Associations of physical activity and fitness with stress reactivity and indices of inhibitory control under stress

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List of abbreviations

ACC	Anterior cingulate cortex
ACTH	Adrenocorticotropic hormone
ANS	Autonomic nervous system
ASP	Arbeitsgemeinschaft für Sportpsychologie in Deutschland
CRediT	Contributor roles taxonomy
CRH	Corticotrophin-releasing hormone
CSA hypothesis	Cross-Stressor-Adaptation hypothesis
DLPFC	Dorsolateral prefrontal cortex
ECSS	European College of Sport Science
EEG	Electroencephalography
ERP	Event-related potential
fMRI	Functional magnetic resonance imaging
fNIRS	Functional near-infrared spectroscopy
HPA axis	Hypothalamus-pituitary-adrenal axis
ISSP	International Society of Sport Psychology
PFC	Prefrontal cortex
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PWC	Physical working capacity
SAM system	Sympathetic-adrenal-medullary system
TSST	Trier Social Stress Test

Summary

Background: Acute psychosocial stress impairs top-down cognitive processes, including aspects of executive functioning. Particularly negative effects on inhibitory control have been highlighted in the literature. During adolescence, the ability to maintain high levels of executive functioning under acute stress is extremely important, because performance in major school exams and finals determines future career opportunities. Moreover, in this age group, brain areas associated with executive functions, such as the dorsolateral prefrontal cortex (DLPFC) are still developing and can be more vulnerable to negative effects of stress. Consequently, research on variables with the potential to mitigate negative effects of acute stress on executive functions is required. Physical activity, fitness, and acute exercise are promising candidates, as research so far suggests that they can reduce stress reactivity and improve executive functioning, including inhibitory control. However, so far these effects have only been investigated separately, and no information is available on associations with executive functioning under stress.

Aims: The overall aims of this dissertation were to investigate whether in male adolescents, physical activity, fitness and acute exercise have health-beneficial effects on stress reactivity, and if these factors improve behavioral and neurocognitive inhibitory control under psychosocial stress.

Methods: One systematic review and two studies were conducted within this research project. The systematic review focused on studies investigating effects of physical activity and fitness on stress reactivity as measured with the Trier Social Stress Test (TSST). Associations of regular exercise and fitness (Study 1, N=42) and acute exercise (Study 2, N=60) with stress reactivity and behavioral as well as neurophysiological inhibitory control under stress were investigated. In both studies, healthy male, right-handed adolescents aged 16-20 years were recruited from local academic high schools. In Study 1, two appointments were scheduled one week apart, with control variables, aerobic fitness and inhibitory control (low stress) being assessed at the first, and stress reactivity and inhibitory control (high stress) at the second appointment. A modified TSST served as the stressor, and endocrine (salivary cortisol), autonomic (salivary alpha-amylase, heart rate) and psychological stress reactivity (state-anxiety) were measured. Inhibitory control was assessed with a computerized Stroop task. The simultaneous measurement of functional near-infrared spectroscopy and electroencephalography allowed for an analysis of DLPFC oxygenation and the N450 component of event-related potentials, respectively. In Study 2, after assessment of control variables and a Stroop task (low stress), participants were randomly assigned to a moderate exercise (30 min on a bicycle ergometer at 70% of maximum heart rate) or a control group (30 min reading). Subsequently, a modified TSST, which included a Stroop task (high stress), was conducted. Stress reactivity and DLPFC oxygenation were measured as in Study 1. In both studies, anthropometric, sociodemographic and psychological control variables were assessed.

Results: Higher aerobic fitness was associated with lower alpha-amylase reactivity, but not with changes in cortisol or psychological stress reactivity. After an acute bout of exercise, compared to a control condition, alpha-amylase and psychological stress reactivity were reduced. Better inhibitory performance at baseline (low stress) was associated with greater N450 negativity and more left-lateralized DLPFC activation. Furthermore, higher aerobic fitness was associated with better inhibitory control at baseline (low stress), which was mediated by N450 negativity, but not by DLPFC lateralization. When comparing high- and low-stress situations, we observed differences in DLPFC oxygenation during tasks demanding inhibitory control. However, inhibitory performance remained unchanged between low and high stress conditions. Acute and chronic exercise had no significant influence on inhibitory control and corresponding DLPFC activity under stress.

Conclusions: We found potentially health-beneficial associations of aerobic fitness and acute exercise with stress reactivity. Our results suggest that exercise might be recommendable to reduce psychological and ANS reactions to acute stress in adolescents, and to improve inhibitory control in low-stress situations. Better conflict monitoring, as indicated by N450 negativity, is suggested as a mechanism underlying the beneficial effects of fitness on inhibitory control. Finally, acute stress had no negative effect on behavioral inhibitory control in our sample of male adolescents, and our data do not support the implementation of acute and chronic exercise to improve inhibitory control under stress.

Zusammenfassung

Hintergrund: Akuter psychosozialer Stress beeinträchtigt höhere kognitive Prozesse einschließlich exekutiver Funktionen. Dies gilt insbesondere für die Fähigkeit der inhibitorischen Kontrolle. In der Adoleszenz ist es von besonderer Bedeutung, eine hohe kognitive Leistungsfähigkeit auch unter Stress aufrecht zu erhalten, da die Leistungen in wichtigen Prüfungen über die berufliche Zukunft entscheiden können. Zudem befindet sich das Gehirn dieser Altersgruppe noch im Entwicklungsprozess, was es möglicherweise anfällig für negative Effekte von akutem Stress macht. Dies gilt vor allem für den dorsolateralen präfrontalen Cortex (DLPFC), der auch für Inhibition verantwortlich ist. Daher sind Untersuchungen zu Faktoren notwendig, die den negativen Einfluss von akutem Stress auf exekutive Funktionen reduzieren können. Vielversprechende Variablen sind körperliche Aktivität, Fitness und Akuteffekte von Sport, da bisherige Untersuchungen zeigten, dass diese Variablen sowohl Stressreaktivität als auch exekutive Funktionen positiv beeinflussen können. Allerdings gibt es noch keine Informationen über den Zusammenhang mit exekutiven Funktionen unter dem Einfluss von akutem Stress.

Ziele: Übergeordnetes Ziel dieser Dissertation ist die Untersuchung von Zusammenhängen von körperlicher Aktivität, Fitness und akuter Sportaktivität mit Stressreaktivität, und mit behavioraler und neurokognitiver inhibitorischer Kontrolle unter akutem psychosozialem Stress. Diese Arbeit fokussiert sich dabei auf männliche adoleszente Studienteilnehmer.

Methoden: Eine systematische Literaturübersicht und zwei Studien waren Teil des Projekts. Die Übersichtsarbeit fokussierte sich auf Studien, die Effekte von körperlicher Aktivität und Fitness auf Stressreaktivität, gemessen mit dem Trier Social Stress Test (TSST), untersuchten. Die beiden Studien untersuchten Zusammenhänge von Sportaktivität und Fitness (Studie 1, N=42) und einer akuten Sporteinheit (Studie 2, N=60) mit Stressreaktivität sowie behavioraler und neurokognitiver inhibitorischer Kontrolle unter Stress. In beiden Studien wurden gesunde, rechtshändige männliche Jugendliche im Alter von 16-20 Jahren rekrutiert, die lokale Gymnasien besuchten. Studie 1 beinhaltete 2 Termine, in denen Kontrollvariablen, aerobe Fitness und inhibitorische Kontrolle ohne Stress (Termin 1), sowie Stressreaktivität und inhibitorische Kontrolle unter Stress (Termin 2) gemessen wurden. Ein modifizierter TSST diente als Stressor, und endokrine (Speichelcortisol), autonome (Speichel-Alpha-Amylase, Herzfrequenz) und psychologische Stressreaktivität (Zustandsangst) wurden erfasst. Eine

Stroop task wurde zur Messung der inhibitorischen Kontrolle verwendet, begleitet von der Messung der DLPFC-Oxygenierung und ereigniskorrelierter Potentiale (N450-Komponente) mittels funktioneller Nahinfrarotspektroskopie und Elektroenzephalographie. Studie 2 begann mit der Messung von Kontrollvariablen, gefolgt von einer Stroop task (ohne Stress). Anschliessend wurden die Probanden randomisiert der Sportgruppe (30 min auf dem Fahrradergometer bei 70% der maximalen Herzfrequenz) oder der Kontrollgruppe (30 min Lesen) zugeteilt. Direkt darauf folgte ein modifizierter TSST, der eine Stroop task (unter Stress) beinhaltete. Stressreaktivität und DLPFC-Aktivität wurden wie in Studie 1 gemessen. In beiden Studien wurden anthropometrische, soziodemographische und psychologische Kontrollvariablen berücksichtigt.

Ergebnisse: Höhere Fitness war mit niedrigerer Alpha-Amylase-, aber nicht mit Veränderungen der Cortisol- und psychologischen Stressreaktivität assoziiert. Nach einer akuten Sporteinheit waren Alpha-Amylase und psychologische Stressreaktivität im Vergleich zur Kontrollgruppe reduziert. Bessere inhibitorische Kontrolle (ohne Stress) hing mit größerer N450-Negativität und linkslateralisierter DLPFC-Aktivität zusammen. Darüber hinaus war höhere Fitness mit besserer inhibitorischer Kontrolle (ohne Stress) assoziiert. Diese Beziehung wurde durch N450 mediiert. Im Vergleich von inhibitorischer Kontrolle mit und ohne Stress zeigten sich Veränderungen in der DLPFC-Oxygenierung, es wurden jedoch keine Unterschiede in der behavioralen Leistung festgestellt. Akute und chronische Sportaktivität hatte keinen signifikanten Einfluss auf behaviorale und neurokognitive inhibitorische Kontrolle unter Stress.

Schlussfolgerungen: Unsere Untersuchungen ergaben potenziell gesundheitsförderliche Zusammenhänge zwischen Sportaktivität und Stressreaktivität. Sport scheint bei Jugendlichen zur Reduktion von psychologischer und autonomer Stressreaktivität, sowie zur Verbesserung der inhibitorischen Kontrolle in stressfreien Situationen empfehlenswert zu sein. Besseres Konfliktmonitoring, angezeigt durch N450-Negativität, ist ein möglicher Mechanismus, der die positiven Effekte von Fitness auf die inhibitorische Kontrolle mediiert. Akuter Stress hatte keinen negativen Einfluss auf behaviorale inhibitorische Kontrolle, und unsere Daten lassen keine Rückschlüsse auf positive Effekte von akuter oder chronischer Sportaktivität auf inhibitorische Kontrolle unter Stress zu.

1 Introduction

1.1 Stress and stress reactivity

1.1.1 Impact on health and cognition

Psychosocial stress is ubiquitous in modern societies and considered a major health issue, as it is a risk factor for many physiological and psychological secondary diseases. For instance, research to this day confirmed that chronic stress is associated with increased risk of metabolic syndrome (Bergmann, Gyntelberg, & Faber, 2014), immune system dysfunction (Puterman et al., 2010; Segerstrom & Miller, 2004), cardiovascular disease (Boutcher, 2017; Kivimäki et al., 2006; Lagraauw, Kuiper, & Bot, 2015), systemic hypertension (Esler et al., 2008), depression (Parker, Schatzberg, & Lyons, 2003), overall psychopathology (Dahl & Gunnar, 2009) and mortality (Chiang, Turiano, Mroczek, & Miller, 2018; Keller et al., 2012), which are all severe burdens for individual and public health. Adverse health effects are not limited to chronic stress conditions. Already the magnitude of an individual's reaction to single psychological stressors is associated with health issues. A recent systematic review including 47 studies on psychological stress reactivity and its relation to future health and disease outcomes found a particularly increased risk of cardiovascular disease and immune system dysfunction in high-responders to acute psychological stress (Turner et al., 2020). While the majority of research focuses on the stress burden of adults, and particularly on occupational stress, it is important to acknowledge that stress and its consequences are phenomena that affect all age groups (Aldwin, 2012; American Psychological Association, 2014; Amirkhan & Auyeung, 2007). Especially the stage of adolescence is characterized by tremendous psychological, social and physiological changes, and because of a rapid increase in potential stressors such as social conflict, social insecurity, performance pressure at school, or anxiety about the future, surveys reported increased stress levels in Swiss adolescents (Eppelmann et al., 2016; Güntzer, 2017).

The effects of chronic stress on the human organism, which can cause ill-health, are often described by the term of allostatic load (Lupien et al., 2015). More than 100 years ago, Walter Cannon postulated that all living organisms strive to maintain a state of equilibrium which is called homeostasis, and that when this complex, dynamic equilibrium is challenged by physical or psychological emergencies (stressors), the organism prepares for either fight or flight (Cannon, 1914). As an extension to Walter's concept of homeostasis, the term of allostasis was introduced by Sterling and Eyer (1988), describing the observation that essentially all physiological processes in the human body maintain stability through constant changes depending on environmental demands (including stressors). The stress response systems are particularly adaptive. If they are overstimulated because of frequent activation, failure to reduce activity after stress, or inadequate responses to stressors, maladaptations and adverse systemic effects occur (McEwen, 2012). This process has been termed allostatic load or overload (McEwen, 1998).

Allostatic load pre-eminently refers to the effect of chronic and cumulated stress and its effects on health. However, stress reactivity can contribute to allostatic load. Greater psychological and physiological responses to a single stressor are linked to potentially prolonged recovery (Linden, Earle, Gerin, & Christenfeld, 1997). Accordingly, in the case of frequently occurring stressors, an overload of the stress response system is more likely in high-responders to acute stress. Additionally, researchers argue that while there is a relative range from higher to lower stress reactivity that can be considered healthy and adaptive (Boyce & Ellis, 2005), evidence suggests that very high (or very low) stress reactivity can be a sign of dysfunctional physiological coping with stress (Cacioppo et al., 1998; Lovallo, 2011). Another argument for the unfavorability of high stress reactivity originates from an evolutionary point of view: As Cacioppo (1998) stated, the processes, which are initiated in reaction to stressors, evolved to support the requirements of fight or flight in dangerous situations (e.g. mobilization of metabolic resources, inhibition of top-down processes, switch to intuitive and experience-based behavior). However, the nature of stressors changed tremendously since the time these mechanisms were established in the human body, with most contemporary (psychosocial) stressors not even allowing a fight or flight response (e.g. school exams or work stress). Metabolic demands in such situations are often low, and high cognitive abilities, such as goal directed behavior, problem solving, control over emotion and inhibition of unfavorable intuitive reactions are required instead. Accordingly, high stress reactivity, which was helpful in our evolutionary past, might be linked with changes in the central nervous, endocrine and autonomic nervous systems that are disadvantageous in the face of typical modern psychological stressors (also see Tsatsoulis & Fountoulakis, 2006). Therefore, research on factors that influence the magnitude of stress reactivity is necessary.

Given the fact that acute stress has a direct influence on our behavior by shifting our mental and cognitive resources to prepare us for fight or flight, it is unsurprising that stress has been shown to have large effects on the brain and its functions (Arnsten, 2009). Over the last decades, research on interactions between stress and the brain intensified. McEwen stated that the brain is “the central organ of stress and adaptation” (McEwen, 2012, p. 17180), meaning that the central nervous system comes into play at many stages of stress reaction (see Section

1.1.2). However, the brain structures involved in these processes are characterized by high plasticity and adaptability and can suffer from maladaptations under severe and repeated stress (Roozendaal, McEwen, & Chattarji, 2009). Research with animals and human subjects showed that particularly the prefrontal cortex (PFC) is sensitive to detrimental effects of stress exposure. On a morphological level, it experiences (reversible) dendritic atrophy and spine loss, and as a result tends to become hyporesponsive (Arnsten, 2009; McEwen, 2012; Roozendaal et al., 2009). Additionally, high levels of noradrenaline and dopamine under stress impair functioning of the PFC (Arnsten, 2009). The result on a functional level is that higher cognitive abilities, which are also processed in the PFC, can be impaired under acute stress (Shields, Sazma, & Yonelinas, 2016). This warrants further research on factors with the potential to buffer such negative effects of stress on cognition and the PFC.

1.1.2 Mechanisms and measurement

As described above, high stress reactivity is problematic and can negatively influence the brain and cognitive functions. Therefore, it is important to look into mechanisms of stress reactivity, and how it can be measured. As the two main stress response systems, the hypothalamus-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS) have been highlighted. Firstly, under acute stress, synaptic networks between limbic system and the hypothalamus stimulate the hypothalamus to release the peptide corticotrophin-releasing hormone (CRH), which in turn stimulates the pituitary to release adrenocorticotropic hormone (ACTH) into the systemic circulation, resulting in the release of cortisol by the adrenal cortex (Foley & Kirschbaum, 2010; Jankord & Herman, 2008). Secondly, the sympathetic branch of the ANS is activated under acute stress, stimulating the adrenal medulla to release adrenaline, thereby preparing the organism for an immediate fight-or-flight response (Allen, Kennedy, Cryan, Dinan, & Clarke, 2014). In the context of stress regulation, the term sympathetic-adrenal-medullary (SAM) system is also used to describe these processes within the ANS (Dawans & Heinrichs, 2017; Schommer, Hellhammer, & Kirschbaum, 2003). Because it is regulated through electrochemical signal transduction, the ANS is considered the faster stress response, while the HPA axis normally becomes effective with a slight delay after stress onset. Activity of both stress axes is closely interrelated, however there is some evidence that they can react differently (Schommer et al., 2003). Supported by initial results from animal studies, some researchers argue that the HPA axis is more related to psychosocial stressors and situations that are characterized by uncontrollability, helplessness or socio-evaluative threat (Dickerson &

Kemeny, 2004), while the ANS is predominantly (but not exclusively) activated in challenging situations which can be mastered actively by effort (Frankenhaeuser, Lundberg, & Forsman, 1980; Henry, 1992).

The activation of both stress axes combined goes along with a number of characteristic changes of functions of the central nervous system, and peripheral functions (Chrousos, 2009). The former include the facilitation of arousal, alertness, vigilance, attention and aggression, the inhibition of vegetative functions (e.g. reproduction, digestion, growth) and the activation of counter-regulatory feedback loops. The latter consist of energy mobilization (i.e. glycogenolysis in the liver), vasodilatation of vessels in the lungs and skeletal muscles, increased cardiac contractility, heart rate, blood pressure, respiration, brain oxygenation, and metabolism (catabolism, inhibition of reproduction and growth), and the activation of counter-regulatory feedback loops including immunosuppression (Chrousos, 2009; Herman et al., 2003). These characteristic changes contribute to focusing resources on dealing with the present situation in the short-term, while delaying processes that are temporarily irrelevant (such as digestion) or have long-term purposes (such as growth and reproduction).

As already briefly mentioned in Section 1.1.1, the central nervous system is involved in virtually all stages of the stress response: It processes afferent sensory information on potentially stressful stimuli, evaluates these stimuli as threatening or not, and initiates the activation of the stress response mechanisms if necessary (Herman et al., 2003; McEwen & Gianaros, 2010; Pruessner et al., 2010). But most importantly, function and activity of both stress axes are constantly readjusted by feedback loops in the central nervous system. Along with the amygdala and the hippocampus, the PFC has been shown to play a pivotal role in the regulation of the stress response. Mostly from animal and lesion studies, it is known that the PFC and hippocampus primarily inhibit the stress response, while the amygdala shows excitatory effects on the HPA axis (Arnsten, 2009; Herman, Ostrander, Mueller, & Figueiredo, 2005; Roozendaal et al., 2009). According to their review on the involvement of the limbic system in stress control, “malfunction of these prominent stress regulatory ‘nodes’ in disease states can result in HPA axis dysfunction” (Herman et al., 2005, p.1202). As cortisol can cross the blood-brain-barrier, it is involved in the feedback loops by influencing brain regions that are involved in the regulation of the stress response (Pruessner et al., 2010). For instance, the PFC has a large number of glucocorticoid and mineralocorticoid receptors, where cortisol can bind (Stark et al., 2006). There, it is believed to cause structural and functional changes in the PFC after prolonged and repeated exposure to stressors (Pruessner et al., 2010; Roozendaal et al., 2009), foreshadowing potential negative effects on other PFC-related functions such as higher cognition (see Section 1.2.3). Analyses on the effects on different age groups revealed, that adolescents' brains are particularly vulnerable to negative effects of stress, as their PFC still continues to develop, and research showed that they potentially express more receptors of the types where cortisol can bind than other age groups (Lupien, McEwen, Gunnar, & Heim, 2009).

Acute psychosocial stress is a phenomenon that occurs in multiple everyday life situations. However, reliably measuring stress reactivity in real-life environments is extremely challenging, since psychosocial stressors vary tremendously, affect individuals differently and may occur and vanish at random times without a distinct beginning or ending (Gerber et al., 2017), making pre-post comparisons of stress parameters often impossible. Therefore, a variety of laboratory stress tasks were developed, allowing a controlled and standardized investigation of stress reactivity with a rigorous measurement protocol. Among these, the Trier Social Stress Test (TSST) has emerged as the most widely used tool. Because of its design as a motivated performance task and the combination of social and cognitive stressors (free speech and mental arithmetic performed in front of a jury after a brief preparation phase), it has a number of advantages. Firstly, it has high ecological validity because having to perform in a socio-evaluative situation (i.e. delivering a presentation in front of a work group or teacher) is a common experience which most people perceive as very stressful because of the threat of negative judgement and the anticipation of an uncontrollable outcome performance (Allen et al., 2017; Campbell & Ehlert, 2012). Secondly, it has been demonstrated that the TSST reliably induces significant increases in the main stress systems, which has been attributed to its inherent combination of several typical features of psychosocial stress such as anticipation, novelty, uncontrollability, and socio-evaluative threat (Campbell & Ehlert, 2012; Dickerson & Kemeny, 2004; Kirschbaum, Pirke, & Hellhammer, 1993). Lastly, it is highly standardized and thus allows for controlled measurements and inter-individual comparisons of the most important stress response parameters (Allen et al., 2014), which are summarized below.

When researchers looked into typical response patterns to psychosocial stressors under controlled conditions, they observed that the perceived psychological stress and the measured physiological stress response are not necessarily interrelated (Campbell & Ehlert, 2012), and that the HPA axis and SAM system can show different response patterns to the same stressor as well (Schommer et al., 2003). Therefore, in order to portray the stress response as a whole and to allow a differentiated investigation, it is considered good practice not to rely on information regarding only one stress axis, but to take different stress response parameters into account when investigating stress reactivity (Allen et al., 2014; Allen et al., 2017; Frisch, Hausser, & Mojzisch, 2015). As a non-invasive marker of the HPA axis, salivary cortisol is used as a gold-standard (Foley & Kirschbaum, 2010), and changes in activity of the ANS are most often represented by increases in heart rate (Forcier et al., 2006) and salivary alpha-amylase (Nater & Rohleder, 2009; Strahler, Skoluda, Kappert, & Nater, 2017). Research showed that both parameters represent different aspects of the ANS and are therefore not redundant (Allen et al., 2014). Psychological reactions to the stressor are often represented by self-reported feelings of anxiety, mood, and calmness (Klaperski, Dawans, Heinrichs, & Fuchs, 2013; Rimmele et al., 2009). An extended summary of biomarkers and psychological markers of stress reactivity in response to the TSST is provided by Allen et al. (2014).

1.2 Inhibitory control

1.2.1 Relevance of inhibitory control

Higher order cognitive abilities include regulation of behavior, thought and emotion, the protection of these processes from internal and external distractions, the inhibition of inappropriate actions and the promotion of task-relevant actions (Arnsten, 2009). Furthermore, they allow us to direct thoughts and actions toward obtaining goals, to adapt to changing environments by shifting the attentional set, and enable us to monitor errors and to change strategies. These capabilities are summarized as executive functions, which are most commonly subdivided in working memory, cognitive flexibility and inhibitory control (Diamond, 2013). Higher executive functioning is associated with better quality of life, mental and physical health, less social problems and higher occupational success (Diamond, 2013). In children and adolescents, higher executive functioning is associated with higher school readiness and school success: studies showed that executive functions are more important for school readiness than other factors such as IQ or entry-level reading or math (Morrison, Ponitz, & McClelland, 2010), and predict better competences in core educational objectives (Borella, Carretti, & Pelegrina, 2010; Duncan et al., 2007). As one of the core executive functions, inhibitory control refers to the ability to “control one’s attention, behavior, thoughts, and/or emotions to override a strong internal predisposition or external lure, and instead do what’s more appropriate or needed” (Diamond, 2013, p.137). Behavior of individuals with low inhibitory control is dominated by habits, implicit preferences, impulses and direct reactions to their immediate environment rather than more reflective precursors such as intentions or long-term goals (Hofmann, Friese, & Roefs, 2009; Miller & Wallis, 2009). Consequently, poor inhibitory control is related to mood disorders (Nigg, 2000), attention deficit hyperactivity disorder (Lipszyc & Schachar, 2010), alcohol and substance abuse (Smith, Mattick, Jamadar, & Iredale, 2014) and eating disorders (Jasinska et al., 2012), while higher inhibitory control is associated with academic achievement (Oberle & Schonert-Reichl, 2013) and favorable health behavior (Allom, Mullan, & Hagger, 2016). Scholars mostly agree that inhibitory control refers to separate but interrelated processes rather than a singular construct, although some disagreed regarding which and how many subdomains can be distinguished (Brydges, Anderson, Reid, & Fox, 2013; Friedman & Miyake, 2004; Nigg, 2000). As a result, most researchers now differentiate between cognitive inhibition, which is often used interchangeably with or is considered a part of interference control, and response inhibition (Diamond, 2013; Shields et al., 2016). Cognitive inhibition (interference control) can be defined as the suppression of a prepotent mental representation (Diamond, 2013), or as the ability to suppress irrelevant information and selectively attend to goal-relevant information (Friedman & Miyake, 2004; Shields, Bonner, & Moons, 2015). It includes resisting unwanted thoughts and intentional forgetting, as well as resisting interference from information acquired earlier (Diamond, 2013). A classic cognitive task representing this domain of inhibitory control is the Stroop task. Its most common version consists of incongruent trials with color words (e.g. “blue”), written in another ink color (“e.g. green”), and congruent trials, where written word and ink color are identical. When asked to ignore the meaning of the word and to only react to the ink color, people tend to be slower in reaction time to the stimulus and make more mistakes in the incongruent condition, because the prepotent response has to be suppressed (Diamond, 2013; Friedman & Miyake, 2004; Vanderhasselt, Raedt, & Baeken, 2009). The response time delay in incongruent trials caused by the increased demand on the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex (DLPFC) is called Stroop interference (Vanderhasselt et al., 2009). Accordingly, while the congruent condition merely serves as an attention task, the incongruent condition requires the higher-order process of cognitive inhibition or interference control.

1.2.2 Neurophysiological correlates

Numerous functional imaging studies illustrated that very specific networks of brain regions contribute to solving cognitive tasks. The cognitive control network encompasses the ACC, the PFC (and particularly the DLPFC), the inferior frontal junction, the anterior insular cortex, the dorsal pre-motor cortex and the posterior parietal cortex (Cole & Schneider, 2007; Rosenbaum et al., 2018). Especially the PFC is considered the highest evolutionary step in brain development, because it plays such a crucial role in higher cognitive functioning and distinguishes us most from other species (Pruessner et al., 2010). The PFC is a cortical area within the frontal lobe, and the DLPFC is situated bilaterally in the dorsal area of the PFC, framing the dorsomedial PFC from the left and right side, and comprising the Brodmann areas 46 and 9, and parts of Brodmann area 8 (Carlén, 2017). The DLPFC is the brain region that is predominantly activated during tasks demanding inhibitory control (Vanderhasselt et al., 2009). For instance, the Stroop task elicits a marked increase in DLPFC activity (Dedovic, D'Aguiar, & Pruessner, 2009). Evidence further suggests that the DLPFC is involved in the cognitive operations of response sequencing, monitoring and manipulation, dual-task coordination, task switching and memory updating (Chaarani et al., 2017). Tasks demanding inhibitory control are often characterized by stimulus conflict or response conflict, and thus require conflict monitoring (Botvinick, Braver, Barch, Carter, & Cohen, 2001). According to the Conflict Monitoring Theory, the ACC signals if a response conflict is present, which is followed by increased recruitment in the DLPFC to increase cognitive control in the subsequent task (Vanderhasselt et al., 2009). As research on neurophysiological correlates of Stroop task performance revealed, these processes do not seem to be congruent over both hemispheres. Higher inhibitory performance is associated with more lateralized DLPFC activity, with greater interference effects in the left, compared to the right DLPFC (Belanger & Cimino, 2002; Vanderhasselt et al., 2009). This finding has been reported repeatedly, and has been replicated with different neuroimaging techniques such as functional magnetic resonance imaging (fMRI) (Spielberg et al., 2011) and functional near-infrared spectroscopy (fNIRS) (Hyodo et al., 2016; Zhang, Sun, Sun, Luo, & Gong, 2014). According to these studies, the leading role of the left DLPFC in this task originates from its activation when distractor incongruence is present during incongruent trials, and when temporally an increase in cognitive control and in the attentional set is required (Vanderhasselt et al., 2009; Zhang et al., 2014).

Evidence in the paragraph above stems from studies using neuroimaging techniques such as fMRI, Electroencephalography (EEG) or fNIRS. Compared to the other two, functional near-infrared imaging is a relatively young neuroimaging technique which is based on the different light absorption properties of oxygenated and deoxygenated hemoglobin in the blood. With optodes mounted to the head, cortical brain regions with changes in the inflow of oxygenated blood can be identified. Neural activity causes an increase in the oxygen metabolism, which at first leads to a local decrease in oxygenated hemoglobin in the blood. Due to neurovascular coupling, this triggers a local increase in oxygen supply. Since this supply is higher than the consumption, the following local increases of oxygenation as detected with fNIRS are interpreted as increased local cortical activity (Herold, Wiegel, Scholkmann, &

Müller, 2018; Scholkmann et al., 2014). Compared to other imaging techniques, fNIRS has the advantage of being relatively robust against movement artefacts (Carius, Hörnig, Ragert, & Kaminski, 2020). It is a small, mobile device that allows the study participant to move freely in-between or even during measurements, making the experience more comfortable for the participants and allowing more flexibility in study designs compared to fMRI. Furthermore, changes over time can be detected with a high temporal resolution (Herold et al., 2018). Zhang et al. (2014) reported that fNIRS measurement during the Stroop task is more sensitive to changes than other neuroimaging tools, and according to Herold et al. (2018), it is suitable for the detection of exercise induced changes in cortical brain activity.

1.2.3 Inhibitory control under stress

As already pointed out in Section 1.1, stress can change morphology and function of the brain, with a particular effect on the PFC. Research suggests that this relates to a change in prioritization from top-down to bottom-up regulatory processes under stress (Arnsten, 2009). In the zone of normal functioning (state of homeostasis), behavior is regulated by top-down processes, with higher-order processes such as executive functions dominating over lower-order processes such as emotions or impulses. This mode of functioning and decision making is characterized as thoughtful, controlled and relatively slow, and requires high involvement of the PFC. Under stress, neuromodulatory changes occur that disrupt PFC network connections and impair PFC functioning, allowing a shift to bottom-up control of behavior. This favors reflexive, intuitive and fast decision making, allowing for rapid responses guided by sensory input and habitual motor responses (Arnsten, 2009). This mechanism is considered evolutionarily advantageous in stressful and potentially life-threatening situations, when fast decisions based on intuition and experience are crucial to survival (fight or flight). However, it may not be optimal for coping with the demands of psychosocial stress, which often requires higher order functioning such as planning, problem-solving or social cognition in real-life situations (Cacioppo et al., 1998; Tsatsoulis & Fountoulakis, 2006).

The empirical research on the effects of acute stress on core executive functions to date is summarized in a systematic review and meta-analysis by Shields et al. (2016). They found predominantly negative effects of acute stress on the domains of working memory and cognitive flexibility. However, it had nuanced effects on inhibitory control: while cognitive inhibition was impaired, aspects of response inhibition improved under stress. This proves the importance of a clear classification of tests investigating different aspects of inhibitory control.

Interestingly, in their analysis, negative effects of acute stress on cognitive inhibition were independent of stress severity, and were not explained by HPA axis reactivity alone. This might show that the stress response is more complex and that we gain more information on effects of acute stress on inhibitory control, if we additionally take the ANS and psychological stress responses into account (see Section 1.1.2).

1.3 Potential buffering effects of physical activity, exercise and fitness

1.3.1 General health effects

According to Sallis (2009), our health is determined by genetics, environment and behavior. Behavior is the domain on which we have the most influence and control, and there is overwhelming evidence for the wide-ranging positive effects of physical activity and exercise behavior on health and well-being. Physical activity is associated with improved mental (Budde & Wegner, 2018) and physical health (Murphy, Lahart, Carlin, & Murtagh, 2019), and better well-being and quality of life (Sudeck & Thiel, 2020). Authors of large cohort studies have repeatedly emphasized the central role of physical activity in the prevention of cardiovascular disease and all-cause mortality (Zhao, Veeranki, Li, Steffen, & Xi, 2019). Furthermore, research showed that physical activity has positive effects on brain health (Blair, 2009): it is associated with increased brain plasticity (Hötting & Röder, 2013), higher gray matter volume in the PFC (Erickson, Leckie, & Weinstein, 2014) and better executive functioning across the lifespan (Ludyga, Gerber, Pühse, Looser, & Kamijo, 2020), including delayed cognitive decline in the elderly (Blair, 2009) (see Section 1.3.3). Even after single bouts of exercise, positive effects on parameters relevant for health and cognition can be observed (Ludyga, Gerber, Brand, Holsboer-Trachsler, & Puhse, 2016; Zschucke, Renneberg, Dimeo, Wustenberg, & Strohle, 2015). Approaching the issue from the other side, studies identified physical inactivity and sedentary behavior as one of the biggest global public health problems of the 21st century (Blair, 2009; Hadgraft et al., 2020; Kohl & Murray, 2012). To some degree, but not entirely, the health-beneficial effects of physical activity and exercise can be deduced to increased physical fitness, which is the adaptation of the organism (i.e. the cardiorespiratory system) to repeated physical exercise (Oja et al., 2015). Studies often do not distinguish rigorously between effects of physical activity, exercise and fitness, as they are highly interrelated (Klaperski, 2017). However, it is important to acknowledge that there are conceptual differences between these variables, and that effects might differ as a result (Klaperski, 2017). For instance, the term physical activity refers to any bodily movement that results in energy expenditure over the course of the day, including gardening, commuting, or exercising, and is very much related to an active or inactive lifestyle and environmental factors (Caspersen, Powell, & Christenson, 1985). Exercise, on the other hand, is defined as planned, structured, and repeated physical activity with the objective to improve physical fitness (Caspersen et al., 1985), and fitness is not only the result of physiological adaptation to behavior, but also has underlying genetic and prenatal determinants (Tikanmäki et al., 2017).

Aside from direct effects of physical activity, exercise and fitness on health, indirect effects are considered as well. On that matter, a prominent and well-investigated assumption is the stress buffer hypothesis (Gerber & Fuchs, 2017; Gerber & Pühse, 2009). It postulates that physical activity and exercise have the ability to buffer the multifold adverse effects of stress on health, which are described in detail in Section 1.1.1. A number of mechanisms such as strengthened personal and social resources, or effects on the perception of and reaction to single stressors are suggested to play a role (Fuchs & Klaperski, 2017; Gerber & Pühse, 2009). Additionally, other authors emphasize that the influence of exercise on metabolic functions such as insulin sensitivity can counteract metabolic disturbances caused by stress and physical inactivity (Tsatsoulis & Fountoulakis, 2006). In their systematic review on studies investigating such stress buffer effects of physical activity and fitness, Gerber and Pühse (2009) observed that about half of the studies provide data that fully or partially support this hypothesis, with evidence from cross-sectional as well as prospective, longitudinal and quasi-experimental investigations. In a more recent, comprehensive overview of the literature, Klaperski (2017) concludes that while many studies corroborate the existence of stress-buffer effects of physical exercise and fitness, underlying mechanisms are still not fully understood.

1.3.2 Effects on stress reactivity

As pointed out in Section 1.3.1, positive effects of physical activity and exercise on health can partly be attributed to buffering effects from negative influences of stress. While such stress buffer effects relate to more long-term outcomes and processes, an increasing body of research focuses on effects of exercise on more short-term stress parameters. In this context, researchers typically refer to the Cross-Stressor-Adaptation (CSA) hypothesis (Gerber, 2017; Sothmann, 2006). It is based on the observation, that physical exercise elicits reactions in the human body that are in part comparable with acute stress. More specifically, exercise that surpasses a minimum intensity of about 50% of maximal oxygen uptake activates the neuroendocrine and autonomic nervous system similarly to acute psychological stress (Budde et al., 2010; Hackney, 2006). However, voluntary exercise does differ from psychological stressors as it lacks harmful features such as uncontrollability and threat, and does not have a negative impact on mood and psychological well-being (Stranahan, Lee, & Mattson, 2008). If the organism is exposed to repeated exercise stimuli, physical fitness increases and another adaptation (habituation) occurs, which is characterized by attenuated neuroendocrine and autonomic responses to the exercise "stressor" (Hackney, 2006). The CSA hypothesis postulates that these adaptations are generalizable to other stressors, in the sense that higher levels of physical activity, regular exercise and better fitness are associated with attenuated reactivity to psychosocial stressors as well, which in turn is associated with better health outcomes (Turner et al., 2020).

The majority of studies investigated potential cross-stressor adaptation effects of physical fitness. An early meta-analysis by Crews and Landers (1987) reported that evidence so far supported the notion of reduced psychosocial stress responses in subjects with higher aerobic fitness. However, study outcomes were predominantly cardiovascular parameters and psychological self-report, and information on endocrine parameters was scarce. These results on cardiovascular stress parameters were mostly corroborated by a later meta-analysis (Forcier et al., 2006). Similar to Crews and Landers, Forcier et al. focused on heart rate and blood pressure as main outcomes, as they have the highest relevance for the prevention of cardiovascular disease. Including a wider range of stress reactivity outcomes such as catecholamine concentrations or skin parameters, Jackson and Dishman (2006) came to a slightly different conclusion in their meta-analysis. Namely, cardiorespiratory fitness only induced marginal changes in overall stress reactivity, and did not mitigate heart rate and blood pressure responses. Thus, the overall meta-analytical evidence provides limited support for the CSA hypothesis, and there is unexplained heterogeneity in the study results. However, the literature cited here is already 14 years old, and more recent studies are available, further broadening the view on effects of physical activity and fitness on stress reactivity of the HPA axis, the ANS, and psychological stress reactivity. Among these studies, a similar overall picture emerges: Several studies reported findings in support of the CSA hypothesis with regard to the HPA axis (e.g. Gerber et al., 2017; Martikainen et al., 2013; Rimmele et al., 2007), the ANS (e.g. Klaperski et al., 2013; Rimmele et al., 2009) and psychological stress reactivity (e.g. Gerber et al., 2017; Rimmele et al., 2007). On the other hand, in some studies, no CSA effects in one or more of these parameters were found (e.g. Childs & Wit, 2014; Jayasinghe et al., 2016; Strahler, Fuchs, Nater, & Klaperski, 2016). Most evidence originates from cross-sectional analyses. The only randomized controlled study, which included a 12-week endurance training program in 96 healthy but mostly inactive office workers, yielded results in support of the CSA hypothesis (Klaperski, Dawans, Heinrichs, & Fuchs, 2014). As the studies cited above (among others) are summarized and analyzed thoroughly in our systematic review, which is included in this thesis, they will not be presented in detail in this introduction, but in Publication 1 (see Section 4.1). Very recently, Wunsch et al. (2019) published another study, where the effects of both habitual and acute exercise were assessed. Compared to the inactive group, habitual exercisers showed lower HPA axis reactivity. Less pronounced effects were reported for ANS reactivity.

The CSA hypothesis refers to the effects of repeated exercise. According to many researchers, comparable effects can be expected for the related constructs of physical activity and fitness (see above). A smaller number of studies investigated, if a single bout of exercise can already elicit similar effects on stress reactivity. In an early study, Steptoe et al. (1993) exposed 36 participants to 20 min of high or moderate intensity exercise or to a control condition, followed by a mental arithmetic and speech task used as a stressor. In reaction to the stressor, the high intensity group showed lower blood pressure, but similar heart rate reactivity compared to the control group. Reviewing effects of acute aerobic exercise on stress-induced blood pressure changes, Hamer et al. (2006) concluded that only studies using a minimum exercise dose of 30 min at 50% of the maximum oxygen consumption had a potentially health-beneficial impact on blood pressure. Only few studies investigated effects on other parameters. Moya-Albiol et al. (2001) compared elite sportsmen to physically active persons. After maximal ergometer exercise until voluntary exhaustion, elite sportsmen showed lower cortisol reactivity and lower slopes in heart rate reactivity than the physically active group, indicating that participants' fitness level might be a modifier of the stress response. Unfortunately, potential conclusions on the effect of acute exercise on stress reactivity are limited by the lack of a control condition to the exercise intervention. More promising results were reported by three more recent studies. Although their study designs varied with regard to use of stressor task, exercise type and intensity, and delay from exercise bout to stressor, they found indications of lower stress reactivity with regard to the HPA axis as well as the ANS in the exercise group compared to the control group (Wood, Clow, Hucklebridge, Law, & Smyth, 2018; Wunsch et al., 2019; Zschucke et al., 2015). In summary, while more studies addressed CSA effects of regular physical activity, exercise and fitness, only few studies investigated CSA effects of an acute exercise bout. However, for both chronic and acute effects, evidence still is inconclusive.

1.3.3 Effects on inhibitory control

As already noted in Section 1.3.1, exercise has beneficial effects on the brain, and particularly on the PFC. Neuroimaging studies using EEG showed that endurance and resistance exercise in particular are associated with improved allocation of attentional resources, faster cognitive processing during stimulus encoding, and better functional connectivity (Hillman, Erickson, & Kramer, 2008; Ludyga et al., 2020). Furthermore, results of studies on event-related potentials indicated increased top-down control during task execution in fitter and physically more active participants (Hillman et al., 2008). Morphological changes, such as increased gray matter volume in the PFC, were demonstrated in fMRI studies (Erickson et al., 2014; Esteban-Cornejo et al., 2014; Hillman et al., 2008). The notion that physical activity is associated with increased brain plasticity is supported by an interesting line of argument by Kempermann et al. (2010). According to them, in our evolutionary past, no separation between physical and cognitive activity occurred, as locomotion was always connected with an increased likelihood of cognitive challenges (such as gathering food, moving forward in difficult terrain, or encountering wildlife). Therefore, physical activity alone already serves as an intrinsic feedback mechanism to the brain, where precursor cells are stimulated to increase proliferation and maintenance over time, in order to overcome the expected cognitive challenges in the future.

Against the backdrop of these beneficial effects of physical activity and fitness on functional and morphological brain parameters, and particularly on the PFC, it is not surprising that many studies investigated the potential influence of acute and chronic exercise on different aspects of behavioral executive performance, as well. With regard to behavioral performance, systematic reviews and meta-analyses of the literature show small to moderate summary effects, indicating better executive functioning in fitter or more physically active study participants, although some groups seem to benefit more than others (Guiney & Machado, 2013; Ludyga et al., 2020; Singh et al., 2019). According to Guiney and Machado (2013), younger participants in developmental stages where cognitive functions are not fully matured yet, benefit most in terms of working memory, inhibitory control and selective attention. In that respect, other summary works by Sibley and Etnier (2003) and Donnelly et al. (2016) revealed that in children and adolescents, higher levels of physical activity and fitness are related to higher inhibitory control, and better performance in many school related cognitive domains such as intelligence, verbal and mathematic tests, academic achievement and academic readiness. The importance of physical activity for cognitive development during childhood and adolescence has also been highlighted in a review of reviews by Biddle et al. (2011). Results of a recent meta-regression analysis by Ludyga et al. (2020) suggested that positive effects of exercise interventions on cognition are more general and less domain-specific, and that male participants seem to benefit more from progressively designed exercise intervention programs than females.

