Digital assessments of motor-cognitive performance in young and older adults - Behavioral and neural correlates

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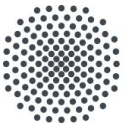

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"Without continual growth and progress, such words as improvement, achievement, and success have no meaning."

Benjamin Franklin

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Abstract

Today's technological advances enable us to have a healthy life. Maintaining mental and physical health is one of the most critical aspects of our healthy life with increasing age. Moreover, one of the many ways to stay healthy is to detect problems of motor or cognitive impairment early and accurately in terms of assessment. Digital assessment can help uncover subtle differences in specific motor and cognitive declines. This early detection can lead to an adequate intervention on time, allowing for preliminary prevention before symptoms occur.

From a different perspective, exercise effect on our bodies and minds is indescribable. Physical exercise induces cellular and molecular changes in our body, which positively change the structure and function of the brain. These positive changes in our brains can result in improved cognitive function. These effects are attributed to physical activity over a long-term period. However, understanding the acute effects of exercise-induced changes is also essential to potentially explain chronic effects. Also, identifying exercise-induced cortical activation patterns should be considered for cognitive function enhancements. For this reason, it is necessary to investigate the effect of exercise protocol composition, such as exercise intensity and duration, on cognitive function based on neural correlates.

Based on these aspects, the present thesis is divided into two parts. In the first part (Part I: Assessment), the paper-pencil version of Trail-Making-Test (ppTMT), a neuropsychological assessment commonly used to investigate cognitive functions, was compared with the digital Trail-Making-Test (dTMT) developed on a tablet version. We verified its reliability and validity by comparing these two versions of TMT. Also, the dTMT was applied in patients with Parkinson's disease to detect subtle differences in fine motor and cognitive performance deterioration. As a strength of the dTMT, the measurement of additional variables for examining the applicability to the clinical field allowed the decomposition of cognitive abilities and observation of changes in performance during the task. The second part (Part II: exercise intervention) investigated the acute effects of exercise-induced cortical activation on cognitive performance using the dTMT. We used functional near-infrared spectroscopy (fNIRS) to measure hemodynamic response in the brain's frontal lobe and motor cortex for immediate and sustained effects of acute exercise with different exercise intensities.

Finally, the interaction of these two parts (assessment and exercise intervention) and the neural mechanisms led to the following discussions. First, we confirmed the value of digital assessment as an early detection tool for motor and cognitive impairment. Second, we identified which exercise intervention positively induces cortical changes in our brain by accompanying the improvement of cognitive performance. The present thesis discussed the role of digital measurement and exercise intervention in maintaining our health and in which direction we should go for our future.

Zusammenfassung

Die heutigen technologischen Fortschritte können uns ein gesundes Leben ermöglichen. Der Erhalt der geistigen und körperlichen Gesundheit ist einer der wichtigsten Aspekte unseres Lebens, insbesondere mit zunehmendem Alter. Eine der vielen Möglichkeiten gesund zu bleiben ist es, Probleme mit motorischen oder kognitiven Beeinträchtigungen frühzeitig und beurteilungsgenau zu erkennen. Die digitale Bewertung kann dabei helfen, subtile Unterschiede in der motorischen und kognitiven Leistungsfähigkeit aufzudecken. Diese Früherkennung kann rechtzeitig zu einer angemessenen Intervention führen und eine vorläufige Prävention ermöglichen, bevor Symptome auftreten.

Aus einer anderen Perspektive sind die Wirkungen von Bewegung auf unseren Körper und Geist sehr vielfältig. Körperliche Bewegung induziert zelluläre und molekulare Veränderungen in unserem Körper, die die Struktur und Funktion des Gehirns positiv beeinflussen. Die positiven Veränderungen in unserem Gehirn können zu einer verbesserten kognitiven Leistung führen. Die Wirkungen werden auf körperliche Aktivität über einen längeren Zeitraum zurückgeführt. Aber auch auf dem Weg zu chronischen Wirkungen ist das Verständnis der akuten Auswirkungen belastungsinduzierter Veränderungen von großer Bedeutung. Die Identifizierung von belastungsinduzierten kortikalen Aktivierungsmustern sollte auch für die Verbesserung der kognitiven Funktion berücksichtigt werden. Aus diesem ist es erforderlich, die Effekte der Konstruktion des Trainingsprotokolls, wie z.B. Trainingsintensität und -dauer, auf die kognitive Funktion basierend auf neuronaler Korrelation zu untersuchen.

Basierend auf diesen Aspekten gliedert sich die vorliegende Arbeit in zwei Teile. Im ersten Teil (Teil I: Assessment) wurde die Papier-Bleistift version des Trail-Making-Test (ppTMT), ein weit verbreitetes neuropsychologisches Testverfahren zur Untersuchung kognitiver Funktionen, mit dem digitalen Trail-Making-Test (dTMT), der auf einer Tablet-Version entwickelt ist, verglichen. Dadurch wurden die Reliabilität und Validität überprüft. Außerdem wurde die dTMT bei Patienten mit Parkinson-Krankheit eingesetzt, um subtile Unterschiede in der Verschlechterung der Feinmotorik und der kognitiven Leistungsfähigkeit zu erkennen. Der dTMT ermöglichte die Messung zusätzlicher Variablen zur Überprüfung der Anwendbarkeit im klinischen Bereich. Außerdem ist eine Dekomposition kognitiver Fähigkeiten und die Beobachtung von Leistungsveränderungen während der

Aufgabe möglich. Der zweite Teil (Teil II: Übungsintervention) untersuchte die akuten Wirkungen der übungsinduzierten kortikalen Aktivierung auf die kognitive Leistungsfähigkeit unter Verwendung des dTMT. Wir verwendeten die funktionelle Nahinfrarot-Spektroskopie (fNIRS), um die hämodynamische Reaktion im Frontallappen und im motorischen Kortex für akute und chronische Auswirkungen unterschiedlicher Übungsintensitäten zu messen.

Schließlich führten das Zusammenspiel dieser beiden Teile (Beurteilung und Übungsintervention) sowie der Erfassung der neuronalen Mechanismen zu den folgenden Diskussionen. Zunächst wurde der Wert der digitalen Bewertung als Früherkennungsinstrument für motorische und kognitive Beeinträchtigungen gelegt. Zweitens wurde identifiziert, welche Trainingsinterventionen positiv kortikale Veränderungen im Gehirn auslösen, mit Verbesserungen kognitiver Funktion. Die vorliegende Dissertation befasst sich mit dem Zusammenspiel von digitaler Messung und Bewegungsintervention zur Erhaltung motorischer und kognitiver Gesundheit und der Frage, in welche Richtung wir für unsere Zukunft gehen sollten.

List of Scientific Publications for Dissertation in cumulative Form

Manuscript 1: Park, S.-Y., & Schott, N. (2021). The trail-making-test: Comparison between paper-and-pencil and computerized versions in young and healthy older adults. *Applied Neuropsychology: Adult*, 29(5), 1208-1220.

Manuscript 2: Park, S.-Y. & Schott, N. (2022). Which motor-cognitive abilities underlie the digital Trail-Making Test? Decomposing various test scores to detect cognitive impairment in Parkinson's disease. *Applied Neuropsychology: Adult*, 1-15.

Manuscript 3: Park, S.-Y., Reinl, M., & Schott, N. (2021). Effects of acute exercise at different intensities on fine motor-cognitive dual-task performance while walking: A functional near-infrared spectroscopy study. *European Journal of Neuroscience*, 54(12), 8225–8248.

Manuscript 4: Park, S.-Y. & Schott, N. (2022). The immediate and sustained effects of exercise-induced hemodynamic response on executive function during fine motor-cognitive tasks using functional near-infrared spectroscopy. *Journal of Integrative Neuroscience*, 21(3), 98.

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Abbreviations

AD	Alzheimer's diseases
BDI	Beck Depression Inventory
BDNF	Brain-derived neurotrophic factor
CBF	Cerebral blood flow
CFRS	Cognitive Functional Rating Scale
deoxy-Hb	Deoxygenated hemoglobin
DLPFC	Dorsolateral pre- frontal cortex
DT	Dual- Task
dTMT	Digital Trail-Making-Test
EEG	Electroencephalography
FDR	False discovery rate
fNIRS	Functional near-infrared spectroscopy
fMRI	Functional magnetic resonance imaging
FPA	Frontopolar area
GLM	General linear models
HC	Healthy control
HIIE	High-intensity interval exercise
HR	Heart rate
IGF-1	Insulin-like growth factor-1
ND	Neurodegenerative diseases
NIR	Near-infrared
M1	Motor cortex
MCE	Moderate-intensity continuous exercise
MCI	Mild cognitive impairment
MoCA	Montreal Cognitive Assessment
MPSTEFS	Mental and Physical State and Trait Energy and Fatigue Scales
oxy-Hb	Oxygenated hemoglobin
PD	Parkinson's disease
PD-MCI	Parkinson's disease with mild cognitive impairment
ppTMT	paper-pencil Trail-Making-Test

PSQ	Parkinson's screening questionnaire
ROI	Regions of interest
RPE	Rating of perceived exertion
TMT	Trail-Making-Test
VEGF	Vascular endothelial growth factor
VO_2max	Maximum oxygen consumption

1 Introduction

1.1 Relevance of early detection of fine motor and cognitive decline using the digital cognitive assessments

As an aging society deepens, the number of people suffering from neurodegenerative diseases (ND) such as Alzheimer's (AD) and Parkinson's disease (PD) is also increasing. Among NDs, AD is one of the most common diseases, belonging to which dementia is a typical form. In particular, around 47 million people worldwide currently have dementia, which is expected to nearly triple by 2050 (WHO, 2021). PD, a common neurodegenerative disease followed by AD, is also not much different. The prevalence of PD is estimated to double between 2005 (4.1 million to 4.6 million) and 2030 (8.7 to 9.3 million) in the world's most populous countries (Dorsey et al., 2007). These challenges will increase the burden on the global health system. As a result of this, the cost will also increase exponentially. In 2015, the global cost of dementia was estimated at USD 818 billion, accounting for 1.09% of the global gross domestic product (Kassebaum et al., 2016). However, if early diagnosis and intervention could delay the onset and progression of the disease by even one year, there would be nearly 9.2 million fewer cases worldwide by 2050, resulting in reduced health-related costs (Brookmeyer et al., 2007). These personal and health costs demonstrate that the early screening of symptoms, such as fine motor control of hand tremors as the representative symptom of PD, and the typical cognitive function problem of AD, is becoming increasingly important. However, assessment tools used by clinicians are primarily subjective, transient, and insensitive (Dorsey et al., 2015) to discriminating subtle differences at the behavioral level, particularly in fine motor control or mild cognitive impairment. Due to insufficient data and poor validation of these assessments, new assessments that provide high reliability and ecological validity are urgently needed (Mahadevan et al., 2020).

In recent years, smartphone- and tablet-based technologies have emerged to monitor changes in fine motor and cognitive performance (Koo & Vizer, 2019). These technological advances enable identifying specific symptoms, such as during drawing and handwriting, involved in fine motor and cognitive control as

digital biomarkers quickly and easily (Danna et al., 2019; Faundez-Zanuy et al., 2021, 2014; Kamble et al., 2021; S. Müller et al., 2017a). The finding of the particular pattern of cognitive deficits and additional information about the performance could save costs for patients and time for clinicians (Scharre et al., 2017). Digitized measures have already observed reduced rater bias, inter-rater variability, and increased sensitivity, which may elucidate significant sub-clinical symptoms (Espay et al., 2016; Lin et al., 2018). Moreover, automatic calculations measured by digital assessments and immediate delivery of results also support easy monitoring of long-term performance development (for a review, see Koo & Vizer, 2019). The digital version of tests isolates cognitive abilities not possible in paper-based tests, allowing measurement of several additional variables that provide additional information for identifying specific cognitive abilities, such as cognitive flexibility, working memory, and set-switching. These transmissions also offer the possibility to capture in detail fine motor control. For instance, movement patterns while drawing or handwriting can be continuously recorded and estimated. Also, movements such as drawing and writing, increasingly attracting attention as digital biomarkers, are among the complex activities of our daily life, involving a complex composition of perceptual-motor, kinesthetic, and cognitive functions that may be sensitive to age-related impairments in cognitive function (Yan et al., 2008). For example, recent studies have already applied a digital spiral drawing to distinguish the degree of hand tremor in PD (Danna et al., 2019; Ishii et al., 2020; Kamble et al., 2021; P. C. Lin et al., 2018). Moreover, the so-called "in air" movement, an additional variable that occurs when moving from lifting the pen to the subsequent motion without applying pressure to the surface while drawing, seems to be a sensitive digital biomarker for dementia patients (Faundez-Zanuy et al., 2014; Müller et al., 2017a, 2017b).

Like handwriting or drawing, the Trail-Making-Test (TMT; Army Individual Test Battery, 1944; Reitan, 1955), commonly used as a neuropsychological test, is also a fine motor-cognitive task consisting of complex manual skills connected with a sophisticated blend of cognitive, sensory, and perceptual-motor elements (Klaming & Vlaskamp, 2018). The TMT is an established neuropsychological test sensitive to cognitive impairment (McAlister et al., 2015) and is preferable for use as a predictor of executive function problems such as inhibitory control, working memory, and cognitive flexibility (Arbuthnott & Frank, 2000;

Salthouse, 2011). Although the TMT can measure these complex cognitive abilities, the goal of the task is straightforward, connecting numbers in ascending order or numbers and alphabets in alternating, ascending order as quickly and accurately as possible. Several digital versions of tablet-based Trail-Making-Test have recently emerged (Baykara et al., 2022; Dahmen et al., 2017; Fellows et al., 2017; Hannukkala et al., 2020; Heimann-Steinert et al., 2020; Lara-Garduno et al., 2019; Z. Lin et al., 2021; Lunardini et al., 2019; Rodriguez et al., 2019; Sacco et al., 2019; Woods et al., 2015; Zeng et al., 2017). Compared to the traditional paper-and-pencil version, the digital Trail-Making-Test (dTMT, see section 2.1) allows quick measurements, provides various information about task performance, and enables tracking of long-term performance change.

In Part I (Assessment) of the present thesis, research on the validity and reliability of the newly developed dTMT integrated with several technologies (Schott et al., in preparation) and its applicability in clinical fields will be introduced in more detail. In the next chapter, the acute effects of exercise on neural mechanisms underlying cognitive functions will be discussed.

1.2 Optical brain imaging supporting changes in neural mechanisms caused by acute exercise

Although the potential positive effects of exercise on cognition and brain health are well known, the mechanisms supporting these associations are not yet fully understood. Physical exercise is one of the best interventions for maintaining our brain health and cognitive function.

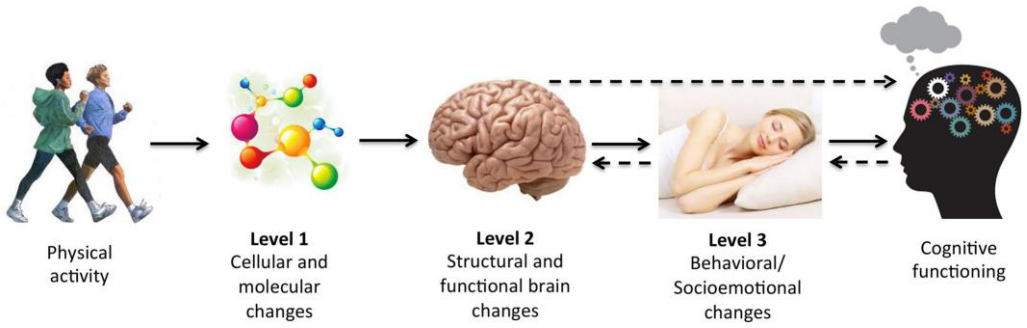


Figure 1. Conceptual model of mechanisms of physical activity at multiple levels of analysis (Stillman et al., 2016).

According to a conceptual model of mechanisms of physical activity by Stillman et al. (2016), the effect of physical exercise on cognitive function comes through a series of various stages (see Figure 1). First of all, physical activity induces cellular and molecular changes (Level 1), altering the structure and function of the brain (Level 2) and thereby resulting in behavioral changes in cognitive function (Level 3). Stillman's model (2016) of the multiple stages of physical activity, followed by cognitive health, is a uniform and simplified description of the interaction between physical and sports activity and cognitive health. The mechanisms of these two interactions are complex and can be detailed from different perspectives, as shown in the figure below. The most studied hypothesis explaining the positive effect of habitual physical activity on cognitive ability is the so-called neurotrophic hypothesis, which is consistent with Stillman's model (2016). Exercise-induced molecular and cellular changes increase growth factors such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF), particularly essential for inducing neuroplasticity (Hötting & Röder, 2013). These increased growth factors lead to the upregulation of neurogenesis, synaptogenesis, gliogenesis, and angiogenesis (Schott, 2020). By upregulating processing neurogenesis and synaptogenesis, physical activity promotes increased gray matter volume, particularly in brain structures repeatedly activated during exercise. Brain structures changed by physical activity cover most areas of the brain: cortical and subcortical motor areas (primary motor cortex and basal ganglia), prefrontal areas (dorsolateral, ventrolateral), limbic system (hippocampus), sensory areas (somatosensory cortex, auditory cortex, visual cortex, sensorimotor integration areas (parietal lobe), and other areas responsible for movement control (cerebellum) (for a review, see Lotze et al., 2019).

Also, these structural changes are likely induced by improved cerebrovascular function as a result of physical activity. Thus, angiogenesis can mediate structural changes in gray matter volume through improved cerebrovascular function and perfusion. This cerebrovascular function enables sufficient blood supply and the delivery of proper nutrients for neurodevelopment. For this reason, improving cerebrovascular function is also essential for neural growth and synapse formation. In addition, exercise-induced structural changes allow efficient use of neural resources and effectively organize connectivity between brain regions (Schott, 2020). Ultimately, these consequences can be caused by regular physical

exercise (chronic exercise) resulting from a steady accumulation of acute exercise, defined as a single bout of physical exercise (Basso & Suzuki, 2017).

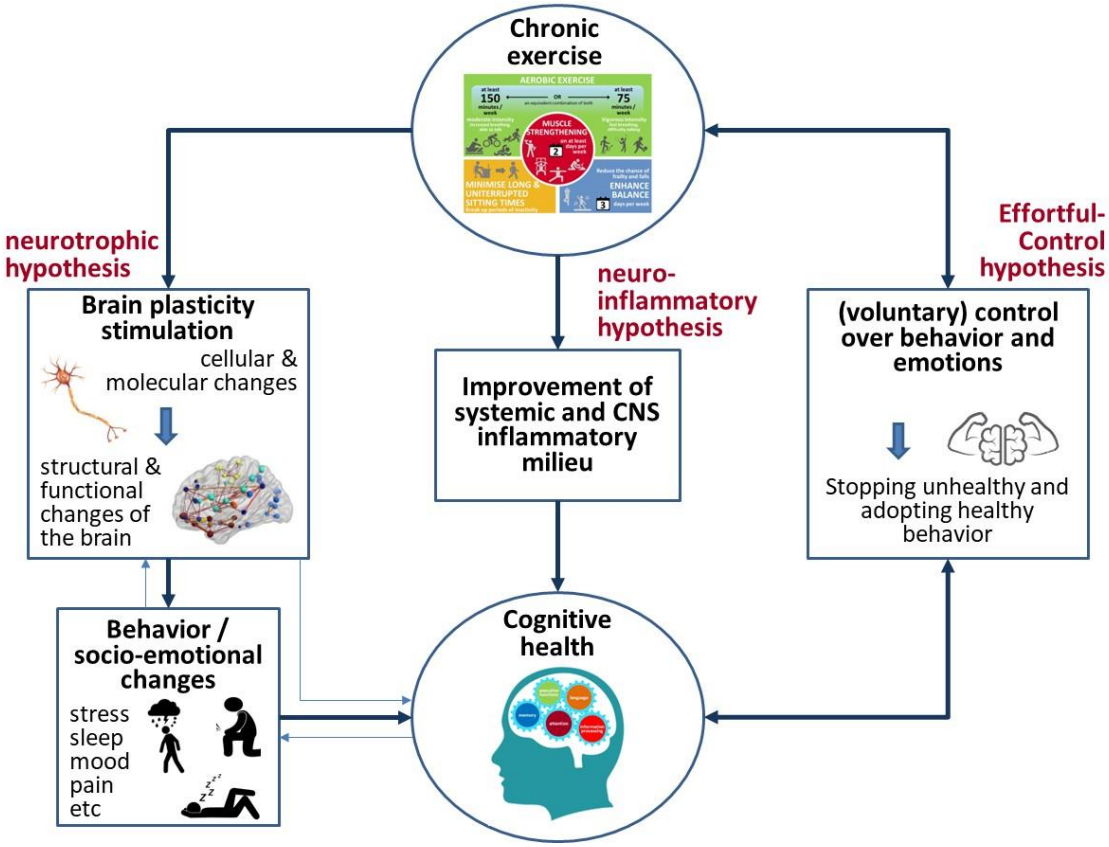


Figure 2. Explanatory approaches for connecting physical and sporting activity and cognitive health (Schott, 2020).

Figure 2 also shows the alternative hypotheses supporting cognitive health: the neuroinflammatory and effortful control hypotheses. According to the neuroinflammatory hypothesis, neuroinflammation, as an immune reaction, responds to a variety of signals, including infections, traumatic brain injury (Ebert et al., 2019), autoimmunity, or toxic metabolites within the central nervous system (Gendelman, 2002), which consists of macroglia, microglia, neurons, and astrocytes. In addition, neuroinflammation plays a role as a pathological mediator in various neurodegenerative diseases (Schain & Kreisl, 2017). However, exercise protects against neurodegenerative disease by raising anti-inflammatory and lowering pro-inflammatory molecule levels (Seo et al., 2019). Finally, the effortful control hypothesis postulates that the coupling of the relationship between physical activity and other healthy behaviors depends on effort control capacity and executive function effectiveness, supported by the strength of neural connectivity within and between brain networks (Audiffren & André, 2019). Overall, the mechanisms by which physical

activity positively affects cognitive health are diverse and complex. As shown in Figure 2, the relationship between physical activity and cognitive health can be explained through the hypotheses described above by mutually complementary interactions. Above all, understanding the acute effects of exercise-induced changes can provide new perspectives for understanding the crucial mechanisms for linking acute and chronic exercise.

Several meta-analyses demonstrated acute exercise's small but positive effect on cognitive performance (Chang et al., 2012; Lambourne & Tomporowski, 2010). In addition, various moderators such as exercise intensity, duration, cognitive task, measurement timing, and individual fitness level have been identified to influence behavioral-related cognitive performance by acute exercise. Several studies have been conducted extensively on these moderator variables for the effects of exercise on cognition (for meta-analyses, see Chang et al., 2012; Lambourne & Tomporowski, 2010; McMorris et al., 2011; McMorris & Hale, 2012). However, there is a limit to explaining the positive effects with only the behavioral change of cognitive performance caused by acute exercise. For this reason, to better elucidate these effects, studies should examine the neural level changes induced by behavioral changes in cognitive performance. However, investigating the effects of acute exercise on neural correlates underpinning behavioral-related cognitive performance is still lacking. Although many neuroimaging methods have been applied to elucidate the interaction between exercise and cognition, each neuroimaging equipment has advantages and disadvantages (for a systematic review, see Herold et al., 2018). For instance, functional magnetic resonance imaging (fMRI) allows measuring activation of the whole brain with a high spatial resolution (e.g., <4.0 mm) but is vulnerable to motion artifacts, so the head is required to be immobilized. While fMRI offers a relatively low temporal resolution, electroencephalography (EEG), which directly measures the neuron's electrical signal by an amplifier, provides a high temporal resolution (e.g., >1000 Hz). EEG enables measurements during movements such as walking or balancing to some extent but is particularly sensitive to physiological artifacts such as sweat and muscle activation. In addition, the disadvantage of EEG lies in its low spatial resolution (e.g., between 5.0–9.0 cm). Due to shortcomings such as body immobilization in fMRI and restricted movement in EEG, research settings investigating the effects of exercise (e.g., walking/running on a treadmill/overground) on cognition are still

limited. A possible alternative, functional near-infrared spectroscopy (fNIRS, see section 3.1), which has been increasingly used in recent research on exercise and cognition, is a relatively new, non-invasive neuroimaging device that adequately compensates for the limitations of fMRI and EEG. Compared to these neuroimaging systems, fNIRS has fairly good spatial (between 1.0–3.0 cm) and temporal resolution (typically up to 10 Hz). Above all, fNIRS is robust against motion artifacts applicable to exercise cognition research (Herold et al., 2018). Therefore, fNIRS may be especially useful for measuring brain activity evoked by motor-cognitive control within movement-unrestricted research settings (e.g., during daily activities such as exercise or walking).

Our brains increase their demand for oxygen and glucose when performing specific tasks, resulting in an oversupply of the brain's local cerebral blood flow (CBF) to meet the increased metabolic demands. Increased CBF in response to increased neural activity is induced by neurovascular coupling (Fabiani et al., 2014; Perrey, 2008). fNIRS can measure increased oxygenated hemoglobin (oxy-Hb) and decreased deoxygenated hemoglobin (deoxy-Hb) resulting from an oversupply in regional CBF on the cerebral oxygenation level of the brain (Agbangla et al., 2017). In addition, increased CBF is commonly seen during physical exercise (Steventon et al., 2020; Thomas et al., 1989). The increased CBF caused by physical exercise results from increased cerebral nerve activity and metabolism (Ogoh & Ainslie, 2009) (see more detailed information in section 3.1). In addition, CBF can shift from areas required for cognitive function to areas needed for motor control and maintenance of vital functions depending on the situation (e.g., during acute exercise) (Moriarty et al., 2019). In this regard, the hypofrontality hypothesis of reticular activation has been previously proposed by Dietrich and Audiffren (2011). This hypothesis states that the decreased neural activity in the prefrontal cortex is responsible for the limited task performance due to increased activation in favor of brain regions involved in sensory and motor processes. This theoretical hypothesis seems particularly evident during high-intensity exercise (Wang et al., 2013) or complex dual-task while walking (DT, e.g., simultaneous performance during walking combined with a cognitive task) (Park & Schott, in preparation). During high-intensity exercise or complex DT, the use of neural resources in the prefrontal cortex for cognitive tasks may be disrupted. However, many fNIRS studies investigating the effects of exercise-induced cortical activation on executive

function have been generally conducted post-exercise. In addition, these fNIRS exercise studies are limited to frontal lobe measurement, so the shifting of CBF to other areas cannot be identified (Damrongthai et al., 2021; Hyodo et al., 2012; Kujach et al., 2018; Yanagisawa et al., 2010). Nevertheless, these studies showed that moderate acute exercise could increase cortical activation of the frontal lobe and enhance cognitive performance. In relation to these findings, a review by Basso and Suzuki (2017) assumes that prefrontal hypoperfusion induced during exercise may increase cerebral oxygenation as a rebound effect in post-exercise, resulting in cognitive improvement.

Furthermore, as pointed out in a systematic review (Herold et al., 2018), most cognitive tasks were set to confirm the reaction time or accuracy induced by one response to one stimulus (e.g., Stroop and Flanker task). Our daily activities usually outweigh the need for sustained cognitive demands, including fine motor control (e.g., texting on a cell phone, button fastening, drawing, or handwriting) rather than an acute response to one stimulus.

With these points in mind, in Part II, we investigated the exercise-induced changes in cortical activation underpinning cognitive performance with two different intensities of acute exercise (high-intensity interval exercise; HIIE vs. moderate-intensity continuous exercise; MCE) using the dTMT and fNIRS. In particular, by measuring two brain regions, namely, the frontal lobe and the motor cortex, changes in cortical activation caused by CBF between these two brain regions were observed. Moreover, based on the neural mechanism of the effects of exercise on cognitive performance, a specific exercise intervention leading to the improvement or maintenance of cognitive function can be proposed.

1.3 Structure of the thesis

The present thesis is primarily divided into two parts. The first part focuses on the TMT assessment, which discusses the shortcomings of the previous paper-pencil version in measuring fine motor control and cognitive performance. Also, to what extent the digital version can compensate for the weaknesses of the earlier version and detect subtler differences will be verified through studies in Part I. The second part will cover exercise interventions. This part will discuss how the performance on the behavioral level induced by acute exercise can be changed and how its

neural correlates can be revealed. Finally, the present thesis will discuss how these two parts (assessment – exercise intervention) should be connected and interact.

2 Part I: Assessment

One of the main challenges in evaluating cognitive performance is detecting subtle differences and overt impairments. With recent technological advances, digital cognitive assessments continue to emerge, particularly enabling obtaining granular outcome measures (Park & Schott, 2021). A digital version of the Trail-Making-Test, one of the most frequently used neuropsychologically established tests, currently exists in several versions, including various techniques such as automatic data calculation and measurement of additional variables other than the current parameter completion time (Baykara et al., 2022; Dahmen et al., 2017; Fellows et al., 2017; Hannukkala et al., 2020; Heimann-Steinert et al., 2020; Lara-Garduno et al., 2019; Z. Lin et al., 2021; Lunardini et al., 2019; Rodriguez et al., 2019; Sacco et al., 2019; Woods et al., 2015; Zeng et al., 2017). In section 2.1, the present study verified the validity and reliability of the newly developed dTMT by comparing it with the existing paper version. Before describing the methods and results of this study, the following section will address the limitations of the paper-pencil version, the current status of the digital version, and its technologies. Finally, at the end of this section, our digital version of TMT will be introduced. In section 2.2,

2.1 Fine motor cognitive control as a possible digital biomarker digital Trail-Making-Test (dTMT)

Although there is still no generally accepted definition of executive function (Wasserman & Wasserman, 2013) as top-down cognitive processes, executive function is an umbrella term with diverse functions such as self-planning, making and recognizing complex, high-level judgments, and organizing and controlling memory processes (Burgess & Simons, 2012; Diamond, 2014). These crucial functions (Botvinick & Braver, 2015) are often divided into three parts: cognitive flexibility, inhibitory control, and working memory (Hofmann et al., 2012; Miyake et al., 2000) and can be severely affected by neurodegenerative processes (Yang et al., 2019).

Among many neuropsychological tests to measure cognitive function, the TMT is a line-drawing task involving cognitive, perceptual-motor, and sensory abilities and is currently widely used in clinical fields. The original paper-pencil version of TMT (ppTMT) consists of TMT-A and -B (Army Individual Test

Battery, 1944; Reitan, 1955). In TMT-A, the numbers in each circle must be connected in ascending order from 1 to 25, and in TMT-B, a more complex task, numbers, and alphabets must be drawn alternately in ascending order (e.g., 1-A-2-B-3-C...). Generally, TMT-A is associated with information processing and visual searching speed (Ríos Lago et al., 2004; Sánchez-Cubillo et al., 2009), whereas TMT-B involves more complex cognitive abilities such as cognitive flexibility, working memory, and inhibitory control (Arbuthnott & Frank, 2000; Gaudino et al., 1995; Kortte et al., 2002b). In addition, fine motor control is involved during the TMT due to the characteristic of the drawing task. Since AD and/or PD are sensitive to the impairment of fine-motor-cognitive control (Danna et al., 2019; Faundez-Zanuy et al., 2021, 2014; Ishii et al., 2020; Kamble et al., 2021; P. C. Lin et al., 2018; S. Müller et al., 2017b, 2017a), Schott et al. (2016) extended TMT with the addition of a control variant to test the fine motor speed (TMT-M). All tasks should be performed as quickly and error-free as possible, and completion time and the number of errors are commonly used as indicators of task performance.

During the TMT, cortical activation measured by fNIRS on the PFC was identified in young adults and the elderly, revealing different activation patterns depending on age (Hagen et al., 2014; Lancia et al., 2018; Müller et al., 2014). In addition, studies on brain activation patterns during TMT using fMRI have already been investigated (Allen et al., 2011; Jacobson et al., 2011; Moll et al., 2002; Zakzanis et al., 2005). According to these studies, increased activation of the extensive brain areas (e.g., dorsolateral prefrontal cortex, inferior/middle frontal cortices, cingulate gyrus, supplementary motor areas, precentral gyrus, the intraparietal sulcus, the left angular gyrus/left middle, and superior temporal gyrus) was observed with TMT-B in contrast to TMT-A (Jacobson et al., 2011; Moll et al., 2002; Zakzanis et al., 2005). Above all, the dorsolateral, the medial prefrontal cortices, and the intraparietal sulcus have been constantly reported to be related to cognitive flexibility, working memory, and set-switching (Moll et al., 2002; Zakzanis et al., 2005). However, in general, TMT includes fine motor control tasks, but because of difficulties in performing tasks in the MRI scanner, an adapted version, i.e., oral TMT or computer version, was used. As a result, an activation pattern different from the conventional TMT may appear. For this reason, fNIRS

covering whole brain regions may be a suitable alternative to analyze activation patterns during TMT.

Although many studies have attempted to validate constructs with other specific cognitive tests or to analyze complex cognitive functions with ratios (B/A) or differences (B-A), these alone are still insufficient to explain the complex cognitive abilities involved in TMT-B (Arbuthnott & Frank, 2000; Gaudino et al., 1995; Kortte et al., 2002a; Salthouse, 2011; Sánchez-Cubillo et al., 2009). Another challenge is that the ppTMT only consists of one variation for each condition. The singular version of neuropsychological tests may thus not be suitable for repeated use for longitudinal evaluation, in which practice effects can occur repetitively (Beglinger et al., 2005; Buck et al., 2008). In addition, the TMT-B has a different path length than the TMT-A, which might explain the difference in the performance of the TMT A and B (Gaudino et al., 1995; Vickers et al., 1996). These limitations may be addressed with a digital version incorporating various functions, such as capturing additional information during the task and generating alternative sheets with equal path lengths. Although many dTMT versions have been published so far (Baykara et al., 2022; Dahmen et al., 2017; Fellows et al., 2017; Hannukkala et al., 2020; Heimann-Steinert et al., 2020; Lara-Garduno et al., 2019; Z. Lin et al., 2021; Lunardini et al., 2019; Rodriguez et al., 2019; Sacco et al., 2019; Woods et al., 2015; Zeng et al., 2017), there are still many methodological limitations (see Table 1). First, a purely fine-motor control condition was not included in any other version of dTMT. Including the control variant is also crucial for identifying the impairments of fine motor skills because it allows us to measure only fine motor control aside from several cognitive functions. In addition, only the group by Maureen Schmitter-Edgecombe integrated additional measures in their dTMT version (e.g., time spent inside/between circles, number/duration of lifts and pauses) and attempted to analyze them in detail (Dahmen et al., 2017; Fellows et al., 2017). Moreover, to avoid the practice effect, several studies have already attempted to create alternative forms in the ppTMT, but without the rearrangement of circles randomly (Atkinson et al., 2011) or only with the rearrangement of circles based on the mirrored image of the original version (only three alternate forms) (Wagner et al., 2011). Unfortunately, only one of the many digital versions solved generating the automatic random alternate sheets with a divide-and-combine approach (Zeng et al., 2017). Although this dTMT integrated

by the algorithm of Zeng et al. (2017) showed possibilities for a reduction in the practice effects and the suitability of their digital version for longitudinal cognitive assessment, only the TMT-A was built. In addition, their algorithm had minor bugs (Maier, 2019). For this reason, the validity and reliability of digital TMT are still required, and research on the TMT as a digital biomarker that discriminates cognitive impairments by applying it to the clinical field should be conducted.

Table 1. T*echnological limitations of the TMT with digital versions.*

Papers by year	Pure fine-motor control condition	Additional measures	Alternative forms
Woods et al., 2015	–	☑	–
Dahmen et al., 2017	–	☑	–
Fellows et al., 2017	–	☑	–
Zeng et al., 2017	–	–	☑
Lara-Garduno et al., 2019	–	–	–
Lunardini et al., 2019	–	–	–
Rodriguez et al., 2019	–	–	–
Sacco et al., 2019	–	–	–
Hannukkala et al., 2020	–	–	–
Steinert et al., 2020	–	–	–
Lin et al., 2021	–	–	–
Baykara et al., 2022	–	–	–

Our version of the dTMT based on the Android application developed by Schott and Maier (in preparation) was designed for a Samsung Galaxy Note Pro (12.2-inch diagonal LED-backlit Multi-Touch display with IPS technology; portrait alignment) in size similar to the paper-pencil version (A4 paper size). Our version of the dTMT consists of three conditions: TMT-A (a number sequencing task), TMT-B (a number-letter switching task), and a fine motor speed task (control task), connecting empty circles along a predefined pathway (see Figure 3). In particular, our version has been improved by integrating the advantages of the current digital versions, including various functions such as measuring additional variables (Dahmen et al., 2017; Fellows et al., 2017) and the divide-combine algorithm for generating alternate sheets (Zeng et al., 2017). Also, an algorithm equally adjusting the random distribution of circles (Vickers et al., 1996) and the path length of the tasks (Gaudino et al., 1995; Vickers et al., 1996) supports a

constant level of difficulty for each variation automatically generated for each task condition. Especially for detailed analysis, additional variables are automatically measured in dTMT in addition to the variables' completion time' and 'number of errors' in ppTMT (see more information about variables in 4.1).

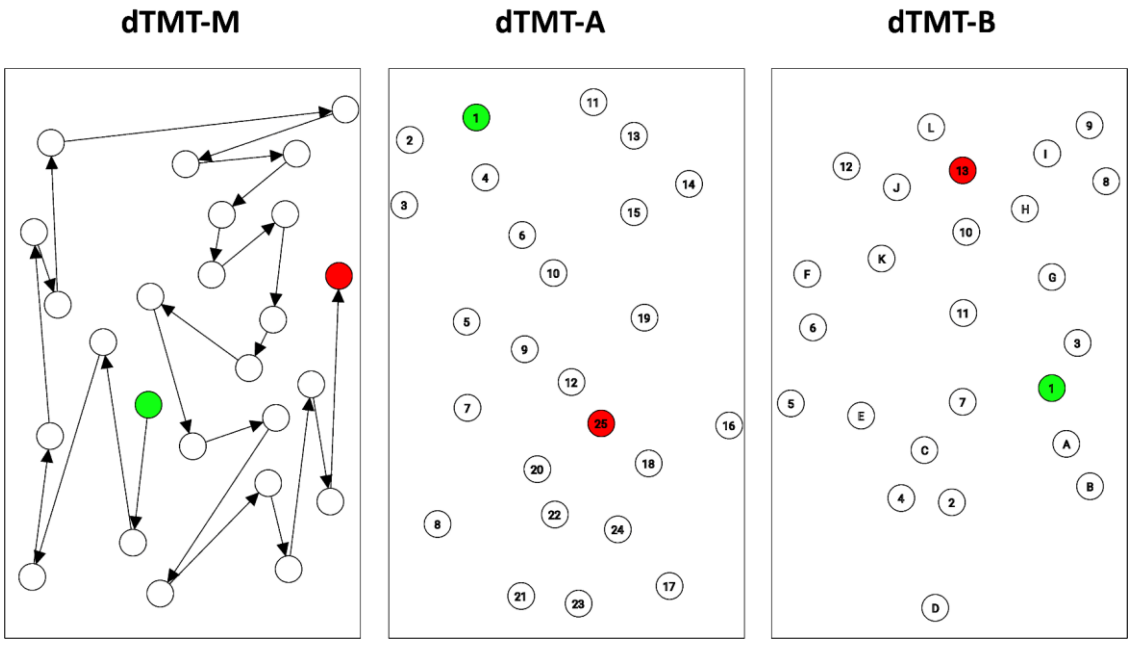


Figure 3. Examples sheet of each condition in dTMT (Park & Schott, 2021).

With these advantages of digital measurement, in Part I (Assessment), we verified the similarity, validity, and reliability of the paper-pencil and digital versions of TMT (ppTMT vs. dTMT) for the completion time (measurable in both versions). Also, a more detailed analysis was attempted by measuring additional variables of dTMT to investigate its applicability to clinical fields to identify PD. Finally, in Part II (exercise intervention), due to difficulties in performance with the conventional ppTMT, dTMT was used to investigate the effects of acute exercise on fine motor and executive functions while walking.

2.1.1 Purpose, procedure, and analysis of manuscript 1

The purpose of the present study for Part I was to investigate (1) reliability, (2) equivalence, and (3) agreement between the ppTMT and dTMT. This study was designed as a cross-over design study. A total of 29 young adults (YA; 22.4 ± 4.47 years, age-ranged between 19–35, 17 male) and 24 healthy older adults (66.2 ±7.48 years, age range between 50–82, 14 male) were recruited for the present study.

Due to the significant difference in the age range, the group of older adults was divided into two sub-groups (12 young-old adults; YOA; age range between 50–65, 8 male, and 12 older adults; OA; age range between 66–82, 6 male). The execution order of ppTMT and dTMT was randomized (ppTMT–dTMT or dTMT–ppTMT) using a counterbalanced design to reduce the potential execution order effects. After the first test version (ppTMT or dTMT), a short break was given. At this time, the questionnaires (demographic information and physical activity) were completed. Then, the remaining test version was conducted. Participants performed each condition of the two TMT versions in triplicate.

As statistical analysis methods, agreements between the two test versions in each condition (TMT-M, TMT-A, TMT-B) were analyzed using Spearman correlations and Bland-Altman plots. Bland-Altman plots contain the difference between the two versions (e.g., dTMT-M – ppTMT-M) and the mean across paired measurements (dTMT-M + ppTMT-M / 2), along with a 95% agreement limit. To compare the equivalence of the overall structure between the two TMT versions and the difficulty of each condition, we conducted 2 × 3 × 3 ANCOVAs with repeated measurements, controlled for years of education and exercise duration as covariates, because these covariates significantly affected the performance of all TMT variants. As for the factors of the ANCOVA, within-subject factors consisted of version (dTMT versus ppTMT) and task condition (TMT-M, TMT-A, and TMT-B), and between-subjects factor as age group (YA, YOA, and OA). As a representative variable for both versions, completion time (average value of three trials in each condition) was used for all analyses.

2.1.2 Results of manuscript 1

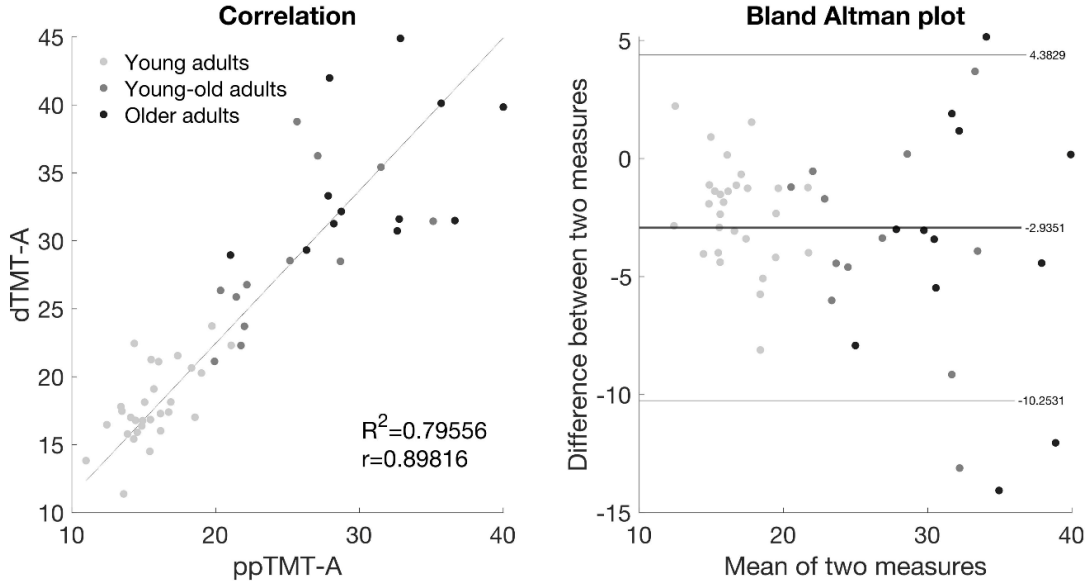
Agreement between ppTMT and dTMT

The construct validity was analyzed using bivariate correlations for the completion times between the ppTMT and dTMT (see Figure 4). Spearman correlation coefficients (r) ranged between .82 and .90 ($p < .001$) for completion times. In addition, the completion time between ppTMT and dTMT demonstrated an explanatory power of 75.4% of the variance in TMT-M, 76.6% in TMT-A, and 75.4% in TMT-B (see on the left side of the graph in Figure 4). In Bland-Altman plots, overall good agreement was observed between test variants, indicating that 96%, 92%, and 94% of data points lie within the limits of agreement. Overall, the mean agreement

indicated a negative value (TMT-M: -4.16, TMT-A: -2.94, and TMT-B: -5.41, see on the right side of the graph in Figure 4), indicating that the participants performed faster in the ppTMT compared to the dTMT.

Equivalence of the two TMT versions

In comparing the difficulty between the two versions of the TMT, ANCOVA with repeated measurement, controlled for years of education and exercise duration, showed a significant effect on task condition and interaction between task condition and age group (see Figure 5). Post hoc analysis demonstrated significant differences between all task conditions ($p < .001$). Completion time increased as task difficulty increased, and this effect also rose with older age. We found no significant main or interaction effect between the TMT version and age group or between TMT version, task condition, or between TMT version, task condition, and age group.



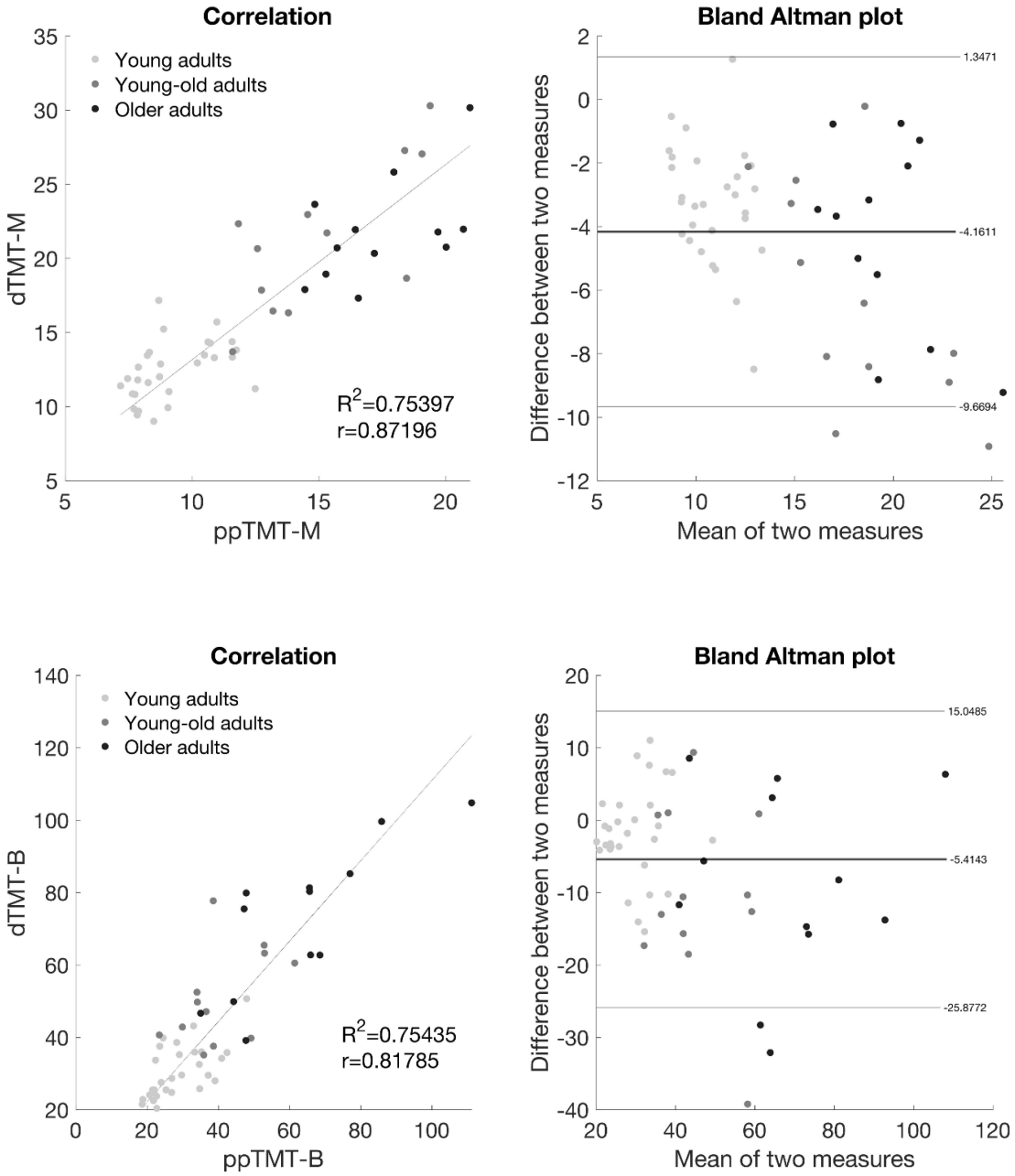


Figure 4. Equivalence between two versions of TMT. Scatterplots with a reference line show a linear regression between ppTMT and dTMT (The left side of the graph). Bland-Altman plots indicate agreements between dTMT and ppTMT (The right side of the figure). (Park & Schott, 2021).

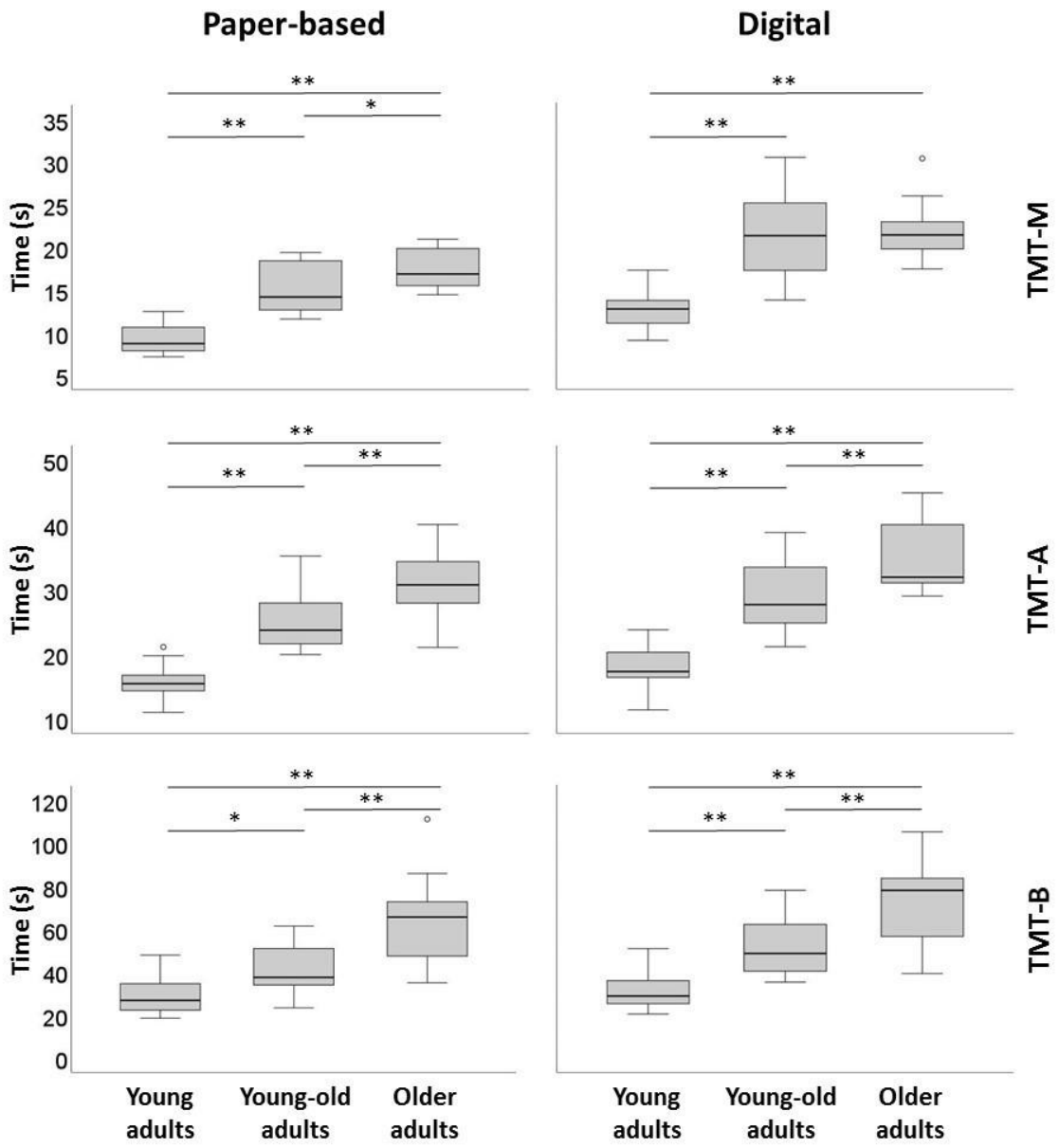


Figure 5. Boxplot of differences in the two versions of TMT for completion time (*p <.05; **p <.01) (Park and Schott, 2021).

2.2 Applicability of dTMT for PD identification in the clinical field

It is already well known that the TMT-B involves many cognitive abilities, such as working memory, inhibitory control, and cognitive flexibility (Arbuthnott & Frank, 2000; Gaudino et al., 1995; Kortte et al., 2002a; Salthouse, 2011; Sánchez-Cubillo et al., 2009). However, these complex cognitive abilities cannot be explained only by completion time and the number of errors in the paper-pencil version. For instance, patients can achieve the same or similar completion time on the dTMT-B, but one person may have difficulty switching tasks. In contrast, another

may have a problem in inhibitory control or working memory or no cognitive problem but only the issue of fine motor control impairment (e.g., resting / action tremor in PD). In this respect, the performance impairments caused by various mechanisms require correct measurement to repair the respective cognitive processes of each other and appropriate interventions based on these mechanisms for patient treatment. Perhaps, the dTMT could enable the decomposition of these complex cognitive functions, detecting specific fine motor and cognitive impairments.

In particular, such a specific problem may suggest the possibility of early detection through dTMT in PD accompanied by, for instance, hand tremors or cognitive impairment. Although PD is a movement disorder with predominantly resting and behavioral tremors, spasticity, bradykinesia, and postural instability, cognitive impairment in PD has recently been increasingly accepted as PD's primary symptomatic non-motor impairment (DeMaagd & Philip, 2015). Among all patients with PD, the prevalence of PD with mild cognitive impairment (PD-MCI) has been reported, typically ranging from 19% to 25% (Aarsland et al., 2009; Caviness et al., 2007; Dalrymple-Alford et al., 2010; Hoops et al., 2009) and up to 53% (Janvin et al., 2006). For this reason, in manuscript 2, dTMT, simultaneously measuring fine motor and cognitive control problems, was applied to PD. Further, we attempted a more detailed analysis through additional measurement variables.

2.2.1 Additional variables measured by dTMT

Especially for detailed analysis, various variables are automatically collected in the dTMT in addition to the variables for completion time and the number of errors in ppTMT (Dahmen et al., 2017):

- **Number of correctly connected circles:** Number of circles that are connected in a specific time (relevant if individual pages in the block design are not entirely completed)
- **Path length:** Path length covered by the test subject (in cm and percentage of the total test length)
- **Number of pauses:** Number of pauses a subject takes while completing the test. A pause is defined as a movement of fewer than 10 pixels for at least 0.1 seconds
- **Pause duration:** Duration of the pauses in milliseconds

- **Number of lifts:** Number of lifts that are made when completing the test
- **Lift duration:** duration of the lifting in milliseconds
- **Time spent between circles:** Time in milliseconds that is required for the path from one circle to the next circle - this time is again divided for the TMT-B into the time before circles with letters and time before circles with numbers
- **Time spent inside the circle:** time spent in milliseconds that elapsed between entering and leaving the circle - this time spent is again divided for the dTMT-B into time inside the circles with letters and time within the circles with numbers.
- **Pressure:** pressure to press the tablet screen with a finger or a stylus

These additional variables are automatically calculated as the average values performed during the task. Most notably, further information about each circle during the task that is not the average value can be provided in our dTMT version (e.g., time of entering and leaving each circle, time spent in each circle, time spent between each circle, path length covered by participants, angle, and orientation between each circle).

2.2.2 Purpose, procedure, and analysis of manuscript 2

The study's purpose was to examine differences between individuals with and without PD with respect to their cognitive status using additional measurable variables by dTMT. We attempted to decompose complex cognitive abilities such as inhibitory control, working memory, and cognitive flexibility. Finally, the dTMT, allowing for analysis in more detail while performing the task, was used to investigate the parameter *time spent in each circle*. This variable can identify which circles a performer has difficulty in and discover performance trends during the task. Through these results, we attempted to identify possible screening symptoms such as fine motor impairment (i.e., freezing of hand movement or tremor) and mild cognitive impairment.

Thirty healthy controls (HC; 66.3±8.61 years, age range 46-82, male n = 17) and thirty individuals suffering from PD (68.3±9.66 years, age range 45-80, male 17) participated voluntarily in the experiment (for more detailed information about demographic data of participants with PD and healthy controls, see Table 2 in Appendix A2). PD participants were recruited via self-help or sports groups

supporting people with PD in Stuttgart, Germany. These groups as the German Parkinson Association, founded in 1981, are a self-help association, including around 450 regional groups that meet monthly to weekly to exchange and support each. Inclusion criteria for the PD patients participating in the present study were (1) a clinical diagnosis of PD according to the United Kingdom Parkinson's Disease Society Brain Bank (Gibb & Lees, 1998), (2) a mild to moderate level of the disease based on Hoehn and Yahr stage (I-III), and (3) ON medication state (Hoehn & Yahr, 1967). The questionnaire results addressing the anamnesis of the PD group are presented in Table 2.

Table 2. *Characteristics of PD (Park & Schott, 2022).*

Characteristics	**PD** (n=30) *M* (*SD*)
Duration of disease (years)	8.19 (6.59)
Duration of medication (years)	7.38 (6.49)
Medication (%)	
L-Dopa / Madopar / Stalevo / Metformin / Neopro Pflaster	56.7 / 30.0 / 6.7 / 3.3 / 3.3
Medication Dose (%)	
600 / 175 / 125 / 100 / 60 (mg)	5.6 / 5.6 / 16.7 / 66.5 / 5.6
Hoehn & Jahr (%)	
I / II / III	47.4 / 21.0 / 31.6
Tremor (e.g., eating, drinking) (%)	
no / left / right / both	50.0 / 10.0 / 33.3 / 6.7
Tremor in resting (%)	
no / left / right / both	70.0 / 6.7 / 16.7 / 6.7

Each dTMT condition was performed in the experiment three times, a total of 9 times (three conditions × three times). The sequence of tasks was constructed randomly, meaning that the task on the same sheet was not performed twice in a row. After that, all participants completed questionnaires for demographic information and sports biography, as well as the Parkinson's screening questionnaire (PSQ, Fereshtehnejad et al., 2014), the Cognitive Functional Rating Scale (CFRS, Kulisevsky et al., 2013), the Beck Depression Inventory (BDI-6, Blom et al., 2012), and the Montreal Cognitive Assessment (MoCA, Nasreddine et al., 2005) for detecting mild cognitive impairment (MCI).

For further statistical analysis, we first subdivided MCI groups (Pathological, Undecide, and Healthy) according to their cognitive abilities based on the MoCA cut-off score from Thomann et al. (2020) and performed the statistical analysis. We first analyzed 2 (PD and HC) × 3 (Pathological, Undecide, and Healthy) × 3 (task condition; dTMT-M, -A, and -B) ANOVAs with repeated measurements on completion time.

We decomposed cognitive abilities (inhibitory control, working memory, and cognitive flexibility) for a more detailed analysis using additional variables. Based on the study by Fellows et al. (2017), we calculated the mean value of each variable related to working memory (number of lifts, duration of lifts, and time spent inside the circle) and inhibitory control (number of pauses, duration of pauses, and time spent between circles). Cognitive flexibility was calculated as the absolute value of subtracting each other the time spent inside circles composed of the numbers and alphabets in dTMT-B. Table 3 shows to which specific cognitive ability each variable measured by dTMT belongs.

Table 3. Variables for d*ecomposition of cognitive abilities*

Inhibitory control	**Cognitive flexibility**	**Working memory**
• Number of pauses • Duration of pauses • Time spent between circles	• Time spent inside circles for numbers • Time spent inside circles for alphabet	• Number of lifts • Duration of lifts • Time spent inside the circle

We assumed that a value closer to 0 indicates better cognitive flexibility, i.e., the ability to switch tasks (from number to alphabet or vice versa). The higher value represents poor cognitive flexibility. On these three variables, we performed 2 (PD and HC) × 3 (Pathological, Undecide, and Healthy) × 3 (decomposed subvariables: inhibitory control, working memory, cognitive flexibility) ANOVAs with repeated measurements. With the three cognitive abilities, we also tested multiple regression with commonality analysis to explore independent variables' unique and common contributions to predicting a dependent variable. For this analysis, we used the questionnaire results (i.e., Fear of falling, CFRS, PSQ, BDI-6, Physical activity in sports clubs) and each dummy variable of PD and MCI-group as predictors.

In order to observe the performance change during the task execution, time spent in each circle for dTMT-B was described as a curve plot. Lastly, we attempted to identify the tendency of each group's performance during dTMT-B. By measuring the variable of time spent in each circle, made possible by our version of dTMT, it is possible to identify where performance difficulties are most pronounced. In addition, there is the possibility of capturing the task performed based on these results to observe individual singularities, such as the problem of cognitive function, freezing of hand movement, or hand tremor.

2.2.3 Results of manuscript 2

Completion time as the primary indicator for fine motor and/or cognitive performance

In the first analysis step, we performed ANOVA with repeated measurements on the completion time, the primary indicator for TMT, over increasing task difficulty to examine the performance change depending on PD-group according to their cognitive state (MCI-group). We found a significant effect of task difficulty and significant interaction effects between PD-group/MCI-group and task difficulty. As the task difficulty increased, overall cognitive performance decreased, leading to considerable differences between groups in dTMT-B. Notably, greater deteriorations in cognitive performance were observed for PD participants and pathological participants of the MCI-group in dTMT-B (see Figure 6). However, there was no significant interaction between PD-, MCI-group, and task difficulty.

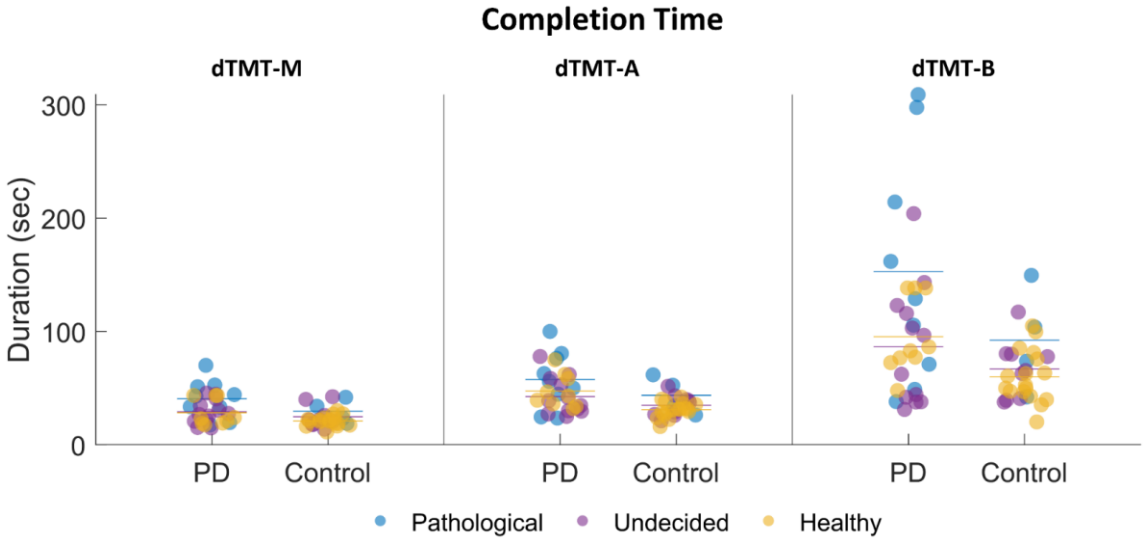


Figure 6. Completion time in each condition by group (PD group: PD vs. HC and MCI group: Pathological vs. Undecided vs. Healthy) (Park & Schott ,2022)

For other additional variables, compared to the PD group, healthy controls required less time to perform tasks, made fewer errors, spent less time inside and between circles, and made less frequency and short duration of lifting the pen in the air. The same was true when comparing healthy controls with individuals at risk for MCI (more detailed information about results for additional variables, see Table 3 in manuscript 2 of Appendix A2).

Decomposition of cognitive abilities using temporal/spatial variables of dTMT-B (Inhibitory control, working memory, and cognitive flexibility)

While comparing sub-variables decomposed from executive function depending on each group condition, we observed a significant main effect of sub-variables and a significant interaction effect between MCI-group and sub-variables. Among the cognitive abilities covered by dTMT-B, working memory was involved with the highest proportion in this complex task, followed by cognitive flexibility and inhibitory control (see Figure 7). Among each sub-variable, inhibitory control was sensitive to the PD group, whereas cognitive flexibility was sensitive to the MCI group. However, working memory had a significant effect on both groups.

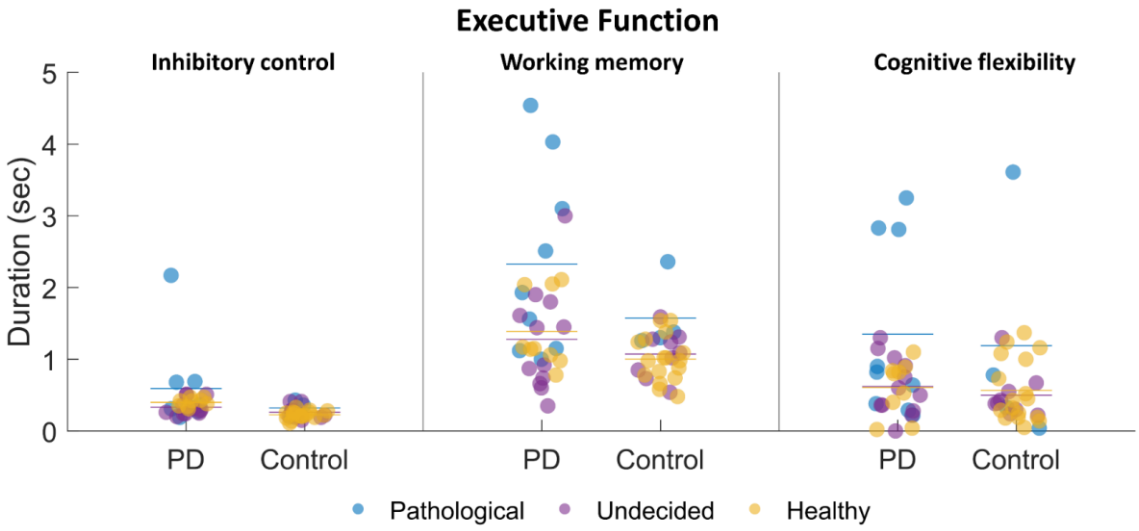


Figure 7. Decomposed sub-variables in executive function by group (PD group: PD vs. HC and MCI group: Pathological

Concerning commonality analysis, Table 4 demonstrates the results of the multiple regression analysis with R^2, β, and the unique and common effects for each model (Model 1: Inhibitory control, Model 2: Cognitive flexibility, and Model 3: Working memory). Model 1 explained 22% of the variance for inhibitory control using MCI-Pathological, Fear of Falling, and PD-Parkinson, $F(3,56) = 5.31$, $p<.001$. In Model 2, a total of 15% of the variance for cognitive flexibility could be explained by MCI-Pathological, Fear of Falling, and Physical activity in sports clubs, $F(3,56) = 3.29$, $p=.02$. Model 3 for working memory showed an explanatory power of 30% of the variance by MCI-Pathological, PD-Parkinson, and PD-CFRS, $F(3,56) = 8.03$, $p<.001$.

Figure 8 presents unique and common effects in the sub-variables (age-adjusted values) for executive function using independent variables selected by relative importance analysis. As the results of commonality analysis within multiple regression, the variable for PD-Parkinson (U3: 52.0%) contributed the greatest unique effect to the prediction of inhibitory control, whereas the variable for MCI-pathological had the most prominent unique contribution to the predictor of cognitive flexibility (U1: 89.3%) and working memory (U1: 52.3%). The common effect between PD-Parkinson and MCI-Pathological explained the variance by a moderate amount in inhibitory control (C2: 16.5 %) and working memory (C1: 13%).