Similar to chronic effects, acute effects of exercise on attention and executive functions have been investigated in many studies (e.g. Budde, Voelcker-Rehage, Pietrabyk-Kendziorra, Ribeiro, & Tidow, 2008; Hillman, Snook, & Jerome, 2003; Koutsandréou, Wegner, Niemann, & Budde, 2016). Reviews and meta-analyses have found small but significant effect of moderate aerobic exercise on executive functions including inhibitory control (Lambourne & Tomporowski, 2010; Ludyga et al., 2016). Ludyga et al. (2016) pointed out that people with low as well as high fitness status seem to benefit from acute exercise, and that age groups undergoing developmental changes are most sensitive to positive effects of acute exercise on executive functioning. Lambourne and Tomporowski (2010) found differential effects of exercise type, with more positive effects in cycling compared to running exercise. Tomporowski (2003) pointed out the importance of the duration of the exercise bout. While bouts of up to 60 min facilitate information processing, extended exercise can compromise executive functioning.

1.4 Summary and knowledge gaps

Within this paragraph, the information contained in the introduction so far is summarized, and knowledge gaps in the current literature are highlighted. Finally, the candidate’s accomplishments within the PhD project are presented.

Psychosocial stress is a major concern in modern, industrialized societies, as it is associated with adverse health outcomes. Among other factors, the incongruence between the evolutionary design of our stress response systems and typical psychosocial stressors might lead to dysfunctional (increased) stress reactivity, which further contributes to allostatic load and the build-up of chronic stress.

Chronic and acute stress further have adverse effects on certain brain structures, and particularly on the PFC, leading to deficits in executive functioning, including the subdomain of cognitive inhibition. This negative effect is highly relevant, because in real-life situations, dealing with acute psychosocial stress often requires the use of higher order cognitive skills and inhibitory control. Higher cognitive control in stressful situations can be a huge advantage and increases the chances to cope well with current and future stressful situations. In front of this background, research on potential remedies and influencing factors is warranted.

In this regard, the investigation of physical activity and fitness, and acute exercise, seems promising. Studies showed that physical activity and fitness can reduce stress reactivity through cross-stressor adaptation effects, and initial evidence indicates that similar effects might already appear after a single bout of exercise. Furthermore, there is compelling evidence for positive effects of acute and chronic exercise on cognition, including inhibitory control. As underlying mechanisms, positive effects of exercise and fitness on brain plasticity in general, and functioning of the PFC in particular, have been suggested.

As the currently available literature reveals, the PFC plays a pivotal role, as it is the nodal point where stress regulation, executive functioning and the positive effects of exercise come together. The PFC is involved in stress regulating feedback loops and downregulates stress reactivity, but is also impaired by high levels of stress. The PFC is at the core of executive functioning, and the DLPFC is particularly involved in inhibitory control. As research showed, these functions decline under stress. Finally, physical activity, fitness and acute exercise have positive effects on the PFC, and can potentially unlock higher capacities of executive functioning under stress.

Within the currently available literature on these complex interactions, three main knowledge gaps have been identified and are explained in the paragraph below. This thesis will make a first effort to contribute to closing these knowledge gaps. Firstly, a systematic synthesis of the recent literature regarding the CSA hypothesis is lacking, and a new, up-to-date review of the literature is warranted for the following reasons. A) The last systematic reviews date back to 2006. While these analyses provided valuable insights into study results with regard to cross-stressor adaptations in the ANS, potential cross-stressor adaptation effects with regard to the HPA axis, and psychological outcomes, were utterly underrepresented at that time. B) While many studies at that time targeted aerobic fitness, measures of physical activity were often not included. C) Furthermore, these analyses included a large variety of physiological and psychological stressors, which can have various effects on stress response parameters (Dickerson & Kemeny, 2004). Oftentimes, cognitive tasks were used as stressors, which other researchers found to be insufficient to elicit a response of the HPA axis (e.g. Budde, Pietrassyk-Kendziorra, Bohm, & Voelcker-Rehage, 2010). Therefore, a new review on studies using a reliable and well validated stressor task is warranted. D) Most importantly, over the last two decades, researchers started to develop and use more standardized psychosocial laboratory stressors with higher transferability to real-life situations (Kudielka, Hellhammer, & Kirschbaum, 2007). Additionally, more sophisticated study designs including measures of psychological stress as well as HPA axis and ANS were implemented (e.g. Gerber et al., 2017;

Klaperski et al., 2013; Rimmele et al., 2007). Most of this research is not represented in these relatively old overviews of the literature. Therefore, the creation of a new systematic review of the current literature was warranted and is presented in Publication 1 of this thesis (Section 4.1).

Secondly, while studies testing the CSA hypothesis targeted children as well as younger and older adults, the stage of adolescence has been neglected in the research so far (Publication 1, Section 4.1). Additionally, only a handful of studies targeted stress reactivity after an acute bout of exercise, and none of them included adolescents in their study population. This is surprising, as this age group is particularly interesting for research on stress reactivity for the following reasons. A) Adolescence is a crucial period for shaping stress responsiveness as an adult, which may afford an opportunity for early intervention (Romeo, 2010). B) This age group has been reported to have higher stress reactivity than others (Dahl & Gunnar, 2009; Kudielka, Buske-Kirschbaum, Hellhammer, & Kirschbaum, 2004; Lupien et al., 2009), so they might also be more exposed to negative effects of higher stress reactivity. C) During adolescence, mechanisms of stress reactivity and coping strategies with stress are not fully developed yet. High or dysfunctional stress reactivity during this developmental period can lead to psychological dysfunction and psychopathologies during adulthood (Dahl & Gunnar, 2009; Romeo, 2013; Sheth, McGlade, & Yurgelun-Todd, 2017). D) Studies already showed promising results with regard to stress reducing effects of aerobic fitness and acute exercise in other age groups (Publication 1, Section 4.1). For these reasons, research on mitigating effects of fitness and acute exercise on stress reactivity in adolescents is necessary, and our findings on this research question are published in Publication 2 (Section 4.2) and Publication 5 (Section 4.5) of this thesis.

Thirdly, although effects of physical activity, fitness and acute exercise on stress reactivity and on inhibitory control have been shown separately, no study so far investigated effects on inhibitory control under acute stress. The following reasons emphasize the importance of such research, and why the phase of adolescence is of particular interest in this context. A) The ability to deliver high cognitive performance under psychosocial stress is of high relevance in modern societies. Across the lifespan, this begins to be particularly relevant during adolescence. For instance, late adolescence is a time when job interests and future career plans start to develop, and performance in school exams defines which career paths can be taken. B) Meta-analytical findings revealed that particularly age groups that are characterized by larger cognitive changes (either improvement during developmental phases, or decline during healthy ageing) can benefit from exercise effects on cognition (Guiney & Machado, 2013; Ludyga et al., 2016). C) During adolescence, the brain and cognitive functions are not fully developed yet (Gunnar, Wewerka, Frenn, Long, & Griggs, 2009). Particularly the PFC is a brain region that only fully matures during early adulthood (Luna, Marek, Larsen, Tervo-Clemmens, & Chahal, 2015). As a result, adolescents with high stress reactivity can experience larger and more long-term negative consequences on cognition than other age groups (Lupien et al., 2009). Therefore, research on effects of regular and acute exercise on executive functioning under stress is necessary. Our results with regard to this topic are presented in the Publications 4 (Section 4.4) and 5 (Section 4.5), respectively.

In the following paragraph, the candidate’s accomplishments within the PhD are summarized briefly. Based on thorough literature research, the candidate identified knowledge gaps, defined aims and hypotheses and, together with the supervisors, developed the design of two studies. Therein, the candidate incorporated the most recent advances in fNIRS methodology for measurement, as well as for analysis, and developed a montage design that allows the simultaneous measurement of both fNIRS and EEG, within a setup combining a psychosocial stress test with a cognitive task. Furthermore, he gained knowledge regarding all required data assessment methods (e.g. saliva sampling for cortisol and alpha-amylase analysis, accelerometry, and fNIRS and EEG data collection). The candidate created the corresponding research proposal and obtained approval from the local ethics committee. During the data collection phase, the candidate organized the recruitment of participants, instructed and supervised five master students and one bachelor student, and was responsible for all measurements. The candidate analyzed all collected data himself except for the analysis of the EEG data. Beyond the two conducted studies, the candidate is the first author of a systematic review. This involved conducting all necessary steps in accordance with the PRISMA guidelines, from design of the research question, over systematic literature search, data extraction, drafting and revising the manuscript, to publication in a high-ranked, peer-reviewed, international journal. Overall, the candidate drafted four PhD-project related publications as the first author, and one as second author (equal contribution of first and second author). Four of the articles are already published in renowned, peer-reviewed, international journals, and one manuscript has been submitted recently. In all publications resulting from the projects, the candidate was responsible for project administration, recruitment of study participants, data collection including maintenance and handling of EEG and fNIRS devices, data analysis (except for EEG data), and writing of the original drafts as well as handling of the revisions. Together with Markus Gerber and Sebastian Ludyga, the candidate conceptualized the sub-projects and developed the methodological approaches, and contributed substantially to the acquisition of supplemental external funding for Study 1. As two of the five publications were published in shared first authorship, the candidate's contribution to these manuscripts are listed in more detail (according to CRediT author statement recommendations) in Publications 3 (Section 4.3) and 4 (Section 4.4). Furthermore, the candidate presented results of the research projects at international congresses on a regular basis (e.g. ISSP, ECSS, or ASP congress). Finally, the candidate engaged in teaching, supervised ten additional bachelor theses, and served the scientific community by writing peer reviews (e.g. for the journals Psychophysiology, Experimental Brain Research, Anxiety, Stress & Coping and European Journal of Sports Science).

2 Aims and hypotheses of the thesis

High stress reactivity has negative effects on health and executive functioning. Particularly negative effects on cognitive inhibition have been highlighted in the literature. Research is needed on variables with the potential to mitigate these negative effects, as maintaining high levels of cognitive functioning under acute stress is important. Physical activity, fitness, and acute exercise have been introduced as behavioral variables with the potential to reduce stress reactivity, and to improve executive functioning. However, so far these effects have only been investigated separately, and no information is available on effects on executive functioning under stress. The PFC has been shown to play a crucial role in these relationships, as it is the agent (facilitation of executive functioning, feedback function on HPA axis), as well as the target organ (inhibited by stress, benefits from exercise).

Therefore, three main goals of this PhD were formulated. The first and second goals were to summarize the literature regarding cross-stressor adaptation effects of physical activity, exercise and fitness, and to investigate such cross-stressor adaptation effects in adolescents, as this age group has been neglected in studies so far. The third goal was to explore potential effects of regular exercise and acute aerobic exercise on inhibitory control under psychosocial stress, as indexed by behavioral performance and changes in DLPFC activity. Therein, the present work focuses particularly on adolescents. This dissertation encompasses one systematic review and two studies. Below, specific aims of the systematic review and the two studies, and hypotheses of the two studies are listed.

2.1 Aims

1) *Systematic review of the literature*

We aimed at summarizing evidence on the effect of physical activity, exercise and fitness on stress reactivity with a special focus on the TSST, and separately for indicators of endocrine, cardiovascular, and psychological stress reactivity; additionally, we aimed to provide an overview of moderators that have been examined in previous studies.

2) *Study 1:* Physical activity and fitness

The aims of Study 1 were threefold: First, we aimed at investigating the association of physical activity and aerobic fitness with physiological and psychological stress reactivity in male adolescents. Second, we aimed at investigating the association of regular exercise with inhibitory control under acute psychosocial stress. Third, we aimed at investigating underlying neurophysiological mechanisms by measuring oxygenation of the DLPFC.

3) *Study 2:* An acute bout of aerobic exercise

The aims of Study 2 were threefold: First, we aimed at investigating the influence of an acute bout of aerobic exercise on physiological and psychological stress reactivity in male adolescents. Second, we aimed at investigating the influence of an acute bout of aerobic exercise on inhibitory control under acute psychosocial stress. Third, we aimed at investigating underlying neurophysiological mechanisms by measuring oxygenation of the DLPFC.

2.2 Hypotheses

Hypothesis 1	*Study 1:* Male adolescents with higher physical activity and fitness show lower physiological and psychological stress reactivity.
	Study 2: Compared to a control task, an acute bout of aerobic exercise elicits lower physiological and psychological stress reactivity in male adolescents.

Hypothesis 2	*Study 1:* Higher levels of regular exercise are associated with better inhibitory performance under acute psychosocial stress. *Study 2:* Compared to a control task, an acute bout of aerobic exercise is associated with better inhibitory performance under acute psychosocial stress.
Hypothesis 3	*Study 1:* Higher levels of regular exercise are associated with more left-lateralized activation of the dorsolateral prefrontal cortex when exerting inhibitory control under stress. *Study 2:* Compared to a control task, an acute bout of aerobic exercise is associated with more left-lateralized activation of the dorsolateral prefrontal cortex when exerting inhibitory control under stress.

3 Overview of the PhD project

This PhD project comprises three sub-projects, which correspond to the formulated research aims. It consists of one systematic review on associations of physical activity and fitness with stress reactivity, and two studies on the association of physical activity and fitness (Study 1), and acute exercise (Study 2), respectively, with behavioral and neurophysiological inhibitory control under stress. To reduce complexity, and for ease-of-reading, this chapter gives a brief overview of the methodological approaches of the three sub-projects and connects them with the corresponding publications in Chapter 4.

The systematic review was conducted in 2018 in accordance with the PRISMA guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009) and included a systematic search within the online databases of PubMed, Web of Science, and PsycINFO, aiming at summarizing data from all studies that investigated effects of physical activity or fitness on stress reactivity as measured with the TSST. Of 645 initially screened publications, 65 full-text articles were assessed after screening, resulting in fourteen studies that met the inclusion criteria. Therein reported data regarding effects on endocrine, cardiovascular and psychological stress reactivity, and potential moderating variables were compiled. The systematic review, as it was published, is presented in Publication 1 (Section 4.1).

Main outcomes of Study 1 and 2 were stress reactivity (salivary cortisol and alpha-amylase, heart rate, and anxiety), and behavioral and neurophysiological representations of inhibitory control with and without psychosocial stress. Behavioral inhibitory control was measured by interference scores on the Stroop task (difference in reaction time and response accuracy between compatible and incompatible test blocks). DLPFC activity (oxygenation differences related to interference) represented inhibitory control on a neurophysiological level. Study 1 investigated the association of physical activity and fitness with these outcomes and was conducted with 42 healthy, right handed, male adolescents aged 16-20 years, all of which were attending an academic high school at the time of measurement. To ensure differences in physical activity and exercise levels, only persons with self-reported leisure-time exercise of either ≥ 6 hours/week or ≤ 1 hour/week were admitted. On the first appointment, anthropometric, sociodemographic and psychological variables, inhibitory control (Stroop task, low-stress condition), and aerobic fitness (Physical Working Capacity 170) were assessed. The second appointment was scheduled one week after the first and consisted of the stressor task (modified TSST), directly followed by a second measurement of inhibitory control (Stroop task, high-stress condition). During the Stroop tasks, DLPFC oxygenation was assessed with fNIRS. In addition, the study included the simultaneous measurement of brain activity via EEG, from which ERPs were extracted. During the seven days between both appointments, physical activity was measured using waist-worn accelerometers. Results of Study 1 were published in Publication 2 (associations of aerobic fitness with stress reactivity, Section 4.2), Publication 3 (associations of aerobic fitness with inhibitory control and neurophysiological pathways, Section 4.3), and Publication 4 (associations of exercise with inhibitory control and DLPFC oxygenation under stress, Section 4.4).

In Study 2, effects of an acute bout of aerobic exercise on the same main outcomes were investigated. Sixty participants were included following the same inclusion criteria as Study 1, except for exercise levels: here, only adolescents reporting 2-6 hours of exercise per week were admitted. After measurement of anthropometric, sociodemographic and psychological control variables and administration of a Stroop task (low-stress condition), participants were randomly assigned to either an acute exercise group (pedaling at 70% of maximal heart rate for 30 min) or to a control group (reading magazines for 30 min). Ten minutes later, participants performed a modified TSST, in which the mental arithmetic task was replaced with a Stroop task under socio-evaluative stress (high-stress condition). Again, during both Stroop tasks, inhibitory control was measured on a behavioral and neurocognitive level by calculating interference scores and assessing DLPFC oxygenation with fNIRS, respectively. Results of Study 2 are presented in Publication 5 (effects of an acute bout of aerobic exercise on stress reactivity, inhibitory control and DLPFC oxygenation under stress, Section 4.5).

4 Publications

4.1 Publication 1: Influence of regular physical activity and fitness on stress reactivity as measured with the Trier Social Stress Test protocol: A systematic review

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SYSTEMATIC REVIEW

Influence of Regular Physical Activity and Fitness on Stress Reactivity as Measured with the Trier Social Stress Test Protocol: A Systematic Review

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Abstract

Background Psychosocial stress is associated with multiple health complaints. Research to date suggests that regular physical activity (PA) and higher cardiorespiratory fitness may reduce stress reactivity and therefore contribute to a reduction of stress-related risk factors. While previous reviews have not differentiated between stressors, we focus on psychosocial stress elicited with the Trier Social Stress Test (TSST).

Objective Our objective was to examine the effect of regular PA and cardiorespiratory fitness on stress reactivity, with a particular focus on the TSST. The TSST is the laboratory task most widely used to induce socio-evaluative stress and elicits stronger stress reactions than most other cognitive stressor tasks.

Methods A systematic search within various databases was performed in January 2018. The following outcomes were considered: cortisol, heart rate, psychological stress reactivity, and potential moderators (age, sex, exercise intensity, assessment mode, and psychological constructs).

Results In total, 14 eligible studies were identified. Cortisol and heart rate reactivity were attenuated by higher PA or better fitness in seven of twelve studies and four of nine studies, respectively. Two of four studies reported smaller increases in anxiety and smaller decreases in calmness in physically active/fitter participants. Three of four studies found that higher PA/fitness was associated with more favorable mood in response to the TSST.

Conclusion About half of the studies suggested that higher PA/fitness levels were associated with an attenuated response to psychosocial stress. Currently, most evidence is based on cross-sectional analyses. Therefore, a great need for further studies with longitudinal or experimental designs exists.

Key Points

Higher physical activity and fitness levels were associated with an attenuated adrenocortical stress reactivity in response to the Trier Social Stress Test (TSST) in about 60% of the studies, indicated by lower increases in salivary cortisol.

Higher physical activity and fitness levels were associated with a reduced cardiovascular reactivity in response to the TSST in about 40% of the studies, indicated by lower increases in heart rate.

Higher physical activity and fitness levels were associated with more favorable psychological responses following the TSST in about half of the studies.

Some evidence indicated a more favorable stress reactivity among people who typically engage in exercise activities with higher intensity levels.

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1 Introduction

In modern societies, psychosocial stress is a major issue associated with psychological and physiological health complaints [1, 2]. While reasonable levels of stress may have beneficial effects on individuals' development, exposure to excessively high and chronic stress that exceeds an individual's coping capacity increases allostatic load and poses substantial health risks across all age groups [3–5]. High subjective stress is associated with a higher risk of cardiovascular diseases [6], stroke [7], metabolic syndrome [8], immune system dysfunction [9] and higher all-cause mortality [10]. Furthermore, cognitive functions can be impaired [11], and stress can contribute to the development of depression or burnout [12].

Most researchers agree that regular physical activity (PA) and higher fitness levels are beneficial to health and well-being [13–16]. Obvious advantages of PA and exercise in comparison with other health-promoting or illness-preventing interventions are cost effectiveness, easy accessibility, and the absence of unwanted side effects, making them increasingly interesting for research [17]. Some researchers argue that PA/fitness not only promotes health through a direct reduction of risk factors for major diseases but also acts indirectly via stress-buffering effects [18–20]. According to a review by Gerber and Pühse [18], half of the reviewed studies supported the claim that people with high exercise levels exhibited fewer health problems if they were exposed to high stress levels.

Several physiological and psychological explanations for a possible attenuating effect of regular PA and better cardiorespiratory fitness on stress have been suggested. According to the cross-stressor-adaptation (CSA) hypothesis, exposure to physical stress (e.g., vigorous exercise) triggers a stress response comparable to that found in reaction to psychosocial stressors [21, 22]. The basic assumption behind the CSA hypothesis is that the (beneficial) adaptation of hypothalamic–pituitary–adrenocortical (HPA) axis activity and the sympathoadrenal medullary (SAM) system during the physical stress of regular exercise can generalize to other, non-physical (e.g., cognitive or psychosocial) stressors [23]. In stress reactivity studies, salivary free cortisol or blood cortisol are usually measured as the main (adrenocortical) parameter [24], with increases indicating a stimulation of the HPA axis. Heart rate (HR) is reported as a criterion for the reactivity of the cardiovascular system, which in turn is modulated by the autonomic nervous system (ANS) [2]. Higher increases in cortisol levels and HR indicate a higher stress response. Less frequently, researchers also assessed blood pressure [25], catecholamine concentrations [26], saliva alpha-amylase [27], or HR variability [28]. Parameters such as anxiety, mood, and calmness are most commonly assessed as psychological outcomes [29–31].

The importance of stress reactivity-related research was highlighted by meta-analytic findings by Chida and Steptoe [32], which showed that a higher stress reactivity, defined as the magnitude of the reaction to acute mental stress, was associated longitudinally with poorer cardiovascular status and a higher risk of subsequent cardiovascular diseases.

The most recent systematic reviews and meta-analyses on the effects of cardiorespiratory fitness on stress reactivity date back to 2006 [33, 34]. In their meta-analysis, Forcier et al. [33] found that participants with higher cardiorespiratory fitness levels showed lower cardiovascular reactivity in response to a wide range of different stressors. More specifically, they reported point estimates of -1.84 ($p<0.005$) and -3.69 ($p<0.001$) for HR and systolic blood pressure, respectively. While these findings suggest that higher fitness levels are associated with a blunted stress reactivity, they cannot be generalized to other physiological parameters or subjective stress reactions. In contrast, Jackson and Dishman [34] included a wider range of physiological outcomes in their meta-analysis (e.g., HR, blood pressure, catecholamines, cardiac function, cortisol). Their study also had a number of strengths, such as the exclusion of studies without maximal or submaximal fitness testing, the exclusion of stressors with a PA component, or the exclusion of studies with a mixed battery of active and passive stressor tasks. A combination of these various reactivity outcomes provided only limited support for the validity of the CSA hypothesis, and high cardiovascular fitness levels were even associated with a small, heterogeneous increase in stress reactivity ($\Delta=0.08$, $p=0.001$). Nevertheless, we hold that this global effect size must be interpreted with utmost caution because different physiological reactivity parameters are regulated by distinct physiological and psychological mechanisms. Moreover, combining different stressors is problematic as different stressor tasks such as physiological stressors (e.g., cold pressor task, forehead cold), cognitive stressors (e.g., Stroop task, mental arithmetic), and socio-evaluative stressors (e.g., public speaking) [33, 35] can elicit different physiological stress reactions [36]. For instance, Dickerson and Kemeny [35] showed that effects on cortisol levels vary greatly across tasks, with highest cortisol reactivity found in motivated performance tasks with the additional element of uncontrollability and socio-evaluative threat.

This may explain why the Trier Social Stress Test (TSST) has become one of the most widely used psychosocial stressor tasks during the past two decades. Developed and validated by Kirschbaum et al. [37], this test consists of an anticipation phase followed by a 5-min mock job interview and a 5-min mental arithmetic task, both in front of a non-responsive jury of two or three people. Over the years, different test versions for children (TSST-C) [38] and for simultaneous measurement in groups of six people (TSST-G) [39] have been developed. The TSST shows high ecological validity and reliability. For instance, the TSST typically induces a two- to threefold increase in cortisol levels from baseline to peak [40, 41]. As shown by Dickerson and Kemeny [35], the socio-evaluative character of the TSST leads to a significantly stronger stress reaction than other cognitive stressor tasks (e.g., simple arithmetic tasks, Stroop task).

Given that the meta-analyses of Forcier et al. [33] and Jackson and Dishman [34] are more than a decade old and were conducted before researchers started using the TSST in CSA studies, we hold that it is time to expand current reviews by examining the effect of regular PA and cardiorespiratory fitness on stress reactivity with a special focus on the TSST, and separately for indicators of adrenocortical, cardiovascular, and psychological stress reactivity.

Considering that the relationship between PA/fitness and stress reactivity might be influenced by a variety of moderating factors, we also aim to provide an overview of moderators that have been examined in previous studies. For instance, as other researchers have pointed out, age might strongly affect physiological and psychological stress responses [34, 42]. Another potential moderator is participants' sex. As highlighted by Kudielka and Kirschbaum [43], glucocorticoid levels were usually higher in females after HPA axis stimulation in animal studies, whereas sex differences in humans seemed to depend on participants' age. Moreover, in a review article on the role of exercise as a stress modifier, Hackney [44] argued that, with increasing exercise intensities, the immediate neuroendocrine stress response (e.g., concentrations of cortisol and adrenocorticotropic hormone in the blood) rises proportionally. He therefore assumed that the intensity with which people typically exercise may have an impact on stress reactivity during psychosocial stressor tasks. Furthermore, scholars have argued that personality affects the perception and regulation of stress, which may also impact on physiological stress reactivity [45, 46]. Personality traits such as competitiveness have been shown to differ between athletes and non-athletes [47] and might lead to variations in cardiovascular stress reactivity [48]. In an attempt to provide a comprehensive model of emotion regulation and dysregulation, Thayer and Lane [49] developed the theory of neurovisceral integration and therein emphasized the importance of inhibitory processes. In a state of dysregulation (e.g., through high perceived or chronic stress), these negative feedback circuits can be disrupted, resulting in perseveration and continued activation of systems. According to Brosschot et al. [50], perseverative cognitions such as rumination, combined with prolonged psychological representations of stressors, can be a factor leading to altered physiological activation in response to stressors.

2 Methods

2.1 Search Strategy

The current systematic review was conducted according to the guidelines provided in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [51]. A research protocol with orientation to the PRISMA-P 2015 checklist was used [52, 53]. The systematic literature search was conducted independently by the first and third author of this article in January 2018 using the online databases PubMed, Web of Science, and PsycINFO. The search terms were ("TSST" OR "social stress*") AND ("physical activity" OR fitness OR exercise OR train* OR sport). As filters within the databases, "abstract availability", "publication date > 1993", and "human subjects" (if available) were used.

2.2 Study Selection and Data Extraction

Studies with cross-sectional and longitudinal design, as well as exercise intervention studies, were eligible for this review. Eligible studies had to (1) investigate the effect of regular PA and/or cardiovascular fitness on stress reactivity, (2) assess stress reactivity with the TSST (studies using an adapted version of the TSST were included if the original structure of the test, consisting of a preparation phase, a free speech task, and a mental arithmetic task, was still recognizable), (3) be published in peer-reviewed journals (in English or German), and (4) focus on healthy human subjects. Studies were excluded if (1) neither cortisol nor HR was measured as a stress reactivity indicator (see Sect. 1), (2) they showed no sufficient differentiation of subjects' PA or fitness levels (e.g., Rohleder et al. [54]), (3) subjects were recruited from non-healthy populations (e.g., Sjörs et al. [55]), or (4) if medication was tested on the subjects (e.g., Sommer et al. [56]). Since the focus of this review was on the effects of regular PA and cardiorespiratory fitness, we further excluded studies investigating the effects of acute bouts of PA on stress reactivity. Given that exposure to psychosocial and socio-evaluative stress is an issue that concerns children, adults, and the elderly (although the effects of acute stress might vary across age groups), no age-specific restrictions were imposed in this review.

After titles and abstracts were screened, full texts of the remaining studies were reviewed with regard to inclusion and exclusion criteria. Additionally, reference lists of available articles and contents of relevant journals were reviewed. If abstracts of studies met the inclusion criteria, but full texts were not available, or if data necessary for the review could not be found in the article, corresponding authors were contacted.

Relevant data were extracted from each article included in the review: age range, number and sex of participants, assessment methods for PA or fitness, group description, TSST version. Table 1 shows the main outcomes. With regard to stress reactivity, saliva or blood cortisol (HPA axis), HR (ANS), and anxiety, calmness, and mood (psychological reactivity) were regarded as main outcomes. Studies were only considered supportive of the CSA hypothesis if group differences or associations were statistically significant ($p < 0.05$).

3 Results

3.1 Overview of Studies

3.1.1 Number of Studies

Figure 1 shows the search process, which was in accordance with the PRISMA guidelines [52]. From the 645 studies initially identified, 14 met the inclusion criteria and are discussed in this review, comprising 13 cross-sectional and one experimental study. Note that the publication by Jayasinghe et al. [57] refers to a subsample of Jayasinghe et al. [26], and Strahler et al. [27] published new data from the study by Klaperski et al. [28].

3.1.2 Participants

In total, 1334 participants (60.7% male) were tested. Sample sizes varied between 34 and 258 participants per study (median 84). Participants' age ranged from 8 to 82 years, with two studies focusing on children [58, 59], seven on young adults aged 18–32 years [25, 29–31, 60–62], four on adults aged 18–65 years [26–28, 57], and one on older adults aged 54–82 years [63].

3.1.3 Stressor Task

As Table 1 shows, 12 studies used one of the TSST standard protocols (five TSST, two TSST-C, and five TSST-G [in groups of three to six participants]), and two studies modified the protocol to some extent (modified speech task to fit the target group [31, 63]).

3.1.4 Assessment of Physical Activity

PA was measured using subjective and objective approaches (Table 1). Validated questionnaires such as the Child Health and Illness Profile—Parent Form [58], the Measurement of Daily Activities and Exercise Questionnaire [28], or the International Physical Activity Questionnaire [62] were administered, or items assessing exercise frequency, duration, and intensity (excluding activities of daily living) were used instead [25, 30, 60, 63]. One study defined different exercise groups via recruitment methods [31]. Objective measurement of PA was achieved via accelerometry over the course of 5–7 days [29, 59].

3.1.5 Assessment of Fitness

Table 1 shows that fitness levels were determined using (spiro)ergometry [26–28, 57], a multilateral fitness test designed for the Swiss army [62], a 4×1000 m running test at increasing subjective exertion [60], or a 3.1 km walking task at an average speed of 5.75 km/h [61].

3.1.6 Outcomes

Twelve of the studies measured cortisol [25–31, 58–61, 63], and nine studies [25, 26, 28–31, 57, 60, 62] reported HR values, as these indicators are known to represent central pathways of the human stress system (see Sect. 1). With regard to psychological parameters, mood [25, 29–31, 60] (five studies) and anxiety and calmness [29–31, 60] (four studies each) were assessed before and after exposure to the stressor.

3.1.7 Calculation of Stress Reactivity

For calculation of cortisol reactivity, most studies used one of the two formulas suggested by Pruessner et al. [64], providing a certain degree of standardization. Accordingly, cortisol reactivity is reported as the area under the curve (AUC) (from baseline to peak) either with respect to the increase from baseline (AUC_I) or with respect to the ground (AUC_G). A different but comparable approach was chosen by Puterman et al. [63], who used multilevel growth curve modeling. Some of the studies also used the difference between peak and baseline cortisol to define reactivity [26, 29, 59]. HR variations in response to the stressor were typically reported as AUC for the time interval from about 5 min before to 5 min after TSST or as the difference between peak and baseline [62]. For reference, some study designs implemented the measurement of resting HR before the TSST instruction in an upright standing position to standardize the conditions (e.g., Jayasinghe et al. [26], Klaperski et al. [28], Gerber et al. [29]).

Table 1 Influence of physical activity and fitness level on TSST outcomes

Study, location	N (M/F); age, years [range (mean)]	Assessment of PA/fitness	Group description	Task	Main outcomes (endocrine, cardiovascular, psychological)
Cross sectional studies					
Childs and de Wit [25], USA	111 (42/69); 18–32 (22.05)	Subjective PA: exercise frequency per week	Sedentary vs. regular exercisers	TSST and non-stressful control task	Cortisol (saliva) → no group differences HR → no group differences Mood → greater decrease in positive affect (elation, friendliness) in non-exercisers
Dockray et al. [58], UK & USA	111 (56/55); 8–13 (10.97)	Subjective PA: CHIP-P questionnaire	Continuous variable (no groups)	TSST-C	Cortisol (saliva) → no association between PA and AUC_I; for girls significant correlation of PA and AUC_I: $r = -0.41$ ($p < 0.05$)
Gerber et al. [29], CH	42 (20/22); 18–31 (21.40)	Objective PA: Accelerometer worn for $M = 5.95$ days (VPA)	Low stress/higher VPA (G1); low stress/lower VPA (G2); high stress/higher VPA (G3); high stress/lower VPA (G4)	TSST	Cortisol (saliva) → group differences in reactivity, with reactivity being highest in G4 and lowest in G1 HR → no group differences State anxiety → no group differences Calmness/mood → group differences in reactivity, with G1 being most calm/having best mood
Jayasinghe et al. [26], AUS	44 F; 30–50 (39.25)	Fitness: $VO_{2\max}$ test	High fit vs. low fit (median split)	TSST	Cortisol (blood) → no group difference; no correlation with $VO_{2\max}$ HR → no group difference; no correlation with $VO_{2\max}$
Jayasinghe et al. [57], AUS[a]	34 F; 30–50 (39.50)	Fitness: $VO_{2\max}$ test	High fit vs. low fit (median split)	TSST	HR → higher reactivity in highly fit women
Klaperski et al. [30], GER	47 F; 18–28 (22.07)	Subjective PA: exercise type, frequency and duration of exercise	Inactive (G1) vs. moderately active (G2) vs. vigorously active (G3)	TSST-G	Cortisol (saliva) → AUC_G differed between groups, being higher in G1 than G2 and G3 HR → average and AUC_G differed between groups (highest in G1) State anxiety → no group differences Calmness/mood → no group differences for calmness; more worsened mood in G3 vs. G1

Table 1 (continued)

Study, location	*N* (M/F); age, years [range (mean)]	Assessment of PA/fitness	Group description	Task	Main outcomes (endocrine, cardiovascular, psychological)
Martikainen et al. [59], FIN	258 (126/132); 8–9 (8.15)	Objective PA: accelerometer worn for mean 5.93 days (overall PA and % of VPA)	Low (G1) vs. intermediate (G2) vs. high overall PA/VPA (G3)	TSST-C	Cortisol (saliva) → overall PA: significant increase only in G1 ($p < 0.001$); lower reactivity in G2 and G3 vs. G1; vigorous PA: significant increase in all groups; lower reactivity in G3 vs. G1 and G2
Puterman et al. [63], USA	46 F; 54–82 (65.41)	Subjective PA: time in vigorous exercise over 3 days	Sedentary vs. active	TSST (modified for elderly)	Cortisol (saliva) → PA did not predict cortisol response; PA moderated the effect of rumination on cortisol response (only in sedentary, high rumination caused an increase in cortisol response)
Rimmele et al. [31], CH	44 M; NR (21.67)	Recruitment-based group differences in endurance training status	Elite athletes vs. untrained men	TSST (modified for athletes)	Cortisol (saliva) → lower cortisol responses in athletes HR → lower HR responses in athletes State anxiety → less state anxiety in athletes Calmness/mood → higher calmness in athletes, less decrease in mood in athletes
Rimmele et al. [60], CH	92 M; 18–32 (24.39)	Fitness: 4 × 1000 m running test (v_{max} and v at 4 mmol/l lactate); subjective PA: frequency and duration of exercise	Elite runners vs. amateur athletes vs. untrained men	TSST	Cortisol (saliva) → significant group differences (lowest cortisol response in elite sportsmen) HR → significant attenuating effect of exercise State anxiety → significant attenuating effect of exercise on state anxiety Calmness/mood → no differences between groups
Strahler et al. [27], GER[b]	115 M; 19–64 (45.70)	Fitness: ergometer test (P_{IAT}/BW)	2- and 3-group-version using age-specific percentiles	TSST-G	Cortisol (saliva) → 2 groups: no group differences; no association between AUC_G or AUC_I and fitness level; 3 groups: significant effect of fitness status
Wood et al. [61], UK	75 F[c]; 18–40 (19.30)	Fitness: HR during a 3 km moderate walk 30 min before TSST	Fit vs. unfit (split at HR = 141)	TSST-G	Cortisol (saliva) → significant lower overall AUC_G in fit group

Table 1 (continued)

Study, location	*N* (M/F); age, years [range (mean)]	Assessment of PA/fitness	Group description	Task	Main outcomes (endocrine, cardiovascular, psychological)
Wyss et al. [62], CH	219 M; NR (20.20)	Fitness: Swiss Army physical fitness test battery; subjective PA: IPAQ	Continuous variable (no groups)	TSST-G	Subjective PA remained insignificant and was not included in the models. HR → positive (enhancing) effect of aerobic fitness (estimated $VO_{2\max}$) and muscle power on HR AUC_G in multiple linear regression ($R^2 = 0.15$); first quartile (highest fitness, high muscle power) with higher reactivity than fourth quartile
Experimental studies					
Klaperski et al. [28], GER	96 M; 19–64 (46.26)	Fitness: ergometer test (P_{IAT}/BW); subjective PA: type, frequency and duration/episode; BSA	Untrained and physically inactive participants	TSST-G	Intervention: 12-week running training program (EG) vs. relaxation training (RG) vs. wait list control (CG); TSST-G and fitness test before (T1) and after (T2) intervention Cortisol (saliva) → within groups: reactivity dropped from T1 to T2 in EG and RG, but not in CG; between groups: higher reactivity improvement in EG vs. CG HR→ within groups: reduction of reactivity from T1 to T2 only in EG; between groups: greater reactivity reduction in EG vs. RG

Studies are presented in alphabetical order

AUC_G area under the curve with respect to the ground, *AUC_I* baseline-adjusted area under the curve, *AUS* Australia, *BSA* Bewegungs- und Sportaktivität Fragebogen (Physical Activity, Exercise and Sport Questionnaire) [86], *CG* control group, *CH* Switzerland, *CHIP-P* Child Health and Illness Profile—Parent Form, *EG* exercise group, *F* female, *FIN* Finland, *G* group, *GER* Germany, *HR* heart rate, *IPAQ* International Physical Activity Questionnaire, *M* male, *NR* not reported, *PA* physical activity, *P_{IAT}/BW* power at individual anaerobic threshold/body weight, *RG* relaxation group, *TSST* Trier Social Stress Test, *TSST-C* Trier Social Stress Test for Children [38], *TSST-G* Trier Social Stress Test in Groups [39], v_{max} maximum velocity, VO_{2max} maximum oxygen consumption, *VPA* vigorous physical activity

[a] Subsample of Jayasinghe et al. [26]

[b] Sample overlapping with Klaperski et al. [28]

[c] From the total sample of 164, only 75 performed the fitness task

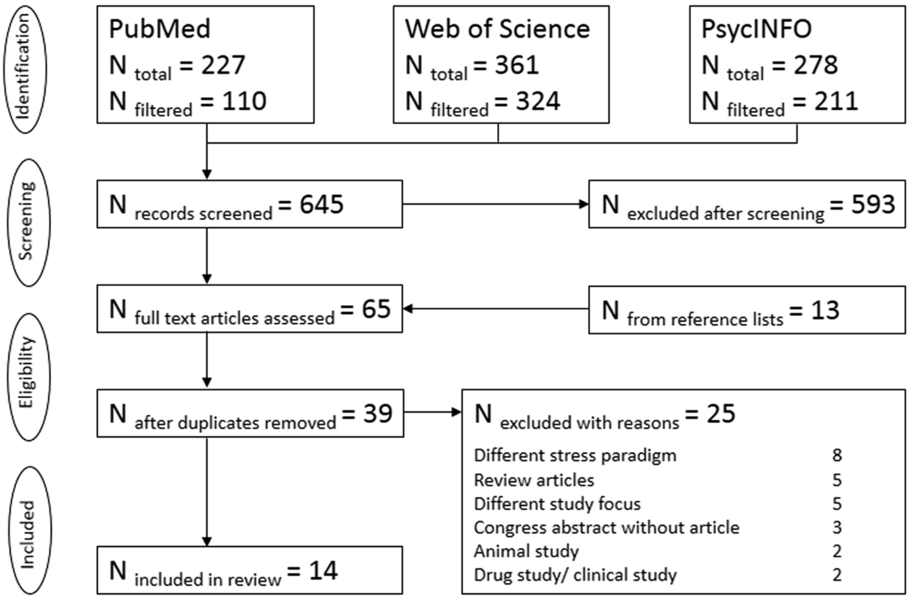

Fig. 1 Flow chart of the different phases of study screening and selection

3.2 General Pattern of Results

3.2.1 Stress Reactivity

In support of the ability of the TSST to induce stress, the measured stress reactivity parameters showed significant changes in response to the TSST in the expected direction across (almost) all studies. Only two exceptions were observed: in Martikainen et al. [59], increases in cortisol levels were detected only in children in the two lower thirds of overall PA, and in Rimmele et al. [31], the stress test did not induce changes with regard to the psychological variable “calmness”.

3.2.2 Cross-Stressor Adaptation Hypothesis

With regard to cortisol, seven of twelve studies fully supported the hypothesis of a reduced reactivity in more physically active or fitter participants, pointing towards an association between increased PA and fitness and a reduced reactivity of the HPA axis in response to psychosocial stress [28–31, 59–61]. Three additional studies found at least partial evidence for the CSA hypothesis [27, 58, 63]. In two studies, cortisol reactivity and PA/fitness were unrelated [25, 26].

With regard to HR, four of nine studies detected lower reactivity in more physically active or fitter participants, indicating that participants with higher PA/fitness levels showed a lower reactivity of the ANS to psychosocial stress [28, 30, 31, 60]. However, three studies found no significant effects [25, 26, 29], and Jayasinghe et al. [57] and Wyss et al. [62] even found that fitter participants showed higher HR reactivity than their less fit counterparts.

With regard to psychological variables, two studies supported the hypothesis that higher PA or fitness levels are associated with lower responses in state anxiety [31, 60] and higher calmness [29, 31] in response to the stressor, whereas two other studies found that this was not the case for state anxiety [29, 30] and for calmness [30, 60]. Moreover, three studies found more positive mood responses to the stressor in participants with higher PA or fitness levels [25, 29, 31]; one study found no significant relationship [60], whereas one study [30] found that vigorously exercising participants displayed stronger decreases in positive mood than their sedentary counterparts.

3.3 Potential Moderators

3.3.1 Age

Five of the reviewed studies included participants’ age in their statistical analysis. In their sample of 111 children aged 8–13 years, Dockray et al. [58] calculated regression analyses on cortisol reactivity, with age and pubertal stage as additional independent variables, finding that age but not pubertal stage was significantly positively associated with stress reactivity in girls. However, there was no association with age or pubertal stage for boys. Gerber et al. [29] used analyses of covariance adjusted for age only if they showed significant associations with physiological and psychological outcomes; however, in their sample of 42 undergraduate students, no significant associations between age and one of the outcomes were present. Klaperski et al. [28] reported participants’ age to be a significant covariate for HR baseline values, but no influence of age was observed on the magnitude of stress reactivity. Puterman et al. [63] replicated all analyses with age as covariate, with unchanged results.

Wood et al. [61] included age as a covariate in their hierarchical multiple regression model but did not report the amount of variance explained by the variable. Nine of the studies did not assess or report the influence of participants' age on their results [25–27, 30, 31, 57, 59, 60, 62].

3.3.2 Sex

With four studies providing information on sex as a potential moderator, our review revealed the following results: For children aged 8–13 years, Dockray et al. [58] found no sex differences in PA and the magnitude of cortisol reactivity, whereas Martikainen et al. [59] found higher levels of overall ($p = 0.01$) and vigorous PA (VPA) ($p = 0.001$) and lower cortisol reactivity ($p = 0.004$) in boys compared with girls. In their sample of young adults, Childs et al. [25] reported significantly higher cortisol ($p < 0.001$, $\eta^2 \rho = 0.16$) responses in men than women but no sex differences in HR and mood responses to the TSST. However, in a similar age group, Gerber et al. [29] found no sex differences regarding cortisol, HR, and psychological reactivity. All other studies investigated either only men or women and therefore did not provide insights into sex as a covariate.