Table 4. *Regression results for variables as predictors of executive function (Park & Schott, 2022)*

Predictor (x)	R^2	R^2_{adj}	***B***	**Sig. of *B***	**Unique**	**Common**	**Total**	**% of R^2**
Model 1	.222	.180						
Constant			.293	<.001***				
MCI-Pathological			.155	.042*	.060	.029	.089	27.0
Fear of Falling			-.027	.053+	.054	-.044	.009	24.5
PD- Parkinson's p			.186	.005**	.115	-.003	.118	52.0
Model 2	.149	.104						
Constant			.766	<.02				
MCI-Pathological			.601	.004**	.134	-.006	.128	89.3
Fear of Falling			-.036	.324	.015	-.007	.008	10.0
Physical activity			-.000	.512	.006	.002	.009	4.40
Model 3	.301	.263						
Constant			.999	<.001***				
MCI-Pathological			.631	<.001***	.157	.058	.215	52.3
PD- Parkinson			.285	.065+	.044	.074	.118	14.7
PD-CFRS			.021	.203	.021	.039	.060	6.87

Note. Model 1: Inhibitory control; Model 2 Cognitive flexibility; Model 3: Working memory; Unique = unique effect; Common = Σ common effects; Total = Σ unique +common effects; % of R^2 = Total/R^2

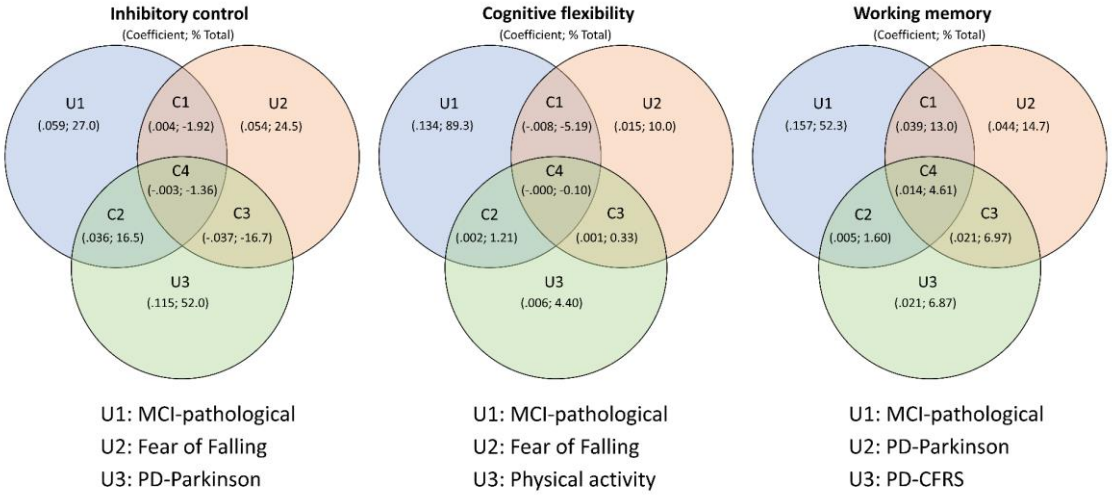


Figure 8. Commonality Diagram for three sub-variables for executive function (Park & Schott ,2022)

Detailed analysis for time spent inside each circle in dTMT-B

We most notably attempted to identify performance trends with the time spent in each circle during the dTMT-B. Figures 9 and 10 highlighted the individual data for time spent in each circle (Figure 9) and averaged data (Figure 10) by the PD and HC groups. As shown in Figure 10, the result of curve fitting using a quadratic polynomial showed an inverse U-curve for all groups, indicating that participants spent the longest time in the 8th circle. After that, their performance gradually improved again. The statistical analysis also demonstrated a significant effect over time calculated as the averaging time spent in each of the eight circles (1-D, 5-H, and 9-L). Besides, there were significant differences between clusters containing eight circles regardless of group, indicating longer spent time duration in circles 5-H than in other circles (1-D and 9-L). Significant differences were also found within the PD group in each cluster, suggesting that the PD-Pathological group spent much more time inside the circle than other groups (see A in Figure 10).

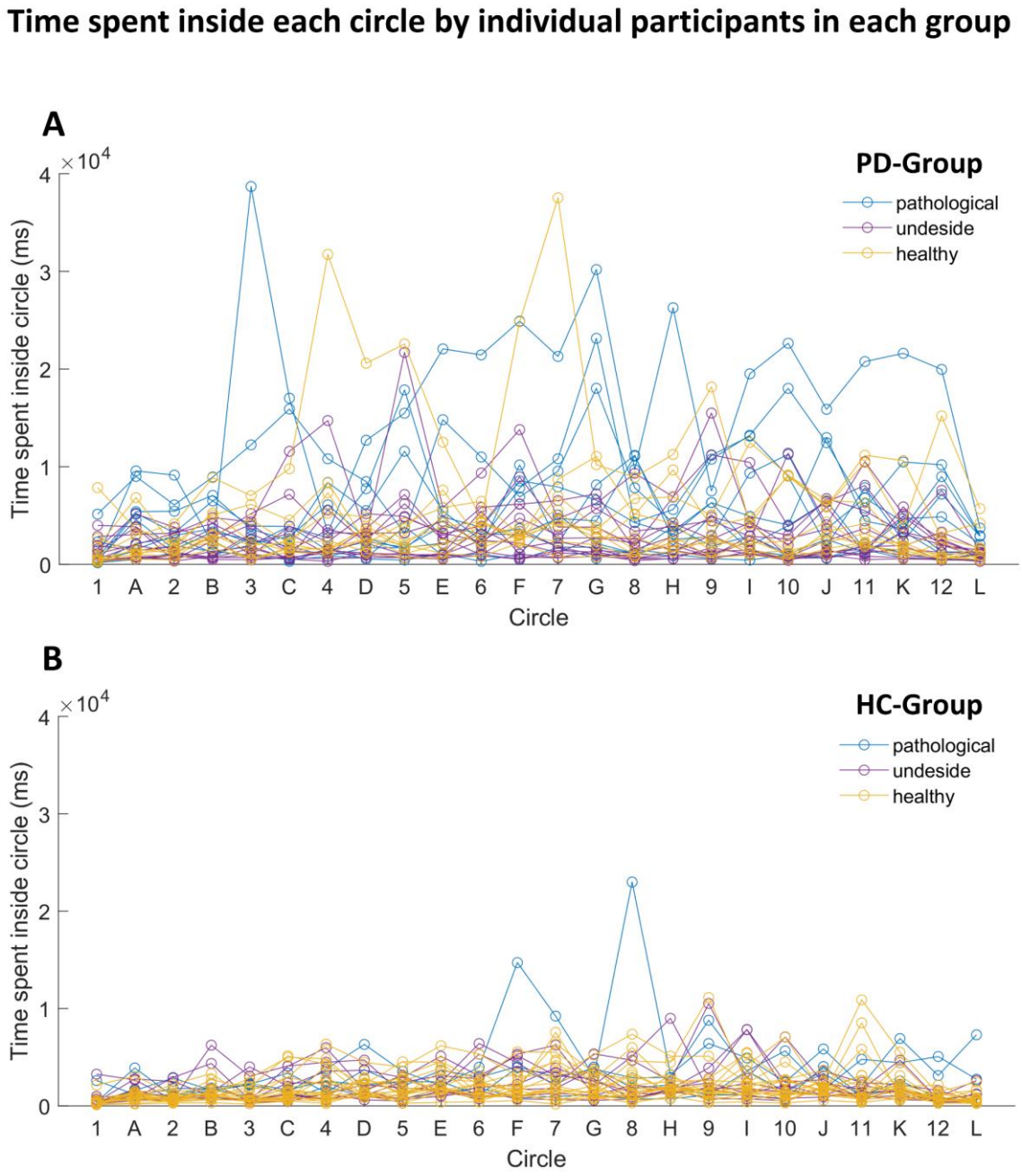


Figure 9. Time spent in each circle for individual data by groups (PD vs Healthy Controls) (Park & Schott ,2022)

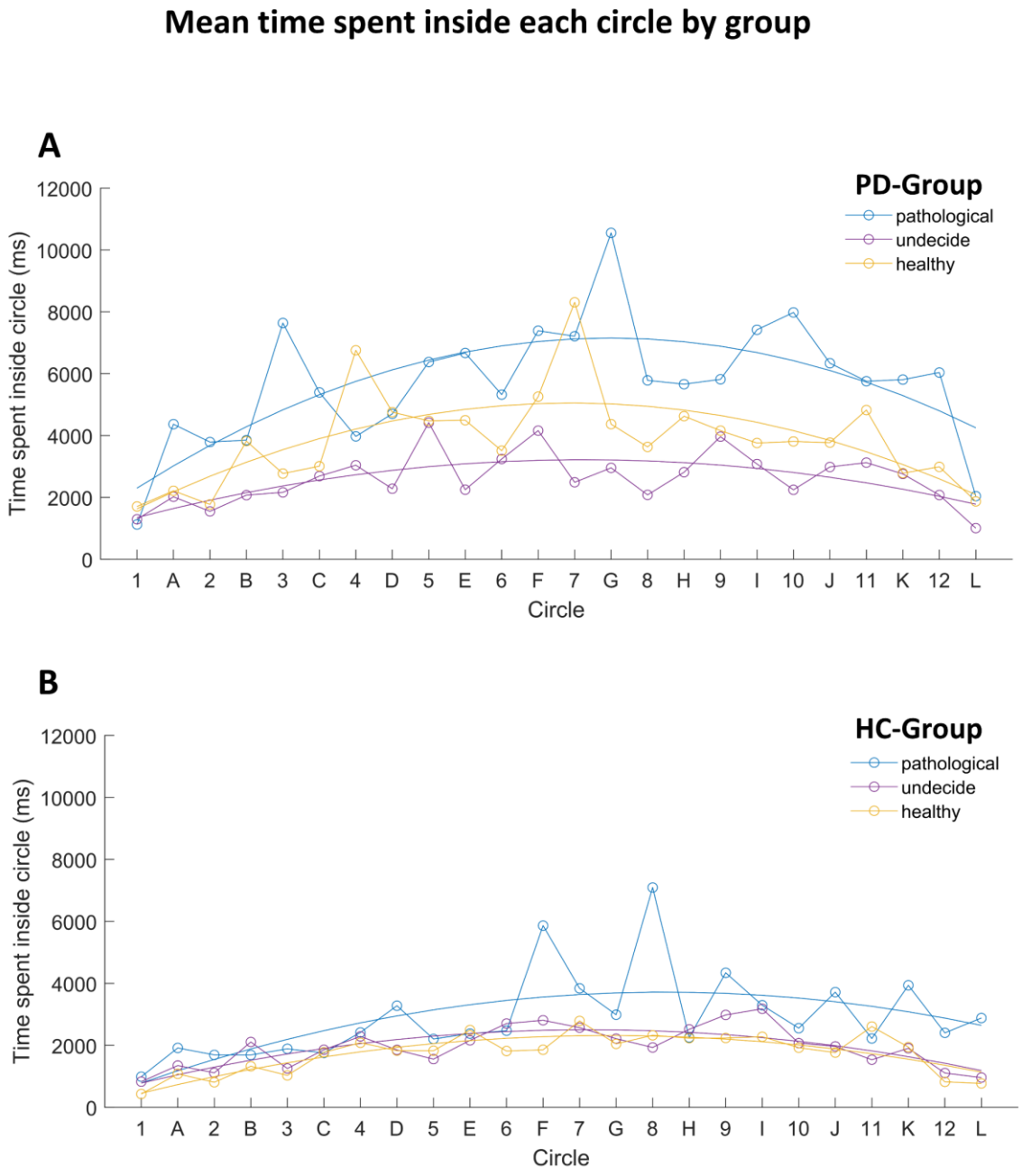


Figure 10. Time spent in each circle for averaged data by groups (Park & Schott ,2022)

3 Part II: Exercise intervention

Physical activity is one of the simplest chronic ways to maintain our brain health with long-term effects (Stillman et al., 2016). Acute exercise, defined as a single bout of physical activity (Basso & Suzuki, 2017), has also shown short-term positive effects on a variety of cognitive functions such as fluid (e.g., working memory, information processing speed, and cognitive flexibility) and crystallized intelligence (e.g., vocabulary, procedural, and declarative knowledge) (Chang et al., 2012; Lambourne & Tomporowski, 2010). However, while crystallized intelligence is generally maintained throughout life, fluid intelligence, including executive functions, declines with aging (Tucker-Drob et al., 2022). Above all, the meta-analysis by Chang et al. (2021) indicated that acute exercise positively affects executive function regardless of other mediators such as exercise intensity, duration, and fitness level. However, in order to elucidate the exercise-cognitive interaction, most studies mainly focus on the response to a given stimulus to investigate executive function (for a systematic review, see Herold et al., 2018). As mentioned in the introduction, cognitive control ability must be required under the cognitive load to control the stimuli perceived from our environment continuously. From this point of view, studies using ongoing cognitive tasks rather than responding to a given stimulus may be more targeted and presumably more sensitive in the detection of effects on the interaction between exercise and cognition. Here, the dTMT as an ongoing cognitive task can be a suitable alternative for investigating the relationship between exercise and cognition. In addition, compared with the existing paper pencil version, the accuracy of measurement sensitivity can be improved through digital assessment, and it may be used as a digital biomarker in the interaction between exercise and cognition.

Although exercise-induced increased cortical activation of PFC has been associated with improved cognitive abilities so far (Damrongthai et al., 2021; Hyodo et al., 2012; Kujach et al., 2018; Yanagisawa et al., 2010), task performance post-exercise was only conducted under a single condition, such as sitting. DT increased prefrontal activation compared to a single condition (for a systematic review, see Pelicioni et al., 2019). However, the effects of acute exercise on DT performance while walking have rarely been investigated. DT, including walking, can be more ecologically valid than a single task (Schott, 2015). Above all, it is

also imperative in our daily life to enhance and sustain DT performance while walking. In particular, this DT that occurred during walking using dTMT enables designing the experiment similar to everyday activities, such as writing a message on a mobile phone or internet searching with a tablet while walking. Also, whether the cognitive function improved by exercise will be enhanced or maintained even during the DT is unknown.

As a function of exercise, the regulation of cortical activation changes also depends on the exercise duration and intensity (for a systematic review, see Rooks et al., 2010). HIIE consists of multiple repetitions of high intensity and recovery intervals. The exercise duration can last from 10 seconds to 5 minutes with an intensity above the anaerobic threshold (90-100% of the maximum oxygen uptake, heart rate, and running speed). The recovery interval between high-intensity intervals can range from 45 seconds to 8 minutes at low intensity (Laursen & Jenkins, 2002). MCE is generally suggested as a habitual exercise (Haskell et al., 2007) that is performed continuously at a steady state for a duration (e.g., 20-60 minutes) while maintaining a certain level of moderate intensity (e.g., 55–69% maximum of heart rate or 40–59% of VO2max) (Keating et al., 2017). Among other things, HIIE produces similar benefits of metabolic and cardiovascular health more time-efficiently than MCE (Helgerud et al., 2007) while demonstrating continuously improved performance in cognitive function compared with MCE (Tsukamoto et al., 2016). However, studies on the immediate and sustained effects of acute exercise, especially HIIE, on neural correlates based on cognitive performance are lacking. Herold et al. (2018) also pointed this out in the systematic review. Exercise-induced alterations in cortical activation and maintenance of cognitive performance are essential to understanding the neural mechanisms leading to acute and chronic effects. In addition, acute exercise interventions have already been shown to improve positive mood states and alleviate negative moods (Yeung, 1996). A recent study found that just 10 minutes of moderate-intensity exercise can improve cognitive performance and positive mood (Damrongthai et al., 2021). There was a significant association between pleasure level, cognitive function, and enhanced cortical activation of the left dorsolateral prefrontal cortex, a critical brain area for inhibitory control and mood regulation (Damrongthai et al., 2021). Although these acute positive effects appear immediately after exercise, how long these positive effects last is also essential. Because these exercise interventions may contribute

to a healthy mood throughout the day post-exercise (Maroulakis & Zervas, 1993; Raglin & Morgan, 1987; Reed & Ones, 2006), acute exercise during a break between classes at school or a break at work should be considered an appropriate exercise intervention to maintain a positive mood and improve cognitive function.

The purpose of the present study of this part II was to investigate the neural correlates underpinning the acute effects of two types of exercise (HIIE vs. MCE) on fine motor-cognitive performance while walking. In addition, immediate and sustained effects were examined on its performance post-recovery. Before reporting the methods and results of the entire study, the following section will explain the mechanism of hemodynamic response to neural activity, the measurement principle of fNIRS, and preprocessing procedures of fNIRS data collected in the present study.

3.1 Functional Near-Infrared Spectroscopy (fNIRS)

fNIRS, a recently emerged non-invasive, safe, and portable optical neuroimaging technique, indirectly measures cortical activation through oxygenated (oxy-Hb) and deoxygenated hemoglobin (deoxy-Hb) in our brain. The elucidation of the mechanisms of hemodynamic and metabolic responses evoked by neural activation consists of two neural couplings (for detailed information in systematic reviews, see Herold et al., 2018, 2020). According to neurometabolic coupling, neural activity increases the oxygen metabolism needed to meet the energy demands of the neural tissue. Simultaneously, energy is generated by consuming oxygen, resulting in decreased oxy-Hb concentration and increased deoxy-Hb concentration (Liao et al., 2013; Pinti et al., 2018; Scholkmann et al., 2014). Conversely, in neurovascular coupling, local cortical hemodynamic responses are triggered by neural activity supply, cerebral blood flow, and volume to activated brain regions, concurrently leading to an increased local supply of oxygen. Consequently, this elevated local oxygen supply increases oxy-Hb and decreases deoxy-Hb (Fabiani et al., 2014; Herold, Gronwald, et al., 2020; Liao et al., 2013; Perrey, 2008). Based on these two neural coupling mechanisms, as a result, increased oxy-Hb, and decreased deoxy-Hb can be observed using fNIRS, and this process is presented in (a) of Figure 11.

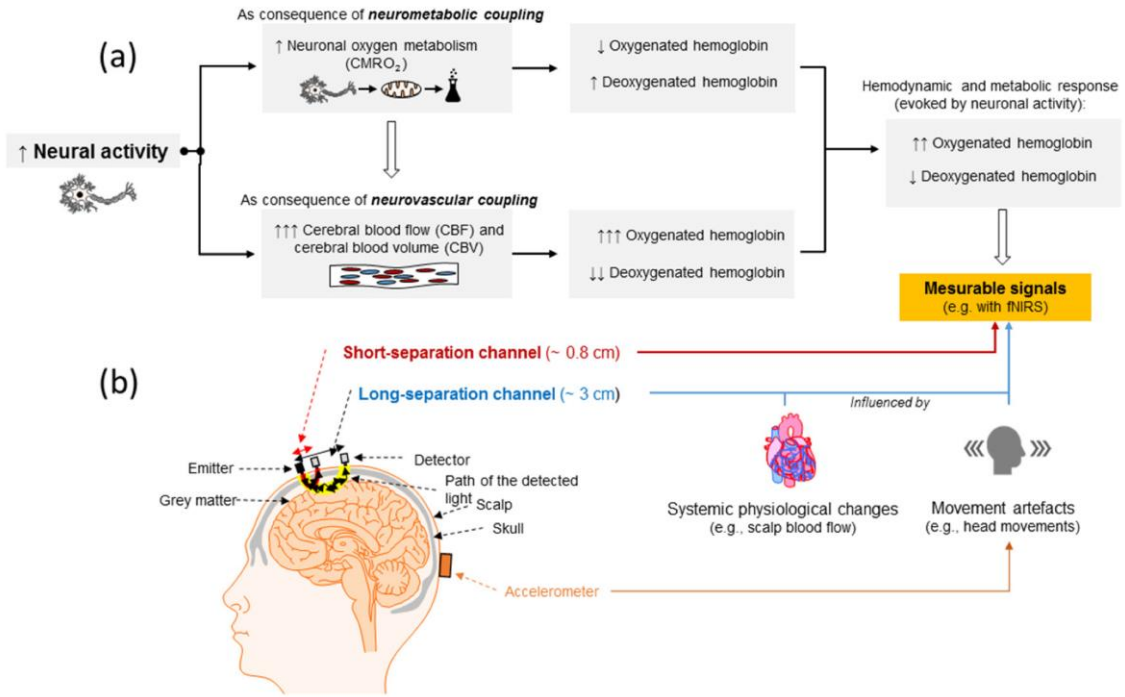


Figure 11. (a) two neural couplings for hemodynamic and metabolic response to neural activity. (b) the measurement principle for short- and long-separation channels of fNIRS; CMRO2: cerebral metabolic rate of oxygen; ↑: increase; ↓: decrease (Herold et al., 2020).

fNIRS measures brain activity by transmitting the near-infrared (NIR) light spectrum. Here, LED photons are attached to the skull to emit different NIR spectra / wavelengths (emitter/source). Then the emitted light reaches the brain's cortex across the scalp, where scattering and absorption of the light occurs, while another photon (detector) receives the amount of light and is recorded. The light must pass through various layers, such as the skin, skull, or cerebrospinal fluid composed of hemoglobin, lipids, melanin, cytochrome-c-oxidase, and water, while reaching the cortex (Pinti et al., 2018). The NIR spectral range is about 650 to 950 nm (optical window). This light can propagate relatively deep, primarily into biological tissue, whereby water, hemoglobin, collagen, and proteins only absorb weak NIR light (Scholkmann et al., 2014). Among them, hemoglobin is the most dominant and physiologically dependent absorption chromophore within the optical window. Each photon can measure oxy- and deoxy-Hb changes with different absorbing properties using different wavelengths (Pinti et al., 2018). For this reason, the more purplish oxy-Hb absorbs wavelengths above 800 nm (arterial blood, 98% saturation). In contrast, the reddish deoxy-Hb absorbs wavelengths below 800 nm (venous blood, 75% saturation) (Pinti et al., 2018). Local changes in light absorption

at two different wavelengths between source and detector (e.g., S-D, Source 1 – Detector 1, called Channel) enable quantifying increased or decreased concentrations of oxy- and deoxy-Hb in the local brain area occurred by neural activity via a modified Beer-Lambert law (Bunce et al., 2006; Pinti et al., 2018). Furthermore, the setting of the proper distance between the source and detector plays an essential role in the measurement depth through which light to the cortex is transmitted. Typically, a source-detector separation of 3.0 cm is used, as shown in (B) of Figure 11. However, while measuring data, this long separation is vulnerable to systemic physiological factors (e.g., heart rate, respiration, scalp blood flow) and motion artifacts (e.g., head movement, walking, or running). For this reason, appropriate filters should be applied to remove any physiological noise or motion artifacts (Barker et al., 2016; Herold et al., 2018; Nguyen et al., 2018; Vitorio et al., 2017; Zhang et al., 2009). Recently, to address these issues, at least systemic physiological changes can be corrected using a short separation channel regression (typically < 1.0 cm, see (B) in Figure 11).

While the emitted light is transmitted to the detector, it undergoes complete absorption or scattering in neural tissue. In this case, the distribution of emitted light leads to light attenuation. Through this process, the concentration of hemoglobin in oxy- and deoxy-Hb is calculated using various factors present in Figure 12 (A: light attenuation, or ΔA(λ): changes in light attenuation at a specific wavelength (λ); IIn: absolute intensity of emitted light; IOut: absolute intensity of recorded light; ε(λ): the extinction coefficient of the chromophore at a specific wavelength (λ); Δc: changes in chromophore concentration; d: distance between source and detector; DPF(λ): differential path length factor for a specific wavelength (λ); g(λ): scattering at a particular wavelength (λ)).

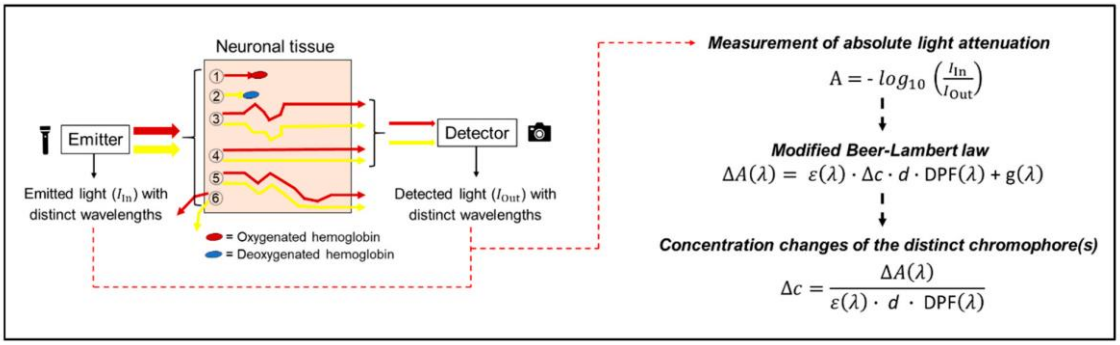


Figure 12. Light propagation through the neuronal tissue between the emitter and detector on the left, and the formula for quantifying concentration changes on the right (Herold et al., 2018).

The concentration value calculated by this preprocessing on the performance of a specific task is statistically analyzed using the value of the mean, median, slope, peak, the area under the curve, or general linear models (GLM) (for reviews, see Herold et al., 2018; Menant et al., 2020; Vitorio et al., 2017).

In the present study for Part II, we used a continuous-wave fNIRS device with multi-channel (NIRSport, NIRx Medical Technologies LLC; 16 sources and 16 detectors; short-separation not configured) to measure changes in cortical activation of the oxy- and deoxy-Hb on the frontopolar area (FPA), dorsolateral prefrontal cortex (DLPFC), and motor cortex (M1) across the right and left brain regions. A probe configuration setup of 32 photons was separated by approximately 3 cm between (long-separation channels) the source and detector to effectively measure the depth sensitivity of cortical activity and high signal quality (Herold et al., 2018). To allow for inter-experimental measurement consistency between participants and sessions, the center of the NIRScaps for photon placement (EASYCAP GmbH, Herrsching, Germany) was marked referencing to international 10–20 system above the vertex (Cz) consisting of the midpoint between nasion and inion, and the left and right preauricular points.

The fNIRS device's data sampling rate, including two infrared wavelengths of light (760 and 850 nm), is 7.81 Hz (Pereira et al., 2007). This device measures oxy- and deoxy-Hb by using a continuous wave system, maintaining the emission of infrared light at a constant intensity and frequency (Scholkmann et al., 2014). The data on hemoglobin concentration were collected by the NIRS Star 14 Software (NIRSport, NIRx Medical Technologies LLC) implemented on the tablet (Microsoft Surface Pro2 128 GB). The task's onset and offset triggers were configured with NIRS Stim Software (NIRSport, NIRx Medical Technologies LLC).

For analyzing neural data in the following two manuscripts, we used the NIRS toolbox (Santosa et al., 2018), a MATLAB-based open-source package (Matlab 2021a; MathWorks, Natick, MA, USA). As the first step in data preprocessing, the relative coefficient of variation (CV in %) was determined with non-filtered raw data to survey the neural data quality as a signal-to-noise ratio. This data quality method is widely used for multi-channel fNIRS measurement (Schmitz et al., 2005;

Schneider et al., 2011). CVs greater than 15% for each channel, calculated for a given whole session duration for the experiment, were rejected from the next preprocessing step through statistical analysis (Piper et al., 2014). After that, a low-pass filter with 0.2 Hz (Scholkmann et al., 2014) was used for subsequent data processing, except for removed channels to eliminate physiological components (e.g., respiration: 0.2 to 0.4 Hz, heartbeats: 0.5 to 2.0 Hz) (Herold et al., 2017; Scholkmann et al., 2014; Tachtsidis & Scholkmann, 2016). Then the low-pass filtered data was converted to optical density. Subsequently, these converted data were corrected for the motion artifacts by the TDDR filter (Temporal Derivative Distribution Repair) using an iterative re-weighting approach to detecting outlier variation during the performing task (Fishburn et al., 2019). These preprocessed data of optical densities were finally computed to oxy- and deoxy-Hb concentrations using modified Beer-Lambert law (Santosa et al., 2018). For the statistical analysis, regions of interest (ROI) were then calculated to distinguish between specific brain areas while averaging a group of each channel between source and detector for six regions: channels with S3-D2, S3-D5 for the left frontopolar area; l-FPA, channels with S6-D5, S6-D7 for the right frontopolar area; r-FPA, channels with S1-D1, S1-D2, S1-D3, S2-D2, S4-D3, S4-D4 for the left dorsolateral prefrontal cortex; l-DLPFC, channels with S5-D6, S7-D7, S8-D7, S8-D8 for the dorsolateral prefrontal cortex; r-DLPFC, all channels above whole left motor cortex for the left motor area; l-M, all channels above whole right motor cortex for the right motor area; r-M1 (see Figure 13). These averaged ROI data were used for the further statistical analysis in the following studies of Part II.

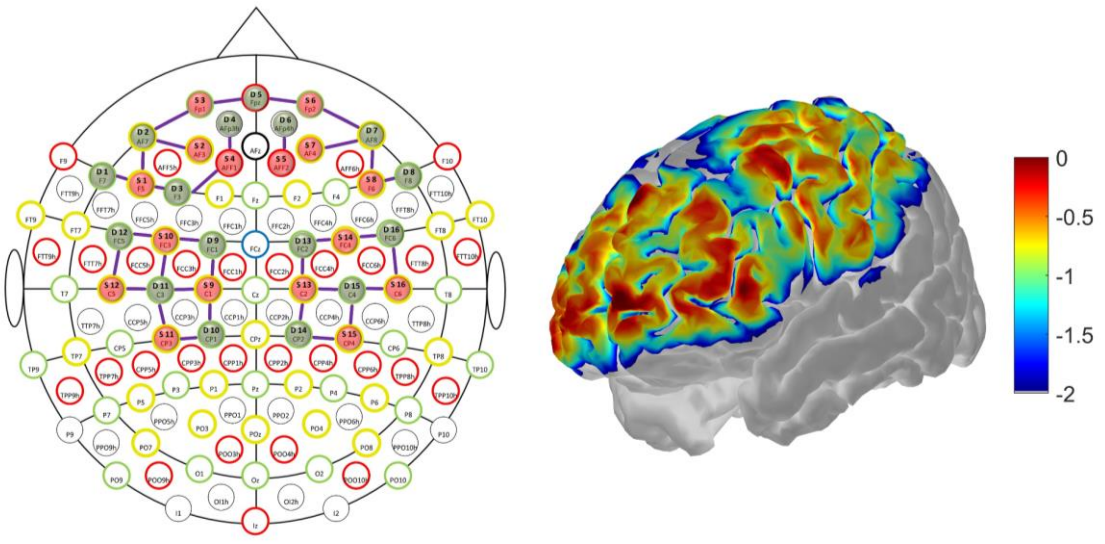


Figure 13. Configuration set up with 16/16 sources/detectors resulting in 34 channels over the prefrontal and motor cortex(Park & Schott, 2022). Sensitivity profile in $\log_{10}$ (mm^{-1}). Visualization using Atlasviewer (Aasted et al., 2015)

3.2 Purpose, procedure, and analysis of Part II (Exercise intervention)

The purpose of the following two studies was to investigate the neural correlates underpinning the acute effects of two different exercise protocols (HIIE vs. MCE) on fine motor-cognitive performance while sitting and walking (dual-task) in post-exercise and -recovery. Due to the extensive data collection in Part II, the study was divided into two sub-studies. The focus of the first sub-study (manuscript 3) here was to investigate the acute effects of two types of exercise on hemodynamic response during dTMT while walking with increasing cognitive load. The focus of the second sub-study (manuscript 4) was to examine immediate and sustained effects only during dTMT-B in post-exercise and -recovery after a 10-minute rest. Among the task conditions of the dTMT, the dTMT-B requires the highest task demands involved in complex cognitive processes, such as inhibition, cognitive flexibility, and working memory. Thus, this task condition serves as the primary cognitive performance on the behavioral level in manuscript 4.

A total of 32 healthy young adults (age-ranged between 19 and 33, 7 female) with at least fair to good cardiorespiratory fitness (VO_2max, 43.5 mL/kg/min or greater for males, 33.6 mL/kg/min or greater for females, American College of Sports Medicine, 2013) were enrolled in this study. This study was designed as a randomized controlled experimental design with repeated measures in a two-armed parallel group (between subjects). Figure 14 shows the experimental procedures of the whole investigation (for more detailed experimental procedures, see Park et al., 2021; Park & Schott, 2022). The first day is composed of two sessions of performing dTMT while sitting (see (1) and (2) of Figure 14). The second day consists of three sessions: two sessions in pre-and post-exercise while walking on a treadmill at a speed of 5 km/h (see (3) and (4) of Figure 14) and the third session performing dTMT in a seated position in post-recovery (see (5) of Figure 14).

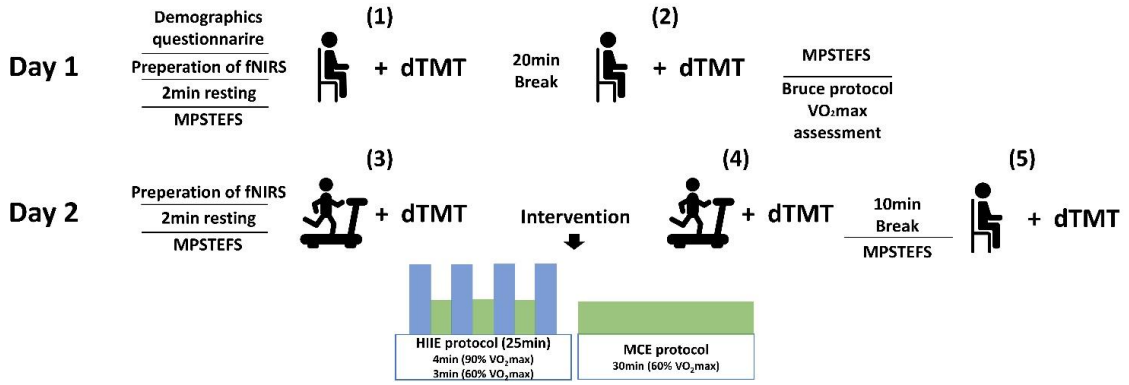


Figure 14. Experimental design and testing procedures (Park and Schott, 2022).

In addition, Figure 15 shows an example of performing the experimental methods.

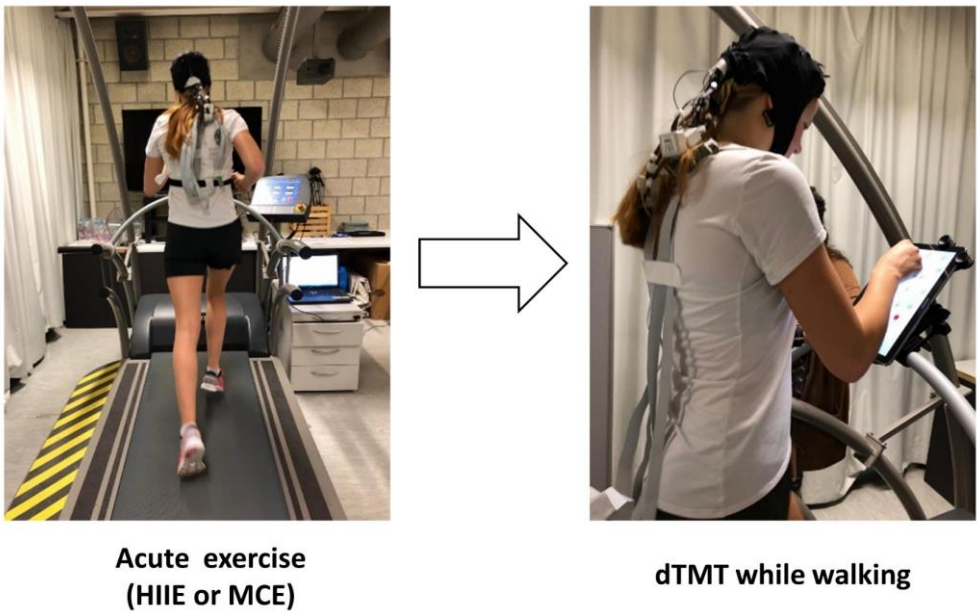


Figure 15. One example for a participant running on the treadmill (left) and performing dTMT while walking on the treadmill (right) (mod. graphical abstract from Park et al., 2022).

As mentioned earlier, HIIE and MCE were used as exercise interventions. HIIE consists of four high-intensity intervals with 90% of the VO_2max for 4 minutes and three relief intervals with 60% of the VO_2max for 3 minutes. The total duration of HIIE was 25 minutes. For MCE, the intensity was consistently composed of 60% of the VO_2max for 30 minutes. Concerning a subtle difference in the whole exercise duration between HIIE and MCE, the duration of the MCE protocol was determined to be the exercise duration required to achieve the same total calorie consumption as that of the HIIE (Magalhães et al., 2020; Tsukamoto et al., 2016). Exercise intensity was determined according to each participant's

cardiorespiratory fitness level (VO_2max) using the Bruce (1972) protocol (for more detailed information about exercise intervention, see Park et al., 2021; Park & Schott, 2022).

The dTMT was used as a cognitive test in the following studies to examine the effect of exercise on executive function. Each task of dTMT was performed in a random order for 30 seconds, followed by resting without a task for 30 seconds (see Figure 16). Depending on each session, this proceeded either while sitting or walking (see Figure 14). The task order of the dTMT conditions (dTMT-M, -A, and -B) with a total of 9 minutes (three times per each condition, including resting between task conditions) was pseudo-randomly designed so that the same condition never appeared twice (for more detailed information about experimental measure of dTMT, see Park et al., 2021; Park & Schott, 2022). Then, additional variables measured by the dTMT (number of connected circles, time spent / speed between circles [inhibitory control], time spent inside circle [working memory]) were utilized for the statistical analysis in the subsequent studies (for detailed information about additional variables of dTMT, see index 4.1).

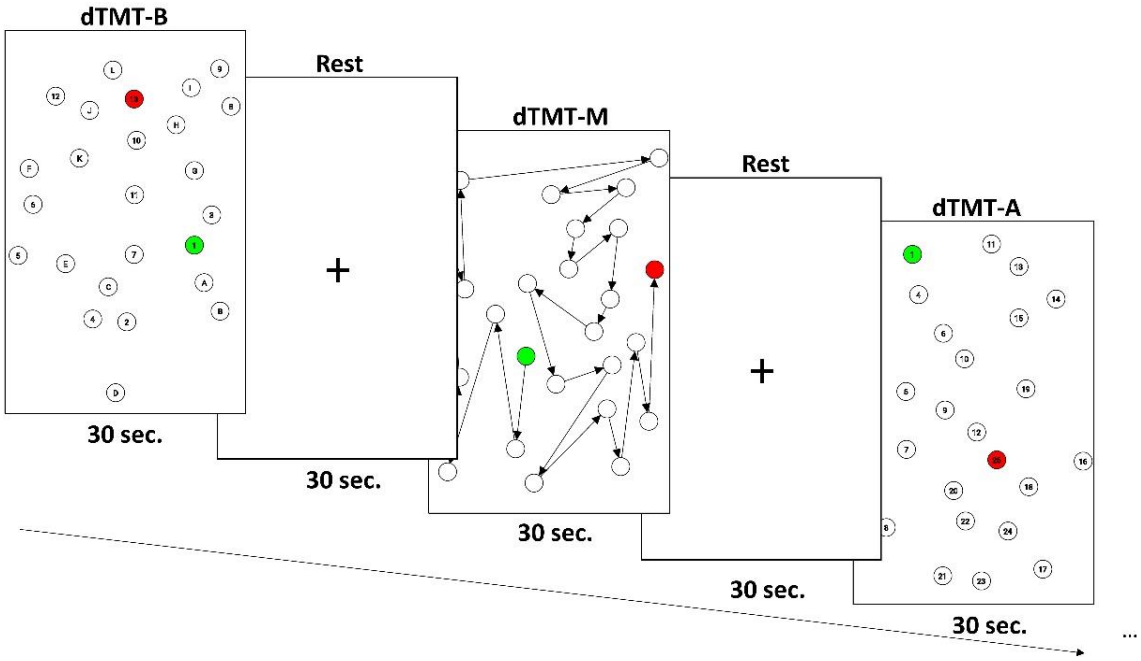


Figure 16. The design of the experimental task for dTMT (Park and Schott, 2022).

To date, various analysis methods such as mean, slope, or GLM have been used for fNIRS statistical analysis. In this regard, there is still no golden standard for fNIRS statistical analysis. Therefore, each manuscript (index 3.3 and 3.4) in

Part II applied different statistical analyses and suggested several fNIRS analysis alternatives. In manuscript 3 of Part II, we averaged two-time windows between 6 and 13 sec (T1) and 25 and 32 sec (T2) for each ROI to observe changes in hemodynamic response while performing the task for 30 seconds. Generally, the hemodynamic response is delayed about 6 seconds after beginning a cognitive task (Herold et al., 2018; Pinti et al., 2020) and also due to the respiratory system during exercise (Seidel et al., 2019). In consideration of this, the time window T1 was determined. We selected the second time window, T2, under the assumption that the concentration peaks at the end of the task (Pinti et al., 2020). In addition, Mandrick et al. (2013) pointed out that the slope method seems appropriate for observing concentration changes in hemodynamic response with the increasing cognitive workload. Therefore, in manuscript 4 of Part II, mean and slope values between 0 and 32 sec during performing tasks were used for statistical analysis. The reason for the time selection of 32 sec was that concentration in hemodynamic response lasts for a few seconds after finishing the task after reaching maximum concentration.

3.3 Results of manuscript 3 (Park et al., 2021)

Behavioral data

For the behavioral data, 2 × 2 × 2 ANOVAs with repeated measurements were conducted with the within-subjects factors "exercise" (pre-and post-exercise) and "dTMT condition" (dTMT-M, -A, and -B) and the between-subjects factor "exercise group" (HIIE and MCE). For all three variables measured by the dTMT (number of connected circles, time spent inside and between circles), there were significant effects of exercise and the dTMT conditions. In contrast, we did not find any interaction effect between group and exercise and/or dTMT condition. Overall, exercise positively affected cognitive performance while indicating significant differences between task conditions, regardless of group. In the present thesis, Figure 17 presents only the variable for the number of connected circles as a primary indicator for cognitive performance in each dTMT condition (for more information about results on the behavioral level, see Park et al., 2021).

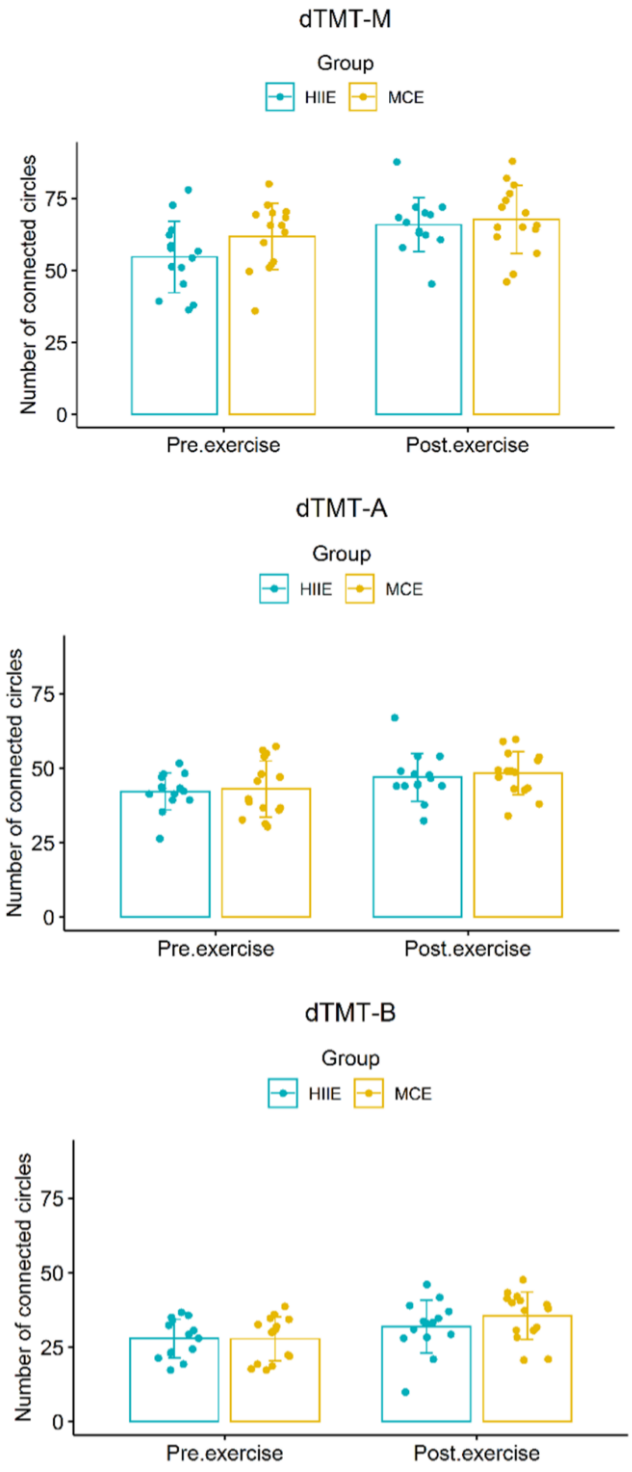


Figure 17. Bar plots with scatter for the variable Number of connected circles in each condition by exercise group.

Neural data

For the statistical analysis of neural data in pre-exercise (while walking), the MANOVA for oxy-Hb over T1 and T2 in each task condition and all ROIs revealed no significant differences between groups in pre-exercise. Figure 18 shows the

change in oxy-Hb time course with T1 and T2 in each ROI. Afterward, the time course of hemodynamic responses (T1 and T2) was analyzed as a function of dTMT conditions in each ROI. The ANOVA with repeated measurement (Time course (2) × task condition (3) × group (2)) for each ROI demonstrated a significant effect of the time course (T1 to T2) in all ROIs. In addition, we observed a significant interaction effect between time course and task condition only in the frontal lobe (for more information about results on the neural level, see Park et al., 2021). In summary, over time, the concentration of oxy-Hb increased while performing the dTMT during walking in pre-exercise, and the task-dependent changes of T2 are localized in the frontal lobe, indicating higher cortical activation in the dTMT-B than in other task conditions.

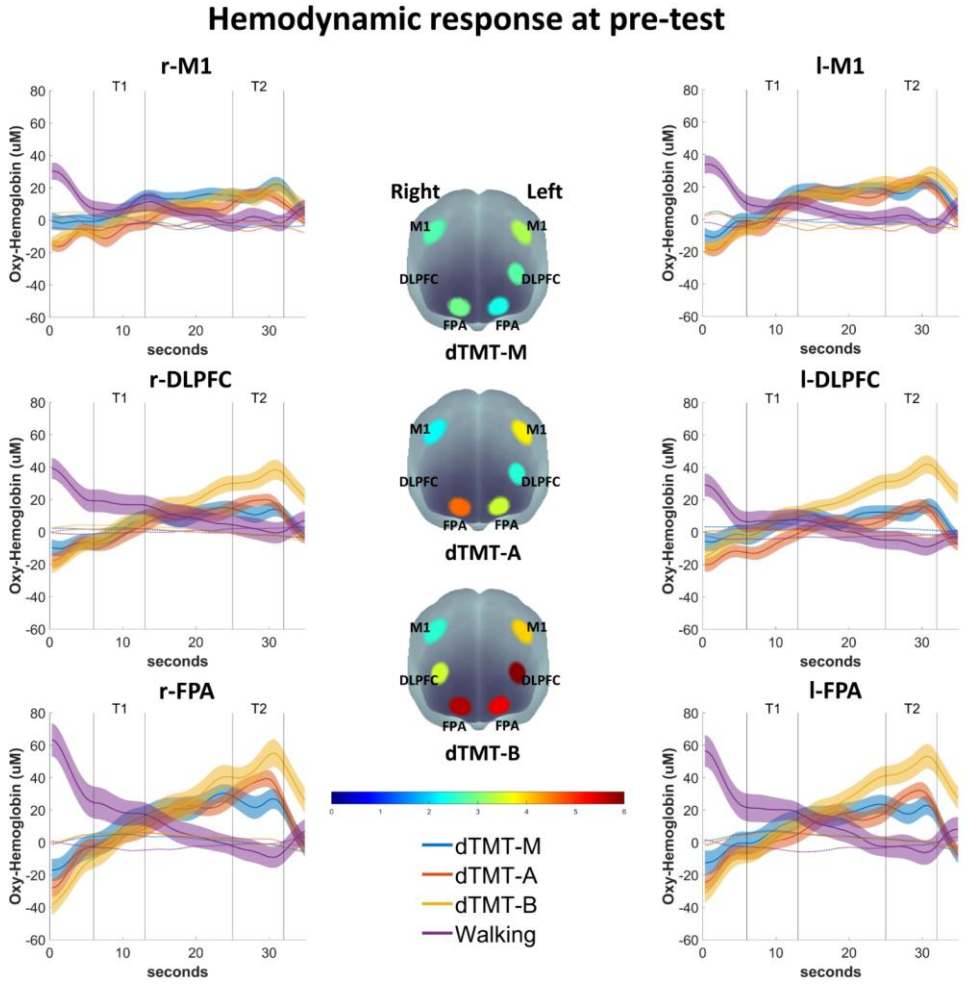
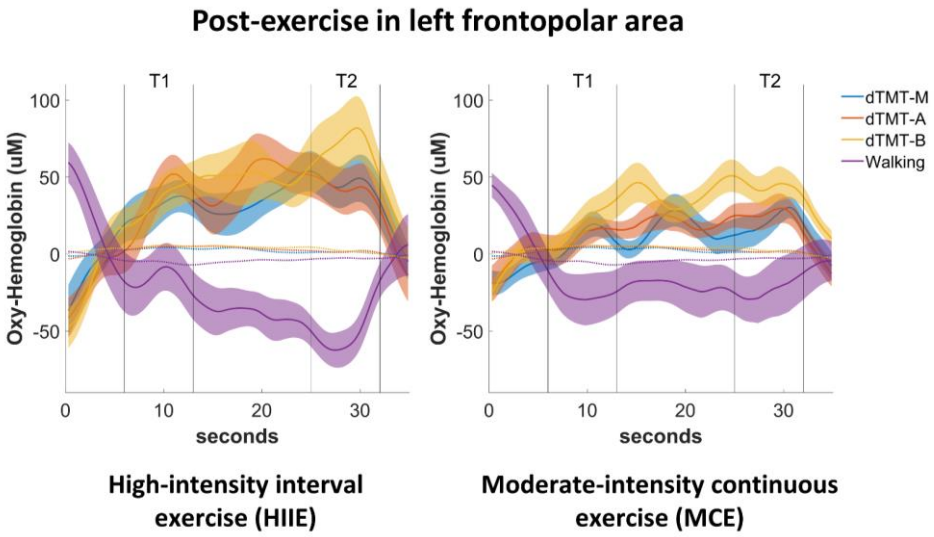


Figure 18. Change in hemodynamic response in pre-exercise while performing dTMT during walking with T1 and T2 (Park et al., 2021).

For the changes of hemodynamic response between pre-and post-exercise, we performed ROI-wise analysis separately by task conditions using 2 × 2 × 2 ANCOVAs with repeated measures, adjusting the change rate of each dTMT performance, with within-subjects factors, "exercise" (pre-and post-exercise) and "time course" (T1 and T2), and with between-subjects factor, "group" (HIIE and MCE). While observing that exercise had an effect of medium or larger size in all areas measured for each task, the interaction between exercise and group was limited to the frontal lobe except for the M1, resulting in higher oxy-Hb induced by HIIE. In all conditions of dTMT, we found interactions with moderate effect size between exercise, time course, and groups only in l-FPA (see Figure 19). To sum up, although increasing oxy-Hb concentrations between pre- and post-exercise regardless of group, HIIE induced higher oxy-Hb at the end of task performance (see Post.T2 in the bottom of Figure 19) in l-FPA than MCE across all dTMT conditions. In addition, through the McNemar test, a robust nonparametric statistical procedure that assesses the correspondence between two incidences (Siegel & Castellan, 1988), we found that HIIE-induced increased cortical activation was associated with positive changes in cognitive performance for almost all ROIs.



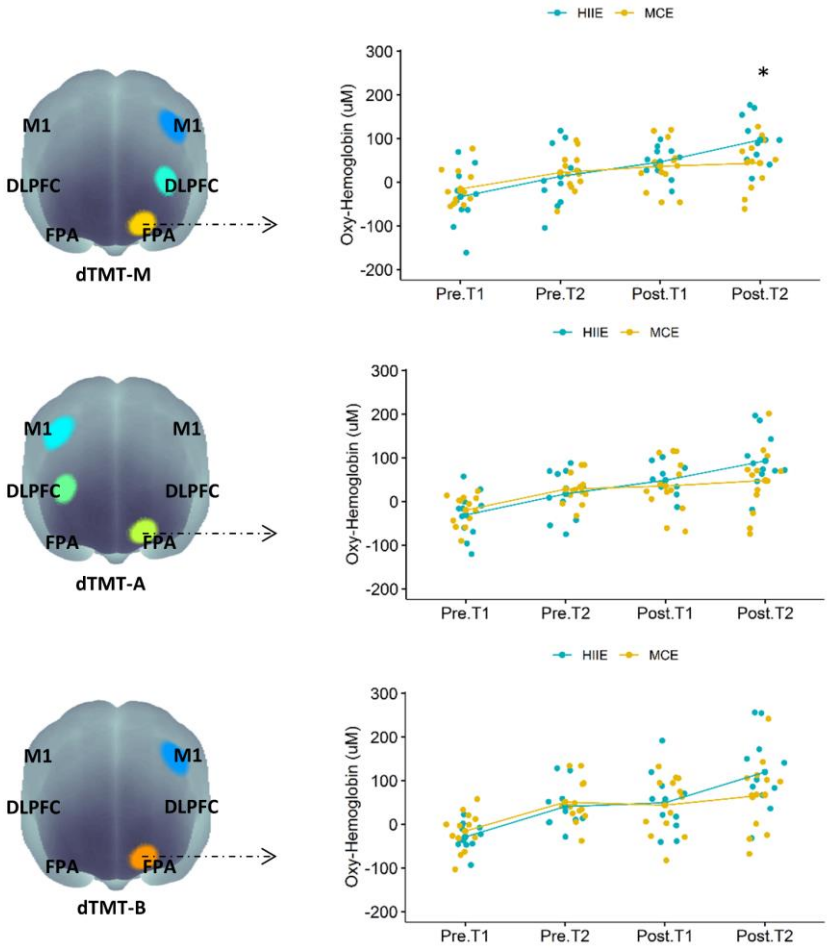


Figure 19. Time course of oxy-Hb for all task conditions in post-exercise in the left frontopolar area by exercise group (the top of Figure); F-map of oxy-Hb changes reflecting the interaction between exercise, time course, and group for each dTMT condition, and mean value in pre- and post-exercise with T1 and T2 in both groups (the bottom of Figure) (mod. graphical abstract from Park et al., 2021).

3.4 Results of manuscript 4 (Park and Schott, 2022)

Behavioral data

To examine the behavioral change in cognitive performance over sessions, 5 × 2 ANOVAs with repeated measurements for the dependent variables of dTMT-B (number of connected circles, time spent inside circle, and speed between circles) were conducted with the within-subjects factors "session" (from first to the last session) and with the between-subjects factor "group" (HIIE and MCE). We found significant session effects for all three variables ($p < .001$), whereas no interaction effects were observed between the session and group. Overall, the performance of the main task (number of connected circles, see Figure 20) enhanced significantly

in both groups in post-exercise and was maintained in post-recovery (Park & Schott, 2022).

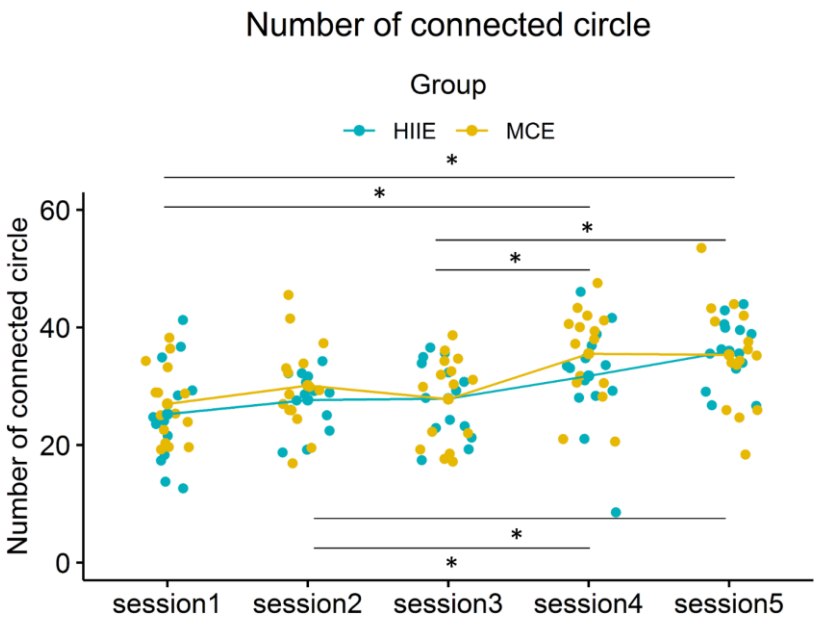


Figure 20. Behavioral data for the number of connected circles from dTMT-B (Park & Schott, 2022)

Neuronal data

On the neural data over sessions, we also performed 5 × 2 ANCOVAs with repeated measurements for the value of mean and slope of the hemodynamic response in each ROI with the within-subjects factors "session" (from first to the last session) and with the between-subjects factor "group" (HIIE and MCE), adjusted for the Δ of the first and last sessions for dTMT performance. The slope value demonstrated significant session effects for all ROIs, whereas the mean value indicated effects with a medium effect size (above 0.06) in all ROIs except for the l-FPA. Most notably, there were interaction effects with a medium effect size only in l-M1 for slope and mean values (see Figure 21 A, only for slope value), resulting in a significant difference with a medium effect size between groups for slope value in post-exercise while walking (p = .073, d = .694) and post-recovery while sitting (p = .027, d = .871), and also a significant difference between groups for mean value in post-exercise (p = .024, d = .886) and post-recovery (p = .026, d = .873) (see Figure 21 B and C, Park & Schott, 2022).

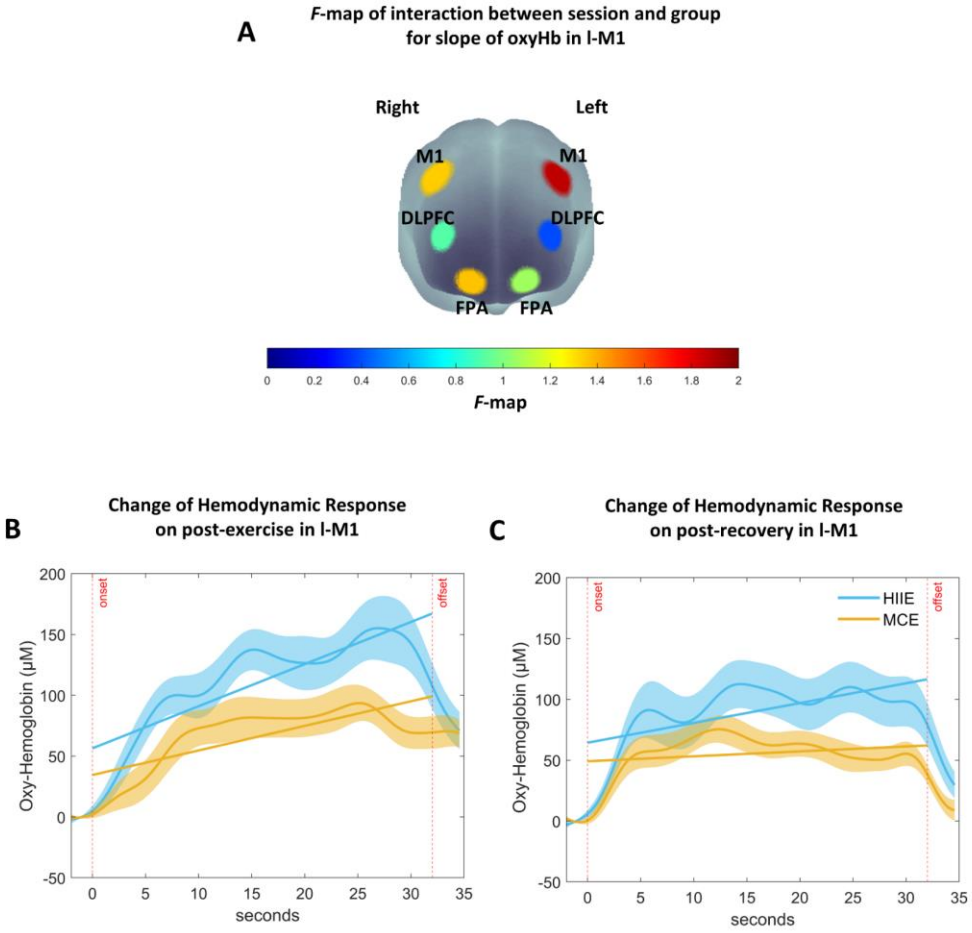


Figure 21. (A) F-map of oxy-Hb signal changes of slope reflecting the interaction between session and group for the dTMT-B performance. Among the six regions of interest, an interaction with a medium effect size can be seen in the left motor cortex (l-M1) (FDR-corrected). F-value is displayed according to color bars. (B) Time course of oxy-Hb changes in response to dTMT-B performance in the l-M1 post-exercise while walking between HIIE and MCE. (C) Time course of oxy-Hb changes in response to dTMT-B performance in the l-M1 post-recovery while sitting between HIIE and MCE. Error bars indicate standard errors (mod. from Park & Schott, 2022).

4 General Discussion

4.1 Interaction between early detection, exercise, and neural mechanism

The present thesis can be divided into two main areas. In the first area, early detection plays an essential role in identifying a fine motor and cognitive problem using digital assessment, the dTMT. In the second area, an exercise intervention, the effects of acute exercise on overall cognitive performance, which type of exercise positively affects our brain health, is of great importance. Figure 22 shows a comprehensive concept explaining the interaction between assessment and exercise intervention based on neural mechanisms. This concept suggests an interaction between the assessment of fine motor and cognitive impairment using dTMT, and exercise intervention to prevent our brain health. At the same time, task- or exercise-related neural correlates support the neural mechanism for these two main areas. Therefore, the first area of the comprehensive concept (assessment) contains manuscripts 1 and 2, and the second area includes manuscripts 3 and 4 (exercise intervention and its neural mechanism).

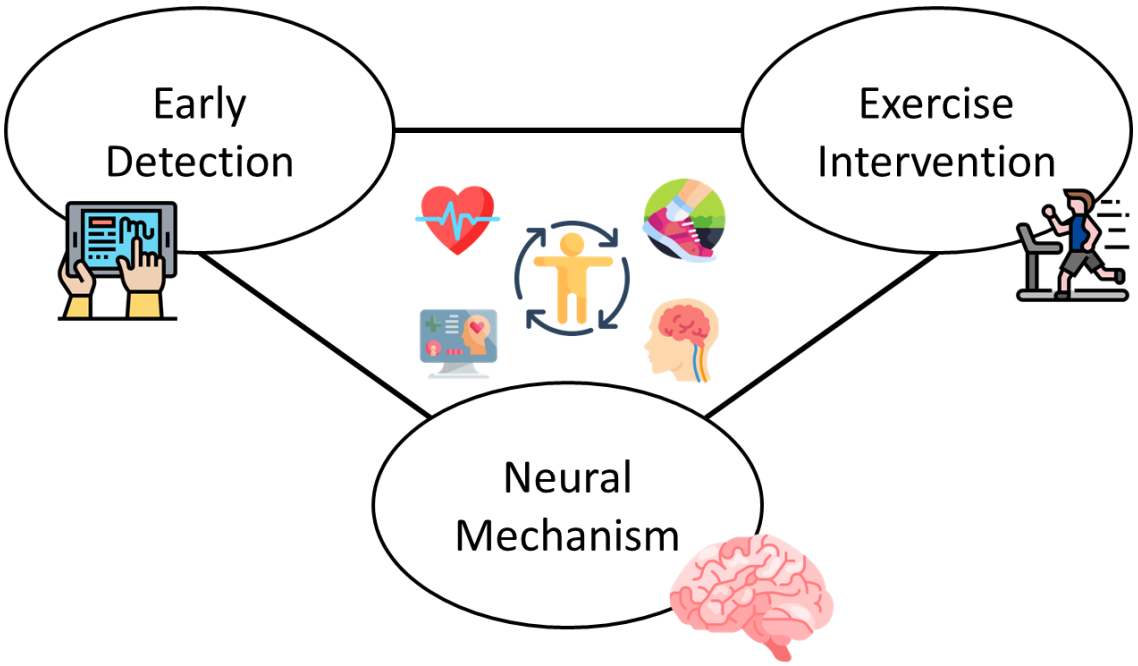


Figure 22. Comprehensive concept between early detection and exercise intervention, supported by neural mechanism.

4.2 Assessment in the comprehensive concept

In the first area of the comprehensive concept, we investigated the reliability and validity of our digital version of the TMT compared to the original paper-pencil version (manuscript 1). When comparing the completion time as the primary indicator of the paper-pencil version with the digital version, faster task performance in the ppTMT could be observed than for the dTMT, consistent with several other studies (Heimann-Steinert et al., 2021; Latendorf et al., 2021). On the other hand, digitized cognitive assessments can lead to poor/ worse performance than the paper version (Heimann-Steinert et al., 2021). This difference may depend on familiarity with technology such as a digital pen or touch screen. However, while finding a high correlation for each condition between the two versions of the TMT, the similarity between the ppTMT and dTMT can be seen by the interaction between task conditions (TMT-M, -A, and -B) and the two versions of the TMT (digital and paper-pencil version). Given these similarities, a digital version with many advantages (e.g., ease of administration, avoiding the inevitable variability, accurate measures, and observing changes in performance in a long-term period) seems to be of considerable value.

In manuscript 2, a more detailed analysis using the digital version with these advantages may enable us to detect PD's fine motor and cognitive impairments. First, using the dTMT, we observed clearly expressed differences in task completion time between groups according to cognitive ability. This result is not surprising. Although numerous studies have already identified that various cognitive functions, such as inhibitory control, working memory, set-switching, and cognitive flexibility, are involved in the TMT-B (Arbuthnott & Frank, 2000; Gaudino et al., 1995; Kortte et al., 2002a; Salthouse, 2011; Sánchez-Cubillo et al., 2009), it is still not enough to explain these complex cognitive abilities in terms of values of completion time, such as ratios (B/A) or differences (B-A). Therefore, we attempted to decompose these into three main executive functions using additional measured variables by the dTMT. As can be seen from the results, PD as a predictor made an enormous unique contribution to inhibitory control, while MCI-Pathological to working memory and cognitive flexibility.

The frontal lobe, particularly the inferior frontal and anterior cingulate gyrus of the right hemisphere, plays an essential role in inhibitory control, a known

problem in patients with PD (Garavan et al., 1999; Konishi et al., 1999; Rubia et al., 2001). During fine motor control, these problems seem to be accompanied by symptoms such as an increased number/duration of out-of-circle pauses or increased time spent between circles. For this reason, these integrated variables for inhibitory control can contribute to identifying fine motor control problems in patients with Parkinson's disease. Generally, performing alternating tasks between two given simultaneous situations plays a critical role in cognitive flexibility. In this regard, cognitive flexibility is considered, for instance, as the ability to switch tasks from number to alphabet or vice versa during dTMT. We thus used the absolute value calculated by subtracting between time spent inside circles of numbers and alphabets. The MCI-Pathological group had a fundamental contribution as a predictor for this dependent variable, which seems to be a natural consequence of impaired cognitive flexibility in this group (Klotzbier & Schott, 2017; Sacco et al., 2019).

Further, working memory appears to be more sensitive to the MCI-Pathological group. Still, PD can also confirm a moderate contribution, resulting in a moderately common effect between the two groups. Also, Parkinson's disease can be accompanied by several other complex cognitive problems (Aarsland et al., 2009; Caviness et al., 2007; Dalrymple-Alford et al., 2010; Hoops et al., 2009; Janvin et al., 2006). In particular, problems with fine motor control due to tremors during the dTMT may appear in variables such as the number/duration of lifts, consequently negatively contributing to working memory in the PD group. Since the time spent inside circles also had a significant difference in each MCI-group of PD and MCI, it seems to be the most critical and sensitive variable for identifying the decline of working memory for both groups. All these decomposed sub-variables collected by dTMT may positively contribute to explaining complex cognitive functions.

We further analyzed more details regarding the variable for time spent in each circle during dTMT-B. Here, for the first time, we identified the trend for performance change during the task. An inverted U-shaped curve could be observed overall by a quadratic polynomial curve. This tendency was an exciting result because we initially expected that the performance would deteriorate due to the number and alphabet combinations that become more complex (e.g., 9-I-10-J) while performing the TMTB task towards the end. One explanation may be that

one-third of the task can be processed at lower complexity, resulting in faster processing. Still, reaching two-thirds of the task while increasing the complexity, the various cognitive functions such as working memory, cognitive flexibility, and inhibitory control become more critical, leading to the increased time spent inside circles. By the end of the task, the number of circles that must be reached is reduced due to the circles already reached, enabling a quick visual search that may result in less time spent in circles than before. The complexity of visual search can be manipulated by contrasting features (Treisman & Gelade, 1980), by diversifying the target-disrupter similarity (Duncan & Humphreys, 1989), or by changing the number of possible goal-defining features (Irons et al., 2012). Above all, manipulating the number of target objects presenting concurrently in a display showed worse performance impairments when processing multiple target objects simultaneously (Huang & Pashler, 2007). In the case of the dTMT, visual processing can work faster by reducing the number of circles processed at the end of the task than at the start and middle of the task.

Moreover, observation of a single case is also required in the clinical field to help enable individual intervention. For example, one participant in the PD-Healthy group showed deteriorated performance during the dTMT-B (long time spent sporadically in several circles). Here, we need a more detailed investigation to check whether there is still a problem in cognitive function or poor performance due to loss of fine motor control. In the latter case, freezing during a handwriting task may be temporarily triggered when moving to the next circle after a long time spent in one circle (seeking the next target circle). In addition, freezing episodes have been reported to occur visibly during gait as well as during upper limb movement resulting in impaired movement output (for a systematic review, see Martins et al., 2022). Freezing of upper limbs was also examined based on changes in motor blocks during point-to-point movement (Ilan et al., 1999; Popovic et al., 2008). As freezing indicators, the high number and long duration of motor blocks in PD were found. In the case of the dTMT, there seems to be a possibility that time spent in each circle can be used as an indicator of freezing of hand movement. However, this symptom may appear more erratic due to the problem of pure fine motor control rather than regular due to cognitive difficulties. As in the former case, if it is a cognitive problem, the need for other cognitive assessments should be involved, such as n-back tasks (working memory), Flanker and Stroop tasks (inhibition),

and/or the Wisconsin Card Sorting Test (cognitive flexibility). Also, the participant showed poor performance on PD-related questionnaires despite his appropriate cognitive ability according to the MoCa z-score (PD-CFRS, PSQ15). For this reason, several factors related to PD, such as fine motor control, freezing during hand movement, or pure cognitive impairment, should be considered. Based on the advantages of the dTMT, we identified applicability with the decomposition of cognitive abilities, detailed analysis of them, and behavioral analysis of individual data as a digital biomarker for early diagnosis in the clinical field.