3.3.3 Exercise Intensity

In this review, seven studies provided information regarding an influence of different exercise intensities and fitness levels. In four studies, a three-group design with different fitness or VPA levels (e.g., sedentary vs. active vs. vigorously active) was created. In three of them, participants classified into the highest PA/fitness group showed a reduced cortisol reactivity compared with participants with moderate PA/fitness levels, and to an even greater degree compared with physically inactive/untrained participants [30, 59, 60]. However, in one study, this was not the case [27]. Furthermore, negative Pearson correlations were reported between cortisol reactivity and PA (only in girls) [58], indicating a linear inverse relationship. In contrast to the aforementioned findings, Jayasinghe et al. [57] reported a positive linear correlation between HR reactivity and fitness level as represented by the maximum oxygen consumption (VO_{2max}), indicating possible different mechanisms in the ANS compared with the HPA axis. However, Jayasinghe et al. [26] reported no significant association between VO_{2max} and cortisol or HR reactivity, respectively.

3.3.4 Objective vs. Subjective Physical Activity

Studies using objective measures of PA [29, 59] were more likely to find changes in cortisol reactivity, which fit the CSA hypothesis, compared with studies using self-report questionnaires [25, 58, 63]. This was not the case for variables concerning psychological reactivity, with only one study showing mixed results [29].

3.3.5 Physical Activity vs. Fitness

When differentiating between PA ($N = 8$) and fitness ($N = 6$), the following pattern emerged: With regard to cortisol reactivity, no systematic differences were found. That is, five of eight studies investigating effects of PA found evidence in favor of the CSA hypothesis [29–31, 59, 60]. Three studies found no [25] or only partial [58, 63] evidence. Two of four studies investigating effects of fitness found evidence in favor of the CSA hypothesis [28, 61]. Two studies found either partial [27] or no [26] evidence. With regard to HR reactivity, three of five studies found lower HR reactivity in participants with higher PA [30, 31, 60], whereas two found no significant between-group differences [25, 29]. However, for fitness, two of five studies showed elevated HR reactivity in fitter participants [57, 62], whereas two studies found no significant results [26, 27]. In contrast, one randomized controlled trial reported lower HR reactivity in participants who engaged in 12-week fitness training compared with a control group [28]. None of the fitness-related studies investigated psychological stress reactivity.

3.3.6 Psychological Covariates

Four studies within this review investigated the influence of psychological factors on the relationship between PA/fitness and stress reactivity. Puterman et al. [63] found that, in women aged 54–82 years, rumination seemed to alter this relationship in the sense that, in less active women, only those with high scores in rumination showed elevated cortisol reactivity, whereas the more active participants exhibited values similar to those of the sedentary low ruminators. Rimmele et al. [60] investigated the stress reactivity of 18 elite and 50 amateur athletes compared with 24 untrained men and reported that the personality trait of competitiveness did not modulate stress reactivity in their sample. Wyss et al. [62] investigated potential moderating effects of the so-called Big Five personality traits (neuroticism, extraversion, openness, agreeableness, and conscientiousness) and found no influence on the cardiac response to the TSST. Finally, Gerber et al. [29] used a four-group design, with groups defined by combining high versus low objectively measured VPA with high versus low perceived stress during the last month. They showed, in a sample of 42 undergraduate students, that those with high chronic stress and low VPA displayed the highest cortisol reactivity and the greatest decrease in calmness and mood, whereas students with low chronic stress and high VPA showed the lowest cortisol reactivity and the least decrease in calmness and mood, underlining the potential of subjective stress perception over a longer period of time to moderate the impact of PA on the stress response.

4 Discussion

The purpose of this systematic review was to evaluate the association between regular PA and cardiorespiratory fitness and stress reactivity and to provide an overview of moderators of this relationship that have been examined in prior investigations. In contrast to previous reviews, only studies that used the TSST to experimentally induce stress were included. The TSST is a highly effective standardized socio-evaluative stressor task that can provoke stronger stress reactions than other (e.g., cognitive) tasks.

Our review shows that, in seven of twelve of the studies, higher PA or fitness levels were associated with an attenuated stress reactivity of the HPA axis. The pattern of reactivity of the ANS was less clear: Four of nine studies supported the CSA hypothesis, whereas three studies found no connection and two other studies showed an increased reactivity in participants with higher PA/fitness. With regard to psychological stress reactivity, two of four studies found less severe anxiety and loss of calmness in more physically active/fit participants, and three of four studies showed more positive mood in more physically active/fit than in less active/fit participants.

Furthermore, preliminary evidence suggests a dose–response relationship, indicating that differences compared with inactive participants are stronger among participants with high PA levels than in those with moderate PA levels. Nevertheless, most evidence is derived from cross-sectional analyses, which precludes conclusions about cause and effect. However, one experimental study (randomized controlled trial by Klaperski et al. [28]) suggested that regular exercise training may indeed lead to a reduced reactivity in response to psychosocial stress. The results of the outcomes addressed in this review are discussed separately in the following sections.

4.1 Cortisol

The reactivity of the HPA axis to acute stress is measured by the glucocorticoid hormone cortisol. The present review confirmed that this parameter reacts sensitively to differences in PA/fitness. Thus, the CSA hypothesis was supported in six cross-sectional studies and one randomized controlled trial. Nevertheless, five studies found no or only limited associations. More specifically, one study showed that, in older women, the variables were only associated in the presence of "rumination" as a moderator, meaning that, in less active women, only those with high scores in rumination showed elevated cortisol reactivity [63]. In Jayasinghe et al. [26], the absent association could be explained by the relatively high fitness scores in the low-fitness group, which precluded observation of the differences that would be expected in a truly low-fit sample. This is the only study in this review measuring total blood cortisol instead of salivary free cortisol. According to the free hormone hypothesis, only the unbound (free) cortisol is considered biologically active [65]. In blood cortisol, the rate of free cortisol is only 6–30%. A comprehensive overview of the issue is given by Levine et al. [66]. Moreover, Dockray et al. [58] reported lower PA-related cortisol reactivity only in girls. However, Martikainen et al. [59] conducted a larger study with participants within the same age range and observed no sex-related differences.

At least two other reasons exist to explain why the CSA was not supported in all studies. As demonstrated by Wolfram et al. [67], cortisol reactivity in response to the TSST and to a real-life stressor is only weakly associated. Following Campbell and Ehlert [68] and Roy [69], emotional involvement might be limited during experimentally induced stress, because failure has no real negative consequences for the participants. In line with this notion, Zanstra and Johnston [70] argued that participants might show less strong stress reactions during laboratory stress than during real-life stress. Another factor might be insufficient statistical power. Based on estimations with G*Power software, we found that at least 128 participants are needed to detect moderate between-group differences (Cohen's $f=0.25$) via analyses of covariance (assuming an alpha error probability of 0.05 and a power of 0.80). As shown in Table 1, only two studies had samples with more than 128 participants [59, 62]. Thus, the majority of the studies did not have sufficient statistical power to detect effects of moderate magnitude. In light of these limitations (which also apply to the other outcomes), it is all the more noteworthy that the CSA hypothesis was supported in almost 60% of all studies.

4.2 Heart Rate

Unlike the HPA axis, the ANS appears to show a more diverse reaction to acute psychosocial stress. Five of nine of the studies did not find the expected reduced HR reactivity in physically more active and fit participants. Beyond that, two studies reported an association in the opposite direction [57, 62]. By contrast, four studies reported lower HR reactivity in highly trained and more active participants. This indicates that a cross-stressor adaptation not only might result in adaptation in the sense of habituation but under certain circumstances may also have a sensitization effect on HR reactivity [71]. Interestingly, Wyss et al. [62] reported the aforementioned changes in reactivity for cardiorespiratory fitness and muscle power but not for balancing, indicating a possible moderating effect of the type of fitness on HR reactivity.

Given that higher cardiovascular fitness levels are generally related to lower resting HR, one could argue that this might have confounded the results. In fact, HR baseline differences between fit and unfit (or physically active and inactive, respectively) participants were found in six of nine studies [25, 28, 30, 57, 60, 62]. However, all studies controlled for this potential bias either by using the AUC_I or baseline minus peak to calculate reactivity or by including baseline HR as a covariate. Nevertheless, as highlighted by Jayasinghe et al. [57], it is still conceivable that a "ceiling" effect prevented participants with a high baseline HR from showing higher reactivity levels.

Moreover, little is known so far about the mechanisms underlying individual differences in physiological stress reactivity. Lovallo [72] created a model with a special focus on stress reactivity regulating brain structures. They argued that dysregulation on the central nervous level (prefrontal cortex, limbic system, hypothalamus, and brain stem), in particular, contributes to poor behavioral homeostasis. Lovallo suggests that "stress reactivity ranging from very low to very high has a normative midrange of intensity and present evidence that negative health outcomes may be associated with both exaggerated and diminished stress reactivity since both tendencies imply a loss of homeostatic regulation" [72, p. 121]. Phillips et al. [73] reported that not only a strongly elevated but in some cases also a (neurally based) blunted stress reactivity might correspond to negative health outcomes. This could explain why Wyss et al. [62] and Jayasinghe et al. [57] obtained results at odds with the CSA hypothesis. As Wyss et al. [62] argued, their results would indicate a shift from an unhealthily low to a normal, healthy stress reactivity. But it remains unclear which magnitude of the individual stress reactivity can be considered healthy and how inter-individual differences can be identified, and their assumption does not explain why about 40% of the studies (including one randomized controlled trial) found evidence supporting the traditional CSA hypothesis. One possible conclusion would be that the CSA hypothesis should be adjusted to state that repeated exercise does not necessarily reduce stress reactivity but instead contributes to a normalization to healthy levels that allow the person to improve their homeostatic regulation. However, as the results of our review suggest, this "range of optimal reactivity" explanation seems to be more evident for adaptations of the SAM system but does not reflect current results of the HPA axis reactivity to psychosocial stress.

4.3 Psychological Stress Reactivity

Earlier studies showed that a physiological adaptation might not necessarily be consistent with the pattern and intensity of psychological stress perception [74]. Accordingly, some of the reviewed studies also collected psychological stress parameters. Findings pointed towards positive effects of PA/fitness on reactions to stressful situations (reduced anxiety, improved mood and calmness), with some inconsistencies. In Klaperski et al. [30], changes in mood in athletes were worse than in non-athletes, which the authors attributed to greater competitiveness and achievement motivation in athletes. However, Rimmele et al. [60] found that competitiveness did not moderate stress reactivity. Both studies used similar assessment approaches; reasons for the contrasting findings remain unclear. According to a review by Campbell and Ehlert [68], dissociation between physiological and psychological stress reactivity is an often observed phenomenon and potentially influenced by assessment features, psychological traits and states, and physiological dispositions. Therefore, the assessment of potential moderating factors is crucial.

4.4 Potential Moderators

According to the CSA hypothesis, exercise acts as a stressor itself and leads to beneficial generalized adaptations of the stress systems. Sufficient exercise intensity seems to be a precondition: According to Hackney [44], a minimum exercise intensity of 50–60% of $V\text{O}_{2\text{max}}$ must be reached to elicit cortisol responses to exercise and thus generate adaptations that would match those required by the CSA hypothesis. The direct dependence of cortisol levels on exercise intensity (during exercise) [44] leads to the assumption that there might be a dose–response relationship regarding the influence of exercise on stress reactivity. The results of this review mostly corroborate this assumption. Rimmele et al. [60] showed that ambitious athletes benefit more in terms of reduced stress reactivity than do recreational athletes. Klaperski et al. [30] found a similar pattern in women. Martikainen et al. [59] demonstrated in a sample of children that differences in VPA, but not moderate PA, account for a reduced reactivity to stress, supporting the hypothesis that a higher exercise intensity is related to more pronounced positive effects on stress reactivity. Nevertheless, prospective studies comparing different exercise intensities are needed to draw more reliable conclusions.

Higher age, e.g., in relation to the amount and intensity of past stressful life events, might contribute to blunted stress reactivity [73, 75]. Strong evidence points towards changes in HPA axis activity with progressing age [34]. However, within this review, only one study reported an influence of participants' age on stress reactivity, and only in girls [58].

More than half of the studies did not include age in their statistical analysis. This might be partly because most of the studies included only participants within a specific age range (e.g., 18–30 years), which might not be sufficient to detect age-specific differences. The study by Dockray et al. [58] was conducted with children aged 8–13 years, an age associated with many behavioral and hormonal changes. This might explain why only these researchers detected significant influences of age on stress reactivity. We therefore suggest that future studies should consider a wider age range in their inclusion criteria to more systematically examine the influence of age on stress reactivity.

Our review revealed that, in the majority of studies, the authors tested either men or women. This likely indicates that sex differences were anticipated and, where possible, avoided as a potential confounding factor. However, within this review, studies that included both male and female participants showed inconsistent results for children [58, 59] and young adults [25, 29]. Interestingly, whereas Martikainen et al. [59] found lower cortisol reactivity in boys than in girls, Childs et al. [25] reported the opposite for young men and women, indicating a possible age-dependent alteration of the influence of sex on cortisol reactivity to acute stress. In their review from 2006, Kajantie et al. [76] focused on sex differences in HPA axis responses to acute psychosocial stress, in the aggregate showing that, between puberty and menopause, women normally show lower reactivity than men of the same age. However, menstrual cycle, intake of oral contraceptives, and pregnancy can alter women's cortisol reactivity [76, 77]. Possible underlying mechanisms that have been investigated in earlier research include sex-specific differences (in premenopausal women and men of similar age) regarding the following hormonal properties: adrenal responsiveness to adrenocorticotropic hormone (ACTH), resulting in different secretion rates of cortisol in the adrenal cortex; production rate of arginine vasopressin (AVP) and HPA axis responsiveness to AVP, which is known to potentiate corticotropin-releasing hormone (CRH)-evoked ACTH release in the pituitary and also directly stimulate cortisol secretion; corticosteroid-binding globulin (CBG), which influences the proportion of circulating unbound, metabolically active cortisol and whose production is stimulated by estrogen; and general sex differences in testosterone and estrogen concentration, whose multiple interactions on a central nervous level are still not fully understood [76]. With regard to children's HPA axis reactivity, a recent review focusing on this topic reported higher reactivity in girls than in boys in a majority of studies [78]. Differences were also explained by possible interactions between the HPA axis and the hypothalamic–pituitary–gonadal (HPG) axis.

As already noted, psychological covariates may play a role in regulation of stress reactivity. Within this review, rumination, agreeableness, extraversion, and stress perception within the last month were shown to moderate the relationship between PA and stress reactivity, whereas competitiveness, neuroticism, openness, and conscientiousness were not found to be involved. According to Bibbey et al. [45], cortisol and cardiovascular stress reactivity are consistently associated with a number of personality traits. In a large middle-aged cohort ($N = 352$), they showed that participants with higher neuroticism scores showed lower cortisol and HR reactivity, and greater agreeableness and openness were associated with higher cortisol and HR reactivity. However, in the studies reviewed by Kudielka et al. [41], personality only influenced stress reactivity after repeated exposure to the TSST. In conclusion, results on psychological covariates are inconsistent and mechanisms remain unclear.

4.5 Strengths and Limitations

A strength of this systematic review is the specific focus on the TSST. While other reviews included a great variety of stressor tasks with different grades of effectiveness and possibly different effects on the human stress system, we concentrated on a stressor task that, compared with other known laboratory stressors, typically triggers a more than twofold increased cortisol reaction and has therefore become the most widespread psychosocial stressor task. Thus, we excluded one factor of potential heterogeneity and decreased the likelihood of a beta error. A second strength is the differentiation between markers of HPA axis, the ANS, and psychological parameters. This allows a more precise analysis of the effects of PA/fitness on the different pathways of stress reactivity. Lastly, within this review, an analysis and discussion of potential moderating factors is offered.

However, some potential limitations need to be taken into consideration. First, some characteristics in terms of study design—for instance, measurement of PA/fitness—still varied across studies. Moreover, in some cases, PA and exercise were not clearly differentiated or were used synonymously [26, 60, 63]. PA was measured variously via validated questionnaires, via self-reported frequency, duration and/or time of exercise (excluding activities of daily living), or, more reliably, objectively via accelerometry [29, 59]. Fitness levels were determined using (spiro)ergometry [26–28, 57], a multilateral fitness test designed for the Swiss army [62], a 4 × 1000 m running test at increasing subjective exertion [60], and a 3 km walking task at 5.75 km/h [61]. While ergometer tests allow a more standardized measurement of fitness status, the latter two correspond more to participants' real-life situations.

Second, cut-offs for differentiation between groups with high and low PA or fitness levels varied across studies, depending on sample characteristics, chosen outcome variables, and study designs. Three different approaches were identified: institutional recommendations for minimum weekly PA were applied [29, 61, 63], a median or tertiary split was performed [26, 27, 57, 59], or arbitrary cut-offs were used [25, 30, 31, 60]. Therefore, the different approaches for measurement and categorization of PA/fitness levels mean that inter-study comparisons of PA/fitness are limited to some extent.

Third, because of changes in cortisol secretion through oral contraceptives and throughout menstrual cycles, obtaining valid cortisol samples in women is challenging [77, 79]. Several strategies were used to control this factor, including exclusion of intake of oral contraceptives [25, 30], controlling for menstrual phase in statistical analyses [61], or scheduling all women during the same menstrual phase (mid follicular: Jayasinghe et al. [26]; luteal: Gerber et al. [29], Klaperski et al. [30]). These different approaches might lead to inconsistent results concerning cortisol reactivity in women.

Fourth, we acknowledge that different versions of the TSST were used in the studies. However, all versions are structured identically (preparation phase, public speech, mental arithmetic) and elicit similar stress reactions [38, 39], reducing the likelihood of a potential bias attributable to different TSST versions.

Fifth, as mentioned in Sect. 2.2, we focused only on significance of study results, meaning that findings were only considered as supporting the CSA hypothesis if they were statistically significant. This might have caused a bias, since the likelihood of identifying significant results is greater in larger samples. As mentioned, most of the studies were underpowered, leading to a relatively conservative interpretation of the current state of the art.

Sixth, while stress reactivity was used as an outcome in the present review, we acknowledge that some scholars have argued that recovery from stress is just as important as stress reactivity [80]. Stress recovery is generally defined as the time elapsed between peak reactivity and return to baseline [81]. However, we decided not to consider stress recovery for the following reasons. (1) Recovery is highly dependent on the peak stress reaction. If a person shows a stronger stress reaction, his/her organism may also need more time to return to baseline. Thus, recovery is to some degree confounded by stress reactivity. (2) In most studies, cortisol concentrations were only assessed in 15-min intervals during the recovery phase, which makes it difficult to establish the exact time at which cortisol levels have returned to baseline. (3) The recovery period was relatively short in some studies, so cortisol concentrations were unlikely to have returned to baseline.

Lastly, no meta-analytical techniques were applied to calculate a summary effect over the individual studies as some of the limitations mentioned above have contributed to a large heterogeneity between studies (e.g., different designs, outcomes, and sample populations). In such a case, examination of the source of heterogeneity rather than calculating a summary effect is recommended [82]. However, the small number of studies do not allow subgroup analysis/meta-regression to further investigate potential moderators.

5 Conclusions and Future Perspectives

Despite methodological differences, 58% of the studies included in this review suggested that higher PA/fitness was associated with an attenuated adrenocortical stress response. Although less marked, a similar pattern was observed for the ANS and for psychological stress reactivity. Some evidence points towards a more reduced stress reactivity with increasing exercise intensity. Study results partly support the notion of an optimal stress reactivity in cardiovascular parameters in particular, and higher PA and better fitness contribute to gaining or maintaining this status.

Elevated or impaired stress reactivity is associated with a variety of health issues, including higher risk of cardiovascular disease [83], musculoskeletal problems [84], or depression [1], with potential negative consequences for health systems and the economy of a country. As our review suggests, people with higher PA/fitness levels may react less strongly than their less active/fit counterparts if exposed to acute stress. However, currently, as most evidence is based on cross-sectional analyses, evidence remains insufficient to draw definite conclusions regarding the question of whether stress reactivity can be deliberately improved by exercise training or by encouraging people to integrate more PA into their daily lives. Therefore, there is a great need for further studies with longitudinal or experimental designs. Future studies should also include health outcomes and examine whether additional factors moderate the relationship between PA/fitness and stress reactivity (e.g., socio-economic status, chronic stress, specific personality traits, influence of genetic factors, or the gene–environment interaction). However, the inclusion of moderating factors should be guided by specific hypotheses and based on theoretical considerations. This is important to mention because, so far, the selection of moderators seems quite arbitrary. Moreover, it is noteworthy that all existing studies were conducted either in the USA or in European countries and mostly focused on Caucasian populations. We therefore suggest that more research is needed in other regions and with more diverse ethnic populations to examine the generalizability of the findings. Furthermore, more basic research is required on underlying mechanisms, especially regarding processes in the brain (e.g., interactions between stress, exercise, and brain structures, such as prefrontal cortex, hippocampus, and amygdala [85]) and genetic factors, which are still not fully understood.

Compliance with Ethical Standards

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4.2 Publication 2: Associations between cardiorespiratory fitness and endocrine, autonomous, and psychological stress reactivity in male adolescents

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Article

Associations Between Cardiorespiratory Fitness and Endocrine, Autonomous, and Psychological Stress Reactivity in Male Adolescents

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Abstract: High stress burden during adolescence can have severe long-term health consequences. While some studies reported that adults with higher fitness levels show lower stress reactivity, research on adolescents is scarce. Accordingly, the aim of the present study was to investigate the association between cardiorespiratory fitness and physiological and psychological stress reactivity in male adolescents. Forty-three healthy, male adolescents aged 16–20 years underwent the Physical Working Capacity 170 bicycle ergometer test to determine cardiorespiratory fitness. The Trier Social Stress Test (TSST) was used to trigger a stress reaction, which was measured physiologically with changes in salivary cortisol and alpha-amylase concentrations, and psychologically using self-rated changes in state-anxiety. Under consideration of potential confounders, hierarchical regression analyses were calculated for each outcome. For cortisol and psychological stress reactivity, fitness did not significantly explain variance. However, 28% of variance in alpha-amylase reactivity were explained by fitness and sleep complaints [adjusted R^2 = .28, $F(2, 36)$ = 8.36, p = .001], with 16% of variance explained by fitness alone ($\beta = -.41$, p = .006). Accordingly, higher fitness was associated with lower stress reactivity of the autonomous nervous system in male adolescents. The promotion of cardiorespiratory fitness may therefore be considered an important factor in preventing negative health consequences of stress in this age group.

Keywords: alpha-amylase, psychosocial stress, HPA axis, SAM system, aerobic fitness

An individual's reaction to a stressor is characterized by the activation of two main physiological pathways: the hypothalamic–pituitary–adrenocortical (HPA) axis, resulting in an increased release of the glucocorticoid hormone cortisol, and the sympathetic branch of the autonomous nervous system, which initiates a number of processes, including the release of epinephrine and norepinephrine in the adrenal medulla (Chrousos, 2009) and changes in the saliva enzyme alpha-amylase (Nater & Rohleder, 2009). These processes are designed to improve our ability to deal with subjectively experienced physiological and psychological challenges (Boyce & Ellis, 2005). If someone is exposed to stressors repeatedly and frequently, with insufficient time for recovery, allostatic load increases – with consequent risk of chronic stress and serious health issues, especially for people with naturally higher stress reactivity (Chida & Steptoe, 2010; McEwen, 1998).

In the case of dysfunctional stress reactivity, a host of research has shown the protective effect of regular physical exercise (Huang, Webb, Zourdos, & Acevedo, 2013) and higher physical fitness (Forcier et al., 2006). Acute bouts of exercise have been shown to elicit neuroendocrine reactions similar to acute stress; depending on exercise intensity and duration, norepinephrine, epinephrine, and cortisol levels increase during exercise, and quickly return to baseline afterward (Hackney, 2006). Following Hackney

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(2006), a minimum intensity of 50–60% of maximal oxygen uptake must be reached during exercise to elicit substantial neuroendocrine responses. Studies further show that repeated, regular physical exercise of sufficient intensity leads to attenuated neuroendocrine reactions to exercise (Rimmele et al., 2009). This can be interpreted as an adaptation of the human stress regulation system, and the cross-stressor-adaptation (CSA) hypothesis postulates transfer effects to other stressors, with high levels of regular exercise being associated with reduced reactivity to psychosocial stressors (Sothmann, 2006). To test this hypothesis in laboratory conditions, the Trier Social Stress Test (TSST) has proven to be a suitable task to induce sufficiently high stress responses among participants (Mücke, Ludyga, Colledge, & Gerber, 2018). The TSST is a socio-evaluative stress test consisting of a mock job interview and a mental arithmetic task in front of a non-responding jury (Kirschbaum, Pirke, & Hellhammer, 1993). As main physiological and psychological stress parameters, most studies assess changes in saliva cortisol and state anxiety (Mücke et al., 2018). As a marker of activity of the autonomous nervous system, measurement of the salivary enzyme alpha-amylase has been proposed. As opposed to blood concentrations of epinephrine and norepinephrine, it can be measured non-invasively and has been underscored as a valid marker of stress-induced activity of the sympathetic nervous system (Nater & Rohleder, 2009).

Although many studies have investigated the CSA effect, systematic reviews still report mixed results regarding this hypothesis (Forcier et al., 2006; Jackson & Dishman, 2006; Mücke et al., 2018). Possible reasons of such incoherent patterns of results may be (a) the use of different and sometimes unstandardized stressor tasks (Dickerson & Kemeny, 2004) and (b) differences in measurement of physical activity and fitness. Many studies rely on subjective reports of physical activity (Childs & de Wit, 2014; Klaperski, von Dawans, Heinrichs, & Fuchs, 2013). Some authors used accelerometry to objectively measure vigorous physical activity (Gerber et al., 2017; Martikainen et al., 2013). Because it is known that only frequent exercise of sufficient intensity can evoke cross-stressor adaptations, effects of different aspects of physical fitness on stress reactivity have also been investigated previously (Jayasinghe et al., 2016; Rimmele et al., 2009). Wyss et al. (2016) investigated the associations of physical activity (as measured with the International Physical Activity Questionnaire) and different aspects of fitness (standardized tests of aerobic fitness, balance, and muscle strength) with stress reactivity and found only aerobic fitness to have health-beneficial effects on stress reactivity to the TSST (especially with regard to the autonomous nervous system), showing that aerobic fitness might be the better parameter to assess potential CSA effects.

Another conclusion that can be drawn from the literature reviews is that the focus of CSA research often lies on stress in adulthood. Health-beneficial effects of regular physical exercise and/or higher cardiorespiratory fitness levels on psychosocial stress reactivity have mainly been demonstrated in adults with cross-sectional studies (Gerber et al., 2017; Rimmele et al., 2007; Wood, Clow, Hucklebridge, Law, & Smyth, 2017; Wunsch et al., 2019; Wyss et al., 2016) and a longitudinal study (Klaperski, von Dawans, Heinrichs, & Fuchs, 2014). Preliminary cross-sectional evidence exists for similar effects in the elderly (Puterman et al., 2011), and in children (Martikainen et al., 2013). However, adolescents are less frequently targeted. Adolescence is defined as the period between childhood and adulthood, which encompasses biological growth as well as major social role transitions (Sawyer, Azzopardi, Wickremarathne, & Patton, 2018). The beginning is usually defined as the onset of puberty, while the end can be defined as the completion of role transitions to adulthood (e.g., completion of education, financial independence, etc.) (Sawyer et al., 2018) or, as a possible biological marker, by abrupt changes in chronotypes around the age of 20 years (Roenneberg et al., 2004). In our recent review on TSST studies on the CSA-hypothesis (Mücke et al., 2018), we only found one study that included some participants at a very early stage of adolescence (up to 13 years of age), showing that in girls, age and pubertal stage, but not physical activity, were positively related to stress reactivity (Dockray, Susman, & Dorn, 2009). By contrast, no data on later stages of adolescence were present. In three different reviews and meta-analyses (Forcier et al., 2006; Huang et al., 2013; Jackson & Dishman, 2006), which also included other stressor tasks, only two studies were identified with adolescent samples. Norris, Carroll, and Cochrane (1992) showed in a sample of 13- to 17-year-old adolescents that higher levels of exercise were related to lower levels of subjective stress. Further, compared to two lower intensity training groups and a control group, participants undergoing a 10-week high intensity aerobic training were able to reduce subjective stress. However, Norris et al. (1992) focused on chronic stress and well-being, and not on acute stress reactivity. Szabó et al. (1994) investigated the association of maximum aerobic power (VO_2max) with cardiovascular stress in reaction to a mental stressor in a sample of 20 adolescent judo athletes. They observed faster stress recovery in participants with higher VO_2max. However, they only tested a small and specific sample, and used a very brief (2 min) stressor task.

The scarcity of such research on adolescents is surprising, as for a number of reasons, the developmental stage of adolescence demands particular attention. During adolescence, behavioral patterns are established that affect adult-age physiological and psychological health (Dahl &

Gunnar, 2009). For a successful transition from adolescence to adulthood, competencies in dealing with stress are necessary (Eppelmann et al., 2016). In case of increased HPA axis reactivity to stress, the risk of psychopathology (Dahl & Gunnar, 2009) and for developing other stress-related health issues like cardiovascular disease (Kivimäki et al., 2006), metabolic syndrome (Bergmann, Gyntelberg, & Faber, 2014), or immune system dysfunction (Segerstrom & Miller, 2004) in the future increases. Recent research shows that in Switzerland, 52% of the adolescents feel stressed or overworked often or very often (Güntzer, 2017), with an increase over previous years (Eichenberger, Kretschmann, & Delgrande Jordan, 2017). Similar results are reported for other countries (Deb, Strodl, & Sun, 2015). The last years before graduation are perceived as particularly stressful (Eppelmann et al., 2016). These points underline the importance of research on stress-reducing factors in adolescents.

Based on the CSA-hypothesis, the purpose of the present study was to explore whether cardiorespiratory fitness is associated with stress reactivity in male adolescents. Lower stress reactivity in fitter participants was hypothesized. This study addresses an important research gap as very few prior studies exist with adolescents. A well-established and validated laboratory stressor task was used, and by measuring endocrine, autonomous and psychological parameters, different perspectives on stress reactivity have been covered. Furthermore, potential confounders identified in prior research were taken into account. Finally, whereas previous studies have relied on self-ratings to assess exercise intensity and duration, we used a validated fitness test in order to objectively measure participants' cardiorespiratory fitness.

Materials and Methods

Participants

In total, 43 participants were recruited via advertisements, flyers, and personal contact. Only male, healthy (nonclinical), right-handed individuals between 16 and 20 years of age were included. To standardize for educational status, only participants currently attending academic high schools were admitted. To achieve two distinct groups in terms of physical activity and fitness level, only adolescents who usually participate in leisure-time exercise and sport activities for (a) less than 1 hr per week or (b) more than 6 hr per week were eligible for the study (assessed via self-report; exercise/sport participation was defined as activities of a duration of at least 30 min that involve sweating and/or getting out of breath; activities during compulsory school physical education lessons were excluded). Participants were informed about the study procedures at least 3 days prior to the data assessment and provided written informed consent. All study procedures were in accordance with ethical principles of the Declaration of Helsinki and approval was obtained by the local ethics committee (Ethikkommission Nordwest- und Zentralschweiz; EKNZ no. 2017-01330, Basel, Switzerland) before the start of the study.

Procedures

To minimize the potential impact of variations in diurnal cortisol levels (Kudielka, Schommer, Hellhammer, & Kirschbaum, 2004), all appointments were scheduled in the afternoon. Tests started either at 13:00 or at 16:00. On the first appointment (T1), participants filled in a questionnaire to assess information about their social and demographic background and other potential confounders. Body height and weight were measured objectively via an electronic scale (Tanita BC-601, Tokyo, Japan) and a stadiometer. Cardiorespiratory fitness was measured using the Physical Working Capacity 170 (PWC170) as described by Bland, Pfeiffer, and Eisenmann (2012). Additionally, a cognitive test (Stroop task) was performed, which is described in more detail in a different publication (Ludyga, Mücke, Colledge, Pühse, & Gerber, 2019). During this task, participants wore a flexible head cap equipped with sensors for measuring brain activity. Seven days later, at the same time of the day, participants were scheduled for the second appointment (T2). Participants were instructed in advance to not engage in moderate-to-vigorous physical activity (activities that make them get out of breath and/or sweat) and to refrain from drinking alcohol or coffee and taking any medication during the 24 hr before the appointment, to refrain from eating and drinking (except water) during the hour before the appointment, and to avoid rushing to the appointment (Klaperski et al., 2013). Upon arrival, participants rested for 10 min in order to reduce the influence of possible stress factors before and/or during arrival. Subsequently, the flexible head cap for measuring brain activity was applied again and a baseline measurement was conducted (brain activity is not addressed in the present article; therefore, these procedures are not described in detail). Then, the TSST was performed as described in section Stress Reactivity. Directly after the TSST, a Stroop task (see Figure 1) was conducted identically to T1, which is not included in this publication. Since the participants were already familiar with this test from T1 and it was not performed in front of the TSST jury, it lacks the elements of uncontrollability and socio-evaluative threat (Dickerson & Kemeny, 2004). Therefore, we do not expect it to influence stress reactivity. However, potential effects of this additional test on the results are covered in the discussion (section Strengths and Limitations). A total of nine saliva

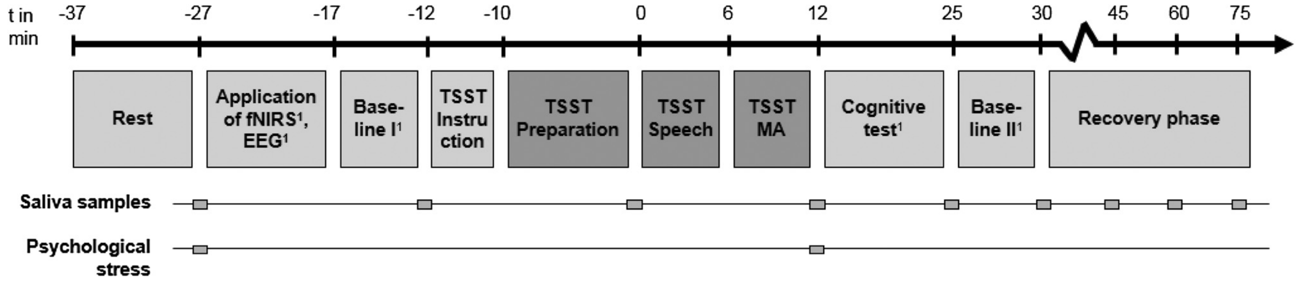

Figure 1. Study procedures during the second appointment. EEG = electroencephalography; fNIRS = functional near-infrared spectroscopy; MA = mental arithmetic; TSST = Trier Social Stress Test. [1]Not included in this publication.

samples were collected before and after the TSST. Additionally, participants completed a brief questionnaire on psychological stress parameters before and after the TSST. For a detailed timeline of the assessments see Figure 1. After debriefing, all participants received financial compensation for their participation in the study.

Cardiorespiratory Fitness

Cardiorespiratory fitness at submaximal intensity is measured with the incremental bicycle ergometer test PWC170. It represents the workload at which a heart rate of 170 beats per minute is achieved (Bland et al., 2012). Submaximal fitness tests have the advantage that they depend less on the participants' motivation than maximal aerobic capacity (VO_2max) tests while being less costly and requiring less equipment. Studies showed high correlations of $r = .70$ to $r = .84$ with VO_2max (Bland et al., 2012; Boreham, Paliczka, & Nichols, 1990), demonstrating the validity of the PWC170 test.

Participants were pedaling at 70–80 revolutions per minute throughout the test and started the first stage at 30 W. Every 2 min, the resistance was increased depending on participants' heart rate during the last 10 s of the previous stage. This stage length was chosen because Bland et al. (2012) showed in a slightly younger sample that 2-min-stages correlate better with VO_2max than longer stage durations. When participants reached a heart rate of at least 165 beats per minute during one stage, the test was terminated at the end of that stage (after 3–5 stages). The maximum power output, measured in watt relative to body weight (W/kg), was used as a measure of cardiorespiratory fitness.

Stress Reactivity

Stress reactivity was measured using the TSST, a psychosocial stress test first introduced by Kirschbaum et al. (1993). It consists of a mock job interview and a mental arithmetic task, thereby combining a motivated performance task with the additional element of uncontrollability and socio-evaluative threat. This test has been shown to be more effective in triggering a physiological stress response than other laboratory stressor tasks (Dickerson & Kemeny, 2004). The standard protocol was slightly modified: after a 10-min preparation phase, participants performed a 5-min free speech in front of a committee of two persons (one male and one female), followed by a 5-min mental arithmetic task. Before the preparation phase (also called anticipation phase), participants were instructed to imagine a situation in the near future when they finished school, are looking for a job and are offered a job interview for their dream job. The committee was introduced to the participants as the manager of the company and an assistant who is specialized in the interpretation of body language and voice frequency. Throughout the speech, the committee showed neutral facial expressions and only used standardized responses (e.g., "You still have time left. Please continue."). The mental arithmetic task consisted of five rounds of counting backward as quickly as possible (from 310 in steps of 9, from 430 in steps of 11, from 450 in steps of 7, from 320 in steps of 13, and from 640 in steps of 8). In case of a mistake, the participant was interrupted and asked to begin again at the last correct number. After the test, participants stayed in the room for another 65 min to assess stress recovery. To standardize conditions, all participants watched a nature documentary movie during the recovery phase.

Physiological Stress Responses

While salivary free cortisol represents the reactivity of the HPA axis (Kudielka, Schommer, et al., 2004), salivary alpha-amylase is known to be reflective of the stress response of the autonomous (more specifically: sympathetic) nervous system (Nater & Rohleder, 2009; Strahler, Skoluda, Kappert, & Nater, 2017). Saliva samples were collected using Salivette® Blue cap (Sarstedt, Nümbrecht, Germany). They were first stored at −20 °C and then sent to the Biochemical Laboratory of the University of Trier, Germany, for analysis of cortisol (in nmol/L) and alpha-amylase concentrations (in U/mL) using time-resolved fluorescence immunoassay. For quality control, all samples were analyzed in duplicates.

Usually, salivary cortisol levels rise with about 10-min delay relative to stressor onset. To be able to find the value that best represents a true baseline, three samples were taken before the TSST onset: (a) 10 min after arrival, (b) before the TSST instruction, and (c) after the preparation phase. Because the average cortisol level was lowest after the preparation phase, we decided to use sample 3 as cortisol baseline. Further samples (no. 4–9) were collected at +12 min, +25 min, +30 min, +45 min, +60 min, and +75 min relative to TSST onset. Based on the group average, peak cortisol was found at sample 5 (25 min after the beginning of the TSST).

Salivary alpha-amylase shows immediate increases after stimulation of the autonomous nervous system and recovers more quickly than salivary cortisol (Rohleder & Nater, 2009). Accordingly, only the first six samples were analyzed (10 min after arrival to +30 min after TSST onset; Figure 1). Since the lowest group average was found at the second sampling occasion, sample 2 was used as the baseline. Peak values (based on the average in the total sample) were found for sample 4 (+12 min after the beginning of the TSST).

Following Pruessner, Kirschbaum, Meinlschmid, and Hellhammer (2003), for cortisol and alpha-amylase the area under the curve with respect to the increase (AUC_I) was calculated. Compared to the area under the curve with respect to the ground (AUC_G), the AUC_I is more reflective of changes over time and therefore more suitable for the research questions addressed in our study. Similar approaches were chosen by Martikainen et al. (2013), Strahler, Fuchs, Nater, and Klaperski (2016) and Gerber et al. (2017). As described above, reactivity onset and recovery time vary across variables. Therefore, different time frames were taken into account: for cortisol, the AUC_I between sample 3 (after the TSST preparation phase) and sample 9 (+75 min after TSST onset) was calculated. For alpha-amylase, the AUC_I between sample 2 (before the TSST preparation phase) and sample 6 (+30 min after the TSST onset) was calculated.

Psychological Stress Responses

Representing psychological stress responses, subjective state anxiety was assessed before and directly after the TSST. With orientation to previously used approaches (Gerber et al., 2017; Klaperski et al., 2013; Rimmele et al., 2007), five items of the State-Trait Anxiety Inventory (STAI, Laux, Glanzmann, Schaffner, & Spielberger, 1981) were selected to reduce expenditure of time (Cronbach's alpha, $\alpha = .82$). After recoding inverted items, a sum score was calculated. It ranges from 5 to 20, with higher scores indicating higher anxiety.

Potential Confounders

In previous studies, younger age (Kudielka, Buske-Kirschbaum, Hellhammer, & Kirschbaum, 2004), lower socioeconomic status (SES, Neupert, Miller, & Lachman, 2006), higher chronic stress (Gerber et al., 2017), sleep complaints (Giese et al., 2013), lower mental toughness (Kaiseler, Polman, & Nicholls, 2009) and dimensions of mental issues (Dahl & Gunnar, 2009) have been shown to aggravate the reactivity of endocrine or other stress markers in reaction to acute stress. Consequently, age (in years), socioeconomic status (one item), sleep complaints (7-item Insomnia Severity Index [ISI], Gerber et al., 2016), chronic stress (10-item Perceived Stress Scale [PSS], Klein et al., 2016), mental toughness (18-item short form of the Mental Toughness Questionnaire [MTQ18], Gerber et al., 2018), and psychopathology (25-item Strengths and Difficulties Questionnaire [SDQ], Goodman, 2001) were assessed as potential confounders. The validity of all psychological instruments has been established previously and all measures showed acceptable internal consistency in the present sample (Cronbach's alpha values for the ISI = .65, for the PSS = .75, for the MTQ18 = .83, and for the SDQ = .72).

Statistical Analysis

For a priori power analysis with G*Power, physiological stress reactivity parameters were defined as main outcomes of interest. Based on results of previous studies, an effect size of $f^2 = .30$ was expected (Gerber et al., 2017; Klaperski et al., 2013; Rimmele et al., 2007). With the parameters linear multiple regression, one-tailed, α-error probability = .05, power = .80, and number of predictors = 3, power calculation resulted in a required sample size of $N = 41$. All analyses were conducted without TSST non-responders, defined as participants displaying values during the stress test that are equal to or lower than baseline (four participants for cortisol analysis, and two participants for alpha-amylase analysis). Effectiveness of the TSST was measured with baseline-to-peak comparisons (paired t-tests) for physiological stress parameters, and pre-post stressor comparisons for psychological stress. Bivariate Pearson correlations between stress reactivity outcomes, fitness and potential confounders were calculated. For each stress reactivity parameter, potential confounders with significant bivariate correlations were included in the subsequent hierarchical linear regression analyses. In the regression analyses, potential confounders were included in the first step and cardiorespiratory fitness in the second step. For interpretation, bivariate correlations of $r = 0.1$, 0.3, and 0.5 were used as thresholds indicating small, medium, and large correlations, respectively (Cohen, 1988). Effect sizes were classified as small ($d = 0.2$), medium ($d = 0.5$), or large ($d = 0.8$) (Cohen, 1988). Significance level was defined as $p < .05$. All statistical computations were performed with SPSS 24 (IBM Corporation, Armonk, NY, USA).

Results

Dropout and Descriptive Data

One participant dropped out after the first appointment because of a sports injury. The data of this participant were excluded from further analysis.

Mean (standard deviation) maximum PWC 170 performance of the remaining 42 participants was 2.9 (0.6) W/kg, ranging from 1.2 to 4.1 W/kg. Mean maximum power output was 206.9 (45.2) W, ranging from 120 W to 300 W.

Mean (standard deviation) baseline and peak values for physiological stress reactivity parameters were as follows: 3.3 (1.4) nmol/L and 9.7 (5.1) nmol/L for cortisol and 196.5 (128.8) U/mL and 377.5 (216.8) U/mL for alpha-amylase. Regarding psychological stress, mean (standard deviation) state anxiety increased from 8.0 (2.1) to 12.8 (3.1). Changes over time in physiological and psychological parameters are presented in Figure 2.

Effectiveness of the Stressor Task

For the total sample (without non-responders), paired *t*-tests revealed a significant increase in cortisol concentrations ($t(37) = 8.85$, $p < .001$, $d = 1.44$), alpha-amylase concentrations ($t(39) = 8.91$, $p < .001$, $d = 1.41$) and state-anxiety ($t(41) = 9.80$, $p < .001$., $d = 1.51$) with large effect sizes for all three parameters.

Physiological Stress Responses

Four participants did not show an elevation in their cortisol level in response to the stressor. They were classified as non-responders and therefore excluded from further analysis. No significant correlations between the potential confounders and cortisol reactivity were found (Table 1). Therefore, only cardiorespiratory fitness was included in the regression equation, with no significant results [Table 2; adjusted $R^2 = -.02$, $F(1, 36) = .18$, $p = .671$].