4.3 Exercise intervention and its neural mechanism in the comprehensive concept

In the second area of the comprehensive concept, we investigated the effects of acute exercise on neural correlates of cognitive performance measured by the dTMT, comparing HIIE with MCE (see Part II of the dissertation). Here, we found that exercise enhanced cognitive performance regardless of the type of exercise. Still, different cortical activation patterns can be observed between the two other exercise protocols in post-exercise and -recovery. Generally, although increased cortical activation was found in the frontal lobe in post-exercise compared to pre-exercise, not dependent on types of exercise protocol, higher cortical activation for each dTMT-condition was more pronounced during HIIE than MCE. Post-exercise, this increased cortical activation may be due to a rebound effect after the hypoperfusion in the frontal lobe responsible for cognitive control induced during exercise (Basso & Suzuki, 2017). Moreover, cognitive performance during the dTMT-B was maintained even post-recovery, and cortical activation was decreased overall but sustained higher activation after HIIE than MCE in M1 responsible for the motor area. Most notably, these results are dependent on types of exercise (e.g., HIIE or MCE, for a systematic review, see Herold et al., 2018), performance conditions (e.g., while sitting or walking, for systematic reviews, see Herold et al., 2017; Pelicioni et al., 2019), and cognitive task features (e.g., dTMT, for a systematic review, see Pelicioni et al., 2019).

Cortical activation increased more while walking post-exercise than sitting post-recovery. It may be possible due to allocating more neural resources to postural control while walking on the treadmill than to fine motor and cognitive

control. Also, this fact might be particularly prominent with physical fatigue induced by high-intensity exercise. However, due to the nature of the cognitive task, cognitive control and additional fine motor control are required during the dTMT. For this reason, to investigate the effect of exercise on the neural correlates of cognitive performance, the frontal lobe and motor area were also measured compared to several studies that measured only the frontal lobe (Damrongthai et al., 2021; Hyodo et al., 2012; Kujach et al., 2018; Yanagisawa et al., 2010). Of course, since the frontal lobe plays an essential role in cognitive function, it is necessary to measure the frontal lobe to examine whether the activation of the frontal lobe induced by exercise positively affects cognitive function. In addition, measuring other brain areas allows us to confirm the distribution of neural resources to other brain areas or other neural mechanisms by the types of exercise. According to a systematic review (Herold, Aye, et al., 2020), the exercise-induced hemodynamic responses measured by fMRI between pre- and post-exercise were mainly observed in the frontal and temporal lobes. This enhanced activation was found after acute exercise with moderate- to high-intensity for 20 – 30 minutes (Li et al., 2014; Mehren et al., 2019). These results indicate improved frontal lobe activation, which is consistent with our findings. However, observation of the distribution of neural resources during exercise is still limited. For this reason, observation of changes before, during, and after exercise using the fNIRS device, which can cover the entire brain, seems essential to elucidate the neural mechanism of acute exercise on cognitive performance.

Concerning performance conditions, DT while walking on the treadmill as an intervention can be applied to improve either cognitive or motor, or both performances. In manuscripts 3 and 4 of Part II, cognitive performance during walking was maintained compared to that performed while sitting (sessions (1), (2), and (3) of Figure 14, see Park & Schott, 2022). Generally, performing a DT while walking is accompanied by problems with motor or cognitive, or both performances via lifespan with an inverted U-shaped curve (Schott & Klotzbier, 2018). However, these results contradict our study. While walking on the treadmill at a fixed speed, cognitive performance seems to be better than during overground walking (Penati et al., 2020). The automatization of the walking movement on the treadmill may lead to focusing on the cognitive task (Clark, 2015; Penati et al., 2020). The DT of walking on a treadmill at a fixed speed as an intervention may trigger a second

postural strategy (Bloem et al., 2006) to focus more on the cognitive task, resulting in enhanced performance.

Besides, DT on the treadmill may be an appropriate intervention in the clinical field for patients with gait disorders such as PD. This DT intervention can enhance gait performance by automatization while walking on the treadmill and simultaneously improve cognitive performance(Clark, 2015; Penati et al., 2020). Based on these theoretical backgrounds above, DT walking also may induce increases in cortical activation of the frontal lobe by supplying additional neural resources to maintain cognitive performance. In particular, the additional supply of these neural resources may have been further facilitated by exercise, allowing a greater allocation of neural resources to a cognitive task during DT walking. Through these neural mechanisms, exercise may contribute to improving both performances. As a result, the two types of exercise protocol with different intensities indicated the same consequence of cognitive improvement. Still, these protocols provoked different cortical activation patterns, which can be seen as effective distribution of neural resources according to the type of exercise and performance conditions. Generally, several studies examining the effects of exercise on cognitive performance demonstrated that exercise with moderate intensity induced high activation in DLPFC accompanied by enhanced cognitive control performance (Damrongthai et al., 2021; Hyodo et al., 2012; Kujach et al., 2018; Yanagisawa et al., 2010). However, these studies did not directly compare with other exercise protocols (moderate versus control group).

In comparison, the study by Moriarty et al. (2019) showed that moderate-intensity exercise produced higher cortical activation in the left PFC than high-intensity exercise. This result is inconsistent with our findings, possibly due to differences in the study protocol. Unlike the study by Moriarty et al. (2019), in which the task was performed while sitting after resting until returning to resting heart rate immediately post-exercise, in our study, the task was executed while walking directly after exercise. Walking activity after high-intensity exercise may lead to higher activation required to perform tasks. Also, in many studies, walking has already been known to promote the activation of the frontal lobe (see Herold et al., 2017; Pelicioni et al., 2019). Unlike the direct locomotor network associated with the primary motor cortex and cerebellar motor areas, neural commands are transmitted to the basal ganglia, hypothalamus, and midbrain motor areas via PFC

and supplementary motor area as indirect motor pathways (see also the systematic review by Herold et al., 2017), resulting in a more pronounced activation in the prefrontal lobe. This synergistic effect through the combination of exercise and walking may further promote prefrontal activation and enable efficient use of increased neural resources, leading to improved cognitive function. As such, the explanation of the effective use of neural resources can be supported based on the neural mechanism for changes in cortical activation induced during a cognitive task or by exercise. Among other things, with this support, comprehensive concept could improve cognitive performance through early detection of a cognitive decline through digital cognitive assessments and optimization of exercise protocol leading to effective neural resource distribution.

4.4 Limitations and View for Future Research

These advantages of the dTMT and the positive effects of exercise were vitally crucial for obtaining the interesting findings of the present thesis. However, one should note our interpretation of these findings in light of some limitations of the present thesis.

Limitation of Methods and Technology of dTMT

Although the sample size for each study was estimated by power analysis using G*Power 3 (Faul et al., 2007), the sample size of all studies in the present thesis was still relatively small. In manuscript 1, although the results were evident for comparing the dTMT and ppTMT, a larger sample would unlikely reach alternative conclusions; a larger sample size will better generalize the results for the overall population. Especially regarding the MoCA score in manuscript 2, groups between PD and control group were divided into subgroups (pathological, undecided, and healthy), leading to six specific groups with a very small sample size that could make it difficult to perform adequate statistical analysis. For this reason, future studies require data collection using dTMT with a large sample size. The homogeneous population recruitment in a clinic or a nursing home is also necessary due to the heterogeneity of the Parkinson's group recruited by the self-help Parkinson's association. Since the effect on task performance may be diminished due to ON medication in the PD group, further studies should be considered comparing groups ON and OFF medication.

From the view of the technology of the dTMT, technical updates are necessary since we found that the involvement rate of cognitive load during dTMT-B showed an inverse U-curve. As the results of manuscript 2, the time spent inside the circle gradually decreases after reaching the peak point during the middle of the task. Concerning these results, increasing engagement in cognitive load at the beginning of the task, such as adjusting the start number and alphabet of the task or temporarily deleting the path covered by the participant after reaching the circle, could contribute to identifying deterioration in fine motor or cognitive control.

In Part II of the thesis, the main limitation was to investigate only healthy young adults with high fitness levels according to the estimation of maximum oxygen consumption. However, due to their high fitness level, which maybe contributes to neural enrichment resources, neural resources can be supplied flexibly and effectively depending on the situation (e.g., sitting and walking), exercise type (e.g., HIIE and MCE), and cognitive tasks (e.g., dTMT and Stroop task) (Herold et al., 2017, 2018; Moriarty et al., 2019; Park & Schott, 2022; Park et al., 2021; Pelicioni et al., 2019). Therefore, various cohorts with different fitness levels (e.g., age group: young and older adults or sports group: experts and novices) should be considered for future studies.

From the view of the design of the experiment, based on speculation from Basso and Suzuki (2017), hypoperfusion of cortical activation in the frontal lobe is caused by increased neural activity forward to sensory- or motor-related other brain areas during exercise (for hypofrontality theory, see Dietrich & Audiffren, 2011) can lead to rebound increased supply to the frontal lobe in post-exercise. In future studies, changes in cortical activation by additional measurements of other brain areas should be examined using more fNIRS channels in addition to the frontal lobe and motor areas. Above all, observing other brain regions, especially during exercise, should be needed to verify the supposition and theory above. We also investigated the sustained effects of post-recovery, but the recovery duration was relatively short. Maintenance of cognitive performance improved by acute exercise play an essential role in predicting positive changes attributed to chronic exercise. Compared to many studies investigating exercise-induced sustained effects (up to approximately 2 hours) on behavior-related cognitive performance level (Barella et al., 2010; Basso et al., 2015; Chou et al., 2021; Hung et al., 2013; Tsukamoto et al., 2016, 2017), sustained effects on changes of task-related

hemodynamic responses after long-term recovery have yet to be studied (Herold et al., 2018). Since maintaining a healthy mood all day after exercise, the sustentation of cognitive performance enhanced by exercise should be observed at the neural and behavioral levels.

Limitation of Results

Furthermore, it is also regrettable that we did not identify the neural correlates by fNIRS during dTMT for the group of Part II. In particular, in the elderly, a different neural activation pattern can be expected in utilizing neural resources compared to young adults. According to the HAROLD model (hemispheric asymmetry reduction in older adults, Cabeza, 2002), the activation in the prefrontal cortex during a cognitive task tends to be less lateralized in the elderly than in younger adults with increasing age. Also, based on the CRUNCH model (compensation-related utilization of neural circuits hypothesis, Reuter-Lorenz & Cappell, 2008), older adults indicate the recruitment tendency of additional neural resources from the brain regions responsible for other neural network processes. This CRUNCH model assumes that older adults could show decreased cortical activation accompanied by performance decline due to high task demands. Thus, utilizing neural resources depends on the task load (Grady, 2012). Therefore, future studies need to identify digital and neural biomarkers during dTMT, especially during the time spent inside a circle or between circles, in patients with neurodegenerative diseases such as Parkinson's or Alzheimer's.

Based on these models mentioned above, it is necessary to investigate how acute exercise affects different neural patterns shown with increasing age compared to young adults. Already acute exercise with moderate intensity demonstrated high cortical activation in the right frontopolar area as compensatory neural resources utilization, associated with enhanced cognitive performance (Hyodo et al., 2012). However, since multiple factors influence the interaction between exercise and cognition, the factors mentioned above (situation, exercise type, cognitive task) and various cohort groups should be considered in future studies to elucidate neural correlates according to these models. Also, it can be expected that by using fNIRS, the change in neural activation pattern, exercise, and the dTMT, it will be possible to confirm the interaction between each other and establish a more specific exercise intervention and neural correlates.

Despite the advantages of dTMT combined with a divide-and-combine technique to reduce the learning effect, this effect by repeated measures should not be neglected entirely. Nevertheless, the absence of a control group is still ambiguous about the positive outcome of the exercise in this part. Still, considering that no significant differences were found between the first and second sessions performed for task familiarity, the divide-and-combine approach of dTMT was especially suitable for the control learning effect. Furthermore, high inter-individual variability of cortical activation measured by fNIRS can also be attributed to the small sample size. For this reason, we emphasized the effect size for the statistical analysis of neural data. However, a control group and a large sample size are still crucial factors that should be considered in future studies.

4.5 Conclusions

The present thesis is an interdisciplinary study in which various fields, such as neuroscience, exercise science, cognitive psychology, and clinical psychology, overlap. On the one hand, we examined the applicability of the TMT, a commonly used neuropsychological test paper, to the clinical field and verified its validity and reliability as a digital version. On the other hand, the positive effect of exercise on task-related cortical activation measured by a newly portable, safe fNIRS equipment was investigated using dTMT to examine fine motor cognitive performance.

As technology advances, the development of these digital assessments will continue. In addition, these digital evaluation tools will be used more and more in clinical fields such as hospitals and nursing homes (Koo & Vizer, 2019). With the advances in digital assessments, early accurate detection of motor and cognitive function problems can contribute to early and timely intervention, such as medication, exercise, or cognitive therapy tailored to the issues. Our version of the dTMT can be introduced as a robust cognitive assessment that combines the strengths of existing versions and adds new technology. Despite the study's limitations, detailed analysis using additional variables provided more specific results. Based on these results, future research using artificial intelligence, such as machine learning and deep learning, should be carried out by accumulating data collected from the dTMT. Moreover, long-term tracking changes for cognitive performance by application to clinical fields should also be needed.

Furthermore, it is already self-evident that physical activity improves cognitive function. However, it is still unclear which exercise protocol contributes to optimally enhancing cognitive performance in terms of exercise intensity and duration. In general, cognitive decline is inevitable with aging. Among them, cognitive control related to the prefrontal cortex includes many activities in our daily life (e.g., walking while talking, reading messages, and texting on a cell phone). As in the results of the previous studies, two different intensities of exercise contributed to the prefrontal cortex's increased cortical activation, accompanied by improved cognitive performance.

Additionally, the increased activation of the motor cortex following high-intensity interval exercise was also found. In the future, it is necessary to investigate how long cognitive performance can be maintained using these two protocols while simultaneously observing the changes in neural correlates. Further, checking the difference according to the exercise duration is also essential. One study already showed increased activation of bilateral frontal lobes with improvement in cognitive performance after 10 minutes of exercise (Damrongthai et al., 2021). Short, time-efficient acute exercise may be the best option for people with low fitness levels because of its simple and safe intervention. In this aspect, neural activation patterns should also be identified according to various intensities and periods. An exercise protocol that fits not only the fitness or behavioral level but also the neural level should also be provided.

If it is possible to individually provide a specific exercise protocol for maintaining cognitive function by identifying changes in cortical activation induced by exercise, the interaction between early detection and exercise intervention will perform well based on neural mechanisms according to the comprehensive concept above.

5 View of central questions in future research

Humans have existed for hundreds of millions of years, and we live now through the continuous development of civilization and technological advancement. In the distant past, when hunting and gathering, we were constantly on the move, fighting to survive. However, now we have made countless advances. As a result, we are living in experiences that were unimaginable at the time, such as smartphones, video chatting, social media, and electric vehicles. However, if there is a bright side, there is also a dark side. Technology is constantly developing, and thanks to that development, we are leading a more prosperous life. We long for a long life and dream of eternal life.

However, on the other hand, prolonging life expectancy is finding genes for neurodegenerative diseases like Alzheimer's. Advances in technology make us more convenient and immobile, which causes many diseases such as obesity and diabetes. The software, that is, our brain understands technology accepts visits and continues to develop, but hardware, our body, is still stuck in the hunting and gathering days and has not kept pace with technological advancement. From an evolutionary point of view, we are still constantly on the move and have to live to survive. (Raichlen & Alexander, 2017).

According to the comprehensive concept mentioned above, efforts should be made to maintain a healthy lifespan with assessment using technological advances and exercise intervention. It is necessary to technically optimize the disadvantages of those mentioned above dTMT and use them in the clinical field to track the change in performance over the long term. At the same time, exercise intervention should be needed to improve brain healthy by observing acute and chronic effects on cognitive performance. In the future fourth industrial era, there will be more and more assessment tools for early detection in the clinical field using artificial intelligence such as machine learning or deep learning. In this regard, dTMT can be highly useful for early detection. Since these advantages of dTMT, such as the simple interface, uncomplicated task instructions, and long-term tracking of task performance, are readily available in clinical fields, dTMT needs to be applied in future studies. In addition, by accumulating a large amount of data for an extended period, we expect the possibility of detecting subtle differences in fine

motor control and cognitive ability using artificial intelligence to prevent early symptoms of Parkinson's or Alzheimer's, a neurodegenerative disease.

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Appendix A1 – Manuscript 1

Accepted manuscript 1:

Park, S. Y., & Schott, N. (2021). The trail-making-test: Comparison between paper-and-pencil and computerized versions in young and healthy older adults. *Applied Neuropsychology:Adult*, 1–13.
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The Trail-Making-Test: Comparison between paper-and-pencil and computerized versions in young and healthy older adults

Abstract

One of the key challenges in assessing cognitive performance is to detect not only apparent impairment but to also pick up on subtle differences. Computerized tests benefit especially from the acquisition of fine-grained outcome measures. However, the equivalency of paper-based and computerized tests cannot be assumed. The Trail-Making-Test is a paper-pencil cognitive assessment tool (ppTMT) that has been used in many research studies to evaluate visuomotor abilities and mental flexibility. A dig-ital version of the extended TMT (including a condition measuring fine motor speed) called the dTMT has been developed. This study aims to test (1) reliability, (2) equiv-alence, and (3) agreement of the ppTMT and dTMT. A total of 53 healthy individuals aged 19 to 82 years of age (22 men, 31 women; mean age 42.2, SD=22.8) completed three trials per ppTMT and dTMT condition. Part M involves following a predefined path, Part A links numbers randomly distributed in space, in ascending order, and Part B alternates between linking numbers and letters. dTMT scores were highly reproduc-ible, correlated strongly with paper-pencil administered durations, and discriminated young from older adults. Measures of reliability, sensitivity, and clinical meaning for dTMT scores were favorable compared with ppTMT-based testing. Our findings sup-port the comparability of TMT-indices in computerized assessments. While many dig-ital biomarker efforts are in progress (e.g., neurodegenerative disorders), the dTMT sets itself apart through its high sensitivity, the alternate forms, and the additional component measures. In this light, it could serve as a starting point for an early diagnostic tool.

Keywords. computerized cognitive assessment; neuropsychological test; executive function; fine motor control; Bland-Altman plots

1 Introduction

Effective early screening of motor and cognitive decline is needed to be able to ascertain whether an individual with possible signs of neurodegenerative diseases (ND) such as Alzheimer's disease (AD) and Parkinson's disease (PD), needs further investigation. In recent years, tablet and smartphone-based applications for assessing motor and cognitive functions have emerged (Koo & Vizer, 2019). Digital-based neuropsychological tests have the potential to detect early – subtle – signs of decline in older adults with and without ND, thus allowing adopting preventive measures (Coravos et al., 2019).

One of the many most frequently used neuropsychological tests to assess executive function across a wide range of neurological conditions is the Trail-Making-Test (TMT; Faria et al., 2015; Reitan, 1955). The TMT consists of a task composed of sequential hand movements that involve fine and complex manual skills relying on a sophisticated mix of cognitive, sensory, and motor components (Klaming & Vlaskamp, 2018). In its original variant as a paper-pencil version (ppTMT), the TMT comprises of two conditions, Part A and Part B (TMT-A, TMT-B; Army Individual Test Battery, 1944). While the TMT-A (connecting numbers from 1 to 25 in ascending order) is largely predicted by visual search and processing speed (Bowie & Harvey, 2006; Ríos Lago et al., 2004), the TMT-B (connecting numbers from 1 to 13 and letters from A to L in alternating and ascending order) is associated with more complex cognitive skills such as mental flexibility, working memory and inhibition control (Arbuthnott & Frank, 2000; Kortte et al., 2002). In addition to evaluating executive functions, the TMT is also a task for measuring fine motor manual performance. To disentangle the contribution of visual search from that of basic perceptual-motor processing in TMT-A and TMT-B, we implemented a condition of the TMT in which visual search is minimized: Participants connect 25 circles, following a predefined path. The extended TMT has already been proven to deteriorate cognitive performance with increasing cognitive load in healthy children and the elderly as well as children with movement disorders and the elderly with Mild Cognitive Impairment (Klotzbier & Schott, 2017; Schott et al., 2016).

The digitization of established neuropsychological tests has the benefit of increasing the ease of administration, the avoidance of the inevitable variability

and uncertainty in manual stopwatch measured by human experimenters, the automation of the presentation of the task, and the possibility to generate alternative forms to avoid practice effects, but also allows the acquisition of additional parameters that enable a better assessment of cognitive and motor performance (e.g., reaction time, correct and incorrect answers, pressure on the tablet, path length). The automatic calculation and immediate provision of the results also support the simple monitoring of the long-term performance development (Berg et al., 2018; Mielke et al., 2015; Ruggeri et al., 2016; Wu et al., 2017) so that changes are objectively recorded at an early stage (Makizako et al., 2013). In recent years, several digitized versions of the original paper-based TMT have been developed that more or less successfully tried to address these aspects (Dahmen et al., 2017; Fellows et al., 2017; Lunardini et al., 2019; Tam et al., 2017; Zeng et al., 2017). First of all, none of these previous versions of the digital TMT included a single-task condition (fine motor control task). Moreover, most computer-based versions of the TMT use at best 10" tablets with the same or lower number of circles (20 vs 25), usually do not generate alternative forms but use the original setup (except Zeng et al., 2017), and only the group around Maureen Schmitter-Edgecombe (Dahmen et al., 2017; Fellows et al., 2017) incorporates additional variables such as path length or the number of lifts into their analytic approach. Recently, our group developed a 12”-tablet-based digital Trail-Making Test (dTMT) from the original variation of the paper-pencil version with an additional trail-tracing task to account for fine motor control, the possibility to generate alternative variations and to run the test with 25 circles or a predefined time (e.g. 30 seconds) as well as the inclusion of additional performance parameters, which now enables large-scale data collection, the richness of measure, and precision (Getchell et al., 2020). Besides, it helps to better describe separately cognitive processes such as processing speed, working memory, inhibition control, and set switching. A deconstruction of the cognitive component processes would, therefore, characterize the specific deficits of individuals with motor and cognitive disorders more clearly (Dahmen et al., 2017).

Only few studies (Bracken et al., 2018; Dahmen et al., 2017; Fellows et al., 2017; Guillaume et al., 2019) investigated the reliability and validity between ppTMT and dTMT, but these digital versions modified the number of circles (20 circles instead of 25) and didn’t use alternate variations. Therefore, in the present

study, we are to compare the psychometric properties of the paper-and-pencil based TMT and our new digitized TMT with young and older adults. Specifically, we examined (1) the reliability, quantifying the relationship between digital- and paper-pencil-based using correlational approaches; (2) the equivalence, the extent to which test results in different settings produce similar overall results; and (3) the agreement, by quantifying acceptable limits to bias and differences between measurement environments. Moreover, we determined the additional component measures of the dTMT that allow us to identify diverse cognitive abilities measured in the condition of dTMT involving processing speed, inhibitory control, and working memory, in healthy young and older adults.

2 Materials and methods

2.1 Power Analysis

This study was powered to detect moderate-to-large differences in test performance between test variants (dTMT vs. ppTMT). The power to detect differences between testing variants was examined using the program G*power 3 (Faul et al., 2007). This indicated that detecting an effect size of 0.4, at 80% power (two-tailed α at .05), would require a sample of 52 in a paired sample test with normal distribution, and between 35 and 47 for the nonparametric equivalent, depending on the underlying distribution of data (Kühberger et al., 2014).

2.2 Participants

A total of 29 young adults (YA; M = 22.4, SD = 4.47, age-range 19–35, 17 male) and 24 healthy older adults (M = 66.2, SD = 7.48, age-range 50–82, 14 male) volunteered to participate in the present study. Since the age range is large in healthy older adults, we divided the elderly group into two groups (12 young-old adults; YOA; M = 60.3, SD = 4.31, age-range 50–65, 8 male, and 12 older adults; OA; M = 72.2, SD = 4.57, age-range 66–82, 6 male). Taking the cognitive decline into account, healthy older adults with a score of 25 or higher on the age- and education-adjusted Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) were enrolled in the study (Santangelo et al., 2015). YA were recruited from the University of Stuttgart, and healthy older adults from sports groups in Stuttgart in Germany.

Exclusion criteria for both groups were comorbidities with other neurological and/ or psychiatric diseases; color-blindness or Colour Vision Deficiency (CVD); visual and hearing impairment incompatible with neuropsychological tests, and the participants must not have any fine motor impairments that could interfere with performing the fine motor-cognitive task. All participants were informed of the nature and aim of the study and signed a consent form. All procedures were in accordance with the Declaration of Helsinki with ethical standards, legal requirements, and international norms. The present study was approved by an internal ethics committee of the University of Stuttgart.

2.3 Measures

2.3.1 Sociodemographic information & physical activity

Basic demographic information (e.g. age, sex, and education, etc.) on the participants was collected. The height and weight of the participants were measured and the body mass index (BMI, kg/m^2) was calculated. To assess physical activity, subjects were asked such as for the type of sport practiced in sports clubs and in leisure time, the number of training units per week, the amount of a training session (Schott et al., 2016).

2.3.2 Trail-Making-Test (ppTMT vs. dTMT)

Both paper-and-pencil-based versions of the TMT were administered for this study, following the guidelines described by Bowie and Harvey (2006). It included three conditions, TMT-M (motor speed), TMT-A, and TMT-B. Figure 1 shows a version of each TMT condition.

here Figure 1

For the ppTMT-M, participants were instructed to connect 25 circles following a predefined pathway. For the TMT-A, participants were told to connect 25 randomly distributed encircled numbers from 1 to 25 in ascending order (*i.e.* 1-2-3-…). For the TMT-B, participants were instructed to connect numbers and letters in alternating, ascending order (*i.e.* 1-A-2-B-3-C…). For all conditions, participants were instructed to draw a continuous line on the paper connecting the different circles. If a subject made an error (e.g., skipped a circle, connected the wrong circles) during the test and did not correct it themselves the research assistant immediately corrected them (e.g., returned the subject to the skipped circle and said

this number (or letter) comes after (preceding stimulus); crossed out the erroneous line and provided immediate feedback, either in terms of ascending connections for part A or alternation for part B). Timing was continued even if the participant made errors (see Bowie & Harvey, 2006). All three versions had to be executed as quickly as possible. The participant's scores were based on their total time to connect all 25 stimuli, the number of errors, the derived scores (difference [B-A]), ratio [B/A]), and dual-task costs (DTC) in each condition. DTC refers to the interference between fine motor and cognitive loss. DTCs are calculated by relating the performance in each task under the DA condition (e.g. completion time of TMT-A or -B) to the respective performance under the single-task condition (e.g., completion time of TMT-M: ([TMT A – TMT M] / TMT M* 100)) (Schott, 2017). To perform the ppTMT, we generated different test runs with the dTMT and produced paper printouts of the same size as the digital version.

The android app-based digital TMT was designed to be similar in structure and size to the paper-and-pencil-based version as it was administered on a Samsung Galaxy Note Pro (12.2-inch diagonal LED-backlit Multi-Touch display with IPS technology; portrait alignment) with a resolution of 2560 x 1600 and Android version 6, which allows the original number of 25 circles. The version of the dTMT used here is based on the digital versions of Dahmen et al. (2017), which mainly introduced numerous additional measurement parameters (e.g. time between and inside the circles, number of lifts, distance length) and the work of Zeng et al., (2017), which is based on a "divide-and-combine approach" making it possible to generate alternative versions. Both approaches have been further optimized: For example, instead of having 25 circles completed at a time, it is now possible to run the test for, say, 30 seconds; also, the algorithm of Zeng et al. (2017) has been optimized so that overlapping paths no longer present any problems. Also, the overall length of all three versions of the TMT was computed to be identical. In this digital version, the time of each condition records automatically from the moment the stylus touches the tablet screen and stopped as soon as the last circle is reached (marked Begin and Stop respectively). Compared to the paper version, which has to rely on the examiner, the administrator informed the participants before the test started that if the wrong circle was touched, it would change its color to red and they must return to the last correct circle, increasing the completion time

as with the ppTMT. The further procedures regarding errors were the same as with the ppTMT.

The dTMT also creates an automated in-app report on the time inside circles (perceptual speed (dTMT-A); visual sequencing ability, visual working memory (dTMT-B)), time between circles (perceptual speed (dTMT-A), inhibition (dTMT-B)), number and duration of pauses (perceptual speed (dTMT-A), inhibition (dTMT-B)), number and duration of lifts (visual working memory (dTMT-B)) (Fellows et al., 2017). Figure 2 shows the execution of the ppTMT and the dTMT by older adults.

here Figure 2

2.4 Experimental design & procedure

A repeated measure design was used where the participants underwent two testing presentations: a paper-based and a digitized version of the same tests using a counterbalanced design to avoid potential order effects: (A) paper-based at the first session and digitized testing at the second session or (B) digitized version at the first session and paper-based testing on the second session (see Figure 3). Testing took place during a single visit. The total assessment duration was between 30 and 45 minutes. All participants entered the study voluntarily and gave written informed consent at the beginning of the study.

All older participants were first given a paper-and-pencil version of the MoCA to examine cognitive decline. Afterward, the different test variants (ppTMT and dTMT) and their conditions (TMT-M, -A, and -B) were explained, and questions were answered. Before testing both variants, each subject was asked to run a short practice version to familiarize themselves with the different TMT conditions (8 circles each).

here Figure 3

Each condition (TMT-M, -A, and -B) of the two variants was performed three times and thus resulted in a total of nine trials per variant. The order of the different conditions was determined using a randomization list. In the paper version, the total time was recorded by stopwatch and the number of errors that occurred was noted, while all variables measured by dTMT were automatically collected. After testing the first variant, the questionnaires (demographic information

and physical activity) were completed including short resting time. After that, the variant of the TMT that has not yet been performed was then tested.

2.5 Data analysis

Statistical analyses were implemented on SPSS v.27 (SPSS, Chicago, IL). The Bayesian statistical analysis was carried out using JASP (JASP Team, 2016; jasp-stats.org). We first explored dependent variables to examine missing data points, normality of distributions, and the presence of outliers. An alpha level of .05 was used for all statistical tests. Potential baseline group differences for continuous variables (i.e., age, height, weight, BMI, physical activity) were assessed using ANOVAs, and categorical demographic variables (i.e., sex) were compared by chi-square test. For ANOVAs, the partial eta^2 (η_p^2) was calculated as effect strength measure. The classification of the η_p^2 also follows the conventions of Cohen (1988): 0.01 small effect; 0.06 medium effect; 0.14 strong effect. With significant results, post-hoc analysis (Bonferroni correction) was used to check which factor levels differ significantly from one another.

Reliabilities, here consistency in performance, were calculated using Intra-class Correlation Coefficients (ICC) using a two-way random-effects model for absolute agreement (ICC (2,1)). This form of the ICC is sensitive to differences between session means. As both measurement error and between-participant variability are important for the interpretation of reliability, we also report the standard error of measurement (SEM) for each variable (Weir, 2005) and the minimum detectable change with a confidence interval of 95% (MDC95). The SEM is the square root of the error variance term in the ICC calculation and reflects the 68% confidence interval around an individual's observed score.

To allow the comparison with reliabilities commonly reported in the literature, bivariate coefficients were computed to measure the strength of the linear association of outcome measures across test settings. Spearman correlations for completion time and derived scores (difference [B-A], ratio [B/A], dual-task costs [DTC]) are reported. Agreement between test settings (TMT-M, TMT-A, TMT-B) was examined with Bland-Altman plots. These plot the difference between assessments (e.g. dTMT-M – ppTMT-M) versus the average across paired measures (dTMT-M + ppTMT-M / 2), along with 95% limits of agreement (Bland & Altman,

1986). The plots serve as a visual check that the magnitude of the differences is comparable throughout the range of measurement. The agreement is considered adequate when 95% of data points lie within the limits of agreement.

Bayesian analyses on completion time and derived scores (difference [B-A], ratio [B/A], dual-task costs [DTC]) consisted of Bayesian paired sample t-tests, conducted with JASP (JASP Team, 2016), which compared the relative support of the data for the alternative hypothesis (B10; evidence for variant differences) to the null hypothesis (B01; evidence for variant equality). The resulting Bayes factor provides an index of the strength of the evidence in support of the null hypothesis (B01) or the alternative hypothesis (B10). We used the default prior in JASP with an effect size of zero for quantifying evidence in favor of the null hypothesis. For the alternative hypothesis, we used the default Cauchy distribution centered on zero with a width of 0.707.

To compare between ppTMT and dTMT and level of difficulty as another indicator for equivalence of the overall structure of the TMT, we calculated 2x3x3 ANCOVAs with repeated measurements (with Greenhouse Geisser correction) for the variable completion time (mean value of three trials in each condition), controlled for years of education and exercise duration as covariates with the within-subject factors “variant” (dTMT versus ppTMT), “task condition” (TMT-M, TMT-A, and TMT-B) and the between-subjects factor “age group” (YA, YOA, and OA).

For the component measures of the dTMT (number and duration of lift, pauses, time between and inside circle that used the mean value of three trials in each condition as a factor), we calculated 3x3 ANOVAs with repeated measurements, controlled for years of education and exercise duration as covariates with within-subject factors “task condition” (dTMT-M, dTMT-A, and dTMT-B) and the between-subjects factor “age group” (YA, YOA, and OA).

3 Results

3.1 Characteristics of the study population

Table 1 summarizes the demographic data including sex, age, height, weight, BMI, handedness, years of education, exercise duration, and MoCA score (only for YOA and OA). There were significant effects for age, weight, BMI, years of education,

and exercise duration. Overall, the results of the post-hoc analysis for group differences showed significant differences between younger and older adults.

Here Table 1

3.2 Reliability

In respect of test consistency across different instances (three times per condition in a randomized order in each TMT version), the relative and absolute reliability measures (ICC, SEM, MDC95) are presented in Table 2. The inter-run reliability was good to excellent for each condition in each TMT variant, with ICC values between 0.90 and 0.95. The SEM fluctuated between 0.98-4.56s for the ppTMT and between 1.51-6.13s for the dTMT. A SEM% ≤ 10% was found in TMT-M and -A for both TMT variants, while SEM% for both TMT variants was a little more than 10%. Besides, the MDC95 about the completion time was between 2.73-12.7s in ppTMT and between 4.20-17.0s in dTMT. Only in both variants of the TMT-B, MDC95% was slightly higher than 30%.

Here Table 2

3.3 Agreement

The construct validity was analyzed using bivariate correlations for the completion times as well as the derived scores between the ppTMT and dTMT (see Table 3, Figure 4). Spearman correlation coefficients ranged between .82 and .90 ($p < .001$) for completion times, and for the derived scores between .51 and .67 ($p < .001$). The variability of the performance decline can be explained by the coefficients of determination between ppTMT and dTMT for the completion times in TMT-M with 75.4%, 79.6% in TMT-A, and 75.4% in TMT-B.

Bland-Altman plots showed overall good agreement between test variants. 96%, 92%, and 94% of data points lie within the limits of agreement. Overall, the mean agreement revealed a negative value (TMT-M: -4.16, TMT-A: -2.94, and TMT-B: -5.41), indicating the faster performance of the ppTMT compared to the dTMT.

here Figure 4.

3.2 Equivalence

Bayesian analyses didn’t support the null hypothesis (H0: no difference between

test settings) over the alternate hypothesis for neither TMT variant (see Table 3). In contrast, the alternate hypothesis, reflecting a difference between test settings, was supported for all direct measures and the dual-task costs, with support being very strong. Effect sizes were in the low-to-large range. However, no difference was found for the difference (B-A) or the ratio (B/A), supporting the overall equivalence between the two variants. Overall, the digital variant resulted in completion times that were 35.6% (TMT-M), 15.1% (TMT-A) and 16.2 % (TMT-B) longer.

here Table 3

Performance of all TMT-durations were significantly affected by age (r = .70 – .87), years of education (r = -.22 – -.40) and exercise duration (r = -.42 – -.61), but not by sex (r = -.03 – -.18). In relation to the comparison of level of difficulty, ANCOVA with repeated measurement (Greenhouse Geisser corrected), controlled for years of education and exercise duration showed a significant effect of task condition, $F(1.09,52.5) = 12.2$, $p < .001$, $\eta_p^2 = .203$, and a significant interaction between task condition and age group, $F(2.19,52.5) = 11.7$, $p < .001$, $\eta_p^2 = .327$ (see Figure. 5). Post hoc analysis confirmed significant differences between all task conditions ($p < .001$). With increasing task difficulty, completion times became longer; in addition, this effect increased with increasing age. There were no significant main or interaction effects for variant x age group or variant x task condition or variant x task condition x age group.

here Figure 5

3.5 Component measures of the dTMT

Performance of most component TMT-measures were significantly affected by age (r = .03 – .82), years of education (r = -.38 – -.19) and exercise duration (r = -.55 – .05), but again not by sex (r = -.29 - .24). Therefore, we employed 3 (task condition: dTMT-M, -A, and -B) x 3 (age group: YA, YOA, and OA) ANCOVAs with repeated measurements for the component measures of dTMT, controlled for years of education and exercise duration.

The analysis on the *number of lifts* demonstrated a significant effect of task condition, $F(1.18,56.9) = 5.67$, $p = .016$, $\eta_p^2 = .106$ and a significant interaction between task condition and age group, $F(2.37,56.9) = 6.15$, $p = .002$, $\eta_p^2 = .204$, indicating an increasing number of lifts with increasing age and task difficulty.

Similarly, we found significant effects for the duration of lifts for task condition, $F(2,96) = 5.86$, $p = .004$, $\eta_p^2 = .109$ and a significant interaction between task condition and age group, $F(4,96) = 3.03$, $p = .026$, $\eta_p^2 = .114$. Post-hoc analysis did not show any significant difference between all groups for the number and duration of lifts for dTMT-M. While a significant difference was found between YA and OA ($p < .001$) for the number and duration of lift in dTMT-A and -B, only YA differed significantly from YOA for the duration of lifts in dTMT-A ($p = .022$) and -B ($p < .001$) (see Figure 6 upper row).

here Figure 6

For the *number of pauses*, there was a significant effect of task condition, $F(1.27,61.0) = 6.57$, $p = .008$, $\eta_p^2 = .120$, but no further interaction effect between task condition and age group. The analysis of the duration of pauses indicated a significant effect of task condition, $F(1.62,77.7) = 6.84$, $p = .004$, $\eta_p^2 = .125$, and a significant interaction between task condition and age group, $F(3.27,77.7) = 8.30$, $p < .001$, $\eta_p^2 = .257$, indicating an increasing duration of pauses with increasing age and task difficulty. Post-hoc analysis of the number of pauses for dTMT-M and -A demonstrated significant differences between YA and the elderly groups ($p < .001$), but for dTMT-B only between YA and OA ($p = .003$). Moreover, a significant difference between YOA and OA was also found in dTMT-A ($p = .015$). Although for the duration of pauses, the post-hoc analysis showed no significant difference in dTMT-M, significant differences between YA and other elderly groups were found in dTMT-A and -B ($p < .001$). Similar to the number of pauses in dTMT-A, the duration of pauses was also found to be significantly different between the elderly groups ($p = .021$) (see Figure 6 middle row).

For the component *time inside circle*, there was a significant effect of task condition, $F(1.14,54.8) = 12.8$, $p < .001$, $\eta_p^2 = .211$, and a significant interaction between task condition and age group, $F(2.28,54.8) = 11.6$, $p < .001$, $\eta_p^2 = .326$, while there was only a significant task condition by age group interaction effect for the time between the circles, $F(3.55,85.3) = 3.82$, $p = .005$, $\eta_p^2 = .151$. Again, we saw increases in duration with increasing age and task difficulty. Post-hoc analysis demonstrated that YA was high significantly different from the two elderly groups in each condition ($p < .001$; but excluding time between circles in dTMT-B). Although, significant differences between the elderly groups were seen for the

time inside circle in dTMT-A (p = .001) and B (p = .013), significant differences with regard to the time between circles were only found between YOA and OA for dTMT-B (p = .008) (see Figure 6 lower row).

4 Discussion

The accuracy and consistency of timing results are crucial for clinically important differences, while manual stopwatch measuring introduces mistakes and uncertainty. A technique that computerized techniques to automate the Trail-Making test and achieve accurate results was investigated here. We examined the comparability of the widely used TMT administered as a computerized version against a typical paper-and-pencil assessment, using a counterbalanced within-subjects design. Furthermore, with various variables measured from the dTMT, we examined the specific cognitive abilities between young adults and healthy elderly to identify the possibility of cognitive decline as a digital biomarker. We imposed strict criteria for comparability, including satisfactory inter-setting reliability, equivalence, and agreement across test settings. Overall, our results support the comparability of performance indices (duration, errors) acquired during the computerized assessments.

The results for the completion times of the ppTMT are comparable to those obtained in previous studies (Klotzbier & Schott, 2017; Schott et al., 2016). Our study showed significant differences between age groups in each condition of the two variants (interaction between task conditions and age group). With increasing age, fine motor, and cognitive deterioration occur (Corti et al., 2017), which suggests that with increasing cognitive load, the performance of young adults and older people also differs. In particular, significant differences were observed between the two older groups as task conditions became more difficult, but not in the fine motor task (TMT-M). These results could be explained by the fact that age-related cognitive decline is more dominant than fine motor control.

The bivariate correlation coefficients between the two test modes ranged from 0.87 to 0.89, which is broadly consistent with previous studies comparing paper-pencil and computer-based assessments in TMT (Bracken et al., 2018; Dahmen et al., 2017; Lunardini et al., 2019). Also, the ICCs were excellent for all variants for all conditions (ICC ρ=0.90-0.95). Also, according to the cross-over

design of the present study, each condition was performed three times in random order in each variant and condition. By calculating the "two-way" intra-class correlation coefficient, the high consistency of the three trials was observed in each condition of the dTMT similar to the ppTMT. A SEM% less than 10% indicates excellent agreement or reliability (Atkinson & Nevill, 1998), although slightly higher than 10% in the TMT-B were observed for both versions. However, the two variants showed similar trends due to the high intraindividual differences in difficult cognitive tasks (Salthouse et al., 2006). Besides, all three conditions of completion time showed acceptable agreement in the Bland-Altman plots. Despite the high correlations between the ppTMT and the dTMT, the participants required longer completion times for the dTMT compared to the ppTMT, as the results of the Bland-Altman plots confirm. Although the Bayesian analyses confirm the difference for the execution times, no difference was found for the difference (B-A) or the ratio (B/A), which supports the general equivalence between the two variants. These discrepancies between the two variants may vary depending on the type of tablets, the developer, and the study design, as already investigated in several previous studies (Bracken et al., 2018; Hannukkala et al., 2020; Rodriguez et al., 2019). In the present study, however, the possible explanation can be attributed to specific characteristics between the digital and paper-based tests. Compared to touching the screen with the tablet's stylus, performing the test with a ballpoint pen on paper has a different sensitivity and may allow better performance. Certainly, the significant differences between the two TMT variants in both older groups may be because familiarity with the technology is lower than in the younger group. Currently, there are various digital versions of Trail-Making-Test, but there is no age- and sex-specific standardized data available yet. However, we developed it similar to the original paper-pencil version by Reitan (1955), and in contrast to the paper version, which should be dependent on the subject who may make measurement errors, dTMT mainly achieved results equivalent to ppTMT, suggesting that translation from the paper-pencil version to a digital version is possible.

Recently, several tablets and smartphone-based digital applications for testing cognitive performance have been developed as digital biomarkers (Koo & Vizer, 2019). In particular, the digital version allows the measurement of various additional variables that provide further information to identify specific cognitive abilities such as cognitive flexibility, working memory and set switching etc., by

separating those cognitive abilities that are not possible in the paper-based tests. These transfers also offer the possibility to capture in detail not only cognitive skills but also fine motor skills. Movement patterns while writing or drawing can be registered and evaluated. One study found that two variables, "movement on paper" (when writing on paper with a pen) and "movement in-air" (when a pen remains in the air without touching the paper) play an important role in distinguishing between PD and control groups during a digitized handwriting task (Rosenblum et al., 2013). Furthermore, this "time in-air" seems to be a possible marker for dementia (Faundez-Zanuy et al., 2014). Patients with amnesic mild cognitive impairment or early dementia of Alzheimer's disease could be distinguished from healthy controls utilizing a tablet-based drawing task. The “time in-air" differed significantly between patient groups and healthy controls, while "time on-surface" only differentiated between AD and control subjects (Müller et al., 2017). Since "time in the air" can be considered as "planning the next movement", a sequential process of handwriting (Ondo & Satija, 2007) that involves cognitive abilities (Werner et al., 2006), this could also be the more sensitive indicator. Therefore, the advantage of measuring a variety of additional variables with a digitized test implies that for each variable a behavioral analysis between different populations is required.

As for the various component measured assessed by our dTMT, they also belong to specific cognitive abilities. Among them, the number and duration of pauses and time between circles are related to inhibitory control, while the number and duration of elevators and time inside the circle are related to working memory (Fellows et al., 2017). In the present study, a significant difference between the groups was observed for the variables in completion time. In particular, these differences between the older groups in dTMT-A and -B were confirmed. As shown in Figure 6, we could identify mainly an age-related cognitive decline in perceptual speed (number and duration of pauses in dTMT-A), inhibitory control (time between circles in dTMT-B), and visual working memory (time inside the circle in dTMT-A and -B) in OA compared to YOA.

In addition, we showed that time inside the circle increases significantly in the elderly groups with increasing cognitive load (significant interaction between task condition and age group), whereas in OA only in dTMT-B an apparent

increase in time between circles was observed. These two-component measures may be important in distinguishing between PD and AD concerning the benefits of measuring additional variables mentioned earlier. For example, the component measuring time inside the circles as an indicator for working memory (Dahmen et al., 2017) can be predicted to be particularly prominent in AD due to the impairment of executive functions such as working memory and set switching (Baudic et al., 2006). As far as the strategy of task execution, in particular, is concerned, the component measures can also enable us to identify the strategy with which the task is to be executed, whether, after reaching the circle, they search for the next circle or the next target while moving between the circles. Therefore, future studies with this digital version should be required in individuals with ND such as AD and PD.

Several limitations of the study suggest the need for future study improvements. First, the sample size for this study was relatively small for this comparison study. Although the results were very clear, and larger samples would be unlikely to reach alternate conclusions, larger samples would provide a better reflection of the overall population, establish the test-retest reliability of the dTMT, and enable an investigation of the different factors such as demographics, or neurodegeneration that may affect performance on a computer-based cognitive test. Second, the study was designed to detect moderate differences between test settings and was not sufficiently focused on detecting subtle differences. Bayesian statistics could qualify the degree of support for the null or alternative hypothesis, but much larger samples would be required to provide stronger evidence for the null hypothesis. Replication in a larger sample is now required to investigate the existence of subtle differences between test settings. Third, at present, no study can be found that has examined the influence of the number of circles in the different TMT conditions. This question was usually only considered to the extent that the number of circles was adjusted to the tablet size used (see Dahmen et al. 2017; however, no adjustment was made in Hannukkala et al., 2020 using a 9.7” IPAD) We have developed a digital version that is most similar to the paper version by also choosing a comparable tablet size to the paper size (12.2”). For early differentiation between normal and impaired cognitive functions, tasks of the broadest possible task difficulty are necessary. In a recent fNIRS study (Park, Reinl, & Schott, under revision) we could show that oxygenation in the prefrontal cortex is highest in the last quarter of the task.

In conclusion, we investigated young adults and older adults with the dTMT, a new digital version of a standardized neuropsychological test, and compared it with its paper-pencil version. First, we found several advantages in measuring reliability, sensitivity, and clinical significance for dTMT compared to the ppTMT. Besides, significant differences between the elderly groups for specific cognitive ability were also observed through additional variable measurement. In the future, the early detection of motor or cognitive decline with advances in technology will play a crucial role in people suffering from ND. While many efforts are underway to develop digital biomarkers, especially for ND, the dTMT is characterized by its high sensitivity, alternative forms, and additional component measurements. Against this background, it could serve as a starting point for an early diagnostic tool. For this reason, future studies should be extended to ND such as AD and PD.

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Table 1. Participant characteristics by age group.

	Young adults (n=29)		**Young-old adults** (n=12)		**Older adults** (n=12)			
Sex (male:female)	12:17		4:8		6:6		$\chi^2(2) = 0.69$	
Handedness (% right)	82.8		100.0		83.3		$\chi^2(4) = 6.08$	
	M	*SD*	*M*	*SD*	*M*	*SD*	*F*(2,50)	η_p^2
Age (years)	22.4	4.47	60.3§	4.31	72.2§,#	4.57	656**	.963
Height (cm)	173	9.17	175	10.3	169	8.77	1.34	.051
Weight (kg)	66.8	11.2	78.0§	12.9	76.3	10.4	5.41**	.178
BMI (kg/m^2)	22.1	2.30	25.2§	1.86	26.5§	1.51	22.4**	.472
Education (years)	15.9	0.70	15.5	2.61	14.1§	3.40	3.37*	.119
Exercise (min/week)	295	198	59.6§	39.8	33.8§	47.1	17.9**	.417
							t(22)	*d*
MoCA-Test (0-30)	NA	NA	27.8	1.64	27.1	1.62	1.13	.429

Note: *M*=mean; *SD*=standard deviation; § significant difference from young adults ($p < 0.05$); # significant difference from young-old adults ($p < 0.05$); BMI: Body-Mass-Index; MoCA: Montreal Cognitive Assessment; NA: not applicable; * $p < .05$; ** $p < .01$.

Table 2. Results for relative (ICC) and absolute (SEM) inter-trial reliability, and MDC95 for each condition (three trial per condition) of the ppTMT and dTMT.

	ppTMT			**dTMT**		
	TMT-M	**TMT-A**	**TMT-B**	**TMT-M**	**TMT-A**	**TMT-B**
ICC	0.95**	0.94**	0.94**	0.93**	0.90**	0.92**
(95% CI)	(0.91-0.97)	(0.90-0.96)	(0.90-0.97)	(0.88-0.96)	(0.85-0.94)	(0.87-0.95)
SEM	0.98	1.89	4.56	1.51	2.60	6.13
SEM%	7.93	8.77	11.63	9.14	9.55	13.7
MDC95	2.73	5.16/	12.7	4.20	6.39	17.0
MDC95%	22.0	24.3	32.2	25.3	26.5	38.0

Note. ppTMT paper-and-pencil Trail-Making-Test; dTMT digital Trail-Making-Test; ICC Intraclass Correlation Coefficients; CI Confidence Interval; SEM standard error of measurement; MDC minimum detectable change; $^{**}p < 0.001$

Table 3. Descriptive data for outcome variables and statistical results for equivalence analyses. Bayesian paired t-test statistics for test setting (paper-pencil vs digital).

	Test setting				**Spear-man**	**Bayesian paired *t*-test statistics**	
Outcome variable	**Digital**		**Paper-pencil**		***rho***	**Bayes Factor H1**	**Effect size δ (95% credible intervals)**
	M	*SD*	*M*	*SD*			
Direct scores (time to completion)							
TMT-M (s)	16.6	5.57	12.4	4.20	.87	9.632e+11	1.44 (-1.05 to 1.84)
TMT-A (s)	24.1	8.34	21.2	7.47	.90	29859	0.76 (-1.07 to -0.45)
TMT-B (s)	44.6	21.3	39.2	18.8	.82	62.2	0.49 (0.21 to 0.78)
Derived scores							
TMT-(B-A)	20.5	15.5	18.0	13.5	.64	1.04	0.27 (0.00 to 0.54)
TMT-(B/A)	1.83	0.49	1.83	0.43	.56	0.15	-0.01 (-0.27 to 0.25)
DTC TMT-A (%)	46.9	22.1	73.2	30.3	.51	5670000	-0.96 (-1.29 to -0.63)

Note. TMT Trail-Making-Test; DTC Dual Task Costs (e.g. ([TMT-B – TMT-M]/TMT-M))

Figure Captions

Figure 1. Examples for the different dTMT conditions

Figure 2. Example for the performance of the ppTMT and the dTMT by an older adult

Figure 3. Design of the present study and procedure of one sample for ppTMT or dTMT

Figure 4. Comparability across TMT variants. Graphs on the left side: Scatterplots with reference line showing a linear relationship between the type of assessment (dTMT vs. ppTMT). Graphs on the right side: Bland-Altman plots of dTMT and ppTMT (M, A, and B from top to bottom) for young, young-old, and older adults: mean difference (solid black line) is close to zero, showing no bias; dashed lines delimit limits of agreement. Comparable magnitudes of difference are seen throughout the range of measurements, and 92 to 96% of the data within limits of agreement.

Figure 5. Boxplot of differences in TMT test durations based on age groups ; median value (solid black line in Box); Interquartile range (lower and upper of the Box); maximum and minimum value (upper and lower whisker); significant differences (* $p < .05$; ** $p < .01$)

Figure 6. Mean and standard deviation of component measures from dTMT (number and duration of lift, number and duration of pauses, time inside circle, and time between circles from top to bottom) (* $p < .05$; ** $p < .01$)

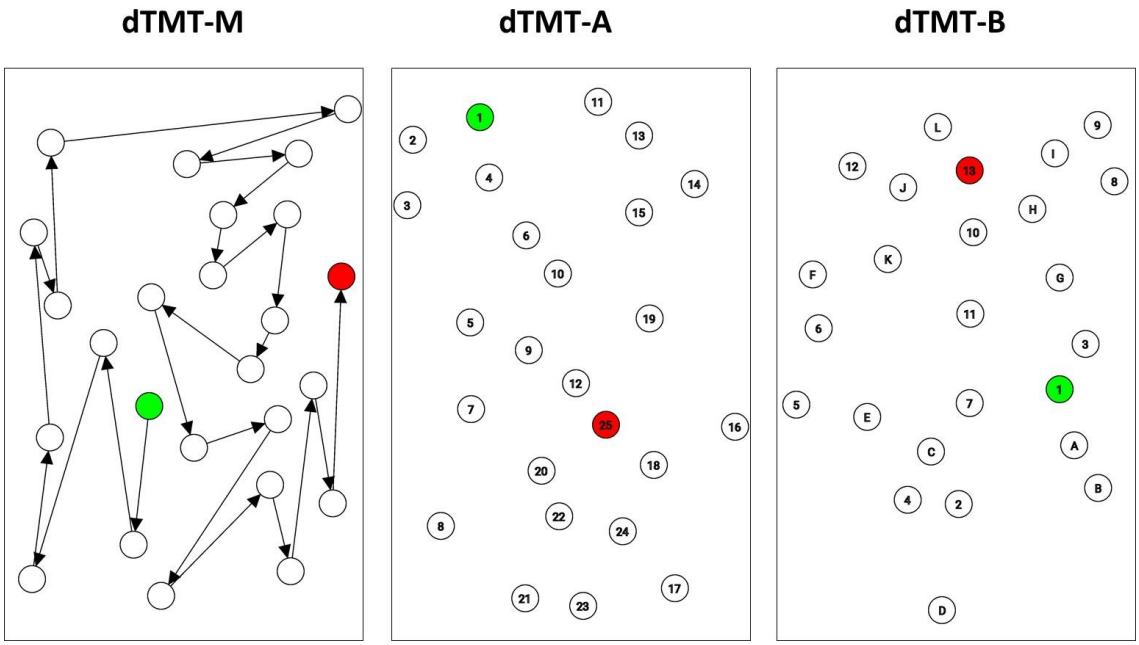

Figure 1

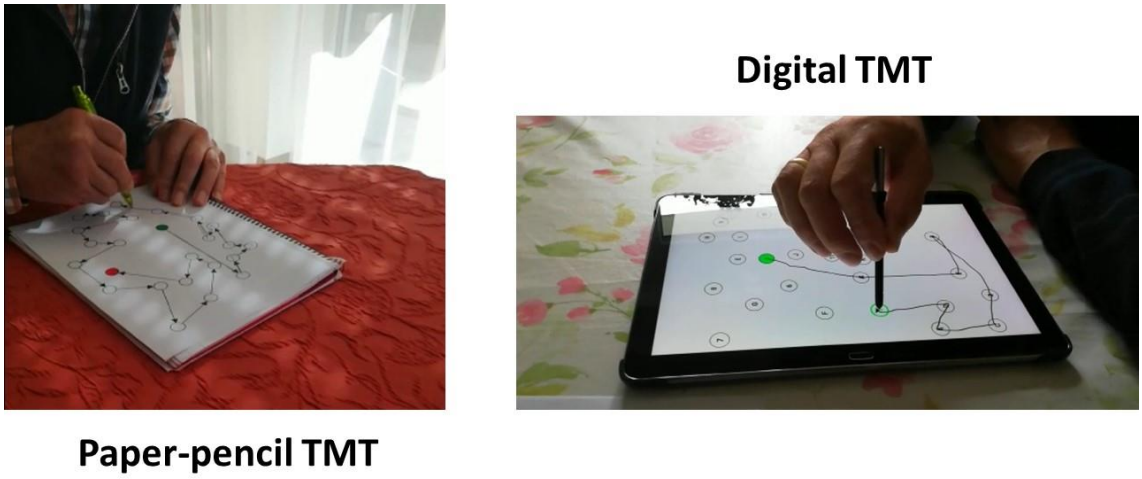

Figure 2

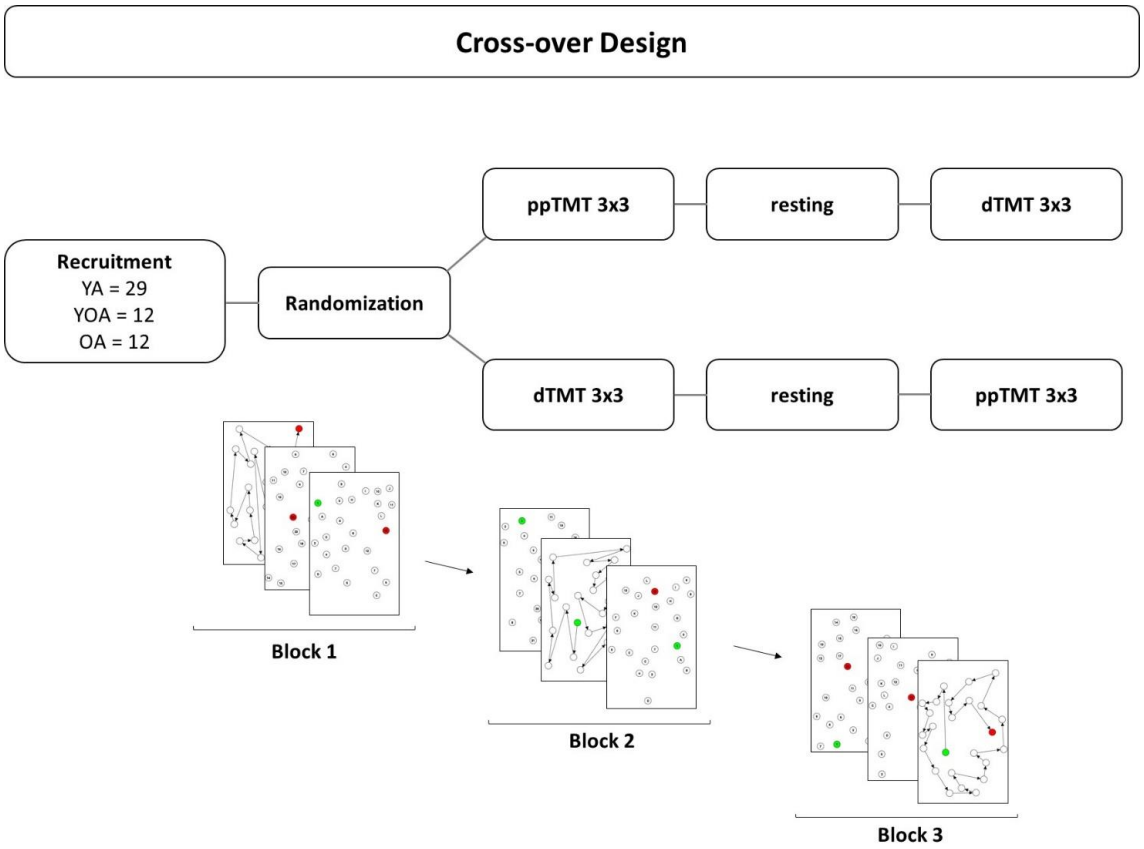
Cross-over Design
Recruitment
YA = 29
YOA = 12
OA = 12
Randomization
ppTMT 3x3
resting
dTMT 3x3
dTMT 3x3
resting
ppTMT 3x3
Block 1
Block 2
Block 3

Figure 3

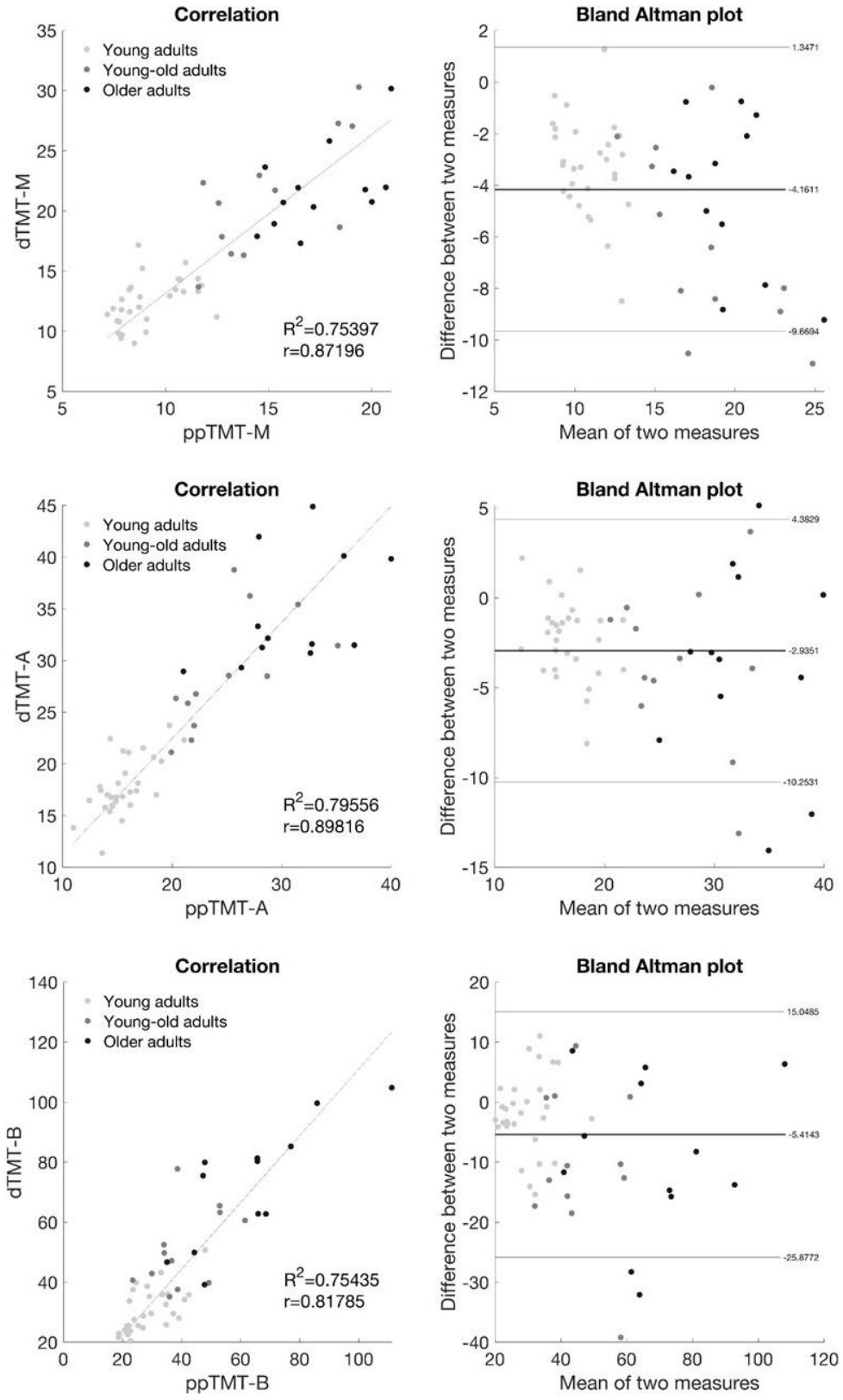
Correlation
Young adults
Young-old adults
Older adults
dTMT-M
ppTMT-M
R²=0.75397
r=0.87196
Bland Altman plot
Difference between two measures
Mean of two measures
1.3471
-4.1611
-9.6694
Correlation
Young adults
Young-old adults
Older adults
dTMT-A
ppTMT-A
R²=0.79556
r=0.89816
Bland Altman plot
Difference between two measures
Mean of two measures
4.3829
-2.9351
-10.2531
Correlation
Young adults
Young-old adults
Older adults
dTMT-B
ppTMT-B
R²=0.75435
r=0.81785
Bland Altman plot
Difference between two measures
Mean of two measures
15.0485
-5.4143
-25.8772

Figure 4

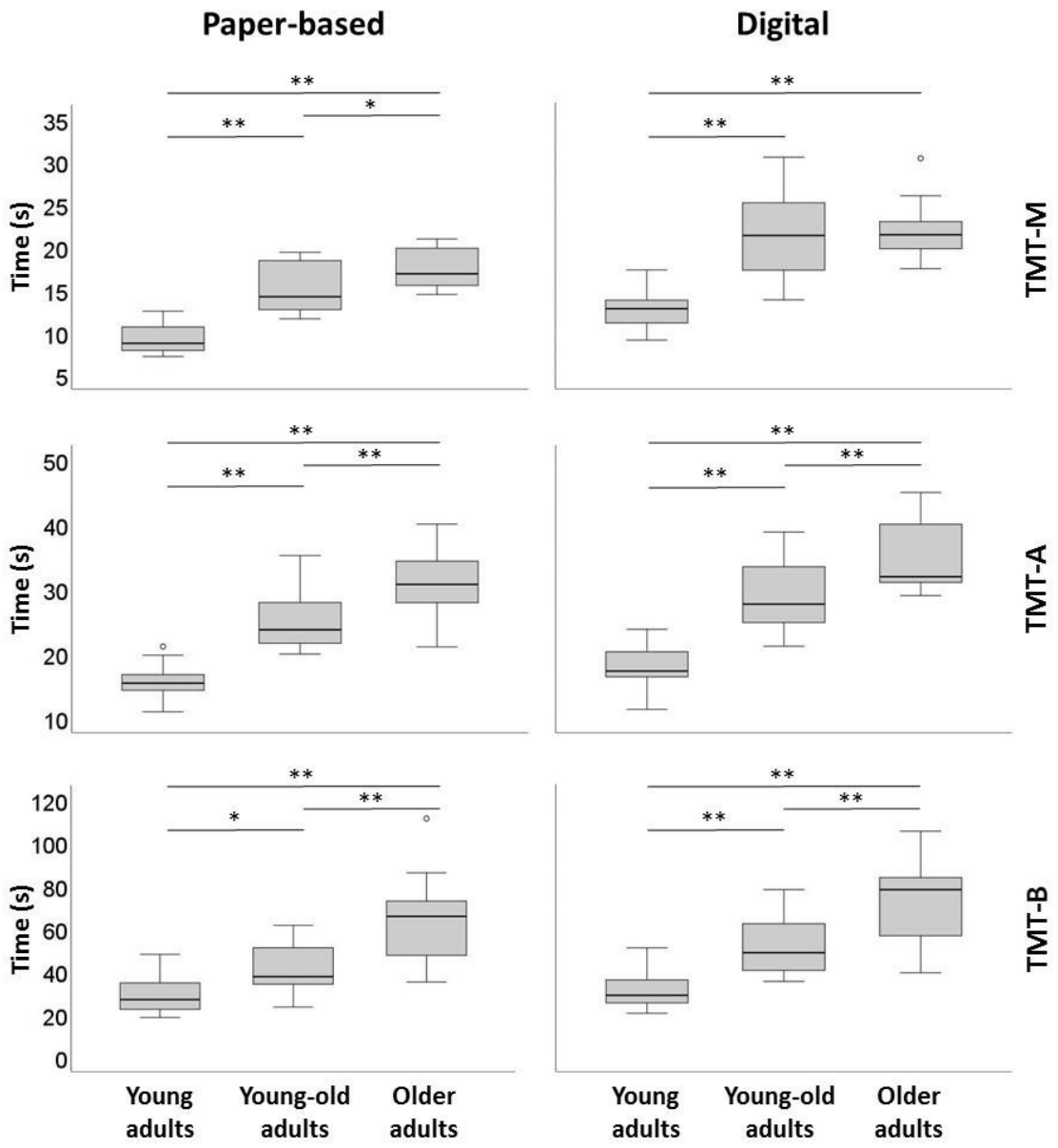
Paper-based
Digital
TMT-M
TMT-A
TMT-B
Time (s)
Young adults
Young-old adults
Older adults

Figure 5

Appendix A2 – Manuscript 2

Accepted manuscript 2:

Park, S.-Y. & Schott, N. (2022). Which motor-cognitive abilities underlie the digital Trail-Making Test? Decomposing various test scores to detect cognitive impairment in Park-inson's disease - A pilot study. *Applied Neuropsychology: Adult*, 1-15. https://doi.org/10.1080/23279095.2022.2147837

Word Count: 8337 (excluding abstract, references, and figure / table legends)
Number of figures: 4; Number of tables: 5

Which motor-cognitive abilities underlie the digital Trail-Making Test? Decomposing various test scores to detect cognitive impairment in Parkinson's disease - A pilot study

Abstract

Since Parkinson's disease (PD) is a heterogeneous disorder with symptoms such as tremors, gait and speech disturbances, or memory loss, individualized diagnostics are needed to optimize treatment. In their current form, the typical paper-pencil methods traditionally used to track disease progression are too coarse to capture the subtleties of clinical phenomena. For this reason, digital biomarkers that capture, for example, motor function, cognition, and behavior using apps, wearables, and tracking systems are becoming increasingly established. However, given the high prevalence of cognitive impairment in PD, digital cognitive biomarkers to predict mental progression are important in clinical practice. This pilot study aimed to identify those components of our digital version of the TMT (dTMT) that allow discrimination between PD patients with and without cognitive deficits. A total of 30 healthy control (age 66.3 ± 8.61) and 30 participants with PD (age 68.3 ± 9.66) performed the dTMT using a touch-sensitive tablet to capture enhanced performance metrics, such as the speed between and inside circles. The decomposition of cognitive abilities based on integrating additional variables in the dTMT revealed that the Parkinson's disease group was significantly more sensitive to parameters of inhibitory control. In contrast, the mild cognitive impairment group was sensitive to parameters of cognitive flexibility and working memory. The dTMT allows objective, ecologically valid, and long-term cognitive and fine-motor performance tracking, suggesting its potential as a digital biomarker in neurodegenerative disorders.