Two participants did not show an elevation in their alpha-amylase level in response to the stressor. They were classified as non-responders and therefore excluded from further analysis. Of the potential confounders, only sleep complaints showed a correlation of $p < .05$ with alpha-amylase reactivity and were thus included in the regression analysis (Table 1). The results indicated that the two predictors explained 27.9% of the variance in alpha-amylase [adjusted $R^2 = .28$, $F(2, 36) = 8.36$, $p = .001$]. As shown in Table 2, more frequent sleep complaints ($\beta = -.48$, $p = .002$) and higher cardiorespiratory fitness ($\beta = -.41$, $p = .006$) were related to lower alpha-amylase reactivity.

Psychological Stress Responses

For poststress state-anxiety, bivariate correlations with SES and mental toughness exceeded the level of $p < .05$ (Table 1). Consequently, these factors as well as pre-stress anxiety were controlled in the regression analysis before introducing cardiorespiratory fitness in the second step. All predictors together explained 19.3% of the variance in state anxiety [adjusted $R^2 = .19$, $F(4, 37) = 3.44$, $p = .017$]. However, fitness did not contribute significantly to the explained variance ($\beta = .20$, $p = .218$; Table 2).

Discussion

This study aimed to investigate the association of cardiorespiratory fitness with stress reactivity in male adolescents, a population so far neglected in this field of research. The key findings of our study are that cardiorespiratory fitness explained 16% of the variance in alpha-amylase reactivity, with higher cardiorespiratory fitness being related to lower stress reactivity. However, cardiorespiratory fitness was not associated with cortisol and psychological stress reactivity. Our results only partly corroborate the validity of the cross-stressor adaptation hypothesis.

Autonomous Nervous System

Changes in alpha-amylase are increasingly used as a marker of the autonomous nervous system (Nater & Rohleder, 2009). This is supported by studies reporting correlations between stress-induced changes in alpha-amylase and other indicators of sympathetic nervous system activity such as norepinephrine, heart rate, heart rate variability, basal skin conductance level, and measures of sympathovagal balance (Thoma, Kirschbaum, Wolf, & Rohleder, 2012). Although some methodological aspects are still the subject of controversial debate (Bosch, Veerman, de Geus,

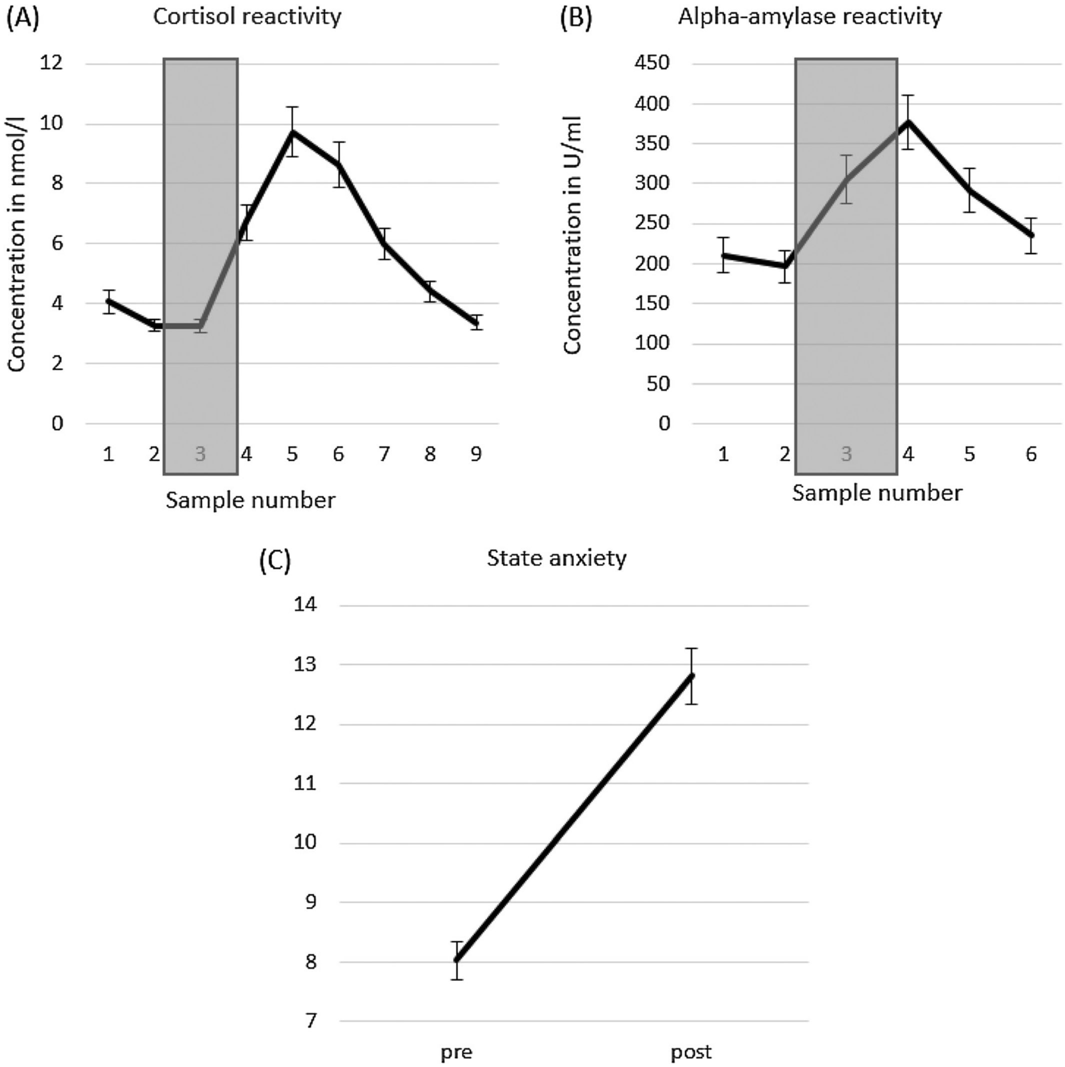

Figure 2. Mean levels of cortisol (A) and alpha-amylase (B) reactivity and changes in state anxiety (C). The shaded area indicates the stress exposure (anticipation phase and stress test). Error bars represent standard errors of the mean (SEM).

Table 1. Bivariate correlations between stress reactivity parameters, cardiorespiratory fitness, and potential confounders

	Fitness	Age	SES	Sleep complaints (ISI)	Chronic stress (PSS)	Mental toughness (MTQ)	Psychopathology (SDQ)
Cortisol (AUC_I) *N* = 38	−.071	−.034	−.055	.218	−.069	−.120	.062
Alpha amylase (AUC_I) *N* = 40	−.320*	−.169	−.257	−.398*	.038	−.118	.041
Post-stress anxiety (STAI) *N* = 42	−.029	.031	−.371*	.178	.281	−.358*	.086

Note. AUC_I = area under the curve with respect to the increase; SES = socioeconomic status. *$p < .05$.

& Proctor, 2011), Nater and Rohleder conclude that in general alpha-amylase “response patterns to both physical and psychological stressors correspond to response patterns of the sympathetic nervous system” (Nater & Rohleder, 2009).

Only few studies have investigated the effect of physical activity or fitness on this stress reactivity parameter. In a sample of 115 male, physically inactive office workers aged 19–64 years, Strahler et al. (2016) found no significant difference in alpha-amylase reactivity to the TSST as a function of physical fitness. One reason for the nonsignificant results in this study might be the lack of highly physically active participants in this sample, which the authors described as mainly sedentary to low-active men. In our present study, we included highly physically active participants who exercise at least 6 hr in their free time as well as physically inactive participants. We could show that in male adolescents, (a) alpha-amylase is sensitive to acute

Table 2. Hierarchical regression analyses explaining variance in physiological and psychological stress reactivity with potential confounders and cardiorespiratory fitness

	Cortisol (AUC$_I$)		Alpha-amylase (AUC$_I$)		State anxiety (poststress)	
Predictor	ΔR^2	β	ΔR^2	β	ΔR^2	β
Step 1						
Potential confounders	–	–	.16*	–	.24*	
SES		–		–		−.40*
Sleep complaints		–		−.47**		–
Mental toughness		–		–		−.26
Prestress score		n/a		n/a		.11
Step 2						
Fitness	−.01	−.07	.16**	−.41**	.03	.20
Total R^2	.01		.32**		.27*	
Total adjusted R^2	−.02		.28**		.19*	

Notes. AUC$_I$ = area under the curve with respect to the increase; n/a = not applicable. All standardized β-weights are presented as they are after step 2. *$p < .05$; **$p < .01$.

stress, and (b) alpha-amylase reactivity to acute stress is related to participants' cardiorespiratory fitness. More specifically, we found that higher fitness levels were associated with lower alpha-amylase reactivity. This is in line with the results presented by Wyss et al. (2016), who investigated the influence of different facets of physical fitness on stress reactivity in 302 male army recruits and found lower alpha-amylase reactivity in participants with higher aerobic endurance capacity.

In their review on the state of the research on alpha-amylase as a biomarker for the sympathetic nervous system, Nater and Rohleder (2009) pointed out that both psychological stress and acute physical activity are strong activators of the sympathetic nervous system. Against this background, one possible conclusion of our study would be that in the sense of the CSA hypothesis, fitness-related adaptations in the autonomous nervous system might influence intensity and pattern of physiological responses to stress.

Besides cardiorespiratory fitness, sleep complaints were also associated with alpha-amylase reactivity, with higher sleep complaints linked to lower alpha-amylase reactivity. In other studies, no effects of sleep parameters on alpha-amylase reactivity to acute stress were found so far (Gehrman et al., 2016; Minkel et al., 2014; O'Leary et al., 2015). However, studies showed that bad sleep quality and sleep deprivation are related to higher waking values (Van Lenten & Doane, 2016) and higher baseline levels of alpha-amylase before a stressor (O'Leary, Howard, Hughes, & James, 2015). While an association of sleep complaints with reduced stress reactivity may sound counterintuitive, previous studies showed that reduced alpha-amylase reactivity can also have negative associations. For instance, blunted alpha-amylase reactivity has in some cases been associated with disruptive (de Vries-Bouw et al., 2012) and antisocial behavior (Susman et al., 2010). While it is very unlikely that this is the case in our sample, since alpha-amylase reactivity did not correlate significantly with the SDQ sum score (Table 1) or any of the SDQ subscales measuring psychopathology, it has to be acknowledged that difficulties remain regarding the interpretation of lessened stress reactivity as "reduced from unhealthily high to normal" or "unphysiologically blunted" (Phillips, Ginty, & Hughes, 2013).

Endocrine Stress Reactivity

Several studies corroborate the assumption that higher levels of fitness reduce HPA axis reactivity in male adults (Klaperski et al., 2014; Rimmele et al., 2007) and in mixed samples (Gerber et al., 2017). However, in a study with 111 university students, Childs and de Wit (2014) found no such association. Jayasinghe et al. (2016) reported similar results in 44 women aged 30–50 years. In our study, a significant increase in saliva cortisol levels in reaction to the stressor was confirmed. However, we did not find evidence for a cross-stressor adaptation regarding HPA axis reactivity, leading to the conclusion that such effects might be smaller or absent in male adolescents. As shown by Stroud et al. (2009), adolescents often present a generally heightened HPA axis reactivity compared other age groups. Gunnar, Wewerka, Frenn, Long, and Griggs (2009) further showed a positive correlation between pubertal stage and HPA axis activity, which is also supported by longitudinal findings by van den Bos, de Rooij, Miers, Bokhorst, and Westenberg (2014). This overall increase in HPA axis responsiveness during late adolescence might cause possible effects of fitness in this particular age group to disappear. Another explanation would be that in this age group, HPA axis activity is predominantly modulated by factors other than fitness. For instance, during adolescence, HPA axis activity interacts with different aspects of personality development and psychopathology (Ryan, 1998). However, in our sample, no correlations of cortisol reactivity with such potential confounders were found.

Our results further suggest that stress reactivity of the HPA axis and the sympathetic nervous system might show different patterns with regard to the association with fitness. According to Rohleder and Nater (2009), the activation threshold of alpha-amylase in response to physical activity is lower than the threshold of cortisol. Therefore, it can be speculated that fitter participants in our sample only reached the minimum exercise intensity threshold for adaptations in alpha-amylase reactivity, but not for cortisol. Furthermore, Schommer, Hellhammer, and Kirschbaum (2003) compared reactivity of HPA axis and sympathetic-adrenal-medullary system to repeated psychosocial stress and found an attenuation only in HPA axis reactivity, thereby showing that both systems might adapt differently to repeated stress exposure.

Psychological Stress Reactivity

In accordance with previous studies, we used changes in trait anxiety to assess psychological stress reactivity (Klaperski et al., 2013; Rimmele et al., 2007). We showed that after the stressor, state anxiety increased. However, we found no relationship of changes in anxiety to participants' level of cardiorespiratory fitness. Post-stress scores were relatively weakly associated with pre-stress scores (bivariate correlation of $r(42) = .29$, $p = .060$). In undergraduate students and in 18- to 28-year-old women, Gerber et al. (2017) and Klaperski et al. (2013), respectively, found no signs of cross-stressor adaptations with regard to state-anxiety, as well. However, in two other studies, significantly lower psychological stress reactivity was found in trained athletes compared to untrained men (Rimmele et al., 2007, 2009). Since all of these studies used the same stressor task (TSST) and similar methodological approaches, the reasons for these different results remain unclear and subject to speculation. Perhaps, with regard to psychological stress reactivity, aspects other than cardiorespiratory fitness related to physical exercise (e.g., social contact, distraction from other stressors or an increase in self-efficacy) contribute more to the health-beneficial adaptations predicted by the CSA hypothesis.

Strengths and Limitations

Our study sheds new light on the impact of cardiorespiratory fitness on stress reactivity among adolescents. The strengths of our study are that we used a well-established, standardized, and validated stressor task. Accordingly, in our sample, the stressor triggered substantial stress responses across all measured stress reactivity parameters. Moreover, this is one of the few studies in which cardiorespiratory fitness was assessed objectively using a standardized submaximal fitness test with high correlation with VO_2max. Another strength of our study is that a specific inclusion criterion was applied to ensure sufficient variance in terms of cardiorespiratory fitness across participants. We also assessed both physiological and psychological outcomes to provide a comprehensive picture of participants' stress reactivity. Based on the existing literature, we considered a broad array of potential confounders, namely the most important sociodemographic and psychological variables, and our sample size was similar to previous studies in the field (Gerber et al., 2017; Jayasinghe et al., 2016; Klaperski et al., 2013; Puterman et al., 2011; Rimmele et al., 2007).

Despite these advantages, our results have to be viewed in light of several limitations which may limit the generalizability of our study. First, our study contains only data on male adolescents with a rather high educational status. Therefore, more research is needed to find out whether similar results occur in female adolescents or peers with lower educational background, respectively. For instance, Kudielka, Buske-Kirschbaum, et al. (2004) showed that in children and young adults, heart rate reactivity is usually higher in female participants, while Kajantie and Phillips (2006) reported lower HPA axis reactivity in women between puberty and menopause compared to similarly aged men. However, research on girls is more challenging, because cortisol levels depend on the menstrual cycle (Kajantie & Phillips, 2006). Second, our results represent cross-sectional data. Therefore, causal inferences are not possible. Third, due to exclusion of non-responders, our calculated sample size was not reached for the parameter cortisol. However, the correlation between fitness and cortisol was very low, so it seems unlikely that potential effects were missed because of an insufficiently large sample size. Finally, with regard to the recovery phase after the TSST, comparability with other studies might be limited. As shown in Figure 1, we performed a cognitive test immediately after the TSST, which may have led to a prolonged recovery phase. To measure brain activity, participants wore a flexible head cap equipped with sensors during the testing (data not shown here). Since the participants were used to this procedure from T1, we do not expect it to have an influence on the stress level before, during or after the TSST, which was conducted at T2.

Conclusions

In male adolescents, changes in salivary alpha-amylase in reaction to a psychological stressor were associated with the level of cardiorespiratory fitness, with higher levels of fitness being related to lower stress reactivity. By contrast, cortisol, and psychological stress reactivity were not associated with participants' fitness. Taken together, our study provides partial support for the validity of the CSA hypothesis, and corroborates that high levels of cardiorespiratory fitness may positively affect stress reactivity of the sympathetic nervous system in male adolescents. These effects may explain how high levels of cardiorespiratory fitness can prevent some of the negative health consequences of stress among young people.

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The authors declare that there is no conflict of interest.

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4.3 Publication 3: A combined EEG-fNIRS study investigating mechanisms underlying the association between aerobic fitness and inhibitory control in young adults

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NEUROSCIENCE

RESEARCH ARTICLE

S. Ludyga et al. / Neuroscience 419 (2019) 23–33

A Combined EEG-fNIRS Study Investigating Mechanisms Underlying the Association between Aerobic Fitness and Inhibitory Control in Young Adults

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Abstract—The current evidence suggests that aerobic fitness is associated with inhibitory control of executive functioning in children and older adults. However, the relative contributions of different neurophysiological mechanisms to this relation remain unclear and have not yet been examined in young adults. The present study aimed to compare inhibitory control between high and low-fit young adult men, and to investigate a possible mediation of fitness effects by conflict monitoring (N450 component of event-related potentials) and lateralized oxygenation difference (LOD) in the DLPFC. For the present cross-sectional study, participants with different physical activity levels were recruited and divided into low-fit and high-fit participants based on relative power on the PWC170. A Stroop Color-Word task was administered and combined EEG-fNIRS was simultaneously utilized to assess the N450 and LOD, because these parameters are linked with behavioral performance. The results of the statistical analysis showed that high-fitcompared to low-fit participants showed less Stroop interference and lower negativity of the N450, whereas no difference was found for LOD. Path-analyses further revealed that the relation between aerobic fitness levels and Stroop interference was indirect and mediated by N450. In contrast, LOD was inversely correlated with Stroop interference, but did not explain the relation of aerobic fitness with behavioral performance. The present findings indicate that greater inhibitory control in high- compared to low-fit young men can be explained by more effective conflict monitoring. Moreover, young adults with left-lateralizedDLPFC oxygenation also show higher inhibitory control, but this oxygenation pattern is not influenced by aerobic fitness.

Key words: Event-related potentials; Cerebral oxygenation; Physical activity; Executive function; Stroop task.

INTRODUCTION

Inhibitory control is considered a core component of executive function and encompasses the ability to control one's attention, behavior, thoughts, and/or emotions while pursuing a cognitively represented goal (Diamond, 2013). In general, executive function has been linked with mental health (Snyder et al., 2015) and academic achievement (Best et al., 2011), whereas its inhibitory component specifically relates to healthy habits in adolescents and young adults. For example, low inhibitory control has been found to be associated with marijuana and alcohol (ab)use (Squeglia et al., 2014) as well as overeating in response to external food cues and negative emotional states (Jasinska et al., 2012). Additionally, inhibitory control shows a more pronounced decline from mid- to late-life (Sweeney, 2001) and at the same time, it partly accounts for general age-related cognitive impairment (Rozas et al., 2008). This highlights the need to unveil the factors that explain differences in inhibitory control in young adults.

On a behavioral level, inhibitory control can be assessed from a Stroop task, in which color words are presented either in the same or different color of ink. The task requires ignoring the meaning of the word and reacting to the color it is written in. When the word meaning differs from the color in which it is written, the need to inhibit a prepotent response is usually accompanied by slower responses and/ or an increased error rate (Vanderhasselt et al., 2009). Evidence suggests that aerobic fitness is one of the factors that accounts for interindividual differences in this interference effect. In this respect, previous studies have shown that high fitness is

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Abbreviations: ACC, anterior cingulate cortices; DLPFC, dorsolateral prefrontal cortex; EEG, electroencephalography; ERPs, event-related potentials; fNIRS, functional Near-infrared Spectroscopy; ICC, intra-class correlation coefficient; ISI, Insomnia Severity Index; PSS, Perceived Stress Scale; PWC170, physical working capacity at 170 bpm; SDQ, Strengths and Difficulties Questionnaire; SES, socioeconomic status.

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associated with less interference and/ or increased accuracy on the Stroop task among children (Buck et al., 2008) and older adults (Prakash et al., 2011; Weinstein et al., 2012). Although a review reported a similar association between aerobic fitness and performance on other inhibitory control tasks as well as other aspects of executive function in both groups (Guiney and Machado, 2013), it should be noted that this link has rarely been examined in young adults.

Moreover, the examination of Stroop interference on behavioral level only does not permit conclusions on the nature of the association between inhibitory control and aerobic fitness. Combined behavioral and neurocognitive assessments promise a deeper understanding of possible mechanisms underlying this link. The utilization of event-related brain potentials (ERPs) recorded via electroencephalography (EEG) allows the examination of different cognitive processes that contribute to inhibitory control. Conflict monitoring in particular appears to be crucial for this aspect of executive function as conflict must be detected adequately to allow for subsequent adjustment of behavior and the implementation of neural resources (Larson et al., 2014). This monitoring process is indexed by the N450 component of ERPs, which is elicited by the stimulus words presented in the Stroop task (Pires et al., 2014). The N450 has a negative polarity in incompatible minus compatible difference waves, appears between 300 and 600 ms after stimulus onset and shows a fronto-central distribution (Larson et al., 2014). In older adults, high physical activity levels and submaximal aerobic fitness have been found to be inversely correlated with N450 amplitude (Gajewski and Falkenstein, 2015). Similarly, elderly individuals who engaged regularly in aerobic exercise showed a smaller N450 amplitude than inactive peers and those who engaged regularly in coordination exercise, which places greater demands on object control and locomotor skills (Chang et al., 2017). Although it remains unclear whether these findings can be generalized to other age groups, they indicate more effective conflict detection in high-fit compared to low-fit individuals. However, it should be noted that previous studies did not examine whether the effect of fitness on N450 accounted for lower error rate and/or reaction time on the Stroop task observed with increased aerobic fitness (Gajewski and Falkenstein, 2015; Chang et al., 2017).

The N450 is primarily generated from anterior (ACC) and posterior cingulate cortices (Beldzik et al., 2015), but neuroimaging findings suggest that the left dorsolateral prefrontal cortex (DLPFC) also contributes to performance on the Stroop task via a rapid and sequential upregulation of the attentional set (Vanderhasselt et al., 2009). Previous studies have investigated the influence of aerobic fitness on DLPFC by employing functional near-infrared spectroscopy (fNIRS), which allows the assessment of the hemodynamic response to cognitive tasks in cortical brain regions of interest (Herold et al., 2018). This is partly due to some first indications that alterations in cerebral circulation may account for exercise-induced cognitive benefits (Stimpson et al., 2018). In this respect, Hyodo et al. (2016) showed that high aerobic fitness was related to lower Stroop interference and greater left-lateralized activation difference in the DLPFC in older adults. Moreover, this activation difference partly mediated the relation between aerobic fitness and behavioral performance. Further cross-sectional findings support shorter reaction times and increased activation of the right inferior frontal gyrus in high- compared to low-fit individuals (Dupuy et al., 2015). However, this activation pattern might be specific for the employed modified Stroop task, which did not allow an assessment of the interference effect.

Considering the current state of evidence, the understanding of the mechanisms underlying the association between aerobic fitness and inhibitory control is limited in two key ways. First, with one exception (Hyodo et al., 2016), previous studies have not examined whether conflict monitoring and left-lateralizedDLPFC oxygenation mediate this relation. Second, these mechanisms have been investigated in isolation and in different versions of the Stroop task, so that their relative contributions to the effect of aerobic fitness on interference remain unclear. Additionally, this limits conclusions on whether conflict monitoring and left-lateralizedDLPFC activity are truly distinct mechanisms. These shortcomings can be overcome by combined EEG-fNIRS recordings, which allow insights into cognitive processing along with the brain's hemodynamic response without electro-optical interference (Chiarelli et al., 2017). Consequently, this technique can be utilized to address the research deficit that exists regarding the effect of aerobic fitness on inhibitory control in young adults as well as its underlying neurocognitive mechanisms.

The present study aimed to compare Stroop interference between high and low-fit young adult men, as well as to examine a mediation of possible fitness effects by conflict monitoring and lateralized DLPFC oxygenation. Based on previous findings, participants with high fitness levels were expected to show less interference (Buck et al., 2008; Prakash et al., 2011), smaller negativity of the N450 amplitude (Gajewski and Falkenstein, 2015; Chang et al., 2017) and a lateral oxygenation difference in favor of the left DLPFC (Hyodo et al., 2016). Moreover, it was hypothesized that smaller N450 amplitude (Larson et al., 2014) and left-lateralizedDLPFC oxygenation would be related to less interference (Vanderhasselt et al., 2009).

EXPERIMENTAL PROCEDURES

Participants

For the present cross-sectional study, 42 male young adults were recruited from local academic high schools in Basel. The choice to include male participants only was based on previous studies reporting significant sex differences for behavioral performance on the Stroop task (Van Der Elst et al., 2006), which are partly due to menstrual cycle phase effects in women (Hatta and Nagaya, 2009), and cerebral oxygenation changes in response to executive function tasks (Kameyama et al., 2004). Further inclusion criteria were less than 1 h or more than 6 h self-reported physical activity (defined as activities involving sweating and/or getting at least a little out of breath) per week within the last 6 months, the attendance of a high school, age between 16 and 20 years, right handedness, corrected-to or normal vision and a head size that fits an electrode cap with a circumference of 56 cm. Physical activity, which is correlated with aerobic fitness (Kristensen et al., 2010), was specified to increase the likeliness of recruiting participants with low and high fitness levels. Participants with color blindness and/ or with an acute or chronic medical condition, which limited the ability to engage in physical activity, were deemed ineligible. Additionally, participants undergoing any pharmacotherapy and those with an intake of medication within 24 h before testing were also excluded. Following the information on possible risks and benefits associated with the study, written informed consent was obtained from all participants. Before the study commenced, its protocol was submitted to and approved by the local ethics committee (Ethikkommission Nordwest- und Zentralschweiz). All study procedures were carried out in accordance with the Declaration of Helsinki.

Study design

The study comprised one laboratory visit, which was scheduled between 1 and 4 p.m. Following the collection of anthropometric measures, all participants were asked to fill in the Strengths and Difficulties Questionnaire (Goodman, 1997), the Perceived Stress Scale (Cohen et al., 1983), the Insomnia Severity Index (Bastien et al., 2001) and to rate the financial situation of their family in relation to other families on a 5-point Likert scale (1 = much worse; 5 = much better). These instruments were used as indicators of psychopathology (Snyder et al., 2015), stress (Williams et al., 2009), sleep (Boonstra et al., 2007) and socioeconomic status (Hackman et al., 2015), and have been found to be associated with executive function. Afterwards, a computer-based, modified version of the Stroop Color-Word test was administered to assess the inhibitory aspect of executive function. During the cognitive test, event-related potentials and the hemodynamic response of the prefrontal cortex were recorded using EEG in combination with fNIRS. Following the cognitive assessment, all participants performed the PWC170 on a cycling ergometer.

Aerobic fitness

The PWC170 is an incremental bicycle ergometer test, which allows for the assessment of aerobic fitness. Studies with both sedentary and highly-active adults showed a high test–retest reliability of the PWC170 and its variants, with ICCs ranging from 0.95–0.98 (Wallman et al., 2003; Rodríguez-Marroyo et al., 2017). In addition, submaximal fitness tests, such as the PWC170, have been suggested to be less biased by the participants' motivation than maximal tests (Sartor et al., 2013). In the present study, the 2-min protocol was used as it showed higher correlations with maximal oxygen uptake than protocols with other stage lengths (Bland et al., 2012). After being seated on a cycling ergometer, participants were instructed to hold their pedaling cadence in a range between 70 and 80 rpm. The initial workload of 30 W was increased every 2 min and the increment was based on the actual heart rate of the participant within the last 10 s of the stage, which was collected with a heart rate monitor (V800, Polar Electro Oy, Kempele, Finland). When the heart rate reached at least 165 beats during a stage, the test was terminated at the end of the stage. For use in statistical analysis, relative power output was calculated by dividing the workload in the final stage by the participant's body weight (Lohman et al., 2008).

Cognitive testing

A computer-based version of the Stroop Color-Word test was conducted to assess the inhibitory component of executive functioning (Homack and Riccio, 2004). In compatible trials of the task, color words appeared written in the same color (e.g. "green" printed in green), whereas in incompatible trials, color words appeared written in a different color (e.g. "yellow" printed in blue). To ensure equal visual content, the German color words "grün" (green), "gelb" (yellow) and "blau" (blue) were used. The participants were asked to press a button corresponding to the color of ink, ignoring the actual meaning of the word. They were further instructed to react as quickly and accurately as possible. The Stroop Color-Word test encompassed six test blocks containing 36 trials each, with 30 s resting periods between the blocks. Prior to testing, two practice blocks with 24 trials each were administered. Compatible and incompatible test blocks alternated and within each block, the stimuli appeared with equal probability and followed a fully randomized order. Color words were presented for 250 ms on black background and responses were allowed within a 1500 ms time window. To avoid habituation, the interstimulus interval varied randomly between 1000 and 1300 ms. Except for the practice trials, no feedback was provided on the participants' accuracy to avoid frequent changes of promotion to prevention focus or vice versa during the task. The interference calculated as the difference between reaction time on incongruent and reaction time on congruent trials was used as the dependent variable. Additionally, average reaction time and accuracy were extracted for both trial types to check whether possible group differences were influenced by speed-accuracytrade-off. Only response-correct trials were used for calculating reaction times.

Brain function

Assessments of brain function were performed in a dimly lit room at an environmental temperature of 21–22 °C. The surrounding noise was reduced to a minimum and participants were instructed to avoid head movements and speaking during cognitive testing. For combined EEG and fNIRS recordings, 32 electrodes and 16 optodes were mounted into a flexible cap, which was then applied to the participant's head. The active EEG electrodes were positioned according to the 10:20 system and AFz served as ground. The EEG signal was amplified by actiCHamp (Brain Products GmbH, Gilching, Germany), recorded at a sampling rate of

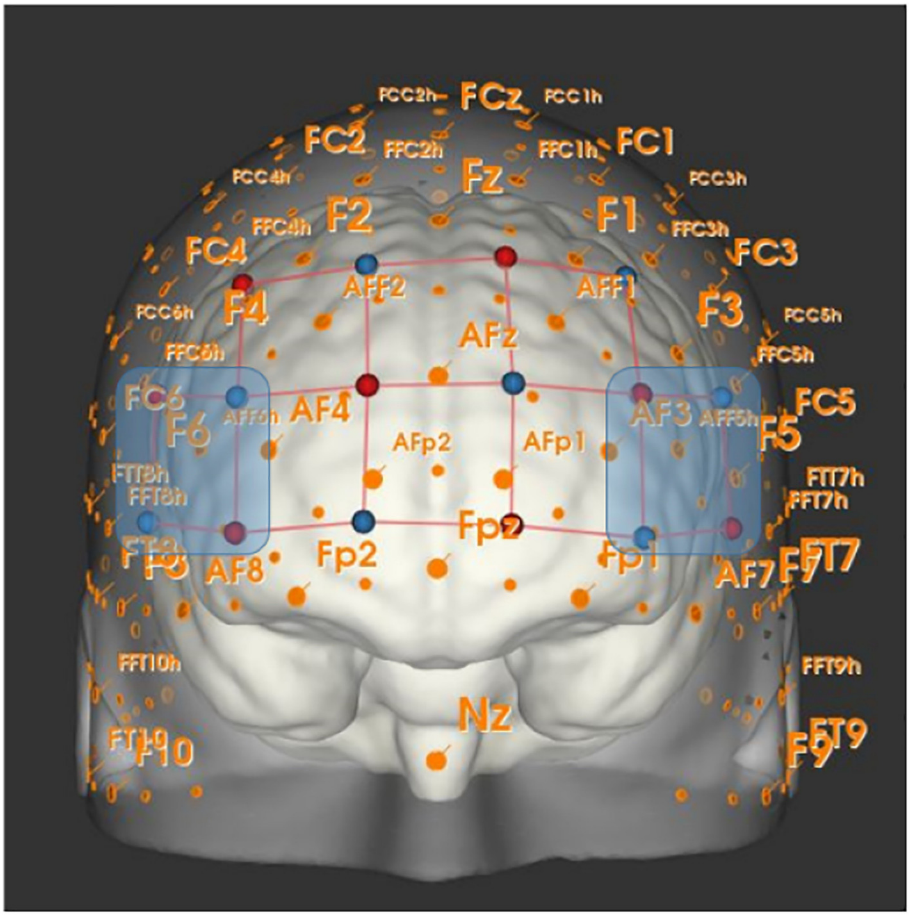

Fig. 1. FNIRS montage in relation to standardized EEG positions. *Note*: Channels used for calculating the lateralized oxygenation difference are highlighted in blue. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

1024 Hz and online-referenced to FCz. Prior to the recordings, impedance was checked and reduced to 10 KΩ or lower by inserting conductive gel between the scalp and the electrodes.

With regard to fNIRS, 16 optodes (8 illumination sources, 8 light detectors) were distributed over the prefrontal cortex as shown in Fig. 1, resulting in a total of 23 channels. Spacers were used to keep the inter-optode distance constant at 3 cm, which is considered the best trade-off between high light penetration depth and sufficient signal-to-noise ratio (Ferrari and Quaresima, 2012; Tak and Ye, 2014). An identical distance across participants was further guaranteed by including individuals with a head size of 56 cm only. A loosely attached, optically opaque overcap was used to prevent ambient light from interfering with the data. The signal acquired by the optodes was recorded at a sampling rate of 7.8125 Hz using a dual-wavelength (760 and 850 nm), continuous-wave fNIRS (NIRSport, NIRx Medical Technologies, Berlin, Germany). During the preparation period, signal quality was assessed, and recordings were initiated when the level was considered excellent as evidenced by an amplification factor lower than or equal to 10^2, signal levels between 0.09 and 1.40 Volt, and a proportion of noise of less than 2.5% of the signal variation. All recording procedures were in line with existing quality standards (Orihuela-Espina et al., 2010) and recommendations for fNIRS assessments in exercise-cognition research (Herold et al., 2018). EEG and fNIRS data were recorded using BrainVision Recorder 1.21 (BrainProducts GmbH, Gilching, Germany) and NIRStar 15.0 (NIRx Medical Technologies, Berlin, Germany), respectively.

Offline processing of fNIRS data was performed with Homer2 version 2.3 (Huppert et al., 2009) and followed the processing stream proposed by Brigadoi et al. (2014). After raw (intensity) data were converted to optical density, signal changes within 1 s intervals exceeding a standard deviation threshold of 50 or an amplification threshold of 0.4 were marked as artifacts. This threshold has been found to be a compromise between the number of motion artifacts identified in noisier data series and the number identified in less noisy data series (Brigadoi et al., 2014). Based on the results of systematic comparisons of artifact correction techniques (Scholkmann et al., 2010; Cooper et al., 2012), spline interpolation was used to correct marked artifacts. Subsequently, artifact detection was performed again and stimuli within the range of artifacts that survived the correction procedure were rejected. The remaining data was submitted to a frequency filter with a low cut-off at 0.01 Hz and a high cut-off at 0.5 Hz to remove baseline drifts, heart beat pulsations and electronic and systemic noise, such as cardiac and respiratory oscillations (Schroeter et al., 2002; Byun et al., 2014; Yennu et al., 2016). In the next step, the modified Beer–Lambert-Law was applied to transform data from optical density to concentration changes (Essenpreis et al., 1993). Differential pathlength factors were adjusted according to the wavelength and the participants' age (Scholkmann et al., 2014). Block averages were created for compatible and incompatible trials with the 5 s period preceding the test block used as reference. The final hemodynamic response function was estimated using a consecutive sequence of Gaussian functions as a basis function and a third order polynomial drift correction algorithm. Interference was calculated by subtracting the oxygenated hemoglobin concentration in response to compatible trials from the oxygenated hemoglobin concentration in response to incompatible trials. Similar to previous studies (Seghier, 2008; Hyodo et al., 2016), the lateral oxygenation difference related to the interference was calculated from the difference between left DLPFC and right DLPFC. In both hemispheres, 4 channels covering the DLPFC were averaged and extracted for statistical analysis, because test–retest reliability has been found to be higher at cluster level (ICC = 0.74) compared to individual optodes (Schecklmann et al., 2008).

For offline processing of EEG recordings, collected data was imported in BESA Research 7.0 (Brain Electric Source Analysis, Gräfelfing, Germany). Following the definition of blinks and eye movements, automatic adaptive artifact correction was applied to continuous data. This method employs principal component analysis to contrast artifacts against the predominant brain activity and uses spatial filtering to subtract the reconstructed artifacts from the original EEG data (Ille et al., 2002). Following high-pass filtering (forward phase shift of 0.3 Hz; slope 6 dB/octave) and baseline correction (−200 ms to stimulus onset), artifacts that survived the correction procedure were rejected using a threshold-based approach on participants' individual amplitudes and gradients within −200 and 1000 ms relative to stimulus onset (Luck, 2005). Subsequently, response-correct segments were averaged separately for compatible and incompatible trials, submitted to low-pass filtering (zero-phase shift of 30 Hz; slope 24 dB/octave) and re-referenced to the average mastoids. Difference waveforms were created by subtracting compatible from incompatible waveforms. Based on previous studies (Qiu et al., 2006; Tillman and Wiens, 2011) and visual inspection of the data, the N450 component was extracted from this waveform and calculated as the mean amplitude from 370 to 470 ms following stimulus onset. The latency window was adjusted according to visual inspection to reduce the influence of preceding and following ERP components on the N450. Amplitude measures were extracted and averaged from Fz, F3, F4, FC1, FC2, Cz, C3 and C4 as the N450 typically shows a fronto-central distribution (Pires et al., 2014). The EEG processing steps were in line with guidelines for the quantification of event-related potential components (Duncan et al., 2009).

Statistics

The statistical analysis of collected data was performed with SPSS 25.0 and the AMOS graphical interface (IBM, USA). Prior to testing the hypotheses, a median-split was conducted on relative power achieved in the PWC170. This procedure was used to verify the extreme group design and to categorize the sample into high-fit and low-fit participants. To check if the resulting groups' aerobic fitness differed from the average, relative power of high- and low-fit participants was tested against the mean ($M = 2.69$) of a large European cohort of healthy young males (Ortlepp et al., 2004) using a one-sided*T*-test. For all analyses, aerobic fitness assessed from the PWC170 was used as independent variable. Prior to the main comparisons, relative power, weight, body mass index, age, socioeconomic status, perceived stress and self-reported sleep were compared between the groups using a series of Student's *T*-test. If variables (except relative power on PWC170) were at least approaching significance ($P < .10$), main outcomes were analyzed using an ANCOVA with group as between-subject factor and such variables included as covariates. Otherwise, Student's T-tests were employed to compare interference, N450 amplitude and lateral oxygenation difference between low- and high-fit groups. Additionally, possible group-differences in reaction time and accuracy were examined to check for a speed-accuracytrade-off. An alpha level of $P \leq .05$ was considered statistically significant.

A possible mediation of the effect of fitness level on interference by N450 amplitude and lateral oxygenation difference was assessed using path-analyses. Model 1 examined the direct relation between fitness level and interference and in model 2, N450 amplitude and lateral oxygenation difference were added as potential mediators and the covariance between both variables was estimated. Standardized betas were calculated to determine the relative strengths of the examined relations. Moreover, the null hypothesis postulating that regression coefficients equal zero was tested and rejected at $P \leq .05$.

RESULTS

Complete data was available from 40 participants as in each group there was one participant with excessive movement artifacts in EEG and fNIRS recordings. These two datasets were removed from the final analysis due to the inability to sufficiently correct or reject these artifacts.

Group comparison

Whereas the initial analysis showed no group differences for anthropometric measures, socioeconomic status, perceived stress, psychopathology and self-reported sleep (Table 1), high- compared to low-fit participants had higher relative power, $T(38) = -7.81$, $P < .001$, $d = 2.47$. Further, low-fit participants achieved a lower relative power, $T(19) = -2.15$, $P = .045$, and high-fit participants a higher relative power, $T(19) = 10.68$, $P < .001$, than the average of a large European cohort of healthy young adults (Ortlepp et al., 2004).

With regard to the main outcomes, Student's *T*-Tests revealed lower interference in high- compared to low-fit participants (Fig. 2), $T(38) = 2.34$, $P = .025$, $d = 0.74$, but no group differences in reaction time and/ or accuracy, $T(38) \leq 0.68$, $P \geq .501$, $d \leq 0.21$. Additionally, lower negativity of the N450 amplitude (Fig. 3), $T(38) = -2.36$, $P = .023$, $d = 0.75$, was found in high- (0.31 ± 1.61 µV) relative to low-fit participants (−0.71 ± 1.05 µV). In contrast, no differences between high- (0.034 ± 0.094 $\mu\text{mol}\cdot\text{l}^{-1}$) and low-fit participants (0.029 ± 0.103 $\mu\text{mol}\cdot\text{l}^{-1}$) emerged for the lateral oxygenation difference, $T(38) = -0.160$, $P = .874$, $d = -0.05$. The waveforms depicting the concentration changes in oxygenated hemoglobin in response to compatible and incompatible trials of the Stroop task are presented in Fig. 4.

Table 1. Comparison of anthropometric data, aerobic fitness, psychopathology, sleep, perceived stress and socioeconomic status between low- and high-fit participants.

	Low-fit (*N* = 20)			High-fit (*N* = 20)			*T*	*P*
	M	*SD*	Range	*M*	*SD*	Range		
Age in y	17.2	1.0	16–20	17.0	1.1	16–20	0.75	.457
Body mass in kg	73.8	15.5	53.7–118.5	69.8	10.0	50.0–83.4	0.97	.338
BMI in kg$\cdot$m^{-2}	23.1	4.8	18.4–38.7	21.7	2.2	17.3–25.7	1.12	.270
PWC170 in W$\cdot$kg^{-1}	2.5	0.4	1.2–2.9	3.4	0.3	3.0–4.1	−7.81	.000
SDQ total score	13.5	8.7	2–35	14.7	6.7	4–30	−0.51	.614
ISI total score	6.4	4.0	2–14	6.4	3.6	2–14	0.02	.988
PSS total score	13.7	5.6	6–25	14.2	3.7	8–21	−0.30	.763
SES	3.1	0.7	2–5	3.5	0.6	3–5	−1.67	.104

BMI = Body mass index; PWC170 = Physical working capacity at 170 bpm; SDQ = Strengths and Difficulties Questionnaire; ISI = Insomnia Severity Index; PSS = Perceived Stress Scale; SES = Socioeconomic status; Range includes minimum-maximum.

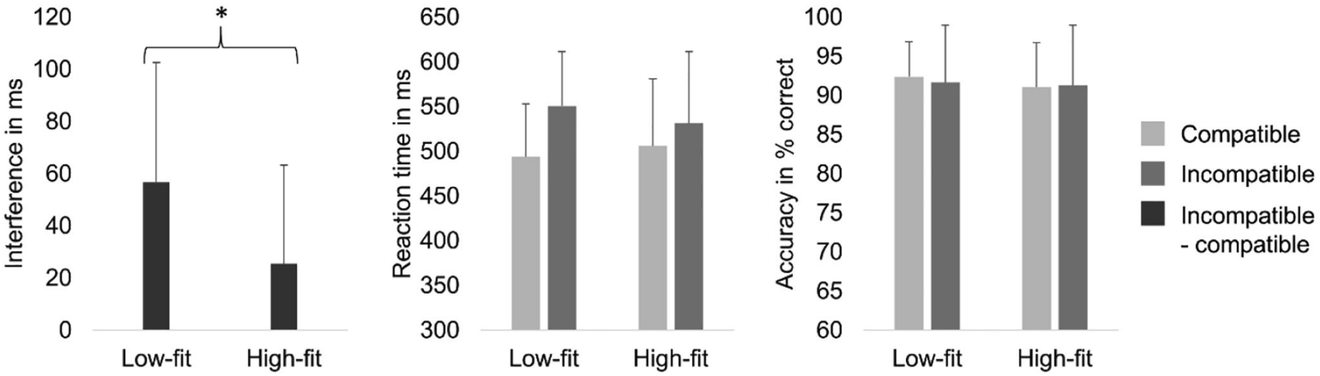

Fig. 2. Low- and high-fit participants' behavioral performance on the Stroop task (means and standard deviation). *Note:* *$P < .05$ for comparison between low- and high-fit participants; interference was defined as the dependent variable.

Mediation model

Based on path-analyses, model 1 showed an inverse relation between fitness level and interference, $\beta = -0.35$, $P = .018$, indicating less interference in high-fit participants. When the N450 amplitude and the lateral oxygenation difference were added in model 2 (Fig. 5), this relation was no longer significant, $\beta = -0.19$, $P = .183$.

Instead, significant associations were found between fitness level and N450, $\beta = 0.36$, $P = .017$, as well as N450 and interference, $\beta = -0.44$, $P = .003$. This indicated that high-fit participants had lower negativity of the N450 amplitude, which in turn was related to lower interference. Moreover, path-analyses revealed an inverse relation between lateral oxygenation difference and interference, $\beta = -0.27$, $P = .050$, but no association of fitness level with lateral oxygenation difference, $\beta = -0.03$, $P = .871$. Regarding the two possible mediating variables, no significant relation was found between the N450 and lateral oxygenation difference, $\beta = -0.25$, $P = .136$.

DISCUSSION

The behavioral findings revealed that high-fit compared to low-fit young adult men showed greater inhibitory control as indexed by less interference on the Stroop task. Based on the investigation of the N450 component of event-related potentials, this behavioral effect was accompanied by more effective conflict monitoring in high-fit participants. A novel result of the present cross-sectional study was that the aerobic fitness level was not directly associated with inhibitory control, because path-analyses indicated a mediation of their relation by conflict monitoring.

Stroop interference

The group differences observed for Stroop interference are in line with previous findings showing that aerobic fitness is related to inhibitory control (Guiney and Machado, 2013). As reaction times and accuracy were not significantly different between high-fit and low-fit participants, the observed effect was not influenced by a speed-accuracytrade-off. Additionally, comparable performance on compatible trials between groups further indicates that less interference in high-fit participants was not due to higher abilities in information processing. Given that previously, the relation between aerobic fitness and inhibitory control has mainly been examined in children (Buck et al., 2008) and older adults (Prakash et al., 2011; Weinstein et al., 2012), the present findings provide novel insights into the influence of aerobic fitness on Stroop interference in young adults. This is important, since experimental evidence is lacking in this age group, whereas beneficial effects of exercise targeting aerobic

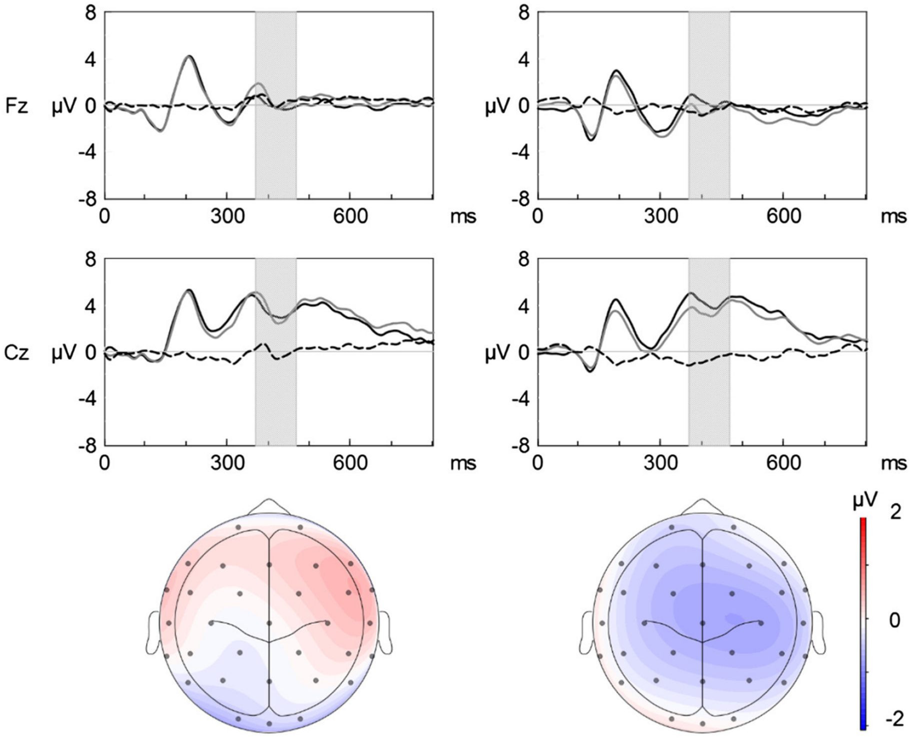

Fig. 3. Compatible (black line), incompatible (gray line) and difference waveforms (dashed line) of grand-averaged event-related potentials and topographic plots from difference waveforms for high- (left panel) and low-fit participants (right panel). *Note*: The waveforms are plotted for Fz and Cz electrodes and for the latency range from stimulus onset to 800 ms. The gray block indicates the latency range used for calculating the N450 amplitude.

fitness for different aspects of executive function are supported in children and older adults. Consequently, the present findings suggest that inhibitory control is sensitive to and partly explained by aerobic fitness in young adulthood, although peak performance on executive function tasks is reached during this age period (Zelazo et al., 2004).

Conflict monitoring

In line with the behavioral findings, the analysis of ERPs revealed a group difference for the N450 component. High-fit participants showed a lower fronto-central negativity, which suggests more effective conflict monitoring compared to their low-fit peers. The pattern of results is similar to previous studies reporting lower N450 negativity in older adults with regular engagement in aerobic training (Chang et al., 2017) and those with high (submaximal) fitness (Gajewski and Falkenstein, 2015). As the Stroop task elicits conflicts at the level of stimulus representations and motor response organization, differences in the N450 negativity indicate changes in monitoring of at least one type of conflict (Larson et al., 2014). Using a modified version of the Stroop task with cues holding relevant or irrelevant information about the required response, the N450 component was found to be associated with stimulus rather than response conflict detection and resolution (Szűcs and Soltész, 2012). Given this relation, high-fit participants in comparison to their low-fit counterparts appear to have a more effective monitoring of incompatible representations of stimulus dimensions that are processed in parallel. This seems to have an impact on behavioral performance, as path-analysis showed an association of lower N450 negativity with lower interference on the Stroop task. Testing the mediation model further revealed that high task performance in participants with high fitness level was explained by differences in this ERP component. These differences may originate from the anterior cingulate cortex (ACC), because source localization studies have found this region to be the major neural generator of the N450 (Larson et al., 2014). The ACC detects conflicts in information processing, probably as an index of task difficulty, and triggers compensatory adjustments, such as increased implementation of control from the DLPFC (Botvinick et al., 2004). A few cross-sectional and experimental findings suggest that high aerobic fitness is associated with more efficient recruitment of the ACC in inhibitory control tasks (Colcombe et al., 2004) and improved resting cerebral blood flow in this region (Chapman et al., 2013). Consequently, lower N450 negativity in individuals with high fitness levels might index more effective conflict monitoring capabilities that generalize to other cognitive tasks with inhibitory demands.

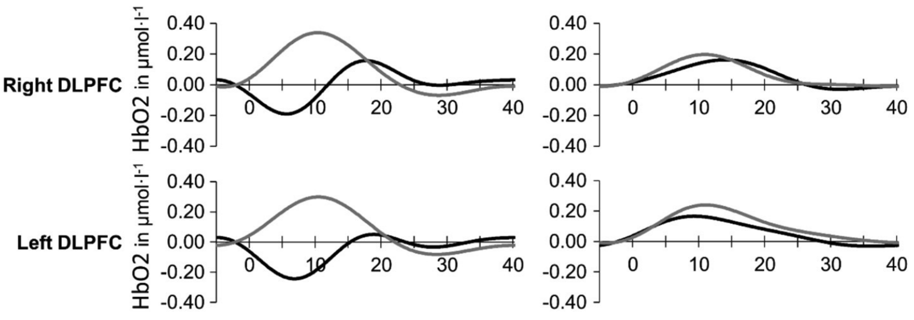

Fig. 4. Concentration changes in oxygenated hemoglobin in response to compatible (black line) and incompatible trials (gray line) of the Stroop task displayed for high- (left panel) and low-fit participants (right panel).

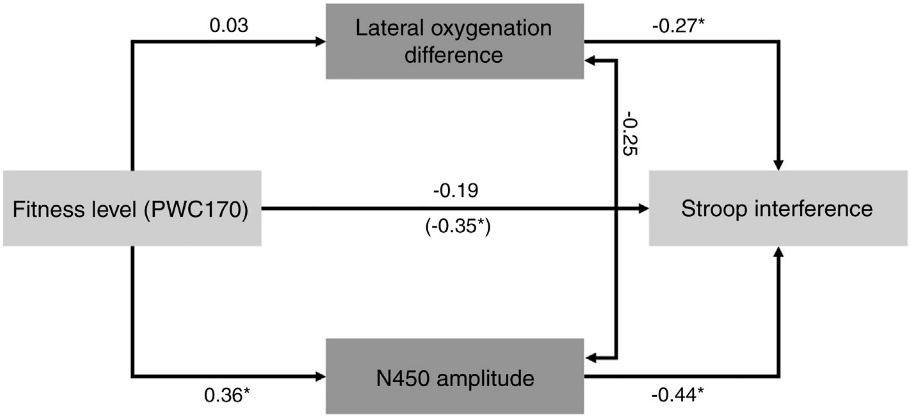

Fig. 5. Association between fitness level (assessed from PWC170) and Stroop interference before (light gray; standardized regression coefficient in brackets) and after (light and dark gray; standardized regression coefficient without brackets) N450 amplitude and lateralized oxygenation difference were entered as potential mediators. *Note*: $^*P < .05$; positive values in lateral oxygenation difference represent left-lateralized DLPFC oxygenation; positive values in N450 amplitude represent more effective conflict monitoring.

Lateral oxygenation difference

With regard to the hemodynamic response of the brain to the Stroop task, no difference between low-fit and high-fit participants was observed for the lateral oxygenation difference. When this parameter was entered in the mediation model along with N450, it did not explain the association between fitness level and behavioral performance. However, higher lateral oxygenation difference indexing left-lateralizedDLPFC oxygenation was linked with lower Stroop interference. The activation of the left DLPFC during the Stroop task is well-documented and has been attributed to the distractor incongruence, which requires the temporal up-regulation of the attentional set, particularly at times of high conflict (Vanderhasselt et al., 2009). As the lateral oxygenation difference was calculated from incongruent minus congruent difference waves, its association with behavioral performance can be explained by the ability to flexibly adjust attentional resources in response to task difficulty or conflict. This ability was not influenced by aerobic fitness in the present study, although an influence of aerobic fitness on the laterality of the DLPFC oxygenation has been reported previously in older adults (Hyodo et al., 2016). This discrepancy might be explained by the inclusion of different age groups. Aging has been associated with a loss of lateralization, so that older compared to younger adults show a more bilateral DLPFC activation in response to tasks with high executive function demands (Spreng et al., 2010). Thus, the lack of group differences in the lateral oxygenation difference might be due to a lower reserve for increased left-lateralizedDLPFC activity. Additionally, Stroop task difficulty may account for a pattern of results that differs from Hyodo et al. (2016). Stroop interference increases with age, suggesting that the same task is perceived as more difficult by older adults (van der Elst et al., 2006). The ACC is involved in conflict monitoring, which is indexed by N450 negativity, and triggers an increased implementation of cognitive control from the DLPFC at high mental effort (Botvinick et al., 2004). Consequently, conflict monitoring processes may contribute similarly to behavioral performance in young and older adults (Chang et al., 2017), whereas an increased recruitment of the left DLPFC might only be necessary to meet the increased relative Stroop task difficulty with higher age. This might account for a mediation of the relation between aerobic fitness and inhibitory control by more effective conflict monitoring, but not a left-lateralization of the DLPFC oxygenation.

Limitations

Although the present findings provide novel insights into the mechanisms underlying the influence of aerobic fitness on a core component of executive function, the findings should be interpreted with caution. First, similar to a previous study (Gajewski and Falkenstein, 2015), a submaximal fitness test was used for the verification of high and low fitness levels. Although the PWC170 may be less biased by participants' motivation, it is possible that the determination of maximal oxygen uptake from a maximal ergometer test would have increased the precision of the mediation model. Second, the mediation was assessed cross-sectionally, which limits inferences about cause and effect. Nonetheless, the present findings provide indications about the mechanisms underlying the effect of aerobic exercise on the inhibitory aspect of executive function in young adults. Future studies are therefore encouraged to further investigate the mediating role of conflict monitoring in a longitudinal design. Third, the small sample size should be noted when interpreting the results. However, it seems unlikely that the path between fitness level and lateral oxygenation difference would reach statistical significance with greater sample size, because the standardized regression coefficient was close to zero. Fourth, stress, socioeconomic status and psychopathology were compared between groups, whereas intelligence was not assessed as a potential confounder. Although inhibitory control has not been related to intelligence in young adults (Friedman et al., 2006), it cannot be ruled out that this variable affects the lateral oxygenation difference and/ or the N450 negativity. Despite the lack of control for intelligence, it was not expected that high- and low-fit participants would show meaningful differences, as they were recruited from academic high school classes that were taught on comparable educational levels. Fifth, the present study included male participants only as performance on the Stroop task and related hemodynamic changes depend on the female cycle phase. Thus, it remains unclear if the findings can be generalized to women and if conflict monitoring or other mechanisms explain possible differences in behavioral performance. Lastly, the present cross-sectional study assessed conflict monitoring and lateral oxygenation difference as possible mediators of the relation between aerobic fitness and inhibitory control. This selection was based on prior findings, which did not examine the role of differences in these outcomes between high- and low-fit participants for behavioral performance. However, it is likely that other ERP components and oxygenation changes in other brain regions might also be sensitive to aerobic fitness and account for variance in Stroop interference.

The present findings indicate that aerobic fitness accounts for interindividual differences in the inhibitory aspect of executive function, with high-fit young adults showing better behavioral performance than their less-fit peers. Based on the analysis of simultaneously recorded EEG and fNIRS data, the relation between aerobic fitness and inhibitory control was mediated by conflict monitoring, but not by a lateralized oxygenation of the DLPFC. This provides first indications on the mechanisms by which aerobic exercise benefits inhibitory control in young adults. Moreover, the association of conflict monitoring and left-lateralizedDLPFC oxygenation with behavioral performance found in the present study may be important for clinical applications, as these indices may be used for understanding and developing interventions for impairments in inhibitory control and related cognitive domains.

CONFLICT OF INTEREST

There is no conflict of interest.

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4.4 Publication 4: Association of exercise with inhibitory control and prefrontal brain activity under acute psychosocial stress

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Article

Association of Exercise with Inhibitory Control and Prefrontal Brain Activity Under Acute Psychosocial Stress

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Abstract: Psychosocial stress has negative effects on cognition in adolescents. The aim of this study was to investigate whether physical exercise can buffer such effects on inhibitory control and associated cortical brain areas. Forty-two male high school students aged 16–20 years and with either low or high exercise levels performed a Stroop task under stress-free conditions and after the Trier Social Stress Test (TSST). Oxygenation of the dorsolateral prefrontal cortex (DLPFC) was measured with functional near-infrared spectroscopy. For inhibitory control, there was no significant primary effect of condition ($F(1{,}40) = 1.09$, $p = 303.$, $\eta p^2 = 0.027$) and no significant condition × group interaction ($F(1{,}40) = 2.40$, $p = 0.129$, $\eta p^2 = 0.057$). For DLPFC oxygenation, a significant primary effect of condition was observed ($F\ (1{,}38) = 6.10$, $p = 0.018$, $\eta p^2 = 0.138$). However, the condition × group interaction ($F\ (1{,}38) = 0.05$, $p = 0.823$, $\eta p^2 = 0.001$) remained not significant. Adolescents' exercise level was not associated with inhibitory control before and after stress. An impact of stress on a neurocognitive level was observed.

Keywords: Stroop interference; sport; executive function; psychological stress; fNIRS; brain oxygenation

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1. Introduction

Performing cognitively challenging tasks, even under high stress, is of great importance in society [1,2]. For example, success or failure in final exams defines whether a higher level of education can be achieved or not, and work success is often related to dealing with performance pressure and time pressure [3]. In recent years, adolescents have been reported to be at increasing risk for high stress [4]. In a study with 1496 Swiss adolescents, 56% of the participants reported being stressed or overworked often or very often [4]. Since the last few years before graduation are usually perceived as particularly stressful [5], there is a need to examine strategies that have the potential to facilitate the maintenance of cognitive function even under stress.

When a stimulus is appraised as harmful or threatening, a physiological stress response is triggered. Typical real-life situations that involve pressure to perform, uncontrollability, and socio-evaluative threat, such as exams or presentations, usually trigger the highest stress responses (i.e., elevation in cortisol levels) [6]. In laboratory conditions, such situations can be well simulated by the standardized Trier Social Stress Test (TSST), which combines a speech task and a mental arithmetic task performed in front of a critical audience [7]. Under acute stress, physiological resources are mobilized and the organism is prepared for a response [8]. The main stress regulation system involved in this process is the hypothalamic–pituitary–adrenal (HPA) axis. Initiated by the limbic system, the hypothalamus releases corticotrophin-releasing hormone, thereby stimulating the pituitary to release adrenocorticotropic hormone, which causes the adrenal cortex to release cortisol [9]. Cortisol has multiple effects on the human body and brain, and is considered a core stress response parameter [6,9].

Executive functions are higher-order cognitive processes that include working memory, cognitive flexibility, and inhibitory control [10]. These effortful processes are necessary for problem solving, reasoning, and planning, and play a crucial role for adolescents' mental health and school success [10]. Acute stress largely affects executive functions and associated brain areas [11,12]. However, the magnitude and duration of stress and the specificities of the cognitive task influence the magnitude and direction of stress effects on cognition. While mild stress often facilitates performance in cognitive tasks with low cognitive load, high stress impairs complex cognitive functions that mainly rely on the prefrontal cortex [12]. Recent meta-analytic findings on the effects of acute stress on core executive functions showed that cognitive inhibition (or interference control) in particular is impaired by acute psychosocial stress [13]. Interestingly, Shields et al. reported that this pattern was relatively robust, as it was independent of sociodemographic and study design parameters, and also independent of stress severity, meaning that even under mild stress, interference control can already be impaired [13].

The potential of regular physical activity and exercise to improve executive functioning has been investigated multiple times. Positive effects on brain plasticity and prefrontal gray matter volume have been reported [14–16], along with higher behavioral performance in a number of cognitive tasks [17,18]. While effects of multiple exercise modalities were found, coordinative exercise and exercise sessions of longer duration seem to be particularly beneficial [19]. With regard to the effects of exercise on inhibitory control, a brain region of greater interest is the dorsolateral prefrontal cortex (DLPFC). It is known that the DLPFC plays a crucial role in tasks tapping interference control, such as the Stroop task [20,21]. Most commonly, the Stroop task consists of two conditions, where color words are presented in compatible or incompatible ink color, and the response time delay in the incompatible condition corresponds to interference [22]. While other cognitive tasks (e.g., Flanker task) also address interference control, studies have shown that the Stroop task is suitable for the measurement of DLPFC activity with functional near-infrared spectroscopy (fNIRS) [23]. The enhanced performance in more physically active and fitter participants in tasks demanding interference control could be associated with improved sensitivity of the DLPFC to conditions of greater conflict [24], and with a more pronounced left-lateralized activity in the DLPFC [23,25]. While the association of exercise with executive functioning has been studied before, no data are available yet on the association of exercise with executive functioning and activity in relevant brain areas under conditions of increased stress, or directly after stress exposure. Interestingly, as a part of the cognitive control network, the DLPFC has also been shown to be activated during psychosocial stress tasks [26–28]. The DLPFC is involved in a negative feedback loop, which (down)-regulates the HPA axis [29]. The other side of the coin is that the DLPFC itself undergoes structural and functional changes when exposed to severe stress [30,31]. Accordingly, regular exercise might have the potential to improve inhibitory control, even under stress, by generally improving the functionality of the DLPFC and thus counteracting detrimental effects of stress on this particular brain region. Another possible mechanism of how exercise could improve executive performance under stress is through a reduction in stress reactivity. Potential positive effects of exercise on stress reactivity have already been demonstrated in an intervention study by Klaperski et al. [32]. A systematic review by Mücke et al. [33] on studies using the TSST showed that around half of the included studies corroborate the notion that exercise is associated with changes in indices of stress reactivity. For this reason, the magnitude of stress reactivity is also taken into account in the present study.

Taken together, in the present study, we aim to investigate the influences of exercise on inhibitory control (more precisely: interference control) and DLPFC oxygenation in the presence of acute psychosocial stress. The DLPFC plays a key role in processing interference control and is influenced by acute stress. Based on the literature, we expected that interference control would deteriorate under acute stress, and that participants who exercised more would show better inhibitory performance under acute stress, in combination with better DLPFC conflict sensitivity and more left-lateralized DLPFC activity (as represented by higher oxygenation), compared to their less active peers.

2. Materials and Methods

2.1. Participants

Overall, 43 participants were recruited with advertisements, flyers, and personal contact. Only male, generally healthy (non-clinical), right-handed individuals between 16 and 20 years of age were included. The assessment of handedness was based on self-report. We focused on male participants because stress research has shown that mechanisms of stress reactivity are different in men and women, and standardized measurement of stress reactivity in women is challenging because of the influence of the menstrual cycle on cortisol levels [34]. To standardize educational status, which has been shown to influence performance in cognitive tasks [35], only participants currently enrolled in academic high schools were admitted. In order to increase the separation between exercise groups, only adolescents who usually participated in leisure-time exercise and sport activities for (a) less than 1 h per week or (b) more than 6 h per week were eligible for the study. The two cut-offs were chosen because they were considerably below and above the minimum exercise recommendations provided by the American College of Sports Medicine (ACSM) [36]. The duration of leisure-time exercise and/or sport activities per week was assessed via self-report, with exercise being defined as regular activities in the past four weeks that caused sweating and getting out of breath, and lasted longer than 30 min. Self-reported exercise levels were used to allocate participants to the low exercise group (<1h/week) or high exercise group (> 6h/week) and were verified with accelerometry (see Section 2.4). At least 3 days before data assessment, participants were informed about the study procedures and provided written informed consent. All study procedures were performed in accordance with ethical principles of the Declaration of Helsinki and were approved by the local ethics committee (Ethikkommission Nordwest- und Zentralschweiz; EKNZ number 2017-01330, Basel, Switzerland) before the start of the study.

2.2. Instruments

For the induction of psychosocial stress, the TSST was used, and saliva cortisol samples were collected to measure the reaction of the HPA axis to the stressor. Both procedures are described in Section 2.6. Inhibitory control was measured with a computerized version of the Stroop task, with simultaneous measurement of DLPFC activity with fNIRS. Details on the cognitive task and DLPFC measurement are presented in Section 2.5. With regard to control variables, body height and weight were measured via a stadiometer and an electronic scale (Tanita BC-601, Tokyo, Japan), respectively, and participants filled in a questionnaire that included socioeconomic status (1 item) and psychological variables. As psychological control variables, chronic stress (perceived stress scale (PSS)) [37], sleep complaints (insomnia severity index (ISI)) [38], and psychopathology (Strengths and Difficulties Questionnaire (SDQ)) [39] were assessed, since these parameters could potentially influence executive functioning. All psychological instruments showed acceptable internal consistency in the present sample (Cronbach's alpha values for the PSS = 0.75, for the ISI = 0.65, and for the SDQ = 0.72), although it should be noted that in the ISI, Cronbach's alpha was slightly below the often-used threshold of 0.7 [40]. Participants' physical activity was measured with accelerometers over the course of 7 days (see Section 2.4).

2.3. Procedure

Figure 1 gives an overview of the study procedures. To minimize the potential influence of variations in diurnal cortisol levels [41], all study appointments were scheduled in the afternoon and started either at 13:00 or at 16:00. At the first appointment, anthropometric data were collected and participants filled in questionnaires. Subsequently, the participants performed a computerized Stroop task under stress-free conditions (C1) while wearing an fNIRS head cap (see Section 2.5).

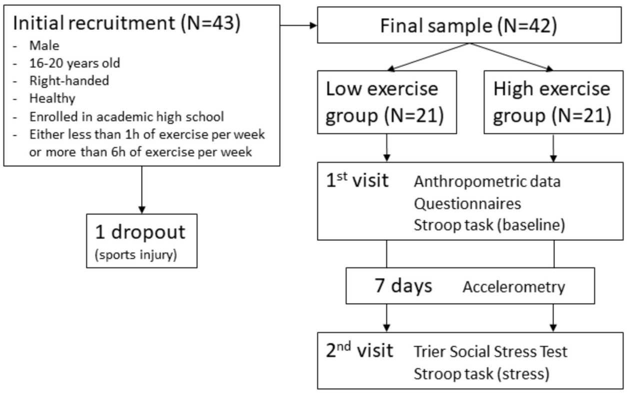


Figure 1. Study procedure.

One week later, at the same time of the day, participants were scheduled for the second study appointment, consisting of the Trier Social Stress Test (TSST) and the Stroop task (C2). Prior to the appointment, participants were instructed to not engage in physical exercise and to refrain from drinking alcohol or coffee and taking any medication during the 24 h before the appointment, to refrain from eating and drinking (except water) during the hour before the appointment, and to avoid rushing to the appointment [42]. Upon arrival, participants rested for 10min in order to reduce the influences of possible stress factors before and/or during arrival. Subsequently, the fNIRS head cap was applied. Then, the TSST was performed as described in Section 2.6. To determine stress reactivity, saliva cortisol was measured after the TSST preparation phase and directly after the Stroop task. Additionally, participants completed a brief questionnaire on psychological stress parameters before and after the TSST. Directly after the TSST, the Stroop task was performed as in C1. This design allows for the comparison of inhibitory performance and DLPFC oxygenation under stress (C2) with both parameters under non-stressful conditions (C1).

Between both study appointments, participants wore accelerometers on the hip for 7 consecutive days (see Section 2.4). After debriefing, all participants received financial compensation for their participation in the study.

2.4. Accelerometry

Physical exercise and physical activity are related constructs [43]. To validate the self-reported exercise levels, and to make sure that participants who reported low exercise levels also showed lower physical activity levels (and vice versa), each participant's physical activity was monitored objectively via waist-worn, triaxial accelerometer (ActiGraph wGT3X-BT, Actigraphcorp, Pensacola, USA) over the course of 7 consecutive days. Non-wear time was determined using the Troiano algorithm [44]. Measured days were considered valid if the device was worn for at least 600 min per day. Total measurements were considered valid if ≥1 valid weekend day, ≥3 valid week days, and ≥5 valid days in total were found [45], leading to the exclusion of the accelerometry data of two participants (one in each group). For calculation of physical activity, an algorithm introduced by Freedson et al. was used, distinguishing between sedentary, light, moderate, vigorous, and very vigorous physical activity [46]. Finally, moderate-to-vigorous physical activity (MVPA) and vigorous physical activity (VPA) were calculated.

2.5. Cognitive Task and Prefrontal Brain Activity

Procedures presented in this section are described in detail in Ludyga et al. [22] and are only summarized here. Assessments took place in a dimly lit room at a temperature of 21–22 °C. Ambient noise was reduced to a minimum and participants were instructed to avoid head movements and speaking during the task. A computer-based version of the Stroop Color and Word task was conducted to assess the inhibitory component (more precisely: interference control) of executive functioning [47]. Computer-based versions have been found to be of high test–retest reliability and they also produce a Stroop-effect comparable to the original pen and paper version [48]. Additionally, a review supports the validity of this task as a measure of executive function and this result was consistent across different variants of computerized Stroop tasks [49]. The employed version consisted of compatible and incompatible trials. In compatible trials, color words were presented in the same ink color (e.g., "blue" printed in blue), whereas in incompatible trials, color words appeared in a different color of ink (e.g., "green" printed in yellow). To ensure similar visual content, the German color words "blau" (blue), "gelb" (yellow), and "grün" (green) were used. Participants were instructed to press a button corresponding to the color of ink, ignoring the meaning of the word they read, and to react as quickly and accurately as possible. The task included six test blocks, which contained 36 trials each. Resting periods between the blocks lasted 30 s. Before testing, two practice blocks with 24 trials each were conducted. Compatible and incompatible test blocks alternated. Within each block, the stimuli were presented with equal probability and in a fully randomized order. For analysis, an interference score was calculated as the difference between reaction time (of response-correct trials) on incongruent trials minus reaction time on congruent trials. A lower interference score equals higher inhibitory control. Additionally, mean reaction time and accuracy were extracted separately for both compatible and incompatible trials to examine whether possible group differences were influenced by a speed-accuracy trade-off.

For measurement of prefrontal brain oxygenation, a dual-wavelength (760 and 850 nm) continuous-wave fNIRS system with a sampling rate of 7.8125 Hz (NIRSport, NIRx Medical Technologies, Berlin, Germany) and the recording software NIRStar 15.0 (NIRx Medical Technologies, Berlin, Germany) was used. Sixteen optodes (8 illumination sources, 8 light detectors) were attached to a flexible cap, which was then fitted to the participant's head. Optodes were distributed over the prefrontal cortex, resulting in a total of 23 channels (montage design; see [22]). Spacers were used to keep the inter-optode distance constant at 3 cm, which is considered to be the best trade-off between high light penetration depth and sufficient signal-to-noise ratio [50,51]. To prevent ambient light from affecting the measurements, participants additionally wore a loosely-attached, optically-opaque overcap. During preparation, signal quality was assessed. Recording procedures were in line with previously established quality standards [52] and recommendations for fNIRS assessments in exercise-cognition research [53].

After recording, fNIRS data were processed with Homer2 version 2.3 [54]. The processing stream followed the one proposed by Brigadoi et al. [55] and is described in detail in Ludyga et al. [22]. Artifacts exceeding defined thresholds were automatically marked and manually verified. Based on the results of systematic comparisons of artefact correction techniques [56,57], spline interpolation was applied to correct marked artefacts, followed by a frequency filter with a low cut-off at 0.01 Hz and a high cut-off at 0.5 Hz [58–60]. Block averages were created for compatible and incompatible trials with the 5 s period preceding the test block used as reference. For this publication, only channels representing left and right DLPFC were used. For each side, the average of 4 channels was calculated because previous studies found test-retest reliability to be higher at cluster level compared to individual optodes [61].

2.6. Stress Induction and Measurement of Stress Reactivity

Psychosocial stress was induced using the TSST [7]. The TSST is composed of a mock job interview and a mental arithmetic task, which are both performed in front of a committee. This combination of a motivated performance task with the additional element of uncontrollability and socio-evaluative threat has been shown to be more effective in triggering a physiological stress response than other laboratory stressor tasks [6]. Participants were instructed to envision a situation in the near future in which they had finished school and were being offered a job interview for their dream job. The committee for the job interview consisted of two persons (one male and one female) and was introduced to the participants as the manager of the company and an associate who is specifically trained in the observation and interpretation of body language and voice frequency. After the introduction and a 10 min preparation phase, participants performed a 5 min free speech facing the committee, which was followed by a 5 min mental arithmetic task. Throughout the speech, the committee showed neutral facial expressions and only used standardized responses if required (e.g., "You still have time left. Please continue."). The mental arithmetic task contained five rounds of counting backwards as quickly as possible in steps of 9, 11, 7, 13 and 8, respectively. In case of miscalculation, the participant was interrupted and asked to begin again at the last correctly calculated number.

Cortisol collected from saliva samples represented the stress reactivity of the HPA axis, the main physiological stress regulation system. Salivary cortisol levels rise with about 10 min delay relative to stressor onset [62]. Accordingly, saliva samples (Salivette® Blue cap, Sarstedt, Nümbrecht, Germany) were collected after the 10 min preparation phase (S1) and directly after the Stroop task (S2). Cortisol reactivity was defined as the value of S2 minus S1. Samples were stored at −20 °C and sent to the Biochemical Laboratory of the University of Trier, Germany, where time-resolved fluorescence immunoassay was applied to analyze cortisol concentrations (in nmol/L).

2.7. Statistical Analysis

For sample size calculation, an a priori power analysis was calculated with G*Power. As the association between exercise and inhibitory control under stress has not been investigated before, a calculation based upon the existing literature was not possible. Therefore, we decided to assume a medium effect size of $f = 0.25$ and to use the knowledge gained through our study for sample size calculations in future studies. With the parameters "repeated measures analysis of variance (ANOVA)," α-error probability = 0.05, power = 0.80, number of measurements = 2, and correlation among repeated measures = 0.5 for inhibitory control, power calculation resulted in a required minimum sample size of $n = 34$.

As a manipulation check, effectiveness of the TSST was measured using a repeated measures ANOVA on cortisol response. Because no group differences with regard to cortisol reactivity to the stressor were found, subsequent analyses were performed without controlling for cortisol.

For both inhibitory performance and DLPFC oxygenation, group differences in baseline values (C1) were examined using independent *t*-tests. To determine the influence of exercise on inhibitory performance under stress, a repeated measures ANOVA was calculated with Stroop interference in reaction time at C1 and C2 as within-subject factors and exercise group as a between-subject factor.

DLPFC activity related to inhibitory control was defined as the mean oxygenated hemoglobin in response to incompatible test blocks minus mean oxygenated hemoglobin in response to compatible test blocks of the Stroop task (Δ_{OXY}). Since studies found indications for different activation patterns in left and right DLPFC [21,63], both hemispheres were included in analysis separately. Thus, the influence of exercise on DLPFC oxygenation under stress was analyzed using a repeated measures ANOVA with condition (Δ_{OXY} at C1 and C2) and hemisphere (Δ_{OXY} of left versus right hemisphere) as within-subject factors and exercise group as a between-subject factor.

For all repeated measures ANOVAs, Greenhouse–Geisser-corrected main effects and interactions were reported. Effect sizes were classified as small ($d \geq 0.2$; $\eta p^2 \geq 0.01$), medium ($d \geq 0.5$; $\eta p^2 \geq 0.06$), or large ($d \geq 0.8$; $\eta p^2 \geq 0.14$) [64]. Significance level was defined as $p < 0.05$ and all statistical computations were performed with SPSS 24 (IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Sample Description

After C1, one participant dropped out because of a sports injury. Therefore, only data of the remaining 42 participants were analyzed. Anthropometric, psychometric, and accelerometry data are presented in Table 1. Additional information on correlations of the control variables with the main outcomes is provided in the Supplementary Materials (Table S1). For verification of the group separation based on self-report, independent samples *t*-tests were calculated and showed that the groups significantly differed in VPA and MVPA (Table 1). None of the control variables showed significant group differences at baseline (Table 1).

Table 1. Sample characteristics of high and low exercise groups.

	Low Exercise Group (n = 21)		**High Exercise Group (n = 21)**		
	Mean	**SD**	**Mean**	**SD**	**T**
Age (years)	17.2	1.1	17.1	1.2	0.14
BMI (kg/m^2)	22.9	5.1	22.0	2.1	0.81
Socioeconomic status	3.1	0.6	3.5	0.8	−2.01
Sleep complaints (ISI)	6.3	3.7	5.9	4.1	0.28
Chronic stress (PSS)	14.3	5.4	13.3	3.6	0.67
Psychopathology (SDQ)	14.8	9.5	13.5	4.5	0.58
VPA (min/day)	6.4	8.6	15.0	7.3	−3.38 *
MVPA (min/day)	60.6	22.4	83.3	20.0	−3.39 *

ISI = insomnia severity index, MVPA = moderate-to-vigorous physical activity, PSS = perceived stress scale, SDQ = Strengths and Difficulties Questionnaire, VPA = vigorous physical activity, * $p < 0.05$.

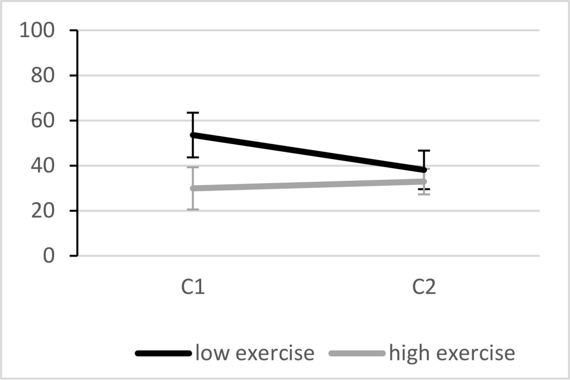
3.2. Effectiveness of the Stressor

The average cortisol level at baseline was 3.5 (standard deviation 1.7) nmol/L. After the TSST, cortisol levels rose to 9.3 (5.1) nmol/L. In the low exercise group, cortisol levels were 3.8 (1.9) nmol/L at baseline and 10.1 (5.7) nmol/L after the stressor, compared to 3.1 (1.4) nom/L and 8.4 (4.5) nmol/L in the high exercise group. Repeated measures ANOVA showed a significant and strong effect of condition $F(1,40) = 60.99$, $p < 0.001$, $\eta p^2 = 0.604$), but no significant condition × group interaction ($F(40) = 0.46$, $p = 0.500$, $\eta p^2 = 0.011$).

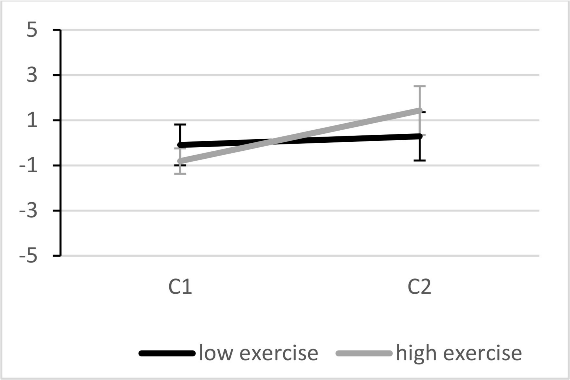
3.3. Inhibitory Performance

Changes in Stroop interference are depicted in Figure 2a. At C1, average reaction time interference in the low exercise group was 53.5 (45.4) ms, compared to 29.9 (39.2) ms in the high exercise group. An independent *t*-Test revealed no baseline (C1) differences between groups (t (40) = 1.81, $p = 0.078$, $d = 0.57$). However, it should be noted that a medium effect size indicated lower (better) interference scores in the high exercise group compared to the low exercise group. At C2, interference scores of 38.1 (42.9) ms and 32.9 (25.9) ms were observed, respectively. To investigate whether potential group differences are related to speed-accuracy trade-offs, we also analyzed response accuracy (Figure 2b). No group differences were present with regard to response accuracy at C1 or C2 for compatible (C1: $p = 0.999$, C2: $p = 0.951$) or for incompatible trials (C1: $p = 0.739$, C2: $p = 0.498$).

The repeated measures ANOVA revealed no significant primary effect of condition ($F(1,40) = 1.09$, $p = 303$, $\eta p^2 = 0.027$) and no significant interaction between condition and exercise group ($F(1,40) = 2.40$, $p = 0.129$, $\eta p^2 = 0.057$). However, for the latter a small-to-medium effect size can be observed (see 4.1).



(**a**)



(**b**)

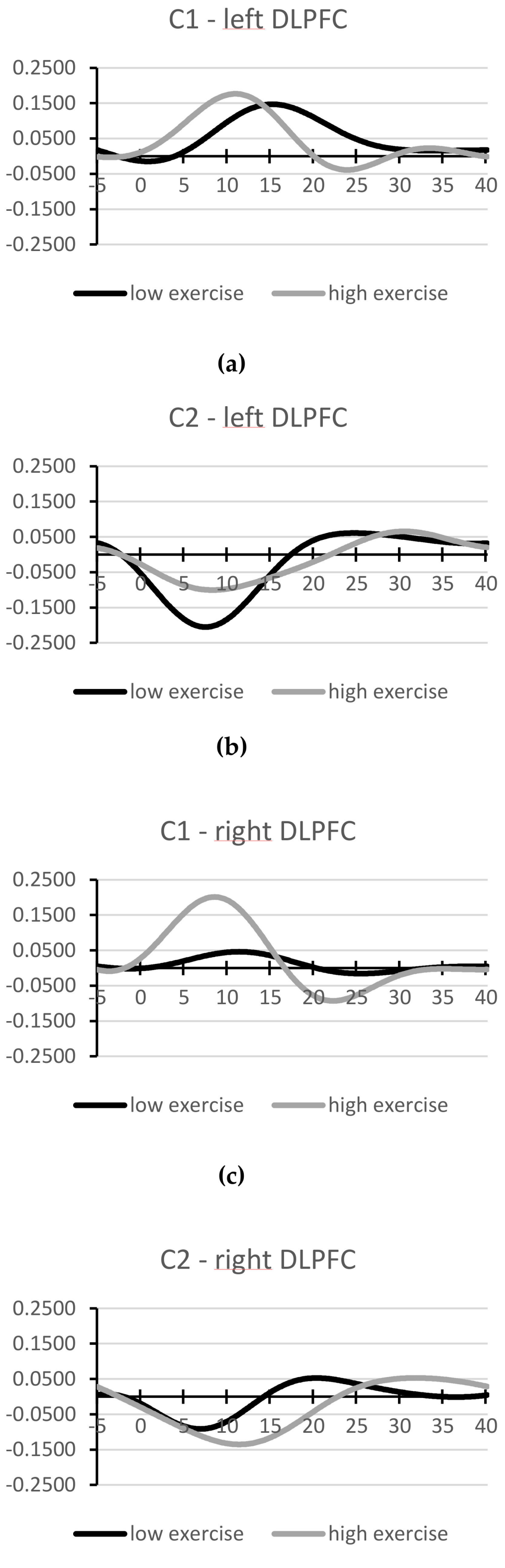
Figure 2. Stroop interference scores (incompatible minus compatible trials) for reaction time ((**a**) in ms) and accuracy ((**b**) in %) in the low and high exercise group. Error bars are standard errors of the mean.

3.4. Oxygenation of Left and Right DLPFC

After signal processing, two participants were excluded from further fNIRS analysis because of overly noisy data. Of the remaining 40 participants, average fNIRS waveforms corresponding to both exercise groups' interference waves (incompatible minus compatible Stroop condition) are depicted in Figure 3. A more detailed image of the averaged waveforms during incompatible and compatible test blocks can be found in the Supplementary Materials (Figure S1).

An independent *t*-test indicated no baseline (C1) differences between groups for Δ_{OXY} of left ($t(38) = -0.67$, $p = 0.509$, $d = 0.22$) and right hemisphere ($t(38) = -1.40$, $p = 0.174$, $d = 0.46$). Recent fNIRS research suggested a leading role of the left DLPFC in tasks demanding inhibitory control [23]. In our sample, when comparing oxygenation interference in both hemispheres at C1, this was only true for participants with lower exercise ($t(20) = 2.09$, $p = 0.049$, $d = 0.46$), but not for those with higher exercise ($t(18) = 0.37$, $p = 0.741$, $d = 0.08$).

The repeated measures ANOVA showed a significant and strong main effect of condition ($F(1,38) = 6.10$, $p = 0.018$, $\eta p^2 = 0.138$), indicating a shift towards lower relative oxygenation during incompatible test blocks and higher relative oxygenation during compatible test blocks after stress induction in both exercise groups (see Figure 3 and Supplementary Materials, Figure S1). No main effect of hemisphere was observed (F (1,38) = 1.11, $p = 0.299$, $\eta p^2 = 0.028$). All interaction terms were not statistically significant ($p > 0.307$). No correlation between DLPFC lateralization and Stroop interference was found at C1 or C2 ($p > 0.514$).



(a)

(b)

(c)

(d)

Figure 3. FNIRS interference waveforms (averaged oxygenation during incompatible test blocks minus compatible test blocks; in mmol/L) of the left dorsolateral prefrontal cortex before (a) and after the stressor (b), and of the right dorsolateral prefrontal cortex before (**c**) and after the stressor (**d**).

4. Discussion

The aim of this study was to investigate whether regular exercise is associated with inhibition (interference control) and corresponding activity in the DLPFC under acute stress. The main findings were that (a) no systematic differences between high and low exercise group were observed with regard to behavioral inhibitory control and DLPFC oxygenation patterns under stress; (b) both groups showed comparable cortisol reactivity to the psychosocial stressor; (c) compared to the stress-free condition, interference control did not change under stress; and (d) across all participants, DLPFC activity was altered under stress, with higher relative oxygenation during compatible test blocks and lower relative oxygenation during incompatible test blocks compared to the pre-stress condition. On a side note, potential group differences in the pre-stress condition occurred: for behavioral inhibitory control, medium effect sizes indicated higher performances in participants with higher levels of exercise.