Keywords. Computerized cognitive assessment; neuropsychological tests; digital biomarkers; executive functions

1 Introduction

Parkinson's disease (PD) is the most common neurodegenerative disease (ND), along with Alzheimer's disease (AD), and its prevalence increases with age (Prince et al., 2015). PD is primarily characterized by movement disorders with the main symptoms of resting and action tremors, rigidity, bradykinesia, and postural instability. Pathologically, PD is caused by the damage of nigrostriatal dopaminergic neurons sent to the striatum and the presence of Lewy bodies in the central, peripheral, and autonomic nervous systems (Jellinger, 2012). However, cognitive impairment has recently been increasingly recognized (Dag Aarsland et al., 2017) as an important non-motor symptom in PD. The prevalence of PD with mild cognitive impairment (PD-MCI)[1] is generally reported to be 19% to 25% (Aarsland et al., 2009; Caviness et al., 2007; Dalrymple-Alford et al., 2010; Hoops et al., 2009) and maybe as high as 53% (Janvin et al., 2006). Therefore, effective early screening of motor and cognitive performance is needed to determine whether an individual with possible signs of PD needs further diagnostic measures.

Biomarkers, for example, from serum or imaging, are objectively measured parameters for normal physiological and pathological processes or pharmacological responses to a therapeutic intervention. Thanks to technological innovations, in addition to classical biomarkers, a new type of biomarker is now available - the so-called digital biomarker. Digital biomarkers provide recognizable data patterns from various sources, such as sensor systems (e.g., digitized boards or accelerometers), from which diagnostic or prognostic values can be derived. Techniques for monitoring motor and cognitive decline have already been developed for early detection of disease progression in motor and cognitive changes, providing information for diagnostic decisions and allowing effective interventions early in the disease process (Arora et al., 2015; Tornatore, 2005). A body of evidence suggests that objective monitoring using technology-based measurements will be a helpful

[1]The 2012 PD-MCI diagnostic criteria consist of level I and II assessments (Litvan et al., 2012). For a diagnosis of PD-MCI, individuals must have a diagnosis of idiopathic PD, a gradual decline in cognitive abilities (noted by the patient, informant, or clinician), cognitive deficits upon testing, and preserved functional independence (with the exception of subtle difficulties with complex tasks). Level I assessment requires impairment on a scale of global cognition (e.g., the Montreal Cognitive Assessment (MoCA)) or at least two neuropsychological tests. Level II assessment requires full neuropsychological testing that includes all five cognitive domains, with impairment on two tests within one cognitive domain or on one test in two cognitive domains.

tool for examining neuropsychological assessments (for a review, see Koo & Vizer, 2019). Moreover, these digitized measurements have already been shown to reduce rater bias and interrater variability and increase sensitivity, so significant sub-clinical changes can be detected for this reason (Espay et al., 2016; Lin et al., 2018). Similarly, the transfer of paper-pencil-based cognitive tests to mobile devices offers the possibility of capturing not only cognitive but also fine-motor performance. For example, using digitized handwriting measurement, Rosenblum et al. (2013) demonstrated that tremor intensity allowed discrimination between PD and healthy controls. In the handwriting task, the two measurement factors "time on surface" and "time in air" should be considered when discriminating between individuals with PD and healthy adults. In particular, the variable "time in air" refers to planning the next movement in the sequential writing process (Ondo & Satija, 2007) and may involve cognitive function (Werner et al., 2006). This variable appears to be a potential digital cognitive biomarker for dementia. Besides, differences have already been observed between individuals with MCI or early dementia of AD and healthy controls during a tablet-based drawing task (Faundez-Zanuy et al., 2014).

Furthermore, in PD, problems with fine-motor control occur when movements are performed sequentially because coordination between the components of the movement sequence has been lost (Cascarano et al., 2019, 2020). These sequential movements are more segmented and characterized by pauses between sub-movements (Bidet-Ildei et al., 2011). Although freezing of gait is currently a common debilitating symptom of PD (Heremans et al., 2016), freezing of the upper limb (manual motor blocks) during handwriting or drawing has rarely been investigated and has received little attention. This symptom may mainly affect the kinematic parameters of handwriting, as the erratic movement during handwriting is more likely to result in higher jerk values and acceleration mismatch after freezing of hand motion (Thomas et al., 2017). Regarding sequential movements, handwriting is a complex human activity requiring fine-motor skills involving complex cognitive, sensory, and perceptual-motor components (Carmeli et al., 2003) and is particularly affected by NDs (de Paula et al., 2016).

The Trail-Making-Test (TMT; Reitan, 1955), a handwriting-like task, is a fine motor-cognitive task consisting of sequential movements involving fine and

complex manual skills based on a sophisticated combination of cognitive, sensory, and motor components (Klaming & Vlaskamp, 2018). The TMT is a well-established neuropsychological testing procedure that is sensitive to various neurological disorders and is therefore preferred as a predictor of executive functions (Arbuthnott & Frank, 2000; Faria et al., 2015). In its original paper-pencil version (Army Individual Test Battery, 1944; Reitan, 1955), the TMT-A (connecting numbers from 1 to 25 in ascending order) is primarily predicted by visual search and information processing speed (Bowie & Harvey, 2006; Ríos Lago et al., 2004). In contrast, the TMT-B (connecting numbers from 1 to 13 and letters from A to L in alternating and ascending order) is associated with more complex cognitive abilities such as cognitive flexibility, working memory, and control (Arbuthnott & Frank, 2000; Kortte et al., 2002b). Recently, our group has developed a digital Trail-Making-Test (dTMT, Park & Schott, 2021) using a 12"-tablet similar to the size of the paper version with an extension of a trail-tracing task to measure a fine-motor control (Schott et al., 2016). Moreover, our version of the dTMT has already been shown to be reliable and valid by comparison with the paper-pencil version of the TMT in healthy older and young adults. The dTMT allows us to deconstruct cognitive abilities, providing a detailed analysis of cognitive processes (Park & Schott, 2021). In fact, given the wide range of cognitive functions required by the TMT-B, it is not surprising that this most task difficult of TMT conditions is sensitive to neurological dysfunction. However, while patients may achieve the same duration in the TMT-B, one may have difficulties with fine-motor control, and another encounters problems with inhibitory control or cognitive flexibility, such as set-switching.

For this reason, only the completion time and the number of errors as measured dependent variables of the task cannot reveal which cognitive functions are individually compromised. Therefore, isolating the TMT components' cognitive processes allows for more clearly identifying specific deficits of the motor and cognitive impairment in patients. Our version of the TMT also offers the possibility to measure additional variables (e.g., the time spent between or within the circles; see methods section) and better describe cognitive processes such as processing speed, working memory, inhibition control, and set-switching (Fellows et al., 2017) separately. Moreover, since the deterioration of fine-motor control has also been observed in older people (Corti et al., 2017), individuals with Alzheimer's (de

Paula et al., 2016; Müller et al., 2017), and Parkinson's disease (Dahdal et al., 2016; Iakovakis et al., 2018; Pradhan et al., 2010), the dTMT, which includes fine-motor control, seems appropriate for use in PD.

This pilot study aimed to identify those components of our digital version of the TMT (dTMT) that allow discrimination between PD patients with and without cognitive deficits. The cognitive function status of PD patients and the healthy control group was only classified with a Level I assessment that requires impairment on a scale of global cognition (e.g., the Montreal Cognitive Assessment (MoCA, Nasreddine et al., 2005); Litvan et al., 2012). Here, we will use a double threshold for the MoCA as it improves clinical and subclinical classification and, using an uncertainty interval (24 to 26), reduces the effect of prevalence on MoCA performance (Thomann et al., 2020). First, we hypothesized that differences between the groups with different cognitive abilities would be more manifest, especially in the dTMT-B, which is the most complex and attention-demanding condition to complete due to the higher cognitive load. Second, we expected that additional variables measured by the dTMT (including time in and between circles, pause length) that allow separate prediction of cognitive processes such as inhibitory control, working memory, and cognitive flexibility would enable a detailed analysis of the two groups according to their cognitive abilities. Finally, we expected that a detailed analysis of the processes within each circle could identify anomalies associated with PD, such as fine-motor impairment (i.e., freezing of hand movement or tremor) and mild cognitive impairment.

2 Materials and methods

2.1 Participants

Estimating sample size calculation was conducted a priori using G*Power (Version 3.1.9.2) (Math.-Nat. Faculty, Düsseldorf, Nordrhein-Westfalen, Deutschland) (Faul et al., 2007). Based on detecting a small to medium effect, we required a total sample size of 54 in the present study with a 5% risk of type 1 error (α), 80% power, and an estimated correlation of $r = 0.5$ between repeated measurements of the cognitive performance measured by dTMT. In addition, A drop-out quota is this taken into account.

A total of 30 healthy control (HC; *M* = 66.3, *SD* = 8.61, age-range 46–82, 17 men) and 30 participants with PD (*M* = 68.3, *SD* = 9.66, age-range 45–80, 17 men) volunteered to participate in this experiment. Participants diagnosed with Parkinson's disease by a clinician at the hospital were found through self-help groups from the German Parkinson's Association and sports groups for people with PD in the Rhein-Neckar area in Germany. The German Parkinson's Association is a self-help association founded in 1981. It includes around 450 regional groups that meet monthly to weekly to exchange and support each other. Inclusion criteria for the PD participants were a clinical diagnosis of PD based on the United Kingdom Parkinson's Disease Society Brain Bank (Gibb WRG & Lees AJ, 1998) and Hoehn and Yahr stage at a mild to moderate level of the disease (I–III) in the ON medication state (Hoehn & Yahr, 1998). The medical history of the PD group (i.e., year of diagnosis, duration of diseases, Hoehn and Yahr stage, and movement disorders such as tremors) is shown in Table 1. The participants for the control group not diagnosed with PD were recruited through acquaintances or, if applicable, were partners or life companions of the participants with PD. Exclusion criteria for both groups were comorbidity with other neurological and/ or psychiatric diseases; visual and hearing impairment incompatible with the neuropsychological tests. In addition, participants were not allowed to have any fine-motor injuries that could have interfered with performing the fine-motor-cognitive task. All participants were informed of the nature and aim of the study and signed a consent form. All procedures were in accordance to the Declaration of Helsinki with ethical standards, legal requirements, and international norms. An internal ethics committee of the University of Stuttgart approved the present study.

Here Table 1

2.2 Measures

2.2.1 Sociodemographic and disease-related information, fall of falling, and physical activity

Basic demographic information (e.g., age, sex, and education) on the participants and their medical history (e.g., medication and number of falls in the last four weeks, fear of falling) were collected. In addition, the height and weight of the participants were measured, and the body mass index (BMI, kg/m^2) was calculated. Participants were asked about the type of sport practiced in sports clubs and leisure

time, the number of training units per week, the number of training sessions, and whether other activities, such as handwork or gardening, are carried out to assess physical activity. In addition, all participants were asked a single question, "How afraid are you of falling?" Participants were asked to respond on a visual analog scale ranging from 1 (not at all anxious) to 10 (exceedingly anxious). This single-item question had a simple structure and was easily administered to individuals with cognitive impairments. Recent studies showed moderate agreement with Fall Efficacy Scale (Belloni et al., 2021). The drug intake and duration, PD diagnosis duration, presence of tremor, and Hoehn and Yahr stage were collected for PD participants.

2.2.2 Parkinson's screening questionnaire (PSQ; Fereshtehnejad et al., 2014)

Parkinsonism characteristics were assessed using the PSQ (Fereshtehnejad et al., 2014). This six-item self-report measure was based on an original collection of 25 questions that were part of existing PD screening measures. Items were selected for the PSQ that best discriminated between PD and an age-matched comparison group based on the negative clinical utility index (Fereshtehnejad et al., 2014). The resulting six-item self-report questionnaire asked about the presence of motor characteristics, to which respondents could answer "yes," "no," or "I do not know." The questions addressed stiffness, tremors, problems with buttoning and dressing, lack of arm swings when walking, feeling stuck to the floor when starting to walk or turning around, and general motor slowing. The frequency of responses to each item and the total number of "yes" responses (PSQ total score) are reported, with higher scores indicating more Parkinson's-related features. The reporting of the total screening score is of particular importance, weighing four of the six PSQ items that independently discriminate PD from healthy controls (Fereshtehnejad et al., 2014). This weighted score is calculated as follows: (2 × stiffness) + (5 × tremor) + (5 × arm swing) + (5 × holding on to the ground). The reliability of the PSQ was reported to be good (Cronbach's $\alpha = 0.88$) (Fereshtehnejad et al., 2014). In the present study, Cronbach's alpha is $\alpha = .77$.

2.2.3 Cognitive Functional Rating Scale (CFRS; Kulisevsky et al., 2013)

The Cognitive Functional Rating Scale is a questionnaire designed to assess a broad range of functional aspects of Parkinson's Disease. It appears to be sensitive

to cognitive impairment in older adults with Parkinson's disease (Kulisevsky et al., 2013). All 12 questions examine with a few examples whether the individual has difficulties performing an activity (0 = none; 1 = sometimes; 2 = most of the time; 8 = the respondent has had the activity in the past), e.g., in handling money, housekeeping, organizing vacations or meetings, handling personal mail, checking medication schedule, organizing daily activities, handling electrical household appliances, understanding how to use public transport, solving unforeseen events, explaining things that he/she would like to say, understand the things he/she reads and use the cell phone. The total of all rating scores is 24. The average of all questions answered 0-2 is calculated, except for question 8, which includes an activity never performed in the past. The CFRS showed an excellent internal consistency (Cronbach's $\alpha = 0.91$) in our study.

2.2.4 Beck Depression Inventory short form (BDI-6; Blom et al., 2012)

The BDI-6 assesses the severity of depression through a self-report questionnaire. In 6 questions capturing sadness, pessimism, past failure, guilt, self-denial, and indecision, the individual is asked to indicate what most closely corresponds to his or her current mood state. To answer, 4 options are given, adding the individual items to a total score of 0-18. The present study's 6-item version of the BDI-II had poor internal consistency ($\alpha = 0.56$).

2.2.5. Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005; validated German version; Thomann et al., 2020)

The MoCA test was administered to assess the cognitive performance of the participants. The MoCA test was developed as a screening test for mild cognitive impairment (MCI) (Duffin et al., 2012; Kenny et al., 2013). Today, it is frequently used to evaluate cognitive performance abilities in research and is considered a suitable screening test for dementia and cognitive functions in individuals with PD (Dalrymple-Alford et al., 2010). The MoCA is a ten-minute, 30-item test with high sensitivity and specificity. It includes tasks on short-term memory, spatial-visual abilities, executive functions, attention and concentration, working memory, language, and orientation to time and place. In the evaluation, all achieved scores are added up. The maximum score that can be achieved is 30 points. Values greater than or equal to 26 points have been shown to be the optimal cut-off value for detecting MCI with high specificity and reliability (Nasreddine et al., 2005).

However, the cut-off value (25/26) for detecting MCI remains controversial. In several other studies, this value has been found to have a specificity of less than 66%, possibly implying an unacceptably high number of false-positive classifications (Carson et al., 2018; Davis et al., 2015; Smith et al., 2007). For this reason, we used a revised cut-off value using a double threshold cut-off value with an indecisive area, according to Thomann et al. (2020). The addition of the indecisive area increases sensitivity and specificity, improving cognitive screening accuracy. In addition, this area of indecisiveness highlights and accurately reflects the difficult realities associated with the early detection of cognitive impairments in the clinical field (Thomann et al., 2020). An adjusted z-score (MoCa z-score) was calculated considering age, gender, and education (Thomann et al., 2020) (z = MoCA total score – (23816.36 + (-175.821 * age [years]) + (472.9053 * education [years]) + (1672.542 * sex [male = 0; female = 1]))) / 4470.258). MoCA scores ≥ -0.19 (27/30) points may be considered unremarkable with high confidence, whereas scores ≤ -1:36 (23/30) points are very likely pathological. For scores between -1.36 and -0.18 (24-26 points; i.e., within the gray zone), either a more comprehensive neuropsychological examination (e.g., Diagnostic and Statistical Manual, 5th Edition) should be arranged or a test repetition in 6 to 12 months should be envisaged (Thomann et al., 2020). A possible MCI classification (pathological group) is defined as an objective result of impairment in one or more cognitive functions, usually memory problems (Albert et al., 2011). For the current study design, we used this MoCA z-score to divide into sub-groups (pathological, undecided, and healthy) within each group (HC and PD).

2.2.6 digital Trail-Making-Test (dTMT)

The Trail-Making-Test (TMT) is a conventional neuropsychological assessment method that is sensitive to various neurological disorders and is, therefore, commonly used worldwide as a predictor of executive function. Its original paper-pencil version comprises two difficulty levels: the TMT-A and TMT-B (Army Individual Test Battery, 1944; Reitan, 1955). The TMT-A requires connecting the numbers labeled on a circle frame from 1 to 25 in ascending order as quickly as possible (1-2-3 .... 25). Compared to the TMT-A, the TMT-B is a more difficult task in which a series of 25 circles must be connected by alternating ascending numbers and letters (1-A-2-B ... 13). The test administrator records the time taken

to complete the task and the number of errors as performance indicators in both conditions. The TMT-A generally predicts visual recall and processing speed (Bowie & Harvey, 2006; Ríos Lago et al., 2004), whereas the TMT-B is related to more complex cognitive functions, such as inhibition and cognitive flexibility, aside from those included in the TMT-A (Arbuthnott & Frank, 2000; Kortte et al., 2002b). The TMT assesses executive function, but it is a manual task requiring fine-motor movements. For this reason, the paper-pencil TMT was expanded by Schott et al. (2016) with a variation that explicitly targets fine-motor control and speed (TMT-M: following a defined path that also connects 25 circles).

The digital TMT (dTMT) developed by a group around Nadja Schott (Park & Schott, 2021) is an android-based app that was presented on a 12.2 "Samsung Galaxy Touchscreen tablet (12.2-inch diagonal LED-backlit Multi-Touch display with IPS technology; portrait alignment) with a resolution of 2560 x 1600 and android version 6, which allows similar structure and size to the paper-and-pencil version with the original number of 25 circles. The dTMT consists of the three condition levels of difficulty, including two difficulty conditions from the original TMT version combined with a trail-tracing task to account for fine-motor control (dTMT-M, -A, and -B, see Figure 1). Furthermore, our version of the dTMT is an optimized version that merges the approaches of existing digital versions with additional measurement parameters (Dahmen et al., 2017) and the divide-and-combine approach (Zeng et al., 2017), allowing the generation of alternative trials for each condition with the same task difficulty and length. In particular, it is possible to isolate the various cognitive processes involved in performing the task by measuring additional variables (Fellows et al., 2017). The dTMT was developed as consistently as possible with the original pen-paper TMT to establish equal concurrent validity. Some improved features were embedded into the design and showed potential use in young and older adult populations (Park & Schott, 2021).

Here Figure 1

Specifically, our version of dTMT can measure variables such as time spent in each circle for more detailed analysis in addition to the existing additional variable measurement such as time spent inside circles, time between circles, number and duration of pauses, number and duration of lifts, and distance length drew by the participant (Dahmen et al., 2017; Fellows et al., 2017; Park & Schott, 2021).

2.3 Experimental design & procedure

In the present research design, we compared the fine motor-cognitive performance using the dTMT between PD and HC with respect to MCI distribution (healthy, undecided, pathological) in the ON-medication condition. The assessments were administered at the participants' homes to avoid taking them out of their familiar environment. In the beginning, the participants gave written consent to participate after being informed about the study and the exact procedure. It was pointed out that participation in the study was voluntary and that withdrawal was possible at any time without giving reasons. Then, the dTMT and its conditions (dTMT-M, -A, and -B) were explained, and open questions were answered. Before the actual test, each participant conducted a short practice run to familiarize themselves with the procedure in each condition. Each condition was performed three times, resulting in a total of nine trials. The order of the different conditions was determined using a randomization sequence built into the program. All variables measured by the dTMT were recorded automatically. All questionnaires and the MoCA test were then administered. The participants were given sufficient breaks between the individual test sections.

2.4 Data analysis

Statistical analyses were performed using SPSS v.27 (SPSS, Chicago, IL). We first explored the dependent variables to examine missing data points, normality of distributions (tested by Kolmogorov–Smirnov tests), and the presence of outliers. The effect sizes of all analyses are presented in Cohen's *d* or partial Eta^2 (η_p^2). The classification of η_p^2 also follows the conventions of Cohen (Cohen, 1988): 0.01 for a small effect, 0.06 for a medium effect, and 0.14 for a strong effect. An alpha level of .05 was used for all statistical tests.

Potential differences between groups for continuous variables (i.e., age, height, weight, BMI, physical activity, medication, falls) were assessed using ANOVAs with "PD-group" (PD and HC) and "MCI-group" (Pathological, Undecided, and Healthy group) as between-subjects factors, and categorical demographic variables (i.e., sex, category of MCI and handedness) were compared using Chi-Square tests. 2 × 3 ANOVAs with "PD-group" (PD and HC) and "MCI-group" (Pathological, Undecided, and Healthy group) as between-subjects factors were

used to examine the differences between PD and HC group according to the MCI distribution for PSQ, CFRS, BDI-6, and MoCA.

Several steps were taken to analyze the variables measured by the dTMT. In the first step, we conducted 3 × 2 × 3 ANOVAs with repeated measurements (with Greenhouse Geisser correction, if the sphericity was not met, $p < .05$) on the completion time (mean value of three trials in each condition) as a dependent variable commonly used in TMT-research with "task condition" (dTMT-M, dTMT-A, and dTMT-B) as within-subject factor, and "PD-group" (PD and HC) and "MCI-group" (Pathological, Undecided, and Healthy group) as between-subjects factor. Then, we used univariate analysis of variance (ANOVA) for all variables measured by the dTMT (except completion time; user speed, distance ratio, number of mistakes, lifts, and pauses, duration of lift, pauses, time spent between and inside a circle; mean value of three trials in each condition) with "PD-group" (PD and HC) and "MCI-group" (Pathological, Undecided, and Healthy group) as between-subjects factors, to determine which variable was more sensitive to which types of group (PD, MCI or PD × MCI).

After confirming the difference of each variable in each condition between the "PD-group" and "MCI-group", a decomposition analysis of executive function (inhibitory control, working memory, and cognitive flexibility) was performed. First, following the analytical steps of Fellows et al. (2017), the values of each variable related to working memory (number of lifts, duration of lifts, and time spent inside the circles) and inhibitory control (number of pauses, duration of pauses, and time spent between circles) were calculated as the average time spent inside and between circles and duration per number of lifts/pauses. The variable calculated for cognitive flexibility was the absolute value obtained by subtracting the time spent in the number circles and the duration spent in the letter circles. It is assumed that the closer the value is to zero, the better the cognitive flexibility, that is, the ability to switch tasks, and that the larger the value, the worse this ability is. Then, we calculated a 3 × 2 × 3 ANOVA with repeated measurements on duration time as a dependent variable with "sub-variable" (inhibitory control, working memory, and cognitive flexibility) as within-subject factors and "PD-group" and "MCI-group" as between-subjects factor.

Given the large effect of age on "sub-variable" (above $r = 0.5$), commonality analysis was performed within multiple linear regression by adjusting these variables (inhibitory control, working memory, and cognitive flexibility) according to age. As the number of predictor variables in the commonality analysis increases, the coefficients also increase exponentially, and the interpretation becomes more complicated (Ray-Mukherjee et al., 2014). For this reason, we selected only three independent variables among demographical variables (i.e., Fear of falling, CFRS, PSQ, BDI-6, Physical activity in sports clubs, PD-dummy-group, and MCI-dummy-group) based on their relative importance. The % of R^2 as effect size according to the unique or common contribution is classified as follows: <1 % negligible, >1 % small contribution, >9 % moderate contribution, and >25 % large contribution (Marchetti et al., 2018). The commonality analysis and selection of variables according to their relative importance were performed using the R libraries yhat 2.0-3 (Nimon et al., 2008) and relaimpo 2.2-6 (Grömping, 2006).

Finally, to further analyze the individual specificity of each group occurring during the task in the dTMT-B in more detail, we extracted the time spent in each circle measured by the dTMT and observed the change during the task. In a further step, the circles for dTMT-B were first divided into 3 groups of 8 circles each (first group of 8 circles: 1 - D; middle group of 8 circles: 5 - H; last group of 8 circles: 9 - L; " time spent in circles in progression"). Then, a 3 × 2 × 3 ANOVA with repeated measurements was performed on time spent in each circle by averaging the time spent in a total of 24 circles as a dependent variable with "time spent in circles in progression" as within-subject factor and "PD-group" (PD and HC) and "MCI-group" (Pathological, Undecided, and Healthy group) as between-subjects factor.

3 Results

3.1 Characteristics of the Study Population

Table 2 presents the summarized demographic data on sex, age, height, weight, BMI, handedness, years of education, physical activity, number of falls in the past 4 weeks, fear of falling, and medication. Among these variables, a significant interaction effect PD x MCI was found for height and weight, indicating significantly smaller values in the HC-pathological group than in the PD-pathological group. In

addition, a significant difference was found between the PD group and the HC group in the number of falls and fear of falling, with the PD group having more fall experiences than the HC group and also greater fear of falling.

Here Table 2

3.2 Parkinson's Screening Questionnaire, Cognitive Functional Rating Scale, Beck Depression Inventory, and Montreal Cognitive Assessment (PSQ, CFRS, BDI-6, and MoCa)

For the PSQ, there was a significant difference between the PD group and the HC group, with a higher number of symptoms for the PD group (see Table 2). In addition, the CFRS also showed a significant difference between the PD groups, with greater limitations in self-rated cognitive performance in the PD group. Furthermore, the expected significant difference between the MCI groups was observed for the MoCa score and the MoCa z-score. However, no interaction effects were found between the PD and MCI groups for these variables. Furthermore, there were no group effects for the BDI-6.

3.3 Parameters in dTMT assessment

3.3.1 Completion time

At the first level of the statistical analysis for the dTMT, ANOVA with repeated measurements on the variable "completion time" across the levels of task difficulty showed a significant effect of "task condition", $F(1.04, 56.3) = 95.4$, $p < .001$, $\eta_p^2 = .639$ and a significant interaction effect between "PD-group" and "task condition", $F(1.04, 56.3) = 5.97$, $p = .017$, $\eta_p^2 = .100$, and between "MCI-group" and "task condition", $F(2.09, 56.3) = 3.13$, $p = .050$, $\eta_p^2 = .104$. In the post-hoc analysis for task condition, significant differences were observed between all conditions ($p < .001$). The post hoc analysis for the interaction between PD-group and task condition showed significant differences between PD and HC in each condition for dTMT-M ($p = .006$), -A ($p = .003$), and -B ($p = .006$). For the interaction between MCI-group and task condition, significant differences were also found between pathological and undecided groups for the dTMT-M ($p = .035$), -A ($p = .047$), and -B ($p = .013$), as well as between pathological and healthy groups for the dTMT-M ($p = .001$), -A ($p = .010$), and -B ($p = .004$). However, there was no significant interaction between PD-, MCI-group, and task condition.

Here Figure 2

3.3.2 Temporal and spatial parameters in the dTMT assessment

Next, we performed multivariate ANOVAs to determine which variable was more sensitive to which group types (PD, MCI, interaction). Statistical results for all variables in each dTMT condition are reported in Table 3.

For the condition of the dTMT-M, "duration of lifts", "user speed", and "speed between circles" showed a significant difference or difference with a medium effect size between PD and HC. In addition, the "number of pauses", "number of lifts", "user speed", "distance ratio", and "time spent inside the circles" indicated a significant difference or difference with a medium effect size between pathological, undecided, and healthy groups.

For the dTMT-A, a significant difference or difference with a medium effect size was found between PD and HC for "number of lifts", “duration of pauses”, “duration of lifts”, “user speed”, “speed between circles”, and “time spent inside the circles”. There were also significant effects between pathological, undecided, and healthy groups for “number of mistakes”, “number of lifts”, “duration of pauses”, “distance ratio”, and “time spent inside the circles”. In addition, a significant interaction or interaction with a medium effect size (between PD and MCI groups) was revealed for “number of mistakes”, “distance ratio”, and “speed between circles.

As the most difficult of the dTMT-conditions, in the dTMT-B, the parameters “number of lifts”, “duration of lifts”, “user speed”, “distance ratio”, “speed between circles”, “time spent inside the circles”, “time spent inside a circle before a letter”, “time spent inside a circle before a number” showed a significant effect or effect with a medium effect size between PD and HC. There was also a significant effect or effect with a medium effect size between MCI groups for the parameters “duration of pauses”, “duration of lifts”, “distance ratio”, “time spent inside the circles”, “time spent inside a circle before a letter”, “time spent inside a circle before a number”. Besides, an interaction effect for PD × MCI with a medium effect size was found for “number of mistakes” and “number of pauses”.

In each case, the expected directions in performance emerged: healthy controls required less time in task performance, made fewer errors, required less time in and between circles, and lifted the pen less frequently with shorter durations

than the PD group. The same was true for comparing healthy controls and individuals with probable MCI.

Here Table 3

3.3.3 Decomposition of cognitive abilities using the dTMT-B

In an ANOVA with repeated measurements for executive function, we found a significant effect of "sub-variable" (inhibitory control, working memory, and cognitive flexibility), $F(2, 108) = 87.4$, $p < .001$, $\eta_p^2 = .618$, and a significant interaction effect between "MCI-group" and " sub-variable", $F(4, 108) = 2.95$, $p = .023$, $\eta_p^2 = .098$. Among the cognitive abilities assessed by the dTMT-B, working memory was involved with the highest proportion in this complex task, followed by cognitive flexibility and inhibitory control. For each sub-variable, significant differences were found for inhibitory control, $F(1, 54) = 5.84$, $p = .019$, $\eta_p^2 = .098$ and working memory, $F(1, 54) = 6.24$, $p = .016$, $\eta_p^2 = .104$ in the PD group, and for cognitive flexibility, $F(2, 54) = 4.25$, $p = .019$, $\eta_p^2 = .136$ and working memory, $F(2, 54) = 4.59$, $p = .014$, $\eta_p^2 = .145$ in the MCI group indicating significant differences ($p < .01$) between the pathological and the other groups (undecided and healthy). However, there was no interaction effect PD × MCI.

Before performing the commonality analysis with multiple regression, three variables were selected by determining the relative importance of each sub-variable. In Table 4, MCI-Pathological, PD-Parkinson, Fear of Falling, Physical activity in sports clubs, and PD-CFRS were identified as important variables for inhibitory control, cognitive flexibility, and working memory.

Here Table 4

Table 5 shows the results of the multiple regression analysis with R^2, β, and the unique and common effects for each model (Model 1: Inhibitory control, Model 2: Cognitive flexibility, and Model 3: Working memory). Figure 3 shows the unique (U) and common (C) effects for each sub-dimensions of the executive function. In Model 1, MCI-Pathological, Fear of Falling, and PD-Parkinson demonstrated an explanatory power of 22.2% of the variance in inhibitory control, $F(3,56) = 5.31$, $p<.001$. Among the variables, PD-Parkinson (U3: 52.0 %) made the greatest unique contribution to the prediction of inhibitory control, and the other two variables, MCI-Pathological (U1: 27.0 %) and Fear of Falling (U2: 24.5 %), also made similar and large unique contributions. The common effect between

PD-Parkinson and MCI-Pathological explained a moderate variance in inhibitory control (C2: 16.5 %), whereas the effect between PD-Parkinson and Fear of Falling was suppressed by a moderate amount of variance (C3: -16.7 %). Other common effects showed suppression effects as effects with low explanatory power contributing to the model (see Fig 3).

Model 2 explained 15.0 % of the variance with MCI-Pathological, Fear of Falling, and Physical activity in sports clubs, and these independent variables were considered significant predictors for cognitive flexibility, $F(3,56) = 3.29$, $p=.02$. As the most important factor in Model 2, the variable MCI-Pathological was observed as having the largest unique contribution (U1: 89.3 %), followed by Fear of Falling (U2: 10.0 %) and Physical activity in sports clubs (U3: 4.40 %) with a moderate and small effect. As a common effect, a suppression effect was found for Fear of Falling with MCI-Pathological (C1: -5.19%), whereas Physical activity in sports clubs showed with other variables a small and negligible common contribution to cognitive flexibility (C2: 1.21 % and C3: 0.33 %, presented in Figure 3).

In Model 3, 30 % of the variance was explained by MCI-Pathological, PD-Parkinson, and PD-CFRS, and these variables served as significant predictors for working memory, $F(3,56) = 8.03$, $p<.001$. As shown in Figure 3, MCI-Pathological made the largest unique contribution (U1: 52.3 %), followed by PD-Parkinson as a moderate effect (U2: 14.7 %) and PD-CFRS as a small effect (U3: 6.87 %). In the common effect, no suppression effect was found. Only MCI-Pathological and PD-Parkinson had a common contribution with a medium effect size (C1: 13 %) for working memory, whereas the common contribution related to the variable of PD-CFRS had a small effect size.

Here Table 5

Here Figure 3

3.3.4 Detail analysis for the variable "time inside each circle in the dTMT-B"

Figure 4 shows the time spent in each circle during the dTMT-B as individual data (A and B) and average data (C and D). In general, the participants of both pathological groups exhibited difficulties compared to the other groups. Still, a person in the PD-healthy group also showed similar difficulties compared to the pathological groups. Furthermore, the mean value of each group was curve-fitted using quadratic polynomials in C and D of Figure 4. The longest retention time for 8

circles in the middle of the task was observed for the entire group, then dropped again. In a statistical analysis of ANOVA with repeated measurements on the variable “time spent in the circles”, we found a significant effect of " time spent in circles in progression ", $F(1.73, 91.6) = 19.7$, $p < .001$, $\eta_p^2 = .271$, indicating significant differences between all ranges (1-2: $p < .001$, 2-3: $p = .001$, 3-1: $p = .016$). In addition, a significant difference was found in all three ranges in each PD group (first range: $p = .008$, second range: $p = .030$, third range: $p = .019$), and a difference with a medium effect size was confirmed only in the third range for the MCI group ($p = .054$). However, there was no interaction effect between the PD- and MCI-groups.