4.1. Associations with Exercise

Our results show no statistically significant association between regular exercise and inhibitory performance under enhanced psychosocial stress. In previous studies investigating this association under stress-free conditions, exercise and fitness have consistently been shown to be positively associated with PFC functioning and cognitive performance [18,65]. Furthermore, research has suggested that stress generally has negative effects on the prefrontal cortex and executive functioning [11], although this relationship might be more complex [13]. We therefore hypothesized that exercise might be able to buffer negative effects of stress on executive functioning. However, our data do not indicate such differences between frequently exercising and inactive adolescents. Possible reasons for non-significant findings could be an insufficient stressor or too little ego-involvement in the stress task. Some of the study participants had never attended a job interview before the study, so the TSST does not represent their current life situation. However, the TSST elicited highly significant increases in saliva cortisol in the participants, indicating the activation of the HPA axis in response to the stressor, and they reported significant increases in psychological stress parameters as well (data not shown). Therefore, it is unlikely that the lack of change in inhibitory control from the stress-free condition to the TSST was due to insufficient stress induction. Another possible issue is the group separation with respect to exercise. Our recruitment strategy of only including participants with self-reported exercise of <1 h or >6 h per week ensured sufficient separation and was verified by significant group differences in MVPA and VPA. However, as the low exercise group showed relatively high MPVA levels (see Table 1), it is possible that the group differences were too little to produce an effect. Furthermore, although exercise has previously been related to executive function, some findings suggest that (fitness and motor) skills targeted by exercise may explain this relation [66]. Other researchers reported that besides fitness, game skills in team sports and aspects of fine motor control predicted inhibitory control, showing that exercise seems to benefit inhibitory control through several pathways [67]. Thus, comparing changes in inhibitory control across conditions between groups differing in motor skills, fitness, and other exercise-related skills might have yielded different results. Additionally, it cannot be ruled out that the stress-buffering role of exercise might only be observable in highly chronically stressed people [68]. Participants in our sample reported relatively low chronic stress levels, and none of them could be classified as highly chronically stressed. It is possible that it is not a single stressor, but repeated and high chronic stress that leads to substantial functional changes in the PFC, and that this condition is required for the buffering effects of exercise on inhibitory performance to be observed [31].

If we extend the discussion of our data to results based on effect sizes, a small-to-medium effect in the condition by exercise group interaction ($\eta p^2 = 0.057$) indicated potential group differences across conditions, with a tendency towards an improvement in inhibitory control from C1 to C2 in participants with lower exercise, while participants with higher exercise showed approximately constant scores from C1 to C2 (see Figure 2a). Considering that a medium effect size indicated that more active participants performed better than their inactive peers at baseline ($d = 0.57$), which is well in line with the current literature [18], one could speculate that while adolescents with low exercise levels show relatively high Stroop interference under non-stressful conditions and manage to improve under stress, adolescents with higher exercise levels perform at a higher level under both conditions and are less affected by acute stress. Byun et al. [58] showed that under certain circumstances, Stroop performance and arousal level can be positively related, which might have been the case in more inactive participants in our sample. However, more research is needed to support or discount this preliminary finding.

With regard to DLPFC activity, we hypothesized that we would find better DLPFC conflict sensitivity (that is: lower oxygenation during compatible and higher oxygenation during incompatible Stroop blocks) and more left-lateralized DLPFC activity in the high exercise group, compared to their less active peers. Consistent with the results on behavioral performance, we did not find any systematic differences in DLPFC conflict sensitivity between high and low exercise groups. Furthermore, no systematic group or condition effects with regard to DLPFC hemisphere were observed. Other researchers reported associations of better Stroop performance with left-lateralized DLPFC activity [23], especially in participants with higher physical fitness [25]. DLPFC lateralization and Stroop performance were not associated in our sample. Perhaps exercise and fitness-related differences in DLPFC lateralization during interference control tasks are age-dependent. The HAROLD phenomenon describes the reorganization of the brain due to age-related structural and physiological decline, resulting in less lateralized brain activity during cognitive tasks [25]. While exercise might have the potential to counteract these changes by delaying the age-related decline, no such effects can be observed in young people. Moreover, Vanderhasselt et al. [21] argued that lateralization effects during the Stroop task are largely influenced by the specificities of the protocol used.

Finally, a significant primary effect of condition indicated that DLPFC oxygenation was altered under stress. That is, across the whole sample, activity during compatible blocks increased and activity during incompatible blocks decreased under stress (in comparison to the stress-free condition). This pattern was more pronounced in the left DLPFC. According to Vanderhasselt et al. [21], during response conflict, the anterior cingulate cortex is activated, leading to recruitment in the DLPFC for increased cognitive control in the task. In our data, this mechanism is represented by the positive interference waves (Figure 3) at baseline, indicating higher DLPFC activity when interference control was necessary. However, under stress, different patterns emerged: during compatible test blocks, which require attention control but no inhibitory performance, DLPFC oxygenation increased, whereas during incompatible test blocks, which require the inhibition of a prepotent response (suppression of word reading), DLPFC oxygenation decreased. This activation pattern suggests a decreased capacity for higher order cognitive function under stress. According to Arnsten [11], p. 415, under acute stress the amygdala initiates high levels of catecholamine release, which, in synergy with increases in glucocorticoid levels, "switch the brain from thoughtful, reflective regulation by the PFC to more rapid reflexive regulation by the amygdala and other subcortical structures." However, in our sample, this change in activation patterns had no effect on behavioral performance. One possibility for this unexpected result is that Stroop performance at C2 is confounded by learning effects. However, this is unlikely since C1 and C2 were seven days apart, and in both appointments, two exercise rounds for the compatible and incompatible conditions were performed. Two other mechanisms seem more likely. On the one hand, it might be possible that due to insufficient task difficulty or duration, no effect of changes in DLPFC oxygenation on inhibitory performance can be observed yet. Plieger et al. [69] showed that stress-related changes in cognitive performance depend on cognitive load. With higher cognitive load, the observed changes in DLPFC oxygenation under acute stress might result in reduced inhibitory performance. On the other hand, the observed changes in DLPFC activation might not originate directly from task-related inhibitory processes but from other stress-relevant processes that are monitored in the DLPFC, such as emotion regulation. Ochsner et al. [70] showed that positive reappraisal of negative situations is accompanied by enhanced activity in the left DLPFC. Other studies reported similar involvement of the DLPFC in emotion regulation [71–73].

4.2. Inhibitory Control Under Stress

The results of our study further suggest that in later stages of adolescence (16–20 years of age in our sample), interference control is neither impaired nor enhanced by acute psychosocial stress. Similarly, Ishizuka, Hillier, and Beversdorf [74], who administered a verbal version of the Stroop task during cold water hand submersion in undergraduate students, found no significant difference to the control condition. In their study on the effect of stress on selective attention, Chajut and Algom [75] administered several versions of the Stroop task. Psychosocial stress was manipulated with psychometric tasks, which had to be performed with or without increased task difficulty, time pressure, and threat to the ego. Interestingly, in their sample of 160 university freshmen aged 20 to 25 years, they observed that under low stress, task performance was affected by task-irrelevant variations, while under high stress, focus on the target attributes was improved. Accordingly, stress was associated with a reduced Stroop interference and an increased inhibitory performance in their study. Studies using other tasks measuring inhibitory control also came to contrasting results. Schwabe, Hoffken, Tegenthoff, and Wolf [76] tested 72 university students and showed improved performance in a stop-signal task after a socially evaluated cold pressor task (SECPT). However, in a similar sample of 97 undergraduate students, Roos et al. [77] found impaired performance in a stop-signal task after the TSST. Similar to the latter, Sänger et al. [78] and Vinski and Watter [79] found impaired performance in cognitive inhibition after the SECPT and the TSST, respectively.

Several factors are discussed as potential causes for these differences in the effect of stress on inhibitory control tasks. In their meta-analysis on the effect of stress on core executive functions, Shields et al. [13] included participants' sex and age, type and severity of stressor, time delay from stressor to inhibition task, outcome type (reaction time versus accuracy based), and inhibition type (response versus cognitive inhibition) as potential moderators. Interestingly, their results show differential effects only with regard to inhibition type: acute stress impairs cognitive inhibition ($\beta = -0.21$, $p = 0.021$)—which Shields et al. [13] used interchangeably with interference control—and enhances response inhibition ($\beta = 0.30$, $p = 0.041$). No influence from other moderators was found. Given that according to Nigg [20] the Stroop task is a classic interference control task, negative effects of acute stress on task performance can be expected. However, this was not the case in our study. One reason might be the particularities of the adolescent sample. However, Shields et al. [13] reported no moderating influence of age. In earlier work, an inverted U-shaped relationship between severity of stress or arousal and cognitive performance has been proposed as an explanation [80]. But again, this notion is not supported by more recent meta-analytical findings [13]. Another possibility is that the influence of stress depends on task difficulty, meaning that while in relatively simple tasks, effects might be absent, performance in more complex tasks might be impaired by stress. In conclusion, more research is needed on the factors underlying the heterogeneous effects of acute stress on inhibition.

4.3. Strengths and Limitations

The primary strengths of our study are (i) the use of an effective and validated stress task which is currently considered as the gold-standard for stimulating neuroendocrine stress responses [62], (ii) a thorough fNIRS data analysis procedure following recent methodological recommendations [53,55], (iii) the verification of the group allocation (high vs. low exercise group) via accelerometry, and (iv) the consideration of major covariates, such as age, BMI, socioeconomic status, and sleep complaints.

The results of this study should be interpreted in light of several limitations. Because our study focused on male adolescents aged 16–20 years, further research on female adolescents and other age groups is necessary. Other inclusion criteria (e.g., regarding educational or socioeconomic status) could have yielded different results. Since no control condition was used in our study, learning effects in the Stroop task from C1 to C2 cannot be fully precluded. However, this is very unlikely, since both appointments were one week apart and during both appointments, exercise trials were performed before testing for both conditions. While our study is a first attempt to examine the association of exercise with inhibitory control and prefrontal brain activity under acute psychosocial stress, our data did not provide support for such an association (i.e., no condition X group interaction). Nevertheless, we acknowledge that our study design does not allow conclusions on whether the lack of any association between outcomes can be generalized to other stressors and other inhibitory control tasks, and the results do not necessarily extend to other executive functions. With regard to the measurement of physical activity via accelerometry, we acknowledge that some types of exercise (e.g., activities in the water or static exercise) are difficult to assess with accelerometry. Additionally, it remains unclear whether a comparison of specific exercise types rather than the total dose would have produced different results. Lastly, our study design does not allow causal inferences with regard to the effect of physical exercise on inhibitory control under stress. Therefore, intervention studies are needed to find out whether executive functioning can be improved with regular exercise training.

4.4. Conclusions

Our study suggests that in healthy male adolescents with higher educational status, acute psychosocial stress does not seem to affect behavioral inhibition. Furthermore, regular exercise was not associated with changes in inhibitory control or DLPFC activity under acute stress. Consequently, our results suggest that the maintenance of high exercise levels does not promise improved inhibitory control under exposure to psychosocial stress in male adolescents. Further studies should consider whether a stress-buffering effect is present in adolescents suffering from chronic stress.

Supplementary Materials: The following are available online at http://www.mdpi.com/2076-3425/10/7/439/s1, Table S1: Zero-order Pearson correlations of the control variables with the main outcomes, Figure S1: FNIRS waveforms of left and right dorsolateral prefrontal cortex during compatible (com) and incompatible (inc) test blocks without stress (C1) and after the stressor (C2) in participants with high and low exercise levels (in mmol/l).,

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Supplementary Material.

Table S1. Zero-order Pearson correlations of the control variables with the main outcomes.

		1	2	3	4	5	6	7	8	9
1	Age (years)									
2	BMI (kg/m^2)	.27								
3	SES	.06	.03							
4	ISI	.15	.24	-.04						
5	PSS	.21	.13	.06	.07					
6	SDQ	.22	.32*	.04	.23	.58**				
7	MVPA	.13	.37*	.09	-.12	-.02	.03			
8	VPA	-.11	.06	.25	-.29	.04	.02	.64**		
9	Cortisol reactivity (S2-S1)	.02	.05	-.18	.28	-.13	-.02	.00	-.06	
10	Stroop interference (C2-C1)	-.15	.01	.09	-.17	.08	.15	.00	.09	-.06
11	fNIRS interference (C2-C1)	-.02	-.19	-.04	.00	-.04	-.08	-.03	-.03	-.08

ISI=Insomnia Severity Index, MVPA=Moderate-to-vigorous physical activity, PSS=Perceived Stress Scale, SDQ=Strengths and Difficulties Questionnaire, SES=Socioeconomic status, VPA=Vigorous physical activity; * $p < 0.05$, ** $p < 0.01$

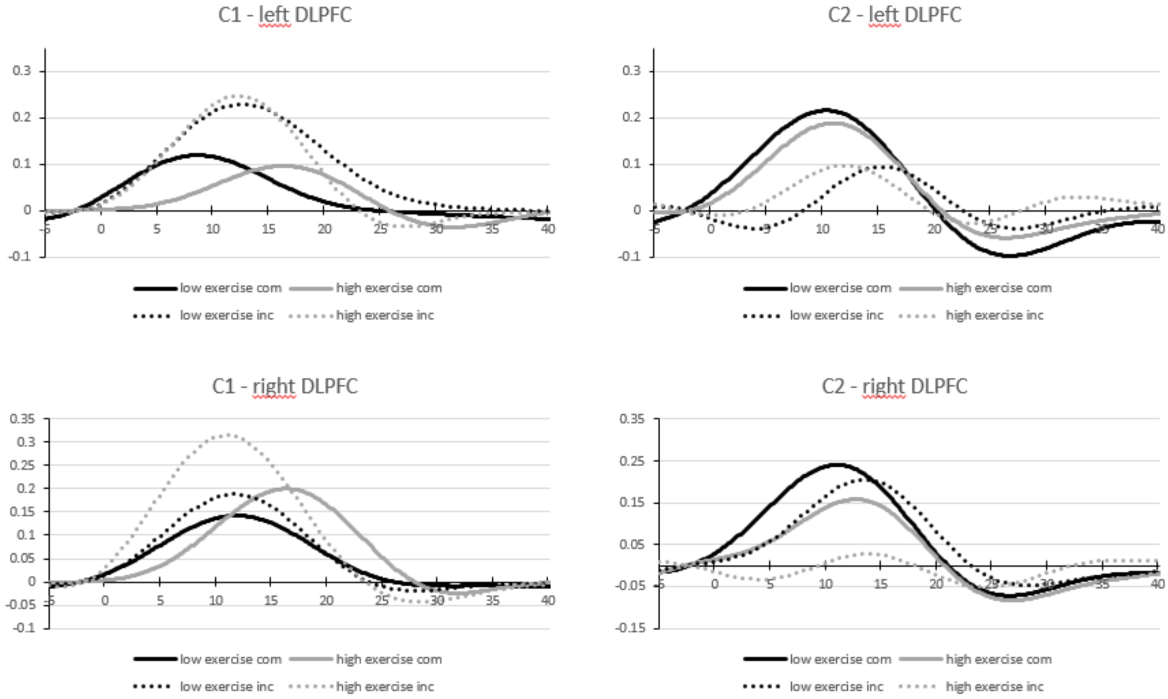

Figure S1. FNIRS waveforms of left and right dorsolateral prefrontal cortex during compatible (com) and incompatible (inc) test blocks without stress (C1) and after the stressor (C2) in participants with high and low exercise levels (in mmol/L).

4.5 Publication 5: The influence of an acute exercise bout on adolescents' stress reactivity, interference control and brain oxygenation under stress

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The Influence of an Acute Exercise Bout on Adolescents' Stress Reactivity, Interference Control, and Brain Oxygenation Under Stress

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Background: High psychosocial stress can impair executive function in adolescents, whereas acute exercise has been reported to benefit this cognitive domain. The aim of this study was to investigate whether an acute bout of aerobic exercise improves the inhibitory aspect of executive function and the associated dorsolateral prefrontal cortex (DLPFC) oxygenation when under stress.

Methods: Sixty male high school students aged 16–20 years performed a Stroop task (baseline condition) and were randomly assigned to an exercise group (30 min on ergometer at 70% of maximum heart rate) and a control group (30 min of reading). Subsequently, all participants underwent a modified Trier Social Stress Test, which included a Stroop task under enhanced stress. The Stroop tasks in both conditions were combined with functional near-infrared spectroscopy to record changes in DLPFC oxygenation in response to the tasks. Stress reactivity was measured with saliva samples (cortisol, alpha-amylase), heart rate monitoring, and anxiety scores.

Results: All stress parameters indicated increases in response to the stressor ($p < 0.001$), with higher alpha-amylase [$t(58) = -3.45$, $p = 0.001$, $d = 1.93$] and anxiety [$t(58) = -2.04$, $p = 0.046$, $d = 0.53$] reactions in the control compared to the exercise group. Controlling for these two parameters, repeated measures analyses of covariance targeting changes in Stroop interference scores showed no main effect of stress [$F(1,58) = 3.80$, $p = 0.056$, $\eta p^2 = 0.063$] and no stress × group interaction [$F(1,58) = 0.43$, $p = 0.517$, $\eta p^2 = 0.008$]. Similarly, there was no main effect of stress [$F(1,58) = 2.38$, $p = 0.128$, $\eta p^2 = 0.040$] and no stress × group interaction [$F(1,58) = 2.80$, $p = 0.100$, $\eta p^2 = 0.047$] for DLPFC oxygenation.

Conclusion: Our study confirms potentially health-enhancing effects of acute exercise on some of the physiological and psychological stress reactivity indicators. However, our data do not support the notion of an effect on interference control and DLPFC activation under stress.

Keywords: executive function, inhibitory control, fNIRS, psychosocial stress, physical activity, TSST

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INTRODUCTION

The physiological response to acute stress is characterized by the activation of the hypothalamus-pituitary-adrenal (HPA) axis, which results in the release of cortisol by the adrenal cortex, and the autonomic nervous system (ANS), which increases the activity of its sympathetic division under stress and initiates a number of processes such as increased release of adrenaline and increase in heart rate (Pruessner et al., 2010). While there is a healthy midrange of stress reactivity that is considered adaptive and useful for coping with certain stressors (Boyce and Ellis, 2005), high stress reactivity can be problematic, as it contributes to allostatic load (McEwen, 1998) and is associated with health concerns. As a recent systematic review revealed, higher levels of stress reactivity are associated with negative long-term effects on health, and in particular with increased risk of cardiovascular disease and immune system dysfunction (Turner et al., 2020).

Studies have also shown that the brain is affected eminently by acute stress. Stress-related changes in architecture and function of the prefrontal cortex (PFC) in particular have been investigated, as it is involved in the regulation of the stress response, but also reacts sensitively to high stress exposure (McEwen and Gianaros, 2010). For instance, cortisol can cross the blood–brain barrier and bind to mineralocorticoid (MR) and glucocorticoid receptors (GR) in the PFC (Lupien et al., 2009), and stress-induced increases in catecholamine levels can indirectly impair PFC functioning as well (Arnsten, 2009). The PFC is considered the highest-evolved brain region, as its principal task is processing higher-order cognitive functions that enable thoughtful, rational and planned behavior (Pruessner et al., 2010; Diamond, 2013). As a part of this, executive functions refer to top-down mental processes requiring working memory, cognitive flexibility or inhibitory control (Diamond, 2013). During homeostasis, behavior is largely regulated through these top-down processes. However, under acute psychological stress, function of the PFC is impaired, and a shift takes place from thoughtful, time-consuming top-down to sensory-driven, rapid bottom-up regulatory processes (Arnsten, 2009). In support of this shift in regulation, meta-analytic findings have shown that behavioral performance in tasks requiring working memory, cognitive flexibility or interference control is impaired under acute stress (Shields et al., 2016).

Interference control, as an important subtype of inhibition, can be assessed with the Stroop color-word task. This task consists of two conditions, where color words are presented either in compatible or incompatible ink color, and requires participants to react to the ink color while ignoring the meaning of the written word. The time delay and/or the increased number of errors caused by the conflict in the incompatible condition is called the Stroop interference effect (Vanderhasselt et al., 2009). Neuroimaging studies suggest that among different brain regions, the dorsolateral prefrontal cortex (DLFPC) in particular is activated during Stroop tasks. This has been associated with the upregulation of the attentional set in order to process the stimulus interference on incompatible trials (Vanderhasselt et al., 2009). Additionally, in studies employing functional near-infrared spectroscopy (fNIRS), better Stroop performance (i.e., less interference) has been associated with the dominance of left-lateralized DLPFC activation (Zhang et al., 2014; Ludyga et al., 2019a).

As recent research has shown, adolescents are particularly at risk of experiencing negative effects of stress on cognition. According to the World Health Organization and national psychological health surveys (American Psychological Association, 2014; Güntzer, 2017; World Health Organization, 2019), adolescents have to cope with an increasing number of psychosocial stressors, while their physiological stress response mechanisms and psychological coping strategies are still developing. It is unsurprising that better stress coping strategies were the main health need reported by Swiss adolescents (Jeannin et al., 2005). Moreover, adolescents have been reported to have higher stress reactivity than other age groups (Romeo, 2010), and there are indications that adolescents might be particularly vulnerable to negative effects of stress on the prefrontal cortex (Lupien et al., 2009). This highlights the need for research on factors that can potentially mitigate negative effects of acute stress on executive functioning in this age group.

In this regard, the investigation of the effects of an acute exercise bout seems promising for a number of reasons. Firstly, moderate acute aerobic exercise has been found to elicit small-to-moderate improvements in inhibitory control and other executive functions (Ludyga et al., 2016). In adolescents, these temporary improvements appear to last at least 60 min after cessation of the exercise session (Ludyga et al., 2019b). Moreover, some studies suggest that acute exercise benefits interference control via increased oxygenation of the DLPFC. Using fNIRS, Ji et al. (2019) and Endo et al. (2013) showed that positive effects of acute exercise on Stroop performance were accompanied by changes in DLPFC oxygenation, and several studies reported that acute exercise at mild (Byun et al., 2014) or moderate intensity (Yanagisawa et al., 2010) evoked a predominantly left-lateralized activation of the DLPFC, also associated with improved Stroop performance. This suggests that acute exercise benefits interference control via a change toward a dominance of the left DLPFC. Secondly, researchers have suggested that exercise has stress-modulating properties. According to the Cross-Stressor-Adaptation Hypothesis, exercise causes stress-like reactions in the human body, and repeated exercise has been shown to cause a reduction of the stress response to exercise (habituation) (Hackney, 2006), which can potentially transfer to other stressors as well (Sothmann, 2006). Systematic reviews of the literature showed that study results on such transfer effects to psychosocial stress are still inconclusive (Jackson and Dishman, 2006; Mücke et al., 2018). However, cross-sectional studies (e.g., Rimmele et al., 2007), and a randomized controlled trial (Klaperski et al., 2014) using the Trier Social Stress Test (TSST), a psychosocial stressor task with high effectivity, reliability and ecological validity, showed attenuated stress reactivity of the HPA axis and the ANS in fitter participants and in those who participated in an exercise program, respectively. Moreover, initial evidence suggests that similar effects already occur after a single bout of aerobic exercise (Zschucke et al., 2015). Accordingly, acute exercise could mitigate potential negative effects of psychosocial stress on executive functioning via two different pathways—either by facilitating executive functioning, or by reducing the magnitude of the reaction to the stressor.

Therefore, the primary aim of the present study was to examine the effects of an acute bout of moderate aerobic exercise on interference control under the influence of psychosocial stress in male adolescents. Studies have found increased performance in interference control to be associated with more left-lateralized activation of the dorsolateral prefrontal cortex (Yanagisawa et al., 2010; Byun et al., 2014). Accordingly, it was hypothesized that compared to a control condition, acute exercise mitigates negative effects of stress on interference control, and is therefore associated with better behavioral interference control and more left-lateralized DLPFC activation than the control condition. As a secondary aim, the effects an acute bout of aerobic exercise on stress reactivity were investigated.

MATERIALS AND METHODS

Participants

In total, 60 participants were recruited via advertisements, flyers and personal contact. Only male, healthy, right-handed (as verified with the Edinburgh Handedness Inventory, Oldfield, 1971) persons between 16 and 20 years of age were included. All participants were fluent German speakers. To standardize educational status, only participants currently attending academic high schools were admitted. Other studies showed that the level of regular physical activity can influence stress reactivity (Klaperski et al., 2014). Therefore, only participants who were not completely inactive, but who reported between two and six hours of exercise per week were included. Participants were informed about the study procedures at least 3 days prior to the data assessment and provided informed consent. All study procedures were in accordance with ethical principles of the Declaration of Helsinki and approval was obtained by the local ethics committee (Ethikkommission Nordwest- und Zentralschweiz, project number: 2018-01775) before the start of the study.

Study Design

The study design is depicted in **Figure 1**. Participants were randomly assigned to the exercise group ($N = 30$) or the control group ($N = 30$). The amount of self-reported regular physical activity was used as a stratum in order to create groups with similar physical activity behavior. As a cut-off, an amount of vigorous physical activity (VPA) of 180 min per week, as reported in the International Physical Activity Questionnaire (IPAQ), was used. This cut-off was chosen because it was the average weekly VPA in a previous study with a very similar sample (Mücke et al., 2020). All appointments were scheduled in the afternoon at either 13:00 or 16:00 to minimize the potential impact of variations in diurnal cortisol levels (Kudielka et al., 2004). Upon arrival, participants rested for 15 min to reduce the influence of possible stress factors before and/or during arrival. Body height and weight were then measured objectively with a stadiometer and an electronic scale (Tanita BC-601, Tokyo, Japan), respectively, and participants filled in a questionnaire including age (in years), socio-economic status (one item), physical activity [International Physical Activity Questionnaire (IPAQ); Craig et al., 2003], sleep complaints [7-item Insomnia Severity Index (ISI); Gerber et al., 2016], chronic stress [10-item Perceived Stress Scale (PSS); Klein et al., 2016], mental toughness [18-item short form of the Mental Toughness Questionnaire (MTQ18); Gerber et al., 2018], and psychopathology [25-item Strengths and Difficulties Questionnaire (SDQ); Goodman, 2001]. The validity of all psychological instruments has been established previously and all measures showed acceptable internal consistency in the present sample (Cronbach's alpha > 0.67 for all psychometric variables). Subsequently, an fNIRS head cap (NIRSport, NIRx Medical Technologies, Berlin, Germany) was fitted to the participants' head, sensors were calibrated and a Stroop Color-Word task was performed (these processes are described in detail in Section "Interference Control and Prefrontal Brain Activity"). During the next 30 min, the control group read an article from a magazine of their choice, while the exercise group performed an exercise session at moderate intensity on a bicycle ergometer (R60, Vision Fitness, Frechen, Germany). After the intervention, the head cap was mounted again. Subsequently, a modified version of the Trier Social Stress Test (TSST) was performed as described in Section "Stress Paradigm and Measurement of Stress Reactivity". The time delay between the end of the exercise or control condition and the beginning of the stress task was approximately 10 min. Within the TSST setup, the Stroop Color-Word task was performed again, with the difference that this time participants were instructed in a way that contributed to an increase in psychosocial stress (see Section "Stress Paradigm and Measurement of Stress Reactivity"). The appointment ended with a 10 min resting period, and all participants received a financial compensation of 70 CHF for their participation. Before and after the Stroop tasks, the intervention (acute exercise vs. reading) and the stress test, and after the resting period, saliva samples were collected with Salivette Blue Cap (Sarstedt, Nümbrecht, Germany) to control for saliva cortisol and alpha-amylase levels (see **Figure 1** and Section "Stress Paradigm and Measurement of Stress Reactivity").

Exercise Session

During the exercise session, participants pedaled at a constant speed (70–80 rpm). Moderate intensity was defined as 70% of maximum heart rate (HR_{max}), which was calculated with the formula $HR_{max} = 208 - 0.7 \times \text{age}$ (Tanaka et al., 2001). Pedaling resistance was continuously adjusted according to the measured heart rate. Furthermore, subjectively perceived intensity was monitored every 5 minutes using rating of perceived exertion (Borg, 1982).

Interference Control and Prefrontal Brain Activity

A computer-based version of the Stroop Color-Word task was used to assess interference control (Homack and Riccio, 2004). It consisted of compatible and incompatible trials. In compatible trials, color words appeared in the same ink color (e.g., "blue" printed in blue), whereas in incompatible trials, color words appeared in a different color of ink (e.g., "yellow" printed in green). To ensure similar visual content, the German color words "grün" (green), "gelb" (yellow), "blau" (blue), and "pink" were

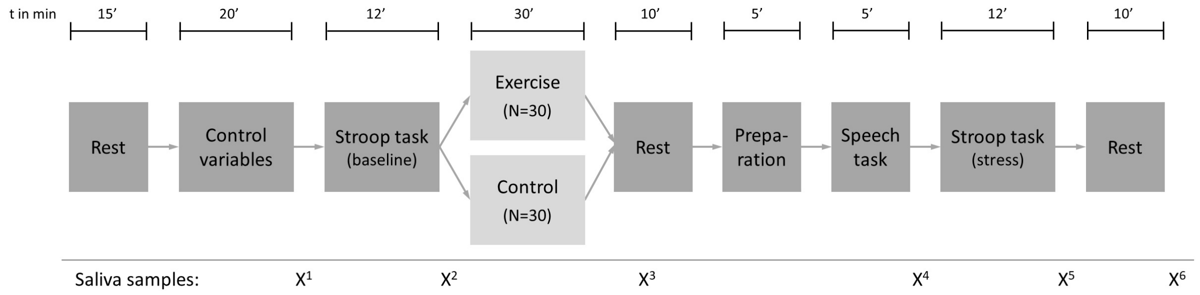

FIGURE 1 | Study design.

used. Participants were instructed to press a button corresponding to the color of ink, ignoring the actual meaning of the word, and to react as quickly and accurately as possible. Stimuli were presented for 250 ms, and responses were collected within a 1250 ms time window. The inter-stimulus time varied randomly between 300 and 500 ms. The task included twenty test blocks, each lasting 22-24 s. The duration of the resting periods between the test blocks varied randomly between 10 and 15 s. Compatible and incompatible test blocks alternated and within each block, the stimuli appeared with equal probability and followed a fully randomized order. Before testing, two practice blocks were conducted for familiarization and to reduce learning effects. Illustrations of the Stroop task sequence and block design are presented in the **Supplementary Material** (**Supplements 1, 2**).

For analysis, an interference score was calculated as the difference between reaction time on incompatible trials minus reaction time on compatible trials. Only response-correct trials with reaction times $\geq$120 ms were used for calculation as shorter response times would be highly likely to indicate guesswork (Zhang et al., 2014). A lower interference score equals higher interference control. To check whether potential group differences were influenced by speed-accuracy trade-offs, response accuracy was recorded as well.

For measurement of DLPFC brain oxygenation during the Stroop task, a dual-wavelength (760 and 850 nm) continuous-wave fNIRS system with a sampling rate of 7.8125 Hz (NIRSport, NIRx Medical Technologies, Berlin, Germany) and the recording software NIRStar 15.2 (NIRx Medical Technologies, Berlin, Germany) were used. Eight optodes (4 illumination sources, 4 light detectors) were mounted into a flexible cap, which was then placed on the participant's head. Optodes were equally distributed over the left and right DLPFC as shown in **Figure 2**. The DLPFC location was defined as described by Carlén (2017), and international 10:10 EEG positions were used as referencing points [for exact probe positions, see **Supplementary Material** (**Supplement 4**)]. The same montage has been used previously by Ludyga et al. (2019a). Spacers were used to keep the inter-optode distance constant at 3cm, which is considered the best compromise between high light penetration depth and sufficient signal-to-noise ratio (Ferrari and Quaresima, 2012; Tak and Ye, 2014). A black overcap was used to minimize the impact of ambient light. Additionally, the surrounding noise was reduced to a minimum and participants were instructed to avoid head movements and speaking during the Stroop task. Recording procedures were in line with existing quality standards (Orihuela-Espina et al., 2010) and recommendations for fNIRS assessments in exercise-cognition research (Herold et al., 2018).

After recording, fNIRS data was processed with Homer2 version 2.3 (Huppert et al., 2009). The processing stream followed the one proposed by Brigadoi et al. (2014) and is described in detail in Ludyga et al. (2019a). Artifacts exceeding defined thresholds were automatically marked and manually verified. Based on the results of systematic comparisons of artifact correction techniques (Scholkmann et al., 2010; Cooper et al., 2012), spline interpolation was used to correct marked artifacts, followed by a frequency filter with a low cut-off at 0.01 Hz (Yennu et al., 2016) and a high cut-off at 0.5 Hz (Brigadoi et al., 2014). Block averages were created for compatible and incompatible test blocks with the 2 s period preceding the test block used as reference. For the calculation of left and right DLPFC oxygenation, the average of all 4 channels on each side was calculated because test-retest reliability has been found to be higher at cluster level compared to individual channels (Schecklmann et al., 2008). Oxygenation related to Stroop interference was calculated as average oxygenation during incompatible minus compatible test blocks (Δ_{OXY}).

Stress Paradigm and Measurement of Stress Reactivity

Psychosocial stress was induced using a modified version of the TSST (Kirschbaum et al., 1993). It consisted of an anticipation phase and a mock job interview, followed by a Stroop task with adapted instructions designed to enhance psychological stress. Both the mental arithmetic task used in the original TSST, as well as the Stroop task implemented in our modified version, have been used as cognitive stressors in previous studies (Dickerson and Kemeny, 2004). In our psychosocial stressor, two motivated performance tasks (speech and cognitive test) were combined with the additional element of uncontrollability and socio-evaluative threat. This combination has been shown to be more effective in triggering a physiological stress response than other laboratory stressors consisting only of a single task (Dickerson and Kemeny, 2004). The following protocol was used: after a 5 min preparation phase, participants performed a 5 min unrehearsed speech in front of a committee of two (one male

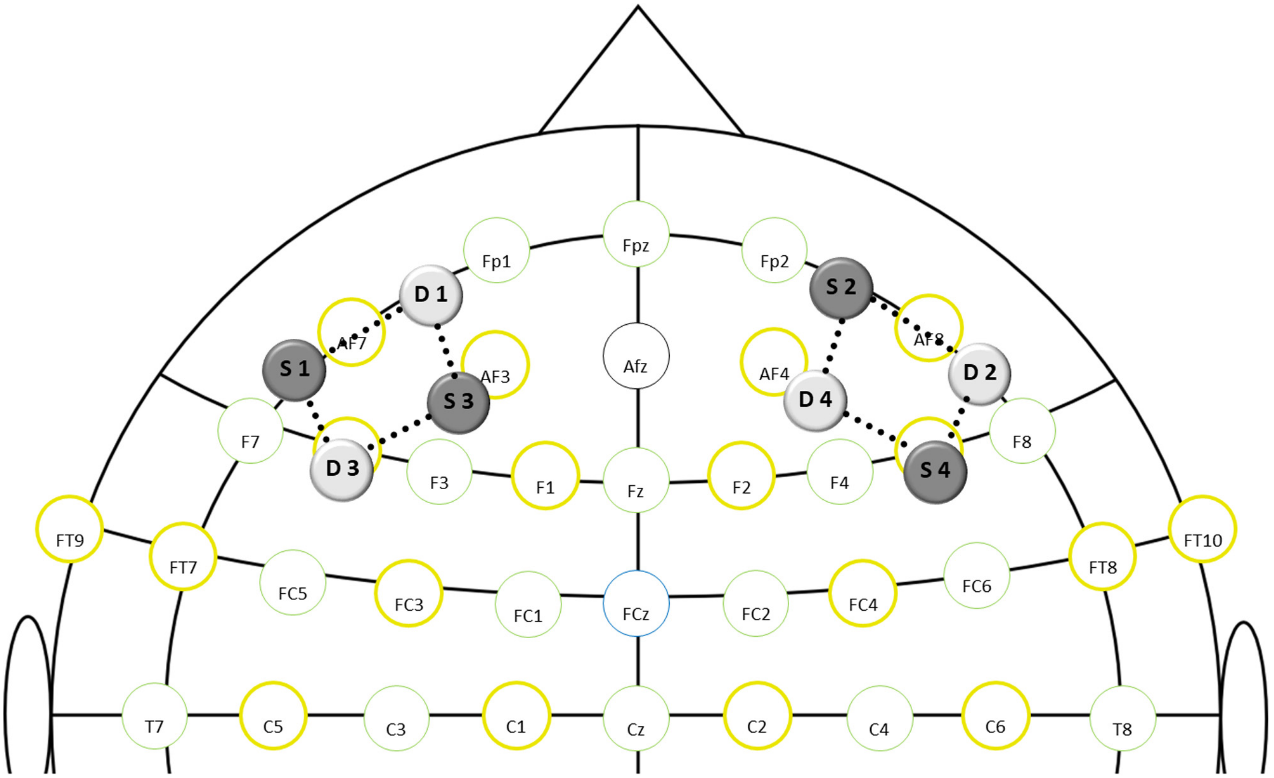

FIGURE 2 | fNIRS montage layout in relation to standard EEG positions (S-source; D-detector; dotted lines-channels).

and one female), followed by a 10 min Stroop task. Participants were instructed to imagine a situation in the near future when they finished school, were looking for a job and were offered an interview for their dream job. The committee was introduced to the participants as the manager of the company and an assistant who is specialized in the interpretation of body language and voice frequency. Throughout the speech, the committee showed neutral facial expressions and only used standardized responses (e.g., "You still have time left. Please continue."). Subsequently, the Stroop task was performed as described in the section above, with the following additions. The committee informed the participant that his test performance was visible on their screen and that they were able to compare his performance directly to other participants' data. The committee further remarked that if he did not perform well, he would not get the job, and the financial compensation for study participation would be reduced.

Stress reactivity was measured using saliva samples (for analysis of cortisol and alpha-amylase concentrations), heart rate monitoring and self-reported state-anxiety scores. While salivary free cortisol represents the reactivity of the HPA axis (Kudielka et al., 2004), salivary alpha-amylase is known to be reflective of the stress response of the autonomic (more specifically: sympathetic) nervous system (Nater and Rohleder, 2009). Saliva samples were collected at several time points during the appointment as shown in **Figure 1**. After data assessment, they were first stored at −20°C and then sent to the Biochemical Laboratory of the University of Trier, Germany, for analysis of cortisol (in nmol/l) and alpha-amylase (in U/ml) concentrations using time-resolved fluorescence immunoassay. As a parameter indicating the activation of the sympathetic nervous system in reaction to stress, heart rate was monitored continuously throughout the stress test. For the purpose of data analysis, 1 min intervals were averaged. Baseline heart rate was measured for 2 min before introduction of the stress test. Psychological stress reactions were measured before and after the stressor using 5 items of the state-anxiety scale of the State-Trait Anxiety Inventory (STAI; Laux et al., 1981; Cronbach's alpha = 0.72). After recoding inverted items, a sum score was calculated. It ranges from 5 to 20, with higher scores indicating higher anxiety.

Statistical Analysis

A power analysis was calculated with G*Power software. As no data on the effects of acute exercise on interference control under stress exists, yet, our power analysis was based on a meta-analysis by Verburgh et al. (2014), who reported moderate effects of acute exercise on interference control in adolescents. It resulted in a minimum number of 52 participants (parameters: repeated measures ANOVA, within-between interaction; effect size f = 0.20; alpha error probability = 0.05; power = 0.80; number of groups: 2; number of measurements: 2; correlation among repeated measures = 0.50; non-sphericity correction = 1).

Following Pruessner et al. (2003), for physiological stress reactivity (cortisol, alpha-amylase and heart rate reactivity), the area under the curve with respect to the increase (AUC_I) was calculated. Since alpha-amylase shows an immediate increase after stimulation of the ANS (Nater and Rohleder, 2009), samples 3–6 (**Figure 1**) were used. Salivary cortisol levels usually rise with about 10 min delay relative to stressor onset (Foley and Kirschbaum, 2010). Therefore, samples 4–6 were used to assess cortisol reactivity. For heart rate reactivity, the 2 min before the introduction of the TSST were averaged and used as a baseline, and the AUC_I was calculated from the subsequent averaged 1 min intervals until stressor cessation. Psychological stress reactivity was defined as the difference of the post-stress minus pre-stress anxiety score. Subsequently, potential group differences in baseline values and stress reactivity (AUC_I) were analyzed using separate independent *T*-tests.

The effect of exercise (compared to the control condition) on interference control under stress was examined using a repeated-measures analysis of variance (rANOVA) with stress (baseline Stroop interference vs. Stroop interference under stress) as within-subject variable and group (exercise vs. control) as between-subjects factor. In a second run of the analysis, stress reactivity parameters that showed group differences were added as covariates.

The effect of exercise on DLPFC oxygenation under stress was investigated using a rANCOVA with stress (Δ_{OXY} at baseline vs. Δ_{OXY} under stress) and hemisphere (Δ_{OXY} left vs. Δ_{OXY} right DLPFC) as within-subject variables and group (exercise vs. control) as between-subject factors. Heart rate during the Stroop task was added as a covariate, because fNIRS data can potentially be affected by systemic changes (Herold et al., 2018). For all rAN(C)OVA, main effects and interactions were reported. Effect sizes were classified as small ($d \geq 0.2$; $\eta p^2 \geq 0.01$), medium ($d \geq 0.5$; $\eta p^2 \geq 0.06$), or large ($d \geq 0.8$; $\eta p^2 \geq 0.14$) (Cohen, 1988). An alpha level of $p \leq 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS 26 (IBM Corporation, Armonk, NY, United States).

RESULTS

Sample Characteristics and Exercise Session

Characteristics of the sample are presented in **Table 1**. The exercise and control groups did not differ significantly in any of the anthropometric, sociodemographic or psychological control variables. During the exercise session, the average (standard deviation) heart rate and rating of perceived exhaustion were 128.5 (7.9) beats per minute and 14.0 (1.0), respectively. Average heart rate during the exercise session was significantly higher compared to the control condition [69.8 (10.0) beats per minute; $t = 24.9$, $p = 0.000$, $d = 6.60$] and represented 65.7 (4.0)% of HR_{max}.

Stress Reactivity

To enable the investigation of interference control under stress, our study design required differences in stress parameters between both Stroop task conditions (baseline and under-stress). As a manipulation check, paired *T*-tests were calculated. All physiological stress parameters indicated higher stress during the Stroop task performed under stress compared to the baseline condition (for cortisol and alpha-amylase directly after both Stroop tasks: $p < 0.001$; for heart rate during both Stroop tasks: $p = 0.03$). When using the measurement points directly after each Stroop task, self-reported psychological stress did not differ between both conditions ($p = 0.80$). However, between both measurement points, the stress test did evoke a measurable psychological stress response (see below).

TABLE 1 | Comparison of group characteristics (independent *T*-test).

	Exercise group M ± SD	Control group M ± SD	*p*
Age in years	17.9 ± 1.2	17.9 ± 1.3	0.999
BMI in kg/m^2	22.9 ± 3.1	22.8 ± 3.2	0.944
Socioeconomic status	3.3 ± 0.6	3.2 ± 0.6	0.667
MVPA in min/week (IPAQ)	308.3 ± 237.4	288.7 ± 157.8	0.707
Chronic stress (PSS)	13.9 ± 4.5	15.0 ± 5.3	0.365
Mental toughness (MTQ18)	45.6 ± 7.3	46.2 ± 6.8	0.730
Psychopathology (SDQ)	9.23 ± 4.1	9.23 ± 4.4	0.999
Insomnia (ISI)	7.6 ± 5.0	6.3 ± 4.1	0.304

BMI, body mass index; IPAQ, International Physical Activity Questionnaire; ISI, Insomnia Severity Index; M, mean; MTQ18, Mental Toughness Questionnaire; MVPA, Moderate-to-vigorous physical activity; PSS, Perceived Stress Scale; SD, standard deviation; SDQ, Strengths and Difficulties Questionnaire.

Changes in physiological and psychological stress parameters in response to the modified TSST are depicted in detail in **Figure 3**. Comparing both groups, independent *T*-tests revealed no baseline difference (that is: after exercise or control intervention, before stress test) for cortisol ($t = -0.07$, $p = 0.943$, $d = 0.02$) and alpha-amylase ($t = 0.11$, $p = 0.914$, $d = 0.03$). However, the control group showed significantly less anxiety ($t = 2.55$, $p = 0.014$, $d = 0.67$) and lower heart rate ($t = 5.57$, $p < 0.001$, $d = 1.46$) before the stress task than the exercise group. With regard to stress reactivity, we found a significant increase across the total sample in all four parameters ($p < 0.001$). However, groups differed in stress responses of alpha-amylase [$t(58) = -3.45$, $p < 0.001$, $d = 1.93$] and anxiety [$t(58) = -2.04$, $p = 0.046$, $d = 0.53$], with large and medium effect sizes, respectively, indicating higher stress reactivity in the control group. No differences between the exercise and control groups were present for cortisol [$t(58) = -0.43$, $p = 0.668$, $d = 0.11$] and heart rate reactivity [$t(57) = -0.48$, $p = 0.636$, $d = 0.13$].

Inhibitory Performance

Figure 4 depicts the reaction times and interference scores for both groups during the baseline Stroop task and the Stroop task under stress. With regard to effects of exercise, and stress, on interference scores, the rANOVA showed no statistically significant main effect of stress [$F(1,58) = 0.01$, $p = 0.925$, $\eta p^2 = 0.000$] and no stress × group interaction [$F(1,58) = 0.05$, $p = 0.826$, $\eta p^2 = 0.001$]. After further including alpha-amylase and psychological stress reactivity, the rANCOVA again showed no statistically significant main effect of stress [$F(1,58) = 3.80$, $p = 0.056$, $\eta p^2 = 0.063$] and no stress × group interaction [$F(1,58) = 0.43$, $p = 0.517$, $\eta p^2 = 0.008$].

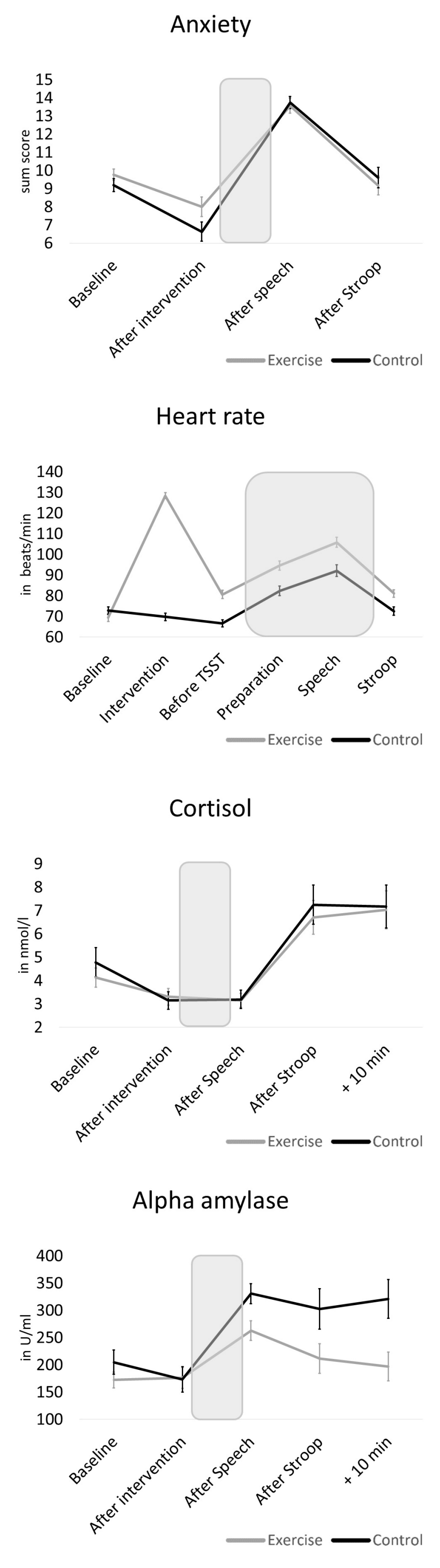

FIGURE 3 | Mean physiological and psychological stress reactivity of the exercise group and the control group. The shaded areas indicate the stressor (preparation and speech task). Error bars are standard errors of the mean (SEM).

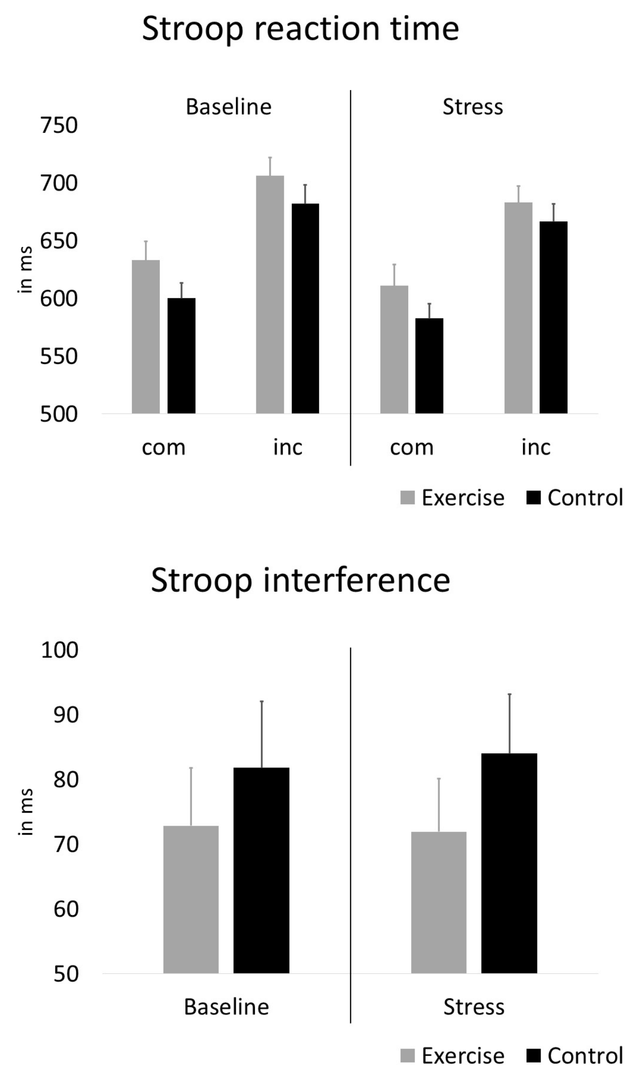

FIGURE 4 | Average Stroop reaction time during compatible (com) and incompatible (inc) test blocks and interference scores before and under stress. Error bars are standard errors of the mean (SEM).

Furthermore, response accuracy interference was analyzed to control for potential speed-accuracy trade-offs. Repeating the same analyses with response accuracy revealed no statistically significant main effect of stress [$F(1,58) = 1.826$, $p = 0.182$, $\eta p^2 = 0.031$] and no stress × group interaction [$F(1,58) = 3.79$, $p = 0.056$, $\eta p^2 = 0.061$]. However, at baseline the exercise group showed lower response accuracy during incompatible trials compared to the control group [$T(1,58) = -2.65$, $p = 0.010$, $d = 0.70$]. Response accuracy scores of both groups are presented in the **Supplementary Material** (**Supplement 3**).

DLPFC Oxygenation

The rANCOVA showed no statistically significant main effect of stress [$F(1,58) = 2.38$, $p = 0.128$, $\eta p^2 = 0.040$], no stress × group interaction [$F(1,58) = 2.80$, $p = 0.100$, $\eta p^2 = 0.047$], and no hemisphere × group interaction [$F(1,58) = 0.76$, $p = 0.387$,

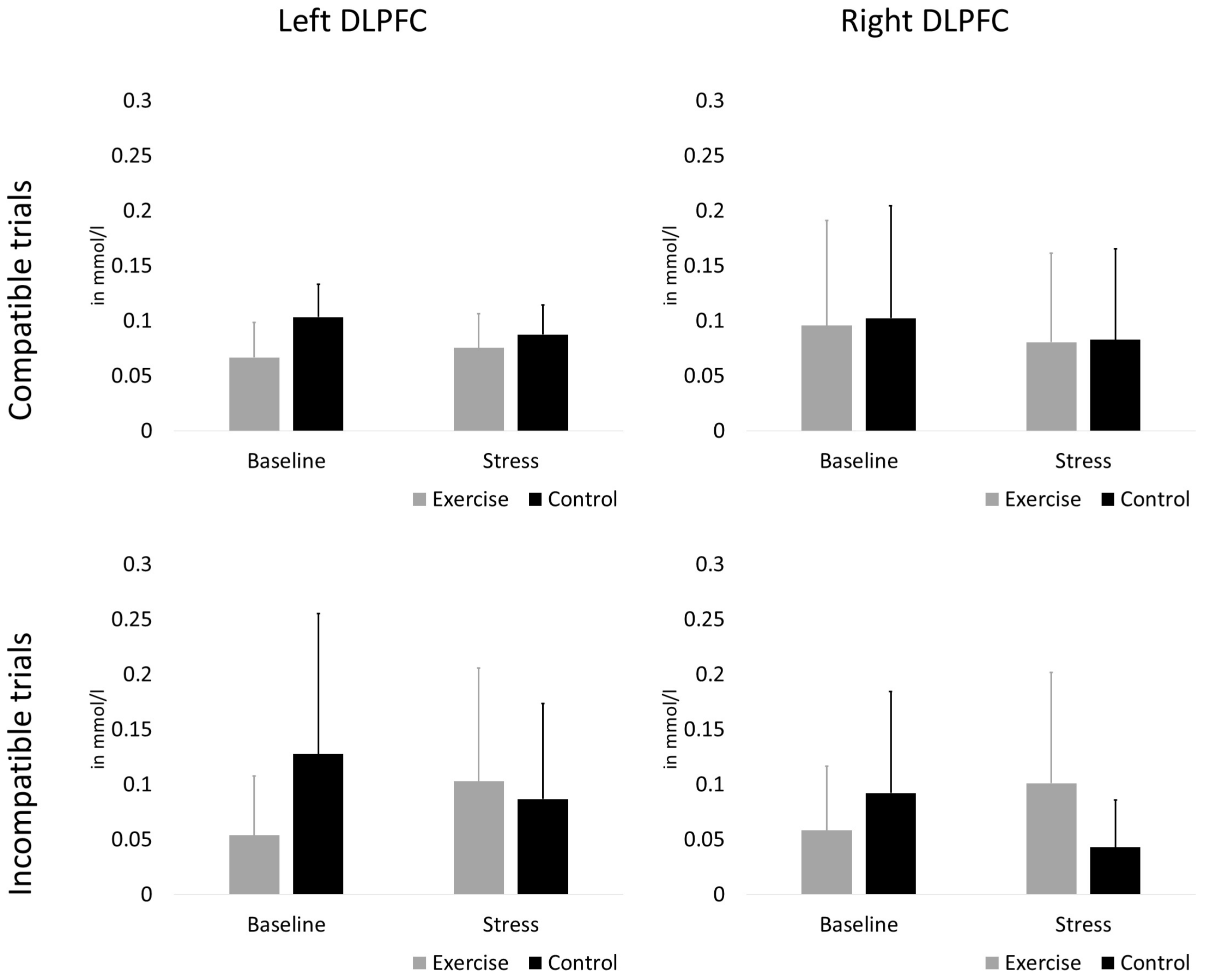

FIGURE 5 | Oxygenation changes in the left **(A,C)** and right **(B,D)**. DLPFC during compatible **(A,B)** and incompatible **(C,D)** test blocks. Error bars are standard errors of the mean (SEM).

$\eta p^2 = 0.013$]. All other main effects and interaction terms did not reach statistical significance ($p < 0.601$). Oxygenation changes in the left and right DLPFC during compatible and incompatible test blocks are presented in **Figure 5**.

DISCUSSION

This study aimed to investigate the effect of an acute exercise bout on interference control under stress and corresponding oxygenation differences in the left and right DLPFC. In our study, we found no indication of differences between the exercise group and control group with regard to interference control under stress, and controlling for differences in stress reactivity did not change this result. Corresponding oxygenation differences in left and right DLPFC also did not differ between groups. While the stress test elicited significant reactions in all stress reactivity parameters and across both groups, we found higher alpha-amylase reactivity and higher increases in anxiety in the control group compared to the exercise group.

Acute Exercise and Interference Control Under Stress

A wealth of studies have already investigated the effects of acute exercise on executive functioning without enhanced stress in various age groups. Systematic reviews and meta-analyses consistently reported small but significant effects, and demonstrated that acute exercise is beneficial for subsequent executive functioning across all age groups (Tomporowski, 2003; Chang et al., 2012; Ludyga et al., 2016), although age groups that are typically characterized by developmental changes seem to benefit more than others (Guiney and Machado, 2013; Ludyga et al., 2016). In a meta-analysis compiling data on preadolescent children (6-12 years), adolescents (13-18 years) and young adults (18-35 years), Verburgh et al. (2014) reported moderate effects of acute exercise on inhibition/interference control in children and adolescents, and small-to-moderate effects in young adults. More recent empirical findings on adolescents corroborated this pattern for interference control (Browne et al., 2016; Peruyero et al., 2017; Park and Etnier, 2019). However, no studies so far looked into the effects of acute exercise on interference control under the influence of psychosocial stress. Previous studies reported negative effects of acute stress on executive functions, including interference control (Shields et al., 2016). As maintaining high executive functioning under stress is of great importance for success in education and professional life, and higher executive functioning under stress has been shown to be associated with better health (Williams and Thayer, 2009; Shields et al., 2017), research on mitigating factors is important.

In this study, we present initial insights into the influence of acute exercise on interference control in the presence of acute psychosocial stress. Despite the promising effects on interference control in situations without additional stress, which previous studies reported to be most pronounced in young people, our study with participants in later stages of adolescence did not show such effects in the presence of acute psychosocial stress. However, these results, which refer to interference scores based on reaction time, can be influenced by differences in response accuracy. In our study, during incompatible trials the exercise group showed worse response accuracy at baseline, but not under stress, and a medium effect size (non-significant, however) pointed toward a stress × group interaction on accuracy interference, indicating potential group differences in response accuracy in favor of the exercise group. These potential group differences in response accuracy might indicate a speed-accuracy trade-off and might have caused effects on the main outcome to disappear. Nevertheless, compared to the results other studies reported for stress-free conditions, exercise effects on interference control appeared to be smaller or absent under stress, and based on our data, we cannot generally recommend acute exercise to enhance interference control under stress. Individuals differ largely in how they perceive and react to stress, and researchers argue that the vulnerability to, and resilience against potential negative effects of acute stress on cognition might vary largely among individuals (Sandi, 2013). While we took the most important anthropometric, sociodemographic and psychological confounders into account, it cannot be ruled out that among other individual factors, the effects of acute exercise were too small to be detected. Our exercise intervention comprised 30 min of ergometer exercise at a constant, moderate intensity (on average 66% of HR_{max}). While interventions of similar type, duration and intensity proved to be effective in enhancing interference control (Alves et al., 2012; Chang et al., 2015), it is possible that under acute stress, different exercise modalities might have yielded more favorable results. For instance, meta-analytical findings by Gu et al. (2019) indicate that open-skill exercise might be more effective for improving cognitive functioning than closed-skill exercise, and Ludyga et al. (2018) showed beneficial effects if aerobic and coordinative demands are combined. On the other hand, ergometer cycling seems to have superior effects on cognitive performance compared to treadmill running exercise (Lambourne and Tomporowski, 2010), and researchers found similar effects for aerobic and strength (Alves et al., 2012) or coordinative exercise (Ludyga et al., 2017) on inhibitory control. To elicit improvements in executive functioning, exercise durations between 20 and 60 min are deemed optimal (Tomporowski, 2003; Lambourne and Tomporowski, 2010). With regard to exercise intensity, studies reported beneficial effects on Stroop performance following low and high (Peruyero et al., 2017), and moderate intensity exercise (Browne et al., 2016; Park and Etnier, 2019). Studies investigating a dose-response relationship suggested an inverted-U-shaped effect, with best results for moderate exercise (McMorris and Hale, 2012). It is noteworthy that depending on intensity, exercise itself can have an impact on stress parameters. According to Hackney (2006), exercise that surpasses an intensity of 50-60% of the maximal oxygen uptake (VO_{2max}) increases circulating concentrations of cortisol. In our study, stress parameters did not rise in response to the exercise session (see **Figure 3**), which means that they might not have surpassed this VO_2 threshold. This might have had an influence on our results, and future studies should look into the effect of exercise intensity and exercise-induced stress on executive functions. Overall, the findings listed above apply to effects of different exercise modalities on executive functioning without the additional element of psychosocial stress, and future studies are encouraged to investigate whether different exercise modalities have distinct effects on executive functioning under stress.

The absence of the hypothesized beneficial effect of acute exercise in our study might in part be explained by the absence of the expected negative impact of stress on interference control. Our results showed no main effect of stress on the interference score, indicating that in our study, the stressor did not change interference control in the overall sample. This was surprising, because other studies reported impaired inhibitory performance under stress (Sanger et al., 2014; Roos et al., 2017), and meta-analytical findings, although based on a small number of studies, suggested that the negative effect of acute stress on interference control is independent of stress severity and stress type (Shields et al., 2016). As our stress reactivity analysis revealed, the stressor elicited significant increases in all measured physiological and psychological indices of stress reactivity. Nevertheless, participants' ratings of anxiety after the baseline Stroop task, and the Stroop task under stress, did not differ significantly (cp. **Figure 3**). Studies showed that impairments in Stroop performance under stress can largely be attributed to subjective stress perceptions (Henderson et al., 2012). However, other studies also found associations of HPA axis and ANS reactivity with impaired inhibitory control (Sanger et al., 2014; Roos et al., 2017). As our study did not include a control condition without stress, we were not able to fully control for the influence of potential practice effects on the results. Participants might have performed better under stress because an assessment of inhibitory control without stress took place beforehand (see limitations). In conclusion, it remains unclear why the stressor failed to elicit the expected decline in behavioral interference control, and more studies on the effect of stress on executive functioning, and on the potential role of exercise, are necessary.

Associations With DLPFC Oxygenation

Along with behavioral parameters, DLPFC oxygenation was measured to account for neurophysiological mechanisms underlying interference control. Recent fNIRS studies demonstrated that more left-lateralized DLPFC oxygenation was associated with higher interference control (Zhang et al., 2014; Ludyga et al., 2019a). This effect has been attributed to differences in left and right DLPFC activation when stimulus conflict is anticipated and up-regulation of the attentional set is required (Vanderhasselt et al., 2009). According to lateralized Stroop studies, interference effects might be greater in the left hemisphere because, compared to the right hemisphere, the left hemisphere presents an overall advantage on most verbal tasks (Belanger and Cimino, 2002). Moreover, research with fNIRS showed that positive effects of exercise on interference control might be mediated by DLPFC lateralization. In 25 young adults, Byun et al. (2014) observed improved performance in a Stroop color-word matching task after a 10min bout of mild ergometer exercise, which was accompanied by pronounced activation of the left DLPFC in relation to Stroop interference. In a sample of 60 older adults, Hyodo et al. (2016) reported correlations between higher aerobic fitness and better Stroop performance, and mediation analysis revealed that this relationship was mediated by more left-lateralized DLPFC activation. In a recent study utilizing a combined fNIRS-EEG approach, our research group investigated mechanisms underlying the association between aerobic fitness and interference control in a sample similar to the present study (Ludyga et al., 2019a). While both left-lateralized DLPFC oxygenation, and greater N450 negativity, were associated with better Stroop performance, only N450 negativity mediated the fitness-interference control relationship. Again, no studies are available that investigated associations between exercise and interference control in the presence of acute psychosocial stress, and the present study provides first insights into this relationship. Overall, our data indicate a tendency toward left-lateralized activation in both groups and in both conditions (cp. **Figure 5**). No systematic differences in DLPFC oxygenation occurred between both groups and conditions. These results match our findings with regard to behavioral interference control, but provide no support for our hypothesis of increased left-lateralized DLPFC activity in the exercise group. From other studies we know that exercise improves interference control via facilitation of DLPFC activation (e.g. Yanagisawa et al., 2010; Byun et al., 2014), and that acute stress affects the PFC (Arnsten, 2009). While our study only assessed stress effects on activation and functioning of the DLPFC, our results do not allow conclusions on the activation of other PFC regions under stress, and potential corresponding effects of acute exercise.

Exercise Effects on Stress Reactivity

In our study, we observed that the acute exercise group showed lower stress reactivity than the control group in the parameters alpha-amylase and anxiety, but not in the parameters cortisol and heart rate. While these group differences in stress reactivity were not related to significant changes in interference control, they are relevant for different reasons. As research shows, the phase of adolescence, compared to other age groups, is characterized by a typical increase in stress reactivity in response to acute psychosocial stressors (Lupien et al., 2009; Stroud et al., 2009). The combination of frequent stress exposure in this age group (American Psychological Association, 2014) and potentially high stress reactivity, increases the risk of corresponding future stress-related health issues (Redmond et al., 2013; Turner et al., 2020). Therefore, a reduction in stress reactivity in the face of psychosocial stressors is often desirable. Our results now show that acute exercise has such potentially health-beneficial effects on stress reactivity.

Changes in stress reactivity in relation to exercise have been observed before, and are often explained with habituation effects of the stress response systems when exposed to regular exercise (Herman et al., 2005; Hackney, 2006), which then transfer to the reaction to psychosocial stressors (Sothmann, 2006). While this has often been demonstrated for regular exercise (Mücke et al., 2018), only few studies investigated such effects after a single exercise bout. Three relatively recent studies investigated the effects of acute exercise on physiological stress reactivity in young adults (Zschucke et al., 2015; Wood et al., 2018; Wunsch et al., 2019). Interestingly, although these studies differed largely with regard to exercise type (walking vs. bicycle ergometer vs. treadmill), exercise intensity (moderate walking vs. 70% of their individual maximum load vs. 60—70% of maximum oxygen uptake), time delay from exercise to stressor (30 min vs. 10 min vs. 90 min delay), stress task (TSST-G vs. Montreal Imaging Stress Task), and control task (passive control vs. light stretching), they consistently reported attenuated cortisol and/or alpha-amylase reactivity in the exercise group, compared to the control group. This initial data demonstrates that the effects of acute exercise on stress reactivity seem to be fairly robust and are related to a wide range of exercise modalities. In our slightly younger sample of male adolescents, and with exercise parameters within the range of these previous studies, we show similar results with regard to alpha-amylase, which represents stress reactions of the autonomic nervous system (Nater and Rohleder, 2009). However, no such effects were observed with regard to cortisol. Different effects of the exercise session on these parameters are unlikely to be the explanation for this result, as directly after the exercise or control condition, alpha-amylase as well as cortisol levels did not differ between groups. Studies have already shown that the reactions of HPA axis and ANS system to psychosocial stressors can be dissociated (Schommer et al., 2003). However, in this particular case, the reasons for these differences remain unclear. Lastly, our study indicated transient effects of exercise on self-reported anxiety. In response to the stressor, we observed lower increases in anxiety in the exercise group, compared to the control group. After the stressor, both groups reported similar anxiety levels. As other studies so far focused on physiological stress parameters, there is a lack of research on acute exercise effects on psychological stress reactivity, and our findings provide initial support for improved coping with stressors that are characterized by uncontrollability and socio-evaluative threat after an acute bout of exercise. Further studies are necessary to confirm these initial results.

Limitations

The results of our randomized, controlled examination have some limitations that need to be considered. As our sample consisted of healthy, male, right-handed adolescents with a rather high educational status, conclusions on other target groups need to be treated with caution. Further research with female participants, different age groups and educational status, or with clinical samples is necessary and could lead to different results. Furthermore, it is possible that different exercise conditions might have changed the results. It is noteworthy that in our study, a modified version of the TSST was used. The mental arithmetic task, as described in the original version by Kirschbaum et al. (1993), was replaced by a Stroop task in order to measure participants' interference control under the direct influence of the psychosocial stressor. Although both mental arithmetic and Stroop tasks have been used as stressors before (Dickerson and Kemeny, 2004), and substantial differences in stress reactivity are therefore unlikely, direct comparisons of our results with other TSST studies are limited. In our study, an acute exercise group was compared to an active control group. However, both groups underwent the complete stressor task, and no "no-stress" control group was present. Therefore, our study did not control for the effects of repeated Stroop task exposure, and our results may be confounded by practice effects. However, other studies reported no such effects after repeated Stroop task administration (Browne et al., 2016), and since it would have affected both groups equally, a change of the general patterns of results because of practice effects is unlikely. Finally, despite its advantages in the assessment of cortical brain activity (Zhang et al., 2014), the use of fNIRS has some limitations. It has been shown that fNIRS measurements can be partially affected by skin blood flow and systemic effects (Tachtsidis and Scholkmann, 2016). However, we expect the effect of such artifacts to be small in our analyses, because all Stroop tasks in our study were conducted under standardized conditions (the participants were instructed to remain seated, to avoid speaking and to breathe regularly throughout the measurement to keep these parameters constant). Moreover, because we calculated Stroop interference related to DLPFC activation as the difference between incompatible and compatible trials, the shared potential global artifacts of both trial types should cancel each other out (Hyodo et al., 2016).

CONCLUSION

Adolescents performing an acute exercise bout appear to show lower stress reactivity of the autonomic nervous system, and a lower increase in anxiety in response to a psychosocial stressor than their non-exercising peers. In contrast, a single exercise session does not seem to influence stress-induced changes in interference control and associated DLPFC oxygenation. Thus, such an exercise paradigm may only be valuable in buffering the autonomous stress response.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethikkommission Nordwest- und Zentralschweiz, Switzerland. Written informed consent was obtained from all participants. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MM, SL, and MG were responsible for the conceptualization and study methodology. SL contributed to the Software. MM, SL, and FC contributed to the formal analysis. MM was responsible for the investigation. UP and MG contributed to the resources. MM contributed to the writing of the manuscript (original draft). SL, FC, UP, and MG contributed to the writing of the manuscript (review and editing). UP and MG were responsible for the project supervision. MM was responsible for the project administration. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2020.581965/full#supplementary-material

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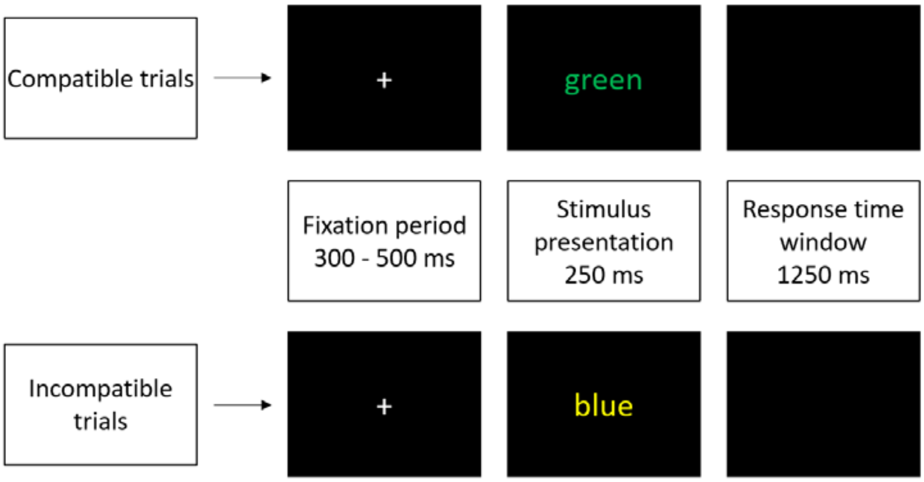
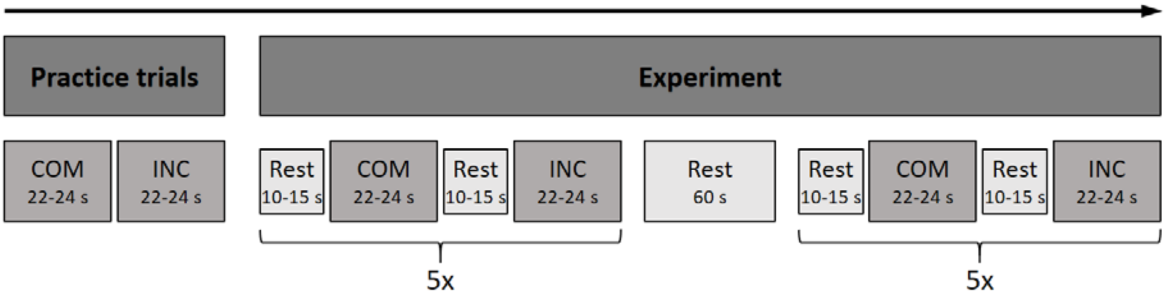
Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

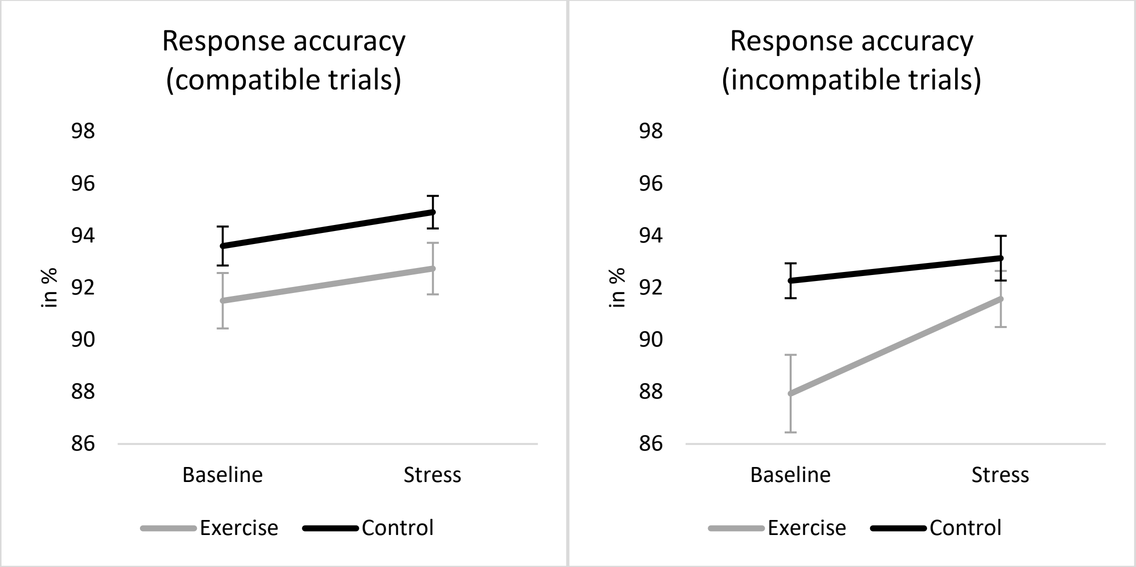
Supplementary material.



Supplement 1. Examples of Stroop task sequence for compatible and incompatible trials.



Supplement 2. Block design of the Stroop task.



Supplement 3. Average Stroop response accuracy during compatible and incompatible test blocks before and under stress. Error bars are standard errors of the mean (SEM).

Supplement 4. fNIRS channel positions

Channel	Azimuth	Elevation
S1_D1	91.109	129.501
S1_D3	80.050	141.226
S2_D2	89.951	50.169
S2_D4	81.382	59.446
S3_D1	81.148	120.368
S3_D3	69.909	132.035
S4_D2	79.835	38.991
S4_D4	70.141	47.932

S-Source; D-Detector

5 Synthesis of the main findings

The publications included in this PhD project correspond to different aspects of the pre-defined hypotheses (Section 2.2). Thus, for ease-of-reading, this chapter gives an overview of the main findings of the publications with respect to the hypotheses. Section 5.1 refers to Hypothesis 1, Section 5.2 is linked to Hypothesis 2, and in Section 5.3, results of our studies corresponding to Hypothesis 3 are summarized.

5.1 Results on physical activity, fitness, acute exercise and stress reactivity

Results of the systematic review. Our systematic overview of the literature uncovered 14 studies investigating potential associations of physical activity and fitness with stress reactivity. Overall, partial support for the CSA hypothesis was found. Seven out of twelve studies reported lower HPA axis activity in more physically active or fitter participants, as represented by cortisol levels, and four out of nine studies showed lower reactivity of the ANS in more physically active or fitter participants, as represented by changes in heart rate. Only five studies reported results on psychological parameters (anxiety, mood and calmness), with inconsistent results. As potential moderating variables, age, sex, exercise intensity, objective vs. subjective measurement of physical activity, physical activity vs. fitness, and psychological covariates were considered. Initial evidence was found for moderating effects of exercise intensity. Results across studies did not indicate different patterns for associations of physical activity and fitness with stress reactivity. Regarding all other potential moderators, results were inconsistent or have not been replicated, yet. A knowledge gap with regard to the age group of adolescents was discovered. Except for one intervention study, all results originated from cross-sectional studies. Overall, it was noticeable that some of the studies reported higher stress reactivity in fitter participants in some of the parameters, which was contrary to the CSA hypothesis. Thus, potential normalizing (and not reducing) effects of physical activity and fitness on stress reactivity are discussed.

Results of Study 1. The first study addressed associations of physical activity and fitness with stress reactivity. In Publication 2 (Section 4.2), results with regard to associations of aerobic fitness with endocrine, autonomous and psychological stress reactivity are presented. In summary, our data provide partial support for the CSA hypothesis. After inclusion of the potential confounders age, socio-economic status, chronic stress, sleep complaints, mental toughness and psychopathology, regression analyses revealed no association of fitness with HPA axis reactivity and psychological stress responses. However, higher fitness was associated with lower autonomic stress reactivity: together with sleep complaints, differences in fitness explained 28% of the variance in stress reactivity of the ANS (as represented by salivary alpha-amylase), with 16% of variance explained by fitness alone.

With regard to associations of physical activity with stress reactivity, Publication 4 (Section 4.4) revealed no association of exercise levels (high vs. low) with baseline-to-peak changes in cortisol following the TSST. After use of the same statistical procedures as described in Publication 2 for calculating associations of physical activity with stress reactivity, no associations of objectively measured moderate-to-vigorous physical activity or vigorous physical activity with stress reactivity of the HPA axis (cortisol levels), ANS (alpha-amylase levels) and psychological parameters (state anxiety, mood, calmness) were observed (data not published).

Results of Study 2. In the second study, effects of an acute bout of aerobic exercise on stress reactivity were examined and compared with an active control group (Publication 5, Section 4.5). Compared to the control group, participants who pedaled on a cycle ergometer at 70% of maximum heart rate for 30 min showed reduced autonomic stress reactivity (salivary alpha-amylase concentration) and lower psychological stress reactivity (self-reported anxiety) in response to a modified TSST. However, with regard to HPA axis reactivity (salivary cortisol concentration) and heart rate as another indicator of the ANS, no group differences were observed.

5.2 Results for inhibitory control under acute psychosocial stress

Results of Study 1. Publication 3 (Section 4.3) focused on mechanisms underlying the association between aerobic fitness and inhibitory control in the pre-stress condition of Study 1. A median split based on aerobic fitness was performed, resulting in a group with significantly lower and a group with significantly higher aerobic fitness than the average fitness of a large European sample of comparable age (Ortlepp, Metrikat, Albrecht, & Maya-Pelzer, 2004). The high-fitness group showed lower interference scores in the Stroop task compared to the low-fitness group, indicating better inhibitory control in fitter participants. When comparing inhibitory performance of frequently exercising and rarely exercising participants in the low-stress and high-stress conditions, different patterns emerged: As indicated in Publication 4 (Section 4.4), no differences in inhibitory control between low- and high-stress condition were found, and no differences between more and less exercising participants emerged with regard to behavioral inhibitory control under stress.

Results of Study 2. Results of Study 2 are presented in detail in Publication 5 (Section 4.5). In summary, before and after controlling for group differences in stress reactivity, no difference in inhibitory control between the acute exercise group and the active control group in both the low- and high-stress conditions were observed. A non-significant effect with medium effect size indicated potential differences in inhibitory control between the low- and high-stress condition across the whole sample.

5.3 Results for corresponding dorsolateral prefrontal brain activity

Results of Study 1. In Publication 3 (Section 4.3), lateralized DLPFC activity was investigated as a potential moderator of the association between aerobic fitness and inhibitory control in the low-stress condition of Study 1. While a more pronounced left-lateralized DLPFC activity was associated with better inhibitory control, no associations of aerobic fitness with DLPFC lateralization were observed. No differences in DLPFC activity and lateralization under stress were observed between participants with high or low exercise levels (Publication 4, Section 4.4). DLPFC lateralization was not associated with inhibitory performance under stress. When comparing DLPFC activity in low- and high-stress conditions across the whole sample, lower relative activity during incompatible test blocks and higher relative activity during compatible test blocks was observed after stress induction, compared to the low-stress condition.

Results of Study 2. The main findings of Publication 5 (Section 4.5) with regard to changes in DLPFC activity were as follows. No difference between the acute aerobic exercise group and the active control group with regard to DLPFC activity and lateralization during the high-stress condition was observed. No difference in DLPFC activity and lateralization was found between the low-stress and high-stress conditions. Controlling for group differences in stress reactivity did not change the pattern of results.

6 General discussion

The overall goal of this thesis was threefold. Firstly, associations of physical activity, aerobic fitness and acute aerobic exercise with stress reactivity were examined. Further goals were to investigate potential effects of physical activity, aerobic fitness and acute aerobic exercise on inhibitory control under psychosocial stress, and to explore underlying mechanisms with a focus on the DLPFC. In the following sections, the main findings will be discussed in light of the current body of research, and separately for each hypothesis (see Section 2.2).

Furthermore, strengths and limitations of the project are highlighted, and conclusions as well as perspectives for future research are presented.

6.1 Associations with stress reactivity

The publications associated with our two studies shed light on the associations of aerobic fitness and acute exercise with stress reactivity in male adolescents. Our main findings were that A) neither aerobic fitness nor acute exercise were associated with altered HPA axis reactivity to psychosocial stress; B) results on ANS reactivity were inconclusive, as associations of better fitness and acute exercise with attenuated alpha-amylase reactivity to the stressor, but not with changes in heart rate reactivity, were found; and C) while aerobic fitness was not associated with altered psychological stress reactivity, participants reported lower psychological stress reactivity (state anxiety) after acute exercise, compared to the control condition. These overall results will now be discussed in light of the literature.

Within our systematic review, we provided a differentiated analysis of CSA effects of physical activity and fitness in TSST studies (Publication 1, Section 4.1). It revealed that study results regarding CSA effects of physical activity and fitness are discordant. That is, different effects were found across studies, and across stress reactivity parameters. With regard to the HPA axis, some studies found marked CSA effects, (e.g. Klaperski et al., 2013; Rimmele et al., 2009) while other studies' results matched our findings (e.g. Childs & Wit, 2014; Jayasinghe et al., 2016). With regard to the effects of an acute exercise bout on stress reactivity, fewer studies are available, but recent studies showed promising results: lower HPA axis and ANS reactivity were reported in comparison to a control condition (Wood et al., 2018; Wunsch et al., 2019; Zschucke et al., 2015). The results of these three previous studies differ from our findings, as in our sample of moderately active adolescents aged 16-20 years, no effect of acute exercise on the HPA axis reactivity to the stressor was found. These differences may be attributed to characteristics of the samples. For instance, participants' age, and their levels of regular exercise, differed compared to our study. Their samples included non-athletic participants aged 18-40 years (Wood et al., 2018), and sedentary and highly trained participants aged 18-30 years (Wunsch et al., 2019), and 20-30 years, respectively (Zschucke et al., 2015). This suggests that people with very high or very low regular exercise levels might benefit more from the effects of acute exercise on stress reactivity than our moderately active sample. The potential influences of exercise intensity and duration, and other study design parameters, are discussed in Publication 5 (Section 4.5). Another explanation for different findings regarding the effects of acute exercise on HPA axis reactivity, which might also apply to our findings regarding the effects of physical activity and fitness, may be the age of the participants in our study, as no other studies on CSA effects focused on the phase of late adolescence. In samples with children, Martikainen et al. (2013) and Dockray et al. (2009) reported that higher physical activity was associated with lower cortisol reactivity, although Dockray et al. found a significant correlation only in girls. In samples of young adults (university students: Gerber et al., 2017; Wood et al., 2018, mostly university-related samples: Childs & Wit, 2014; Klaperski et al., 2013; Rimmele et al., 2007; Zschucke et al., 2015, various: Wunsch et al., 2019), findings mostly corroborated the CSA hypothesis with regard to the HPA axis as well (except Childs & Wit, 2014). However, although the differences in participants' age compared to our studies are small and partly overlapping, a direct comparison of our results with these studies is difficult for two reasons. Firstly, while some of the older participants in our study (aged 19-20 years) were of a similar age to the younger participants in other studies, they differ largely in their current life situation (academic high school vs. university students). From a psychosocial point of view, this is a defining step for the transition from adolescence to adulthood that might also be reflected in different reactions to stressors (Stroud et al., 2009). Secondly, many studies emphasize how adolescents react differently to acute stress compared to other age groups (Stroud et al., 2009). The often-observed higher stress reactivity in adolescents has been attributed to large hormonal changes (Romeo, 2010), and to increased expression of mineralo- and glucocorticoid receptors in adolescents' brains, which influences the feedback loops on the stress response systems (Lupien et al., 2009). Under these premises, positive effects of physical activity and fitness on HPA axis reactivity might be smaller in this particular age group, which might be an explanation for our results.

In the available literature on the CSA hypothesis, a similarly differentiated picture emerges with regard to ANS reactivity, with studies showing lower (e.g. Klaperski et al., 2014; Rimmele et al., 2009) or unchanged heart rate reactivity to psychosocial stressors (e.g. Childs & Wit, 2014; Gerber et al., 2017) in fitter or more active participants. Interestingly, two studies reported inverse effects on heart rate reactivity (Jayasinghe et al., 2017; Wyss et al., 2016). Despite being a relatively recently established marker of ANS reactivity (Nater & Rohleder, 2009), salivary alpha-amylase has only been investigated in a few studies. In samples of young adults (Wunsch et al., 2019) and male office workers (Strahler et al., 2016), studies found no association of habitual exercise and fitness, respectively, with alpha-amylase reactivity. However, in a sample of male Swiss army aspirants, Wyss et al. (2016) found alpha-amylase results in support of the CSA hypothesis. Again, no studies on adolescents are available, hampering comparability. Our results now provide first insights into CSA effects in adolescents and highlight differences in alpha-amylase reactivity depending on participants’ fitness level, with lower reactivity in fitter adolescents.

Additionally, after an acute exercise bout (compared to the control condition), participants not only showed lower alpha-amylase reactivity, but also reported smaller increases in anxiety in reaction to the stressor. This is important because studies showed that anxiety and negative emotion at least partially account for the magnitude of the physiological stress response (Feldman, Cohen, Hamrick, & Lepore, 2004). Researchers showed that exercise leads to short-term changes in affect, with most pronounced effects for moderate intensity exercise, as indicated by an increase in positive mood, and a reduction in negative affect (Sudeck & Thiel, 2020). Perhaps exercise puts people in a more positive, sanguine and confident state of mind, which might help them to meet oncoming psychosocial stressors with fewer increases in anxiety. As other studies on the effect of acute exercise on stress reactivity have only focused on physiological parameters (Wood et al., 2018; Wunsch et al., 2019; Zschucke et al., 2015), our study is the first TSST study to report such effects for psychological stress parameters. Overall, our findings regarding ANS and psychological reactivity are of high relevance, as high stress reactivity is associated with adverse physical (Turner et al., 2020) and psychological health outcomes (Dahl & Gunnar, 2009). Adolescents are in a particularly vulnerable phase for experiencing such negative consequences of stress (Lupien et al., 2009; Romeo, 2010), and our results indicate that aerobic fitness might be a factor contributing to healthier levels of stress reactivity, although we could only show this for psychological stress reactivity, and reactivity of the ANS.