Here Figure 4

4 Discussion

In the present pilot study, we examined fine-motor and cognitive control between a PD group and a control group with and without cognitive deficits by combining the digital version of the TMT with additional, more detailed technologies and analysis compared to other existing digital versions. Furthermore, by analyzing various complex changes, such as previously unattempted analyses, performance changes during tasks, and decomposition of cognitive abilities into additional variables that can be measured by the dTMT, we convey the potential and capabilities of our digital version of the dTMT as a screening tool, as well as the technical limitations that need to be addressed in the future.

Similar to many previous studies using the paper version of TMT (Gaudino et al., 1995; Kortte et al., 2002a; Park & Schott, 2021; Salthouse, 2011; Sánchez-Cubillo et al., 2009; Schott et al., 2016), our study found a significant effect on task condition and group on task completion time, which can be used as a representative predictor for motor and/or cognitive performance. The reliability and validity of our digital version were already verified in a previous study comparing it with the paper-pencil version (Park & Schott, 2021). Most importantly, the usefulness of the dTMT was also confirmed through significant effects in our study's PD- and MCI-groups. However, we did not find an interaction effect between these two group factors. The small effect size found for this interaction effect is most likely due to the small sample size. In addition, differences with medium to large effect

sizes were found between the sub-groups; in particular, these differences were larger between PD- and HC-Pathological groups than for the other sub-groups. In a future study, we must further increase the value of our results by using them when computing a power analysis.

Especially given the diverse cognitive functions required for the TMT-B, it is not surprising that it reacts sensitively to cognitive deficits. Many studies have already verified various cognitive functions such as inhibitory control, working memory, set-switching, and cognitive flexibility in the TMT-B (Arbuthnott & Frank, 2000; Gaudino et al., 1995; Kortte et al., 2002a; Salthouse, 2011; Sánchez-Cubillo et al., 2009). However, processing time or different ratio quotients (B/A; B-A) are not sufficient to clarify a detailed analysis of the cognitive functions involved in the TMT. For this reason, additional parameters derived from the dTMT could explain on-task behavior and allow the decomposition of cognitive functions. We noted to this effect that each additional parameter was sensitive to either the PD- or MCI-group (see Table 3) but was still difficult to interpret. Two parameters should be highlighted among these parameters: the time spent inside the circles and between the circles. Cognitive decline may increase the time spent inside a circle while looking for the next circle, whereas problems with fine-motor control may increase the time spent moving between circles. In Table 3, significant differences were observed for the parameters of time spent inside and between circles in the PD-group. In contrast, the MCI-group showed a significant difference only in time spent in the circles. This does not appear to be a problem with fine-motor control of time spent moving between circles. However, since the symptoms of Parkinson's patients are associated with cognitive impairment with increasing disease duration (Aarsland et al., 2009; Caviness et al., 2007; Dalrymple-Alford et al., 2010; Hoops et al., 2009; Janvin et al., 2006), it seems to be sensitive to these two variables.

In addition to these two parameters, a decomposition of cognitive abilities may be possible with various additional parameters. First, in a construct validity analysis by Fellows et al. (2017), the number and duration of pauses, and the time spent between circles were related to inhibitory control. In contrast, the number and duration of lifts and the time spent inside the circles were associated with working memory. Although analysis of the construct validity of set-switching, i.e.,

cognitive flexibility, has not yet been conducted, we hypothesized that the parameters for time spent inside the circles with numbers or letters would be related to cognitive flexibility. By integrating each parameter, each executive function's subcategory consisting of inhibition regulation, cognitive flexibility, and working memory could be established and analyzed. First, the MCI-Pathological group showed a relatively large unique contribution in the sub-variables except for inhibitory control (moderate contribution). In contrast, in the PD-group, a large unique contribution was found in inhibitory control and a moderate contribution in working memory (see Fig. 3).

Inhibitory control problems are common in Parkinson's patients. The frontal lobe, particularly the inferior frontal gyrus and the anterior cingulate gyrus in the right hemispheric, plays an essential role in inhibitory control (Garavan et al., 1999; Konishi et al., 1999; Rubia et al., 2001). Deficits in inhibitory control could be observed even after a basal ganglia lesion (Rieger et al., 2003), indicating a close interaction between the basal ganglia and the prefrontal cortex (Alexander et al., 1990; Galvan et al., 2015). Most importantly, we confirmed that the PD-group made a unique and significant contribution to the inhibitory control. For example, problems in fine-motor control can be mapped with an increased number/duration of pauses outside of circles or increased time between circles. These integrated parameters for inhibitory control suggest that they may contribute positively to identifying fine-motor control problems in patients with Parkinson's disease early on. In addition, fear of falling is a common and serious problem in individuals with PD. This factor is also an important predictor for inhibitory control because inhibitory control plays a role in resisting a fall (Bolton & Richardson, 2022)

The contribution of the MCI-group reached approximately 89% to cognitive flexibility, and it is not surprising that the cognitive flexibility function was impaired in the MCI-group (Klotzbier & Schott, 2017; Sacco et al., 2019). The dTMTB requires the ability to switch tasks to alternate numbers and letters in each circle. In addition, the parameter “time spent inside each circle of number and letter” can be considered an indicator of cognitive flexibility. Nevertheless, an analysis of the construct validity of this variable using other cognitive tests related to cognitive flexibility should be performed in future studies. As other factors, physical activity in a sports club and fear of falling are also important predictors

of cognitive flexibility. Above all, fear of falling may be an early marker of a decline in global cognitive functioning (Peeters et al., 2019). Physical activity is also widely known for maintaining and improving cognitive function and has protective effects against memory and cognitive decline, particularly in people with Parkinson's and Alzheimer's disease (Paillard et al., 2015). Generally, a high level of physical exercise is related to a lower risk of PD. Also, participation in physical activities in people with PD may contribute to a lower risk of falls and fractures and improved quality of life (Mantri et al., 2018). Therefore, consideration of other factors should not be neglected.

Working memory also appears to be more sensitive to limitations in the MCI-group, but being a member of the PD-group may also contribute moderately. In particular, a moderately common effect between the two groups can also be detected. In this regard, Parkinson's disease may also be accompanied by several other complex cognitive problems (Aarsland et al., 2009; Caviness et al., 2007; Dalrymple-Alford et al., 2010; Hoops et al., 2009; Janvin et al., 2006). In particular, problems with fine-motor control may occur due to hand tremors during dTMT in parameters such as the number/duration of lifts, resulting in the PD group contributing to working memory performance. Since the time spent inside the circles showed a significant difference in both groups compared to the healthy controls, it seems the most critical and sensitive parameter for identifying the decline of cognitive function. PD-CFRS is also a validated questionnaire for differentiating mild cognitive impairment in Parkinson's patients as a factor for working memory.

In addition to the decomposition of cognitive abilities, a more detailed analysis can be made based on the changes in performance during the tasks. As shown in Figure 4, the PD group was found to have worse performance than the HC group, and the pathological group was able to confirm the worst performance in each group. However, one participant with strikingly poor performance was found in the PD group. This single case should also be specifically looked at: Despite adequate cognitive ability according to the MoCa z-score (0.04), the duration of PD was long (14 years), and poor performance was also observed on the Parkinson's disease-related questionnaires (PD-CFRS, PSQ15). Here, a more detailed investigation is needed to determine whether it is still a problem of cognitive function or whether the poor performance is due to a loss of pure motor control. In the latter

case, freezing may be briefly triggered during a handwriting task when moving to the next circle after remaining in one circle for an extended period of time (searching for the next target circle). These manual motor blocks may be due to a problem with fine-motor skills rather than cognitive deficits. However, suppose it is a cognitive deficit, as in the former case. In that case, the need for concomitant other – more specific - cognitive function tests, such as n-back tasks (working memory), Flanker and Stroop tasks (inhibition), and/or the Wisconsin Card Sorting Tests (cognitive flexibility), should be included.

In addition, the general trend could be observed with a quadratic polynomial curve fit corresponding to the change in time spent in each circle. This trend may result in faster processing due to the lower complexity of the task until the first third. However, as the complexity of the task increases at about two-thirds of the task, various cognitive functions, such as working memory, cognitive flexibility, and inhibitory control, are involved, increasing the time spent inside the circles. In the last third of the dTMT-B (e.g., 9-I-10-J), the number of circles to be reached decreases due to the circles already completed, which allows for rapid visual search that may result in less time spent in the circles than in the first and second third of the task. We found through advanced analysis that cognitive skill involvement was greatest in the middle phase during TMT-B, which made the task most difficult. Technical supplementation is also needed to examine performance by increasing the proportion of involvement for cognitive abilities by adjusting the starting number and alphabet (e.g., 43-F-44-G-45-H) to determine the drop in fine-motor or cognitive control performance.

Although this is a pilot study, there are some limitations to the present study. First, we examined a small sample size; in particular, grouping was performed considering cognitive abilities according to the MoCA, resulting in a very small sample size for a given group. Second, the information about the Parkinson's group recruited by the Parkinson's Association self-help group could have been more comprehensive. For this reason, information indicating disease was lacking. However, participants were diagnosed with PD by a clinician at the hospital (e.g., missing the scores of the Unified Parkinson’s Disease Rating Scale). The background on the PD-group was supplemented by other questionnaires such as PD-CFRS and PSQ. Recruiting a larger additional sample of community-dwelling older adults

with PD or from a clinic would help generalize our explanations. Also, since the PD group was on medication, this may have reduced task performance (Tomlinson et al., 2010). Comparing motor and cognitive performance in ON- and OFF-medication status should inform further studies.

Conclusions

The present pilot study attempted a more detailed analysis and decomposition of cognitive function, which differs from other digital versions of the Trail-Making Test available on the market due to the convergence of new technologies. Here, cognitive abilities were decomposed by integrating the variables representing inhibitory control, cognitive flexibility, and working memory. The PD-group contributed largely to inhibitory control, and MCI-group to cognitive flexibility and working memory. In addition, the moderate contribution of the PD group to the working memory was also not negligible. Decomposing cognitive abilities demonstrated the potential as a digital cognitive biomarker through additional parameters that can be measured with our dTMT and confirming which group each cognitive function is more sensitive to specific parameters.

In addition, the analysis of the time spent in each circle showed the performance with a quadratic curve fit between groups during the task. These results indicated that time spent in each circle increased at the midpoint due to enhanced cognitive load related to complex cognitive functions and decreased again due to the already reached circle. More accurate identification of cognitive impairments in complex cognitive abilities should also require adjusting for technically different conditions (i.e., changing the starting points of numbers and letters).

Future longitudinal studies should be conducted in GP clinics to investigate the feasibility of the dTMT as a screening tool that can quickly and efficiently diagnose fine-motor and cognitive control problems by learning specific patterns through dTMT using artificial intelligence such as machine learning or deep learning.

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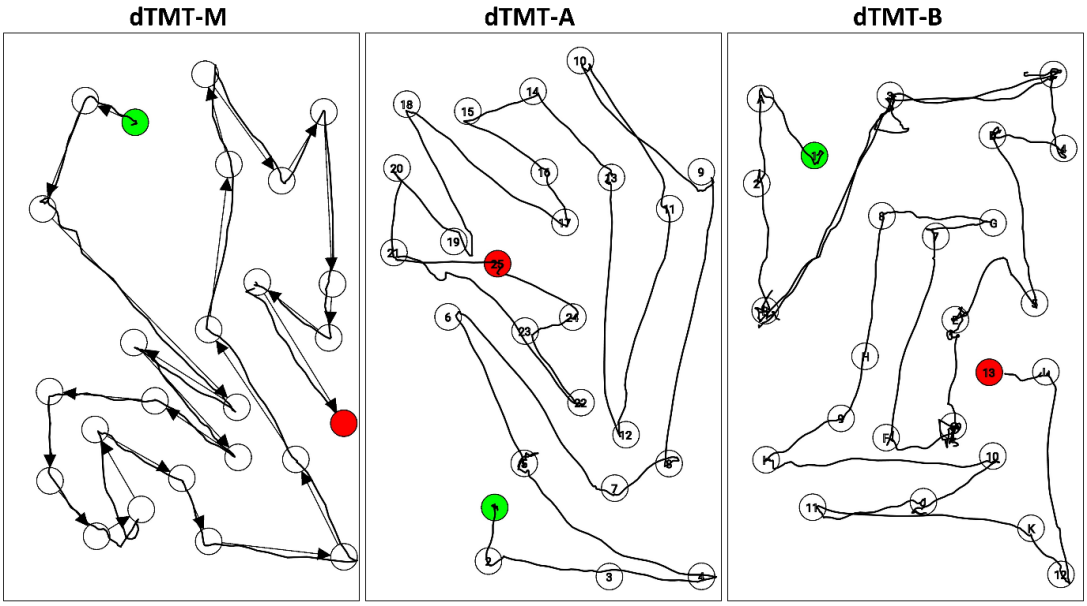

Figure 1. Example of a PD patient in dependence of the respective test conditions of the dTMT.

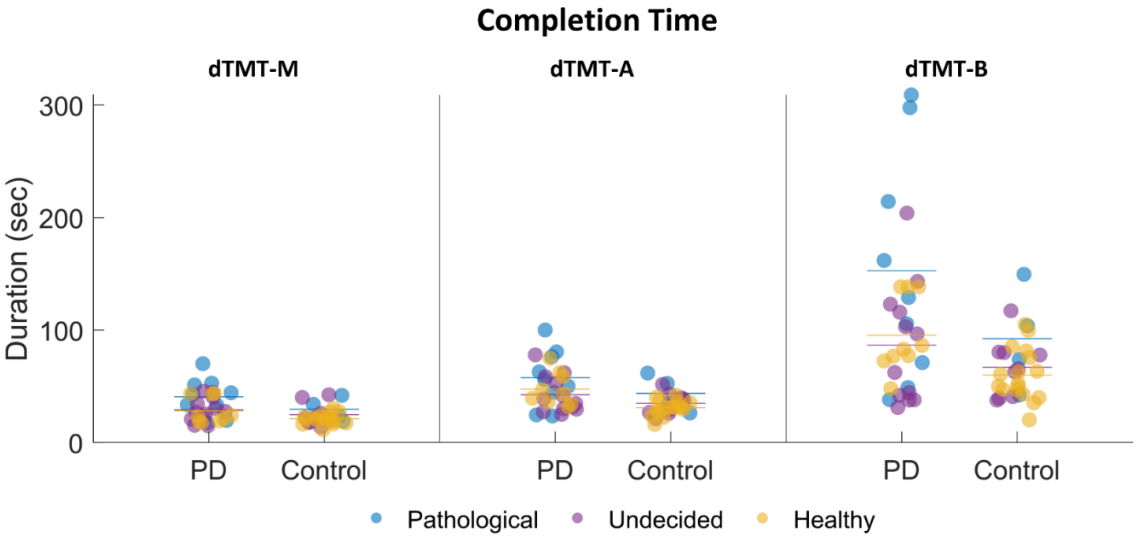

Figure 2. Dot plot demonstrating the duration of the completion time for the dTMT in the different diagnostic groups: Parkinson's Disease with and without Mild Cognitive Impairment and control participants with and without Mild Cognitive Impairment. The horizontal lines indicate the median (mean?) for pathological (blue), undecided (purple), and healthy (yellow).

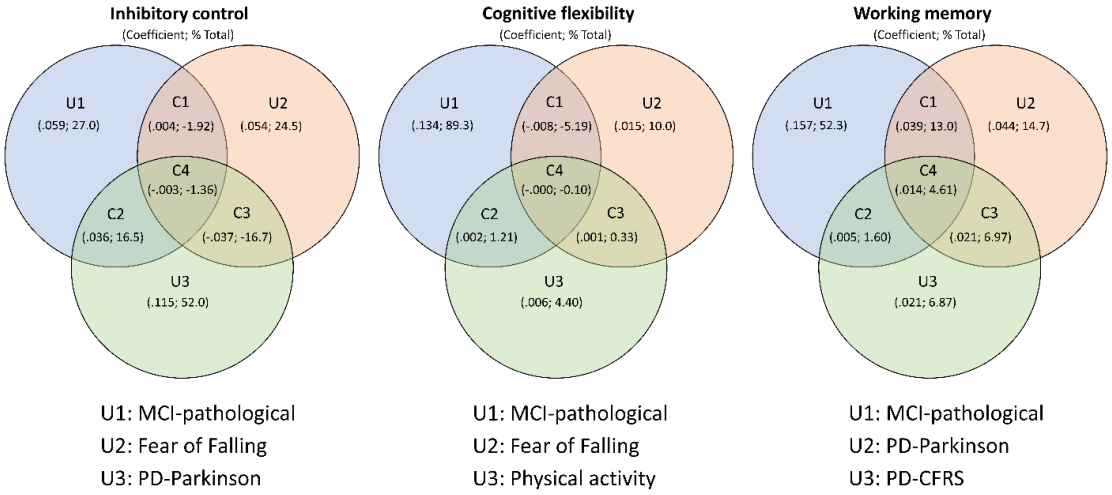

Figure 3. Commonality Diagram for the three dependent variables inhibitory control, cognitive flexibility, and working memory

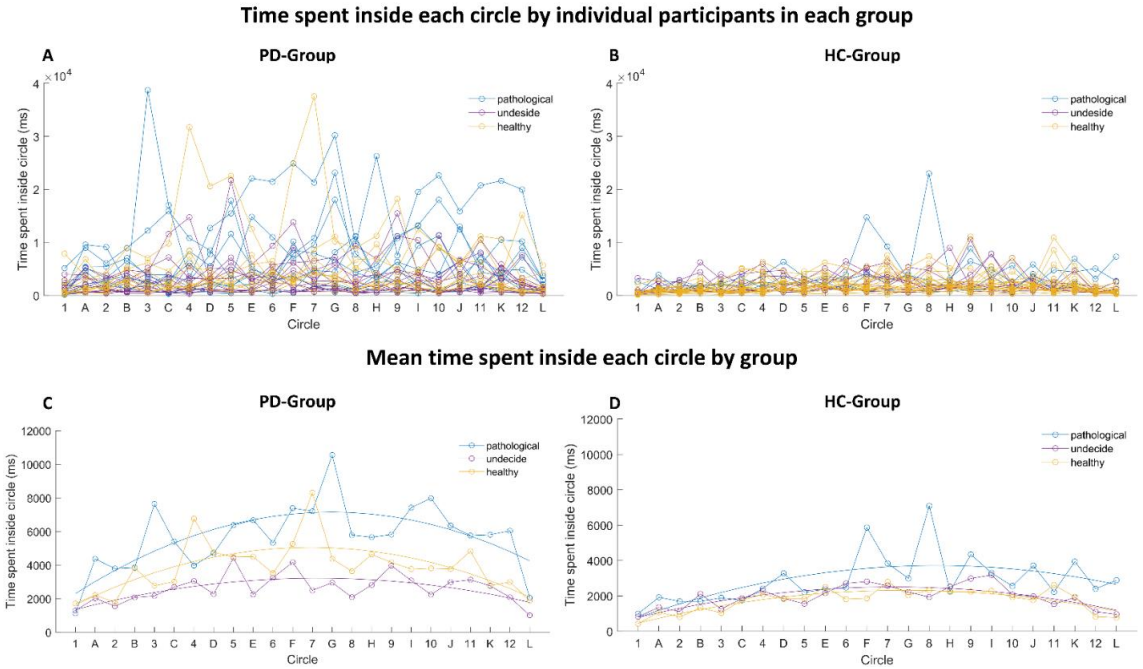

Figure 4. Time spent inside each circle by individual participants (A: PD-group, B: HC-group, according to their cognitive status) and averaged time spent inside each circle by group (A: PD-group, B: HC-group, according to their cognitive status)

	PD healthy (n=9) *M* (*SD*)	**PD undecided** (n=12) *M* (*SD*)	**PD-MCI** (n=9) *M* (*SD*)
Duration of diesases (years)	8.00 (6.63)	7.58 (4.50)	8.89 (9.20)
Duration of medication (years)	7.00 (6.28)	6.46 (4.24)	9.00 (9.18)
Medication (%)			
L-Dopa / Madopar / Stalevo /	66.7 / 22.2 / 0.0 /	54.5 / 27.3 / 18.2 /	44.4 / 44.4 / 0.0 /
Metformin / Neopro Pflaster	11.1 / 0.0	0.0 / 0.0	0.0 / 11.1
Medication Dose (mg)	475 (265)	368 (184)	438 (161)
Hoehn & Jahr (%)			
I / II / III	88.9 / 11.1 / 0.0	33.3 / 33.4 / 33.3	44.4 / 11.1 / 44.4
Tremor (e.g., eating, drinking) (%)			
left / right / both	0.0 / 33.3 / 0.0	8.3 / 50.0 / 0.0	22.2 / 11.1 / 22.2
Tremor in resting (%)			
left / right / both	11.1 / 11.1 / 0.0	0.0 / 16.7 / 0.0	11.1 / 22.2 / 22.2
CFRS	4.44 (3.60)	4.92 (5.07)	6.33 (4.44)
PSQ6	3.22 (1.20)	3.42 (1.16)	4.00 (1.73)

Table 1. Characteristics of the Parkinson's cohort by cognitive diagnosis

Note: *M*=mean; *SD*=standard deviation; CFRS: Cognitive Functional Rating Scale; PSQ: Parkinson's screening questionnaire

	PD (n=30) *M* (*SD*)	**HC** (n=30) *M* (*SD*)	**PD-Group**	**MCI-Group**	**Interaction (PD x MCI)**
Sex	17 M, 13 F	17 M, 13 F	$\chi^2(1) = 0.00$, $p = 1.00$		
Distribution of MCI	P: 9, U: 12, H: 9	P: 4, U: 9, H: 17	$\chi^2(2) = 4.81$, $p = .09$		
Age (years)	68.3 (9.66)	66.3 (8.61)	$F(1,54) = -0.18$, $\eta_p^2 = .003$	$F(2,54) = 1.36$, $\eta_p^2 = .048$	$F(2,54) = 0.68$, $\eta_p^2 = .025$
Height (m)	1.73 (0.09)	1.71 (0.10)	$F(1,54) = 1.98$, $\eta_p^2 = .036$	$F(2,54) = 2.26$, $\eta_p^2 = .079$	$F(2,54) = 4.65^{*}$, $\eta_p^2 = .149$
Weight (kg)	75.7 (16.3)	76.3 (11.4)	$F(1,54) = 0.19$, $\eta_p^2 = .004$	$F(2,54) = 1.90$, $\eta_p^2 = .067$	$F(2,54) = 6.65^{*}$, $\eta_p^2 = .200$
BMI (kg/m^2)	25.1 (3.92)	25.9 (1.85)	$F(1,54) = 0.54$, $\eta_p^2 = .010$	$F(2,54) = 1.68$, $\eta_p^2 = .059$	$F(2,54) = 2.96$, $\eta_p^2 = .100$
Handedness (% right)	96.7	93.3	$\chi^2(2) = 1.02$, $p = .601$		
Education (years)	14.6 (2.34)	14.8 (3.33)	$F(1,54) = 0.01$, $\eta_p^2 = .000$	$F(2,54) = 1.06$, $\eta_p^2 = .038$	$F(2,54) = 0.24$, $\eta_p^2 = .009$
Physical activity (min/week)					
in sports clubs	69.5 (64.2)	62.3 (80.4)	$F(1,54) = 0.20$, $\eta_p^2 = .000$	$F(2,54) = 2.04$, $\eta_p^2 = .070$	$F(2,54) = 0.34$, $\eta_p^2 = .013$
in leisure time	126 (141)	176 (230)	$F(1,54) = 0.36$, $\eta_p^2 = .007$	$F(2,54) = 0.84$, $\eta_p^2 = .030$	$F(2,54) = 0.75$, $\eta_p^2 = .027$
Falls last 4 weeks	0.40 (0.89)	0.03 (0.18)	$F(1,54) = 4.99^{*}$, $\eta_p^2 = .085$	$F(2,54) = 0.82$, $\eta_p^2 = .029$	$F(2,54) = 0.87$, $\eta_p^2 = .031$
Fear of falling	3.70 (2.47)	2.17 (1.91)	$F(1,54) = 7.06^{*}$, $\eta_p^2 = .116$	$F(2,54) = 0.15$, $\eta_p^2 = .005$	$F(2,54) = 1.86$, $\eta_p^2 = .064$
Medications	1.14 (1.06)	0.93 (0.98)	$F(1,54) = 0.97$, $\eta_p^2 = .018$	$F(2,54) = 0.35$, $\eta_p^2 = .013$	$F(2,54) = 0.65$, $\eta_p^2 = .024$
MoCA-Score	23.5 (2.49)	25.1 (2.34)	$F(1,54) = 1.64$, $\eta_p^2 = .030$	$F(2,54) = 61.0^{***}$, $\eta_p^2 = .693$	$F(2,54) = 0.12$, $\eta_p^2 = .004$
MoCa-Z Score	-0.77 (0.84)	-0.10 (1.00)	$F(1,54) = 1.36$, $\eta_p^2 = .025$	$F(2,54) = 98.8^{***}$, $\eta_p^2 = .785$	$F(2,54) = 1.34$, $\eta_p^2 = .047$

	PD (n=30) *M* (*SD*)	**HC** (n=30) *M* (*SD*)	**PD-Group**	**MCI-Group**	**Interaction (PD x MCI)**
CFRS	5.20 (4.41)	2.73 (4.65)	$F(1,54) = 4.19^{*}$, $\eta_p^2 = .072$	$F(2,54) = 0.28$, $\eta_p^2 = .010$	$F(2,54) = 0.75$, $\eta_p^2 = .027$
PSQ6	3.53 (1.36)	0.60 (0.77)	$F(1,54) = 85.6^{***}$, $\eta_p^2 = .613$	$F(2,54) = 0.50$, $\eta_p^2 = .025$	$F(2,54) = 0.39$, $\eta_p^2 = .014$
PSQ weighted	8.63 (4.72)	0.27 (0.69)	$F(1,54) = 73.2^{***}$, $\eta_p^2 = .575$	$F(2,54) = 0.61$, $\eta_p^2 = .018$	$F(2,54) = 0.29$, $\eta_p^2 = .011$
BDI-6	1.70 (1.62)	1.03 (1.27)	$F(1,54) = 3.37$, $\eta_p^2 = .059$	$F(2,54) = 0.17$, $\eta_p^2 = .006$	$F(2,54) = 0.58$, $\eta_p^2 = .021$

Table 2. Clinical and demographic data of participants with PD and healthy controls
Note: *M*=mean; *SD*=standard deviation; PD-Group: PD vs. HC; MCI-Group: Pathological (P) vs. Undecided (U) vs. Healthy (H); MoCa: Montreal Cognitive Assessment; CFRS: Cognitive Functional Rating Scale; PSQ: Parkinson's screening questionnaire; BDI: Beck-Depressions-Inventar

Variables		dTMT-M			dTMT-A			dTMT-B		
		F	*P*	η_p^2	*F*	*P*	η_p^2	*F*	*P*	η_p^2
Number of Mistakes	***PD*[1]**	1.88	.176	.034	.566	.455	.013	1.71	.196	.031
	***MCI*[2]**	.165	.849	.006	1.77	**.179**	.061	1.13	.330	.040
	Int.[2]	.404	.669	.015	1.99	**.146**	.068	3.06	**.055**	.102
Number of Pauses	***PD*[1]**	2.17	.147	.038	1.78	.187	.032	1.91	.171	.034
	***MCI*[2]**	3.42	**.039**	.112	1.58	.213	.055	.108	.897	.004
	Int.[2]	.164	.849	.006	.771	.467	.027	3.05	**.055**	.101
Number of Lifts	***PD*[1]**	.000	.991	.000	5.22	**.026**	.088	4.59	**.036**	.078
	***MCI*[2]**	6.53	**.002**	.194	2.68	**.077**	.090	2.17	.123	.074
	Int.[2]	1.01	.367	.003	1.41	.252	.049	.331	.719	.012
Duration of Pauses	***PD*[1]**	1.11	.296	.020	7.42	**.008**	.121	2.77	.101	.048
	***MCI*[2]**	.930	.400	.033	2.95	**.061**	.099	3.18	**.049**	.105
	Int.[2]	.570	.568	.020	.651	.525	.023	.362	.697	.013
Duration of Lifts	***PD*[1]**	10.2	**.002**	.159	9.46	**.003**	.149	4.23	**.044**	.072
	***MCI*[2]**	.869	.425	.031	.772	.466	.027	3.72	**.030**	.121
	Int.[2]	.868	.425	.031	.421	.658	.015	1.08	.345	.038
User Speed	***PD*[1]**	5.44	**.023**	.091	11.4	**.001**	.174	4.36	**.041**	.074
	***MCI*[2]**	2.37	**.102**	.081	.791	.458	.028	1.33	.270	.047
	Int.[2]	.025	.974	.000	.145	.864	.005	.249	.780	.009
Distance Ratio	***PD*[1]**	.098	.754	.001	1.51	.224	.027	3.46	**.068**	.060
	***MCI*[2]**	2.28	**.111**	.078	4.04	**.023**	.130	2.83	**.067**	.095
	Int.[2]	1.11	.336	.039	3.85	**.027**	.124	1.42	.248	.050
Duration between Circles	***PD*[1]**	9.62	**.003**	.151	8.02	**.006**	.129	6.16	**.016**	.102
	***MCI*[2]**	3.11	**.053**	.103	3.91	**.026**	.127	1.61	.210	.056
	Int.[2]	.443	.645	.016	.749	.478	.027	.616	.544	.022
Duration inside Circle	***PD*[1]**	2.78	.101	.049	8.79	**.004**	.140	6.05	**.017**	.101
	***MCI*[2]**	6.79	**.002**	.201	2.57	**.085**	.087	3.63	**.033**	.118
	Int.[2]	.731	.486	.026	.546	.582	.019	.603	.550	.021
Duration inside Circle before Letter	***PD*[1]**							9.09	**.003**	.144
	***MCI*[2]**							2.50	**.091**	.084
	Int.[2]							1.17	.316	.041
Duration inside Circle before Number	***PD*[1]**							5.89	**.018**	.098
	***MCI*[2]**							3.68	**.031**	.120
	Int.[2]							.452	.638	.016

Table 3. ANOVA (PD × MCI) for all temporal and spatial parameters of the dTMT
Note: [1]: *F*(1,54); [2]: *F*(2,54); PD: PD x HC vs. HC; MCI: Pathological x Undecided x Healthy; Int.: Interaction between PD and MCI

Relative Importance	Inhibitory Control		Cognitive Flexibility		Working Memory	
	Predictor	R^2	**Predictor**	R^2	**Predictor**	R^2
1	MCI-Pathological	.061	MCI-Pathological	.115	MCI-Pathological	.178
2	Fear of Falling	.056	Fear of Falling	.019	PD-Parkinson	.092
3	PD-Parkinson	.054	Physical activity in sports clubs	.013	PD-CFRS	.040

Table 4. Relative importance of variables for Inhibitory control, Working memory, and Cognitive flexibility

Predictor (x)	R^2	R^2_{adj}	***B***	**Sig. of *B***	**Unique**	**Com-mon**	**To-tal**	**% of R^2**
Model 1	.222	.180						
Constant			.293	<.001***				
MCI-Pathological			.155	.042*	.060	.029	.089	27.0
Fear of Falling			-.027	.053+	.054	-.044	.009	24.5
PD-group			.186	.005**	.115	-.003	.118	52.0
Model 2	.149	.104						
Constant			.766	<.001***				
MCI-Pathological			.601	.004**	.134	-.006	.128	89.3
Fear of Falling			-.036	.324	.015	-.007	.008	10.0
Physical activity in sports clubs			-.000	.512	.006	.002	.009	4.40
Model 3	.301	.263						
Constant			.999	<.001***				
MCI-Pathological			.631	<.001***	.157	.058	.215	52.3
PD-group			.285	.065+	.044	.074	.118	14.7
PD-CFRS			.021	.203	.021	.039	.060	6.87

Table 5. Regression results for variables as predictors of executive function

Note. Model 1: Inhibitory control; Model 2 Cognitive flexibility; Model 3: Working memory; Unique = unique effect; Common = Σ common effects; Total = Σ unique +common effects; % of R^2 = Total/R^2

Appendix A3 – Manuscript 3

Manuscript 3:

Park, S. Y., Reinl, M., & Schott, N. (2021). Effects of acute exercise at different intensities on fine motor-cognitive dual-task performance while walking: A functional near-infrared spectroscopy study. *European Journal of Neuroscience*, 54(12), 8225–8248. https://doi.org/10.1111/ejn.15241

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SPECIAL ISSUE ARTICLE

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Effects of acute exercise at different intensities on fine motor-cognitive dual-task performance while walking: A functional near-infrared spectroscopy study

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Abstract

Studies on the effects of acute exercises on cognitive functions vary greatly and depend on the duration and intensity of exercise and the type of cognitive tasks. This study aimed to investigate the neural correlates that underpin the acute effects of high-intensity interval (HIIE) versus moderate-intensity continuous exercise (MCE) on fine motor-cognitive performance while walking (dual-task, DT) in healthy young adults. Twenty-nine healthy right-handers (mean age: 25.1 years ± 4.04; 7 female) performed the digital trail-making-test (dTMT) while walking (5 km/h) before and after acute exercise. During task performance, the hemodynamic activation of the frontopolar area (FPA), dorsolateral prefrontal (DLPFC), and motor cortex (M1) was recorded using functional near-infrared spectroscopy (fNIRS). Both HIIE and MCE resulted in improved dTMT performance, as reflected by an increase in the number of completed circles and a reduction in the time within and between circuits (reflecting improvements in working memory, inhibition, and decision making). Notably, HIIE evoked higher cortical activity on all brain areas measured in the present study than the MCE group. To our knowledge, these results provide the first empirical evidence using a mobile neuroimaging approach that both HIIE and MCE improve executive function during walking, likely mediated by increased activation of the task-related area of the prefrontal cortex and the ability to effectively use, among other things, high fitness levels as neural enrichment resources.

KEYWORDS

digital Trail-Making-Test (dTMT), fine-motor control, motor cortex, prefrontal cortex, running

Abbreviations: BDNF, Brain derived neurotrophic factor; CBF, Cerebral blood flow; DLPFC, Dorsolateral prefrontal cortex; DT, Dual-Task; dTMT, Digital Trail-Making-Test; EEG, Electroencephalography; FDR, False discovery rate; fNIRS, Functional near-infrared spectroscopy; FPA, Frontopolar area; HbO, Oxygenated hemoglobin; HbR, Deoxygenated hemoglobin; HIIE, High-intensity interval exercise; HR, Heart rate; M1, Motor cortex; MCE, Moderate-intensity continuous exercise; MPSTEFS, Mental and Physical State and Trait Energy and Fatigue Scales; ROI, Regions of interest; RPE, Rating of perceived exertion; TMT, Trail-Making-Test; VO_2max, Maximum oxygen consumption.

Edited by: Teodoro Solis-Escalante

1 | INTRODUCTION

There is a consensus that exercise positively affects the brain's various cognitive functions and functional modalities. Several meta-analyses related to behavioral changes in cognitive function have concluded that acute exercise has a small but positive effect on cognitive functions such as working memory, attention, and the processing speed of visual information, especially after training (Chang et al., 2012; Lambourne & Tomporowski, 2010; McMorris et al., 2011). The magnitude of the effect depends mainly