However, some open questions remain. While both main stress systems reacted to the stressor as expected, only the ANS, but not the HPA axis, was sensitive to differences in fitness in our sample. As demonstrated in our systematic review (Publication 1, Section 4.1) and in the meta-analysis by Jackson and Dishman (2006), such inconsistencies between HPA axis and ANS reactivity have been observed in other studies as well. Researchers emphasized that stress reactivity is highly adaptable, with large differences between individuals that might cause such differences (Chrousos, 2009; Dickerson & Kemeny, 2004). Furthermore, Schommer et al. (2003) found that the HPA axis quickly habituates to repeated exposure to the same psychosocial stressor, while the ANS showed more uniform activation patterns among repetitions. Kudielka et al. (2007) argued that both systems might be sensitive to different types of stressful situations, with the HPA axis being primarily activated during situations that are perceived as threatening, incontrollable and distressful, while the ANS is more associated to situations demanding effort without distress. Accordingly, Schommer et al.'s results could be interpreted to mean that through repetition, the (already known) stressor loses its threatening, uncontrollable character to the participants, which leads to a reduction in HPA axis reactivity. In conclusion, effects of fitness on both stress response systems might depend on which system is primarily activated in the individual during the stressor, which in turn depends on how severe, controllable or distressful individual judges the stressor to be.

Within the ANS, the most often used markers in studies investigating the CSA hypothesis are heart rate (Publication 1, Section 4.1) and blood pressure (Hamer et al., 2006), followed by alpha-amylase (Wunsch et al., 2019) and catecholamine concentrations in the blood (Jayasinghe et al., 2016). It is striking that results regarding these parameters are inconsistent across studies. This might be attributable to differences in study designs (e.g. use of stressor task, sampling intervals, or intensity of exercise). But as some studies measured more than one ANS related outcome and received diverging results (e.g. Wyss et al., 2016, and our Study 2), it seems more likely that mechanisms within the ANS are the underlying reason. Under acute stress, the activation of the sympathetic nervous system stimulates the adrenal medulla to release catecholamines, which initiate multiple processes in the organism that prepare the body for "fight or flight", including changes in cardiovascular parameters. An increase in heart rate is one of the results, which, compared to catecholamine concentrations in the blood, is more easily and non-invasively measureable and therefore favored by many researchers (Dawans & Heinrichs, 2017). Alpha-amylase is a saliva enzyme produced in acinar cells with the main function of digesting starch. Alpha-adrenergic and beta-adrenergic mechanisms contribute to alpha-amylase secretion, which is why it can be used as another non-invasive marker for sympathetic activation in response to psychosocial stress or exercise (Nater & Rohleder, 2009). As the acinar cells are innervated by both branches of the ANS, and parasympathetic activity influences saliva flow rate, parasympathetic activation or withdrawal may also contribute to a fraction of the total amount of salivary alpha-amylase (Nater & Rohleder, 2009; Strahler et al., 2017). Nater and Rohleder (2009) summarized the evidence with regard to associations among these parameters of ANS reactivity, and found limited evidence for a direct correlation between catecholamine and alpha-amylase concentrations. Interestingly, Chatterton et al. (1996) showed that the correlation between these parameters was higher in response to exercise, but low and non-significant in response to psychosocial stress. In comparison, small-to-moderate correlations are reported between alpha-amylase and cardiovascular parameters (Nater & Rohleder, 2009). Overall, these insights might explain the differential effects of exercise we found for heart rate and alpha-amylase reactivity, as they suggest that because of different pathways of activation, heart rate, alpha-amylase and catecholamine reactivity to stress are not necessarily related.

Another point worth discussing is the direction of possible CSA effects of exercise. In our systematic review, we observed that in some studies better fitness was associated with increased stress reactivity, and previous meta-analyses contradicted each other, as Forcier et al. (2006) reported a reduction, and Jackson and Dishman (2006) a small increase in stress reactivity with higher fitness across studies. Although such inverse effects were not replicated in our own empirical findings, these results might be important to better understand the effects of fitness on stress reactivity. Researchers often focus on negative effects of high stress reactivity on health-related parameters. But studies have also shown that unphysiologically blunted stress reactivity can be a sign of dysfunction and poor health status, too (Lovallo, 2011; Phillips, Ginty, & Hughes, 2013; Turner et al., 2020), and that a more reactive stress system can also be interpreted as advantageous and adaptive to changing situations (Wyss et al., 2016). This indicates that the truth might be more complex. Based on this evidence, Lovallo (2011) hypothesized that exaggerated and blunted stress reactivity are both signs of a loss of homeostatic regulation, and that a midrange stress reactivity is healthiest. Therefore, we suggested that physical activity and fitness might not necessarily cause a general reduction in stress reactivity, but maybe a normalization to a healthy, physiologically adaptable range (Publication 1, Section 4.1). In that case, the preponderance of studies reporting reductions in stress reactivity in fitter and more active participants might be a sign of a higher proportion of participants in their samples with exaggerated, compared to blunted, stress reactivity. For studies finding no effect, one might speculate that this indicates that most of their participants already showed a healthy (normal) stress reaction. The human stress response systems are complex and still not fully understood; although this reading of the CSA hypothesis would explain some of the inconsistencies in the literature to date, more research is necessary to gain a better understanding of underlying physiological mechanisms to prove or discard this hypothesis.

An important issue to discuss with regard to laboratory stress studies is the transferability to the complexity of real-life situations. Because laboratory stress tasks might not be perceived as personally relevant (ego-involvement), and people can detach from the stressor, researchers assume that physiological stress reactions might be much higher in real-life stress situations (Gerber, 2017; Zanstra & Johnston, 2011). However, studies directly comparing the TSST to real-life stressors are rare. When comparing student teachers’ cortisol reactivity to the TSST with a real-life demonstration lesson, Wolfram et al. (2013) reported peak cortisol levels in the real-life stressor that were almost twice as high as in the TSST, and found no direct correlation between real-life and laboratory stress reactivity in their relatively small sample (N=21). Subjective ratings of the two stressors lead to equal ratings in anticipated mastery, threat, strain and challenge, while the TSST was rated more novel, but less important to master, than the real-life stressor. These different subjective rating profiles might contribute to differences in HPA axis reactivity. In a sample of 25 university students, Loeffler et al. (2017) compared the TSST with a seminar presentation and reported higher heart rate reactivity in the TSST, and similar emotional strain in both conditions. In both studies, stress reactions peaked earlier in the real-life condition, with highest levels during anticipation and a downregulation during the real-life stressor, while stress levels continued to rise during the TSST. When comparing three different laboratory stressors to a real-life stressor (public defense of PhD thesis), von Doornen and van Blokland (1992) found that mental and physiological laboratory stressors can adequately predict real-life stress, if they are able to trigger a common physiological mechanism (i.e. increase in noradrenaline release). Other studies also reported similarities between physiological and psychological reactions to laboratory and real-life stressors (Kidd, Carvalho, & Steptoe, 2014; Rajcani, Solarikova, Turonova, & Brezina, 2016). In summary, laboratory stressors seem to have some predictive value for real-life stress reactions because of common physiological mechanisms, but ecological validity differs across studies.

An important consideration with regard to the effects of real-life challenges on stress reactivity is the differentiation between habituating and facilitating effects on the HPA axis. Researchers demonstrated that repeated exposure to similar or predictable stressors leads to gradual decreases in HPA axis reactivity (habituation), and repeated exposure to novel or unpredictable stressors enhances HPA axis reactivity (facilitation) (Herman et al., 2005). In a TSST study with actors, and students in other fields, Jezova et al. (2016) supported the notion of habituation effects, as in their study, the actors showed no elevation in heart rate in response to the TSST, and lower cortisol, blood pressure and anxiety reactivity than participants who were not accustomed to public speaking. Accordingly, the effect challenges have on stress reactivity seems to depend on the novelty and predictability of the stressor. While exercise tends to be mostly predictable as a stressor in real-life situations and is therefore likely to cause habituation effects (Hackney, 2006), many psychosocial stressors are often more complex and variable and could cause gradual increases in stress reactivity over time, with the already described negative effects on psychological and physiological health. With regard to the CSA effect of physical activity and fitness on the reactions to psychosocial stress, real-life experiments are still rare, possibly because of the technical and methodological challenges (Gerber & Fuchs, 2017). However, initial evidence shows that health-beneficial effects on stress reactivity are not limited to laboratory stressors, but can also be replicated in real-life studies. Haaren et al. (2015) found lower emotional stress reactivity during academic examinations in university students participating in a 20-week aerobic exercise intervention. And in a sample of 201 Swiss police officers, Schilling et al. (2020) reported lower physiological stress reactivity in fitter officers in response to occupational stressors, but no effect of fitness on affect. Overall, although the TSST has been proven to be an effective psychosocial stressor that mimics a stressful situation with high insecurity and cognitive demands that most people can relate to, it is still not entirely clear how well this and other laboratory stress tests represent real-life stressors. More research is necessary to draw dependable conclusions on ecological validity of laboratory stress test results. However, it is noteworthy that health beneficial effects of exercise and/or fitness on stress reactivity have already been demonstrated in laboratory (e.g. Publication 2, Section 4.2), as well as in real-life studies (e.g. Schilling et al., 2020). Studies reported associations of laboratory stress reactivity with long-term health outcomes (as reviewed by Turner et al., 2020), which demonstrates that stress reactivity results obtained in the laboratory have important implications for real life.

6.2 Associations with inhibitory control under stress

Study 1 indicated that fitter participants showed better behavioral inhibitory control at baseline (Publication 3, Section 4.3), but exercise levels were not associated with inhibitory control under stress (Publication 4, Section 4.4). In comparison to the control task, an acute bout of exercise did not yield better inhibitory control under stress (Study 2, Section 4.5). In both studies, inhibitory control did not differ between the low-stress and high-stress conditions across the whole sample.

Firstly, our results suggested that in male adolescents, higher aerobic fitness might be beneficial for the inhibitory component of executive functioning (Publication 3, Section 4.3). As our results originate from cross-sectional data, causal inferences have to be treated with caution. However, since meta-analytical findings on long-term effects of randomized controlled trials indicate similar beneficial effects of exercise on cognition (Ludyga et al., 2020), a causal relationship seems very likely. This is an important finding, as better inhibitory performance during this developmental stage is associated with higher academic achievement (Oberle & Schonert-Reichl, 2013), favorable health behavior (Allom et al., 2016) and lower likelihood of psychopathology (Jasinska et al., 2012; Lipszyc & Schachar, 2010). Although the largest developmental steps are typically observed during childhood, the PFC and executive functions are still advancing during adolescence, and compared to other executive functions, the development of inhibitory control is typically delayed, with continued improvement until early adulthood (Crone & Steinbeis, 2017; Park & Etnier, 2019; Zelazo, Craik, & Booth, 2004). Therefore, adolescents can benefit more from positive effects of exercise on the brain than adults (Guiney & Machado, 2013). Our results are in line with the existing literature. In summary works, small-to-moderate positive effects were found (Donnelly et al., 2016; Guiney & Machado, 2013; Ludyga et al., 2020). Other studies with adolescents reported similar positive effects of aerobic fitness (Westfall et al., 2018) and regular exercise on inhibitory control (Ludyga, Gerber, Herrmann, Brand, & Pühse, 2018), and positive effects of an acute bout of aerobic exercise have been demonstrated repeatedly, as well (Ludyga et al., 2016). Our findings with regard to potential neurophysiological mechanisms underlying this relationship are discussed in Section 6.3. Based on these known positive effects on executive functions, we hypothesized that higher levels of regular exercise, and acute exercise, would be associated with better inhibitory control under stress. This is of high relevance, because better executive functioning under stress is not only highly beneficial for academic and occupational performance and success, but also mitigates the effects of recent life stress on health. This is underlined by Shields et al., who found that “better executive function during acute stress, but not in the absence of stress, was associated with an attenuated link between participants’ recent life stress exposure and their current health complaints” (Shields, Moons, & Slavich, 2017, p. 92). However, our data do not support our hypothesis, and based on our results, we cannot generally recommend regular or acute exercise as a facilitator of inhibitory control under stress. Potential reasons for our findings are discussed in the paragraph below.

As reported in Publications 4 and 5, in both of our studies the modified TSST failed to elicit the expected decline in inhibitory performance, regardless of group allocation. This might explain why no potential buffering effects of regular or acute exercise (as hypothesized in Section 2.2) could be observed. In support of the absent effect of the stressor on inhibitory performance in our studies, a meta-analysis of studies using exogenous cortisol administration to simulate effects of HPA axis activity on core executive functions also found an overall non-significant effect on inhibition (Shields et al., 2015). However, when actual stressors were used to elicit endogenous stress reactivity mechanisms, meta-analytical results clearly indicated impairments of cognitive inhibition under psychosocial stress (Shields et al., 2016), showing that besides HPA axis activity, other factors contribute to the effects of acute stress on executive functioning. For instance, in addition to the binding of cortisol to receptors in the PFC (Lupien et al., 2009), the shift from top-down to bottom-up regulation initiated by increased sympathetic activity (Arnsten, 2009) has been discussed previously. Thus, the absence of a difference in inhibitory control between low-stress and high-stress conditions in both of our studies was unexpected, and potential reasons for this need to be discussed. One possibility is an influence of the time delay between stressor and cognitive task (Sandi, 2013). Shields et al. (2015) found that immediately (15-135 min) after the stressor, the likelihood of positive non-genomic effects of exogenous cortisol administration on inhibition might increase, with negative effects becoming more likely only after a delay of more than 135 min. But again, this does not seem to apply to endogenous stress reactivity, as results show negative effects of stress on inhibition independent of the time delay (Shields et al., 2016). However, as in our studies the cognitive test was performed immediately after the stressor, such delay effects cannot completely be ruled out. Another possibility is that the stressor might have been insufficient and therefore without an effect on inhibitory control. However, in both of our studies, significant increases in HPA axis, ANS and psychological stress reactivity were observed. While the heart rate dropped back to just above baseline levels during the Stroop task, cortisol levels, alpha-amylase levels and self-reported anxiety remained significantly elevated throughout the task. In Study 2, self-reported anxiety levels after the Stroop task under stress were higher than at baseline, but similar to the Stroop task without stress. Therefore, insufficient subjective stress levels might in part account for the absence of stress effects on inhibitory control in our data. Future studies should consider potential effects of the psychological stress profile on cognitive performance (Kassam, Koslov, & Mendes, 2009). However, it is noteworthy that there is no consensus on the effects of different stress intensities on inhibitory performance. Many researchers cite the Yerkes-Dodson Law of arousal and performance, stating that in difficult tasks, arousal has an inverted U-shaped influence on performance, so that a stressor that elicits moderate increases in arousal might actually improve performance (Diamond, 2005; Yerkes & Dodson, 1908). But arousal does not equal psychosocial stress, as it lacks the elements of adversity and distress. This differentiation is very important, because exercise-induced arousal improves executive functioning (Byun et al., 2014; Lambourne & Tomporowski, 2010), but psychosocial stress has been reported to have opposite effects (Shields et al., 2016). Furthermore, research suggested that effects of acute stress seem to be highly domain-specific. For instance, with regard to effects of stress intensity on memory performance, Sandi (2013) pointed out that that for implicit memory, a roughly linear relationship has been shown, but the relationship with explicit memory is best characterized by said inverted U-shape, with optimal performance at moderate stress levels (also see Lupien, Maheu, Tu, Fiocco, & Schramek, 2007). Little empirically grounded knowledge exists on the effect of stress intensity on inhibitory control, and although so far meta-analytical findings suggest that stress impairs cognitive inhibition regardless of stress intensity (Shields et al., 2016), differential effects of stress intensity on subdomains of inhibitory control cannot be completely ruled out. The difficulty of the task is another potential moderator of the stress-cognition relationship. Research showed that high levels of stress impair performance in difficult tasks that involve higher cognitive functions, but might facilitate performance in simpler (e.g. attention) tasks (Diamond, 2005). However, it is unlikely that this was an issue in our studies, because in both studies a congruent and incongruent Stroop condition was used, thereby accounting for both attention and cognitive inhibition, respectively. Furthermore, in Study 2, difficulty was increased compared to Study 1 because four instead of three different colors were used in the Stroop task, but results remained unchanged.

Nevertheless, although we found no negative effects of stress on cognitive inhibition, regular and acute exercise could still have had an effect on Stroop performance under stress. In Publication 4, we suggested that physical activity and exercise might positively influence cognitive inhibition under stress via two different pathways: either through a reduction in stress reactivity, or by counteracting negative effects of acute stress on executive functioning. In Study 1 and 2, we found indications of reduced ANS reactivity in more active participants and after an acute exercise bout, respectively, and Study 2 additionally indicated a smaller increase in anxiety in response to the stressor compared to the control group. However, this reduction in stress reactivity had no impact on inhibitory performance. Furthermore, when controlling for differences in stress reactivity, no group differences in inhibitory performance under stress were found either. Thus, our studies did not find evidence for either of the two expected pathways. Sandi pointed out the “existence of important differences in the way individuals are affected in their cognitive capabilities when exposed to particular stress conditions” (Sandi, 2013, p.247). Perhaps, even when controlling for the most important confounders, the effects of physical activity on inhibitory control under stress are too small to be detected among other, larger, interindividual variations. However, it is possible that larger effect sizes can be found when the properties of physical activity and exercise are modified. When looking at the effects on stress reactivity and executive functions alone, there are indications that different types and intensities of exercise might moderate the effects. With our systematic review, we detected initial evidence for larger effects on stress reactivity in participants who reported higher intensities of physical activity and exercise (Publication 1, Section 4.1), and some studies observed better speed of processing and cognitive performance with higher exercise intensities as well (Chang & Etnier, 2009; Ludyga et al., 2020). Furthermore, while most studies focus on aerobic exercise, promising effects were also shown for resistance training (Chang & Etnier, 2009), coordinative training (Budde et al., 2008) and combinations of the former (Ludyga, Gerber, Kamijo, Brand, & Pühse, 2018). In their systematic review, Gu et al. (2019) looked into the effects of open skill versus closed skill exercise on cognitive function. They concluded that while both types benefit cognitive functions, open skill exercise might have superior effects. The two studies presented within this thesis are the first to focus on the effects of regular and acute exercise on cognition under stress. We did not find such effects for the different levels of regular exercise (Study 1, Publication 4, Section 4.4) and a single bout of moderate, closed skill exercise (Study 2, Publication 5, Section 4.5). Further studies are encouraged to investigate the effects of different exercise modalities on this relationship.

6.3 Underlying neurophysiological mechanisms

Along with behavioral inhibitory performance, neurophysiological mechanisms were assessed in our studies. As the principal region of interest, the DLPFC was identified, and its activity was measured using fNIRS. Furthermore, Publication 3 (Section 4.3) contains the analysis of the N450 component of Event-Related Potentials (ERP), as measured using EEG during the Stroop task in the low-stress condition. Compared to participants with lower fitness, their fitter peers showed better behavioral inhibitory control in the low-stress condition. Analyses of response accuracy and reaction time showed that the group differences were not caused by a speed-accuracy trade-off, and as both groups showed comparable performance in compatible Stroop blocks, the differences in inhibitory performance cannot be explained by faster information processing in the fitter group either. Instead, path-analyses revealed that the association of fitness with inhibitory performance was mediated by N450 negativity. N450 is an ERP component that indexes conflict monitoring, which is an important aspect of executive functioning because the correct detection of conflict precedes the implementation of further neural resources and adjustments in behavior (Larson, Clayson, & Clawson, 2014). Our results suggest that the process of conflict monitoring might be more efficient in adolescents with higher fitness, compared to their less fit peers, and underlie their improved inhibitory control (for more details, see Publication 3, Section 4.3). The ACC is the major generator of the N450 (Larson et al., 2014). Studies have suggested that in the case of stimulus conflict (e.g. in the incompatible condition of the Stroop task), the ACC triggers the activation of the DLPFC to increase cognitive control (Botvinick et al., 2001; Yeung, 2013), and Vanderhasselt et al. (2009) showed that more effective inhibitory control is characterized by more left-lateralized DLPFC activation. Consequently, in our study, both indices were associated with inhibitory performance, with higher performance linked to greater N450 negativity and more left-lateralized DLPFC activity. However, as the association of DLPFC lateralization with participants' fitness did not reach statistical significance, only the mediation via N450 was confirmed in our study. This result differs from Hyodo et al. (2016), who found that in elderly men, the association of aerobic fitness with Stroop performance was mediated by DLPFC lateralization. Overall, the findings of Publication 3 indicate that in adolescents, aerobic fitness is associated with changes in neurophysiological indices of cognitive functioning that benefit inhibitory control. This is an important finding because inhibitory control is a core aspect of executive functioning, and in the age group of adolescence, higher inhibitory control is associated with better academic performance, fewer social problems, and better physical and mental health (Diamond, 2013). With regard to methodology, it is noteworthy that because of the technical difficulty, only few studies so far had attempted to measure EEG and fNIRS simultaneously before the beginning of our study in 2017. Our study underscores the feasibility of simultaneous measurement of EEG and fNIRS during cognitive tasks and highlights the added value of such multimodal assessments of brain activity for the exploration of neurophysiological mechanisms.

The paragraph above refers to inhibitory control during the low stress condition of Study 1. With regard to inhibitory control under stress, the results of Study 1 and 2 were more complex. First of all, we found a statistically significant and large main effect of condition on DLPFC oxygenation, indicating that acute stress had an influence on DLPFC activation during the Stroop task (Publication 4, Section 4.4). That is, relative DLPFC oxygenation during compatible trials increased, and relative DLPFC oxygenation during incompatible trials decreased under stress, compared to the low-stress condition. Under stress, behavioral regulation changes from top-down to bottom-up processes. This shift favors the processing of sensory stimuli, enhances attention and encourages intuitive reflexes, while potentially impairing higher-order cognitive processes (Arnsten, 2009). The compatible condition of the Stroop task is a relatively simple choice-reaction task that requires the allocation of attentional resources, and the incompatible condition is characterized by an increased demand for inhibitory control. Therefore, our results might be a consequence of this shift in regulatory processes. The increase in oxygenation during the compatible trials, and the decrease in oxygenation during incompatible trials, indicate that under stress, more resources were allocated to tasks demanding attention, and fewer to tasks additionally demanding inhibitory control. A logical consequence of this change in oxygenation would be a measurable deterioration in inhibitory performance under stress (Shields et al., 2016). However, this was not the case in both of our studies (Publications 4 and 5, Section 4.4 and 4.5, respectively). It appears that the participants were able to compensate for this change in allocation of resources.

One explanation for the unexpectedly good cognitive performance under stress is a priming effect of the stressor task. The TSST is an effective stressor because it combines different aspects of psychosocial stress, one of which is cognitive challenge during both the speech and the mental arithmetic task component. Neuroimaging studies on brain activation patterns during the TSST (Rosenbaum et al., 2018) and mental arithmetic alone (Nagasawa et al., 2020) showed an activation of the cognitive control network including the DLPFC, and increased bilateral oxygenation of the PFC, respectively, during the task. Similar results have been reported for the Montreal Imaging Stress Test (MIST), which is specifically designed for simultaneous fMRI measurement (Dedovic et al., 2005; Dedovic et al., 2009; Zschucke et al., 2015). Maybe the pre-activation of cognitive networks during the TSST facilitated subsequent inhibitory performance, and other, non-cognitive stressors, might have yielded different effects. However, this does not sufficiently explain the discrepancy between DLPFC oxygenation and inhibitory performance under stress, which we observed. In this regard, Allen et al. (2014) suggested that the increase in plasma lactate in response to the TSST, which the brain can use temporarily as an alternative source of energy, might have an influence on cognitive performance directly after the stressor. Perhaps, while our data suggest that participants were still able to compensate for the changes in allocation of resources, results might have been different under more severe, prolonged or delayed stress exposure (Roozendaal et al., 2009), or with greater differences in task difficulty (Sandi, 2013).

Many studies showed that aside from overall DLPFC activation, the lateralization of DLPFC activity is an important indicator of performance during tasks demanding inhibitory control. For instance, Zhang et al. (2014) used fNIRS to detect hemispheric differences in oxygenation of the PFC during the Stroop task in 13 healthy, right-handed participants aged 20-26 years. Despite the small sample size, they found marked associations between left-lateralized activity and behavioral performance. Similar results were obtained with different samples and methodologies (Vanderhasselt et al., 2009) and have been attributed to the verbal nature of the task (Zhang et al., 2014), to hemispheric differences in speed of processing (Belanger & Cimino, 2002), and to the up-regulation of the attentional set when conflict is anticipated, which is related to an activation of the left DLPFC (Vanderhasselt et al., 2009). Therefore, we hypothesized that higher levels of regular exercise (Study 1), and an acute bout of exercise (Study 2), respectively, would be associated with more left-lateralized DLPFC activity during the Stroop task in the stressful condition. Only few studies have tackled the association of acute and chronic exercise with Stroop performance and DLPFC lateralization under stress-free conditions, and no study has investigated this association under stress, to date. In older adults, Hyodo et al. (2016) reported correlations between higher aerobic fitness, lower Stroop interference and greater left-lateralized DLPFC activation. Furthermore, they showed that DLPFC lateralization mediated the association between fitness and Stroop performance. They argued that while young adults and those with higher inhibitory control can rely on unilateral activation of the (left) DLPFC during the task, older participants and those with lower inhibitory control use bi-hemispheric DLPFC activity to compensate for their reduced neural capacity and efficiency. They concluded that fitness might improve neural efficiency in tasks demanding inhibitory control and delay the cognitive decline in the elderly (Cabeza, 2002; Hyodo et al., 2016). Similar results were found in young adults as well: Byun et al. (2014) showed that ergometer exercise at light intensity (30 % of maximum oxygen consumption) improved Stroop performance five minutes after the exercise session, and was again associated with more left-lateralized DLPFC activation. In the light of these findings, our results were rather unexpected. Studies 1 and 2 revealed no effect of regular and acute exercise, respectively, on DLPFC activation patterns under stress. Our hypothesis of more left-lateralized DLPFC activation under stress in participants with higher exercise levels and after acute exercise, respectively, was not corroborated by our data. The neurophysiological findings of our studies match our findings on a behavioral level – overall, no significant effect of regular and acute exercise on behavioral and neurophysiological inhibitory control was observed. The reasons for this result are unclear, and because no other studies have targeted this research question before, only speculations based on the existing literature on sub-categories of our research question are possible.

In her narrative review on stress and cognition, Sandi (2013) pointed out that large variations among individuals are possible regarding the effect of stress on cognition, as some are more vulnerable, and some more resilient for a wide range of possible reasons. Although we tried to minimize confounding factors by using a narrow sample with strict inclusion and exclusion criteria (only healthy, male, right-handed adolescents aged 16-20 years, with higher educational status were admitted), and controlled for the most important confounding variables known in the literature, it is possible that the effect of regular and acute exercise on DPLFC functioning under acute stress is smaller than it has been reported under stress-free conditions, and thus too small or too heterogeneous to be detected in our sample. Another possible reason might lie in the changes in activation patterns during cognitive tasks across the life span. In adolescents, changes in functional connectivity might be more important than the activation of single regions of interest (Crone & Steinbeis, 2017). Furthermore, studies showed that while children utilize more diffuse activation of wider brain areas, more distinct activation patterns of smaller brain areas are observed in adults when performing the same cognitive task (Brydges et al., 2013). Therefore, slighter systematic changes in activation patterns might be more difficult to detect in younger people. However, this is unlikely to be the case in our two samples of participants aged 16-20 years, as people at that age usually already show more adult-like activation during cognitive tasks (Brydges et al., 2013). Future studies are encouraged to further investigate the effects of acute stress on adolescents' brains and cognitive performance, and to explore the mechanisms of exercise and other potential moderating factors.

6.4 Strengths and limitations

This thesis comprises the first two studies to investigate the association of regular and acute exercise, respectively, with inhibitory control under stress. Furthermore, CSA effects of physical activity, fitness and acute exercise in adolescents were tested. The strengths of our studies include the use of the TSST for the induction of psychosocial stress, which is considered the gold-standard for psychosocial laboratory stressors, and the multi-dimensional approach to the measurement of stress reactivity, including the two main physiological stress response systems (HPA axis and ANS), as well as psychological stress parameters (Allen et al., 2017). High quality of stress reactivity data was maintained by scheduling all appointments in the afternoon to minimize the effects of circadian changes in HPA axis (Kudielka, Schommer, Hellhammer, & Kirschbaum, 2004) and SAM system activity (Strahler, Mueller, Rosenloecher, Kirschbaum, & Rohleder, 2010). Applying a laboratory test design allowed for a controlled environment and a reduction of confounding factors. Inhibitory control was measured using the well-established Stroop paradigm, and behavioral performance as well as neurophysiological indices were included. On that account, one of the achievements of our studies is the development of a montage and study design that facilitated the simultaneous measurement of fNIRS and EEG during a cognitive task, thereby combining the advantages of both methods in the search for underlying neurophysiological mechanisms. This multimodal approach has only rarely been utilized before (e.g. Wallois, Mahmoudzadeh, Patil, & Grebe, 2012), and is new to the field of sport psychology. Further strengths of the project include the verification of subjectively reported physical activity and exercise levels with objective accelerometry measurement over the course of seven days (Study 1), the integration of the Stroop task in the stressor in order to measure the effects of acute exercise on inhibitory control under stress (Study 2), and the inclusion of potential confounders that were reported in the literature and are discussed in the respective Publications in Chapter 4.

However, the studies have limitations that need to be considered. First of all, our results are limited to healthy, right-handed male adolescents with above average educational status, and conclusions on clinical samples, or adolescents with lower educational status have to be treated with caution. Potential effects of gender and reasons for the restriction to male participants are discussed in Publication 2 (Section 4.2). It is important to mention that our results, with regard to associations of physical activity and fitness with stress reactivity and inhibitory control under stress, are cross-sectional. Further longitudinal and intervention studies are necessary to confirm assumptions about causalities. In our studies, we used a modified TSST as a laboratory stressor. As effects can be stressor-specific, other laboratory or real-life stressors might lead to different results. Furthermore, our modifications of the TSST to meet the requirements of EEG and fNIRS measurement might have changed the effectiveness of the stressor, and the comparability with other TSST studies is somewhat limited. In both of our studies, participants wore a head cap with EEG and/or fNIRS sensors during the TSST. As participants were not used to wearing such measurement devices, this might have added to the perceived psychological stress. In Study 2, the mental arithmetic task within the TSST was replaced by another cognitive stressor (Stroop task). This integration of the Stroop task in the TSST had the advantage that inhibitory control under the direct influence of psychosocial stress could be measured. Both mental arithmetic and the Stroop task have been used as single stressor tasks before (Dickerson & Kemeny, 2004), and we took measures to increase perceived stress during the Stroop task (Publication 5, Section 4.5). Thus, it is unlikely that this modification of the TSST caused substantial changes in stress reactivity compared to the original version. Within the field of laboratory stress research, some scholars recommend a differentiation between stress reactivity and stress recovery (Linden et al., 1997). Our results focus explicitly on the aspect of stress reactivity. We used area-under-the-curve analyses to estimate the magnitude of the response curve as recommended for the calculation of stress reactivity (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). Therefore, possible effects of a faster stress recovery might be implicitly included in our results. However, we acknowledge that potential differences between the constructs of stress reactivity and recovery exist. For instance, Forcier et al. (2006) reported greater effects of fitness on stress recovery, than on stress reactivity. On the other hand, some scholars emphasize that stress reactivity and recovery are intertwined and cannot be regarded separately (Smyth et al., 2018). Future studies are encouraged to additionally investigate potential CSA effects on stress recovery in adolescents in order to cover both aspects of the stress response.

As already discussed in Section 6.1, laboratory stressors might not completely represent the nuances of real-life stressors. However, while correlations between laboratory and real-life stress seem to be minor, stress buffer and CSA effects of exercise have been reported in real-life and laboratory conditions, and lower reactivity in response to laboratory stressors is linked to future health outcomes (Turner et al., 2020). Nevertheless, more research is necessary to gain a better understanding of how laboratory stress reactivity is connected with real-life stress reactivity.

Furthermore, potential limitations concerning the cognitive task and measurements of brain activity need to be considered. Studies have shown that the Stroop task can potentially be confounded by practice effects (Edwards, Brice, Craig, & Penri-Jones, 1996). These effects can occur when the same test is performed repeatedly. Such effects were unlikely in Study 1 because the low-stress and high-stress Stroop tasks were performed seven days apart. In Study 2, both conditions were performed on the same day, making the influence of practice effects on the results more likely. To reduce such effects, all Stroop tasks were preceded by two practice rounds. In an attempt to explore potential practice effects, a re-analysis with only the last ten (of twenty) test blocks in Study 2 was performed; the general pattern of results remained unchanged (data not shown). The use of fNIRS has some important limitations. For our measurements, we used a standardized optode montage that allows for a simultaneous measurement with a 32-channel EEG positioned according to the international 10:20 standard. Spacers were used to guarantee equal inter-optode distances across participants, which is important to keep the light penetration depth constant. However, head sizes and shapes vary individually, which is why coverage of the prefrontal brain regions might vary across participants within the range of a few millimeters. To minimize the impact of such variations, we did not rely on single-channel, but on channel-cluster analyses (Schecklmann, Ehlis, Plichta, & Fallgatter, 2008). Considering these precautionary measures during analysis, and that fNIRS works with lower spacial resolution than fMRI or PET, differences in head size and shape are unlikely to impact the results. Tachtsidis and Scholkmann (2016) pointed out two other methodological issues with fNIRS: changes in respiratory and cardiovascular parameters (e.g. breathing frequency or heart rate) can confound fNIRS data, and measured data might not only contain cerebral, but also extracerebral changes in blood flow and oxygenation. This can be an issue especially when participants exercise, speak or shift body positions (e.g. from sitting to standing) during the measurement. Recently, to tackle this issue, “short channels” were introduced to fNIRS methodology (Sato et al., 2016). As this technology was not available for our system, we followed the procedures recommended in fNIRS quality guidelines, which recommend to kept these parameters constant during the measurement to minimize interference with task-related changes in cerebral oxygenation (Orihuela-Espina, Leff, James, Darzi, & Yang, 2010). In our studies, this was achieved by instructing the participants to remain seated, to breathe regularly and freely, to minimize body movements and to avoid speaking during the Stroop task. On a final note, within the limitations of the available software, there are numerous modalities of fNIRS data analysis, and steps of analysis have to be chosen carefully, as they might have an influence on the results (Tak & Ye, 2014). For this reason, we closely followed already established processing streams (Brigadoi et al., 2014), used artifact correction algorithms that were considered superior in previous investigations (Cooper et al., 2012; Scholkmann, Spichtig, Muehlemann, & Wolf, 2010), adapted the differential pathlength factors to participants' age as recommended by other researchers (Scholkmann & Wolf, 2013) and analyzed the data based on channel clusters to increase reliability (Schecklmann et al., 2008). Nevertheless, despite this rigorous approach, it cannot be ruled out that different data analysis procedures might have yielded deviating results.

6.5 Conclusion and perspectives

Previous research has shown that adolescents with high stress reactivity are at risk for experiencing negative health consequences (Turner et al., 2020). Moreover, acute psychosocial stress potentially elicits changes in the PFC that can impair executive functions including inhibitory control (Arnsten, 2009). Thus, adolescents with high stress reactivity may not be able to retrieve their full cognitive potential in stressful situations, which might, for instance, compromise their performance in important exams and finals, and limit their career opportunities. Our findings shed light on associations of exercise and fitness with stress reactivity and inhibitory control under stress in male adolescents, and have important implications. We could show a reduction in ANS reactivity to psychosocial stress in fitter adolescents. After an acute exercise bout, both ANS and psychological stress reactivity were reduced. Consequently, acute exercise, and regular exercise targeting an increase in fitness, seem to be recommendable for adolescents who suffer from negative consequences of high stress reactivity. This opens up many possibilities for future investigations. Studies should investigate which exercise modalities (e.g. exercise type, duration, intensity) have the highest effect on stress reactivity, and whether these effects can be repeated with female adolescents, different types and severities of stressors, and in real-life stress situations. Clinical samples often show disturbed stress reactivity, and in people with psychopathologies, stress reactivity is often unhealthily blunted (Phillips et al., 2013). Further studies on the effect of exercise on participants with initially blunted stress reactivity (e.g. participants with depression, Gerber et al., 2020) could disentangle whether exercise causes a reduction, or a normalization of stress reactivity mechanisms. Furthermore, future studies could look into the reasons why exercise seems to differentially affect HPA axis and ANS reactivity to acute psychosocial stress.

Moreover, our data suggested an association of better fitness with higher inhibitory control, which is well in line with other studies on children and adolescents (e.g. Khan & Hillman, 2014). This is an important finding, as inhibitory control is a prerequisite of self-regulation and goal-directed behavior, and better inhibitory control is associated with higher academic achievement and better health behavior (Diamond, 2013). With regard to the measurement of underlying mechanisms, we further showed that the combined used of EEG and fNIRS is feasible in research within the field of sport psychology, and that it has added value, as our results revealed that conflict monitoring, but not DLPFC lateralization, seems to underlie the association of fitness with inhibitory control. This is an important contribution, because although the associations of exercise and fitness with executive functions have been shown multiple times on a behavioral level, underlying mechanisms are complex and still not fully understood (Hillman et al., 2008). Even less is known about associations with executive functions under stress. Our studies revealed that in healthy adolescents, acute stress does not seem to influence behavioral inhibitory control, although Study 1 showed changes on a neurocognitive level. This suggests that healthy adolescents seem to be able to compensate for these changes caused by acute stress. Hence, there might be no pressing need for intervention in this group. However, it remains unclear whether this would still be the case with different stress severity or different task difficulty, and improving inhibitory control in situations of high psychological stress still is desirable. In this regard, our studies provide first and novel insights into the potential of acute and regular exercise. Despite associations of fitness with inhibitory control in low-stress situations, our data do not support the notion of effects of acute or regular exercise on inhibitory control under stress, and based on our results, we cannot generally recommend exercise to improve inhibitory control in stressful situations. Again, our results relate to generally healthy adolescents, and future studies should target clinical samples, or more vulnerable individuals (e.g. with high chronic stress), as these samples might show a greater influence of stress on inhibitory control, and exercise might have more beneficial effects.

There are multiple possible starting points for future investigations on this important issue. Most importantly, as our studies are the first to provide insights into associations of acute and regular exercise with inhibitory control under stress, longitudinal investigations and intervention studies are necessary to verify potential causal relationships. Furthermore, it would be of interest to test the effects of different exercise modalities. For instance, exercise intensity has been reported to moderate exercise effects on inhibitory control without stress (Peruyero, Zapata, Pastor, & Cervelló, 2017). Future studies should also look into other executive and cognitive functions, as effects might vary (Shields et al., 2016). Finally, more research on neurophysiological mechanisms is needed to better understand the effects of stress on cognition, and to further evaluate the contribution of acute and regular exercise to executive functioning under stress. In this regard, approaches combining different methods to measure brain activity are strongly encouraged.

7 References

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Appendix

A Curriculum vitae

Manuel Mücke

Date of Birth:	01-12-1987 (Lutherstadt Wittenberg, Germany)
E-Mail:	manuel.muecke@unibas.ch
ORCID:	0000-0002-5303-9289

Academic Qualifications

04/2016 – 09/2020	**Doctoral candidate** University of Basel, Supervisor: Prof. Dr. Markus Gerber
10/2010 – 03/2014	**Master of Science (M.Sc.) in Rehabilitation and Prevention** University of Leipzig
10/2010 – 03/2014	**Master of Science (M.Sc.) in Diagnostics and Intervention** University of Leipzig
10/2007 – 09/2010	**Bachelor of Arts (B.A.) in Sports Science** University of Leipzig
08/2000 – 04/2007	**Abitur** Liborius Gymnasium Dessau

Professional Experience

Since 04/2016	**Researcher (PhD candidate)** Department of Sport, Exercise and Health, University of Basel
01/2015 – 02/2016	**Researcher** Department of Sports Sciences, Martin-Luther-University Halle-Wittenberg
10/2011 – 12/2014	**Scientific assistant** Institute of Social Medicine, Occupational Health and Public Health (ISAP), University of Leipzig

09/2013 – 06/2014	**Freelancer** (Sports Therapist) Gesundheitssportverein Leipzig e.V.
10/2013 – 02/2014	**Scientific assistant** Institute of Sport Psychology and Sport Pedagogy, University of Leipzig
02/2011 – 04/2012	**Research Internship** Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig

Supervision and Teaching

Master students:	Supervision of 5 master theses
Bachelor students:	Supervision of 11 bachelor theses
Teaching activities:	Mental training – visualization (seminar); Functional near-infrared spectroscopy during exercise (seminar and practical lecture); Project coordination for bachelor and master theses

Peer-Review contributions

European Journal of Sport Science; Experimental Brain Research; Psychophysiology; Anxiety, Stress & Coping and others

Research Grants

Bangerter-Rhyner Foundation:

Ludyga, S., Mücke, M., Gerber, M. (2017). The impact of physical activity on stress reactivity, executive function and brain activity during and after experimentally induced stress (4.400 CHF)

Membership in Professional Associations

European College of Sports Science (ECSS)

Conference Contributions

Oral presentation: Swiss Society of Sport Science (SGS),
12th annual conference, *Basel*, 2020
Swiss Society of Sport Science (SGS),
11th annual conference, *Fribourg*, 2019
European College of Sports Science (ECSS),
23rd annual congress, *Dublin*, 2018
Swiss Society of Sport Science (SGS),
10th annual conference, *Magglingen*, 2018
Swiss Society of Sport Science (SGS),
9th annual conference, *Zurich*, 2017
German Spine Association (DWG),
9th annual congress, *Leipzig*, 2014
World Psychiatry Association (WPA),
16th world congress, *Madrid*, 2014

Poster presentation: European College of Sports Science (ECSS),
24th annual congress, *Prague*, 2019
International Society of Sport Psychology (ISSP),
14th world congress, *Sevilla*, 2017

Publication list

2020

Mücke, M., Ludyga, S., Colledge, F., Pühse, U. & Gerber, M. (submitted). The influence of an acute exercise bout on stress reactivity, interference control and brain oxygenation under stress. *Frontiers in Psychology*.

Mücke, M., Ludyga, S., Brand, S., Andrä. C., Gerber, M. & Herrmann, C. (under review). Associations between physical activity, basic motor competencies and automatic evaluations of exercise. *Journal of Sports Sciences.*

Mücke, M. [1], Ludyga, S. [1], Colledge, F., Pühse, U. & Gerber, M. (2020). Association of exercise with inhibitory control and prefrontal brain activity under acute psychosocial stress. *Brain Sciences*, *10*, 439.

[1] contributed equally

Mücke, M., Ludyga, S., Brand, S., Colledge, F., Pühse, U., & Gerber, M. (2020). Associations between cardiorespiratory fitness and endocrine, autonomous, and psychological stress reactivity in male adolescents. *Journal of Psychophysiology, 30,* 1-12. https://doi.org/10.1027/0269-8803/a000258.

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[1] contributed equally

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B Graduate education

Course	Institution	ECTS
Academic Writing in the Health Sciences Phase I (Annegret Mündermann)	University of Basel	1
Academic Writing in the Health Sciences Phase II (Annegret Mündermann)	University of Basel	2
Brain Mind Institute Symposia: Stress in Health and Disease (Carmen Sandi)	EPFL, Lausanne	1
Conflict Management (Alba Polo)	University of Basel	1
Creating the Job-Hunting Package: Finding Opportunities Outside the University and Building Applications (Verity Elston)	University of Basel	1
Fragebogenerstellung (Harald Seelig)	University of Basel	-
Lecture: Neurobiology (Peter Scheiffele, Rainer Friedrich, Silvia Arber)	University of Basel	2
Meta-Analysis in Social Research and Survey Methodology (Bernd Weiß, Jessica Daikeler)	GESIS summer school, Cologne	2
Mindful Career Planning (Anya Häusermann)	University of Basel	1
Nachwuchstagung der Arbeitsgemeinschaft für Sportpsychologie, 2017	asp, Bern	-
Nachwuchstagung der Arbeitsgemeinschaft für Sportpsychologie, 2018	asp, Köln	1
Nachwuchstagung der Arbeitsgemeinschaft für Sportpsychologie, 2019	asp, Halle (Saale)	1
NIRx workshop on recent developments in fNIRS methodology (Christoph Schmitz, Baris Yesilyurt)	NIRx medical technologies, Berlin	-
Project Management for Researchers (Dimitrije Krstic)	University of Basel	1
Raus mit der Sprache! - Stimme und Körpersprache als Erfolgsfaktoren (Katharina Padleschat)	University of Basel	1
Supervising students – Dealing with roles and relationships (Markus Weil)	University of Basel	-
Total ECTS		**15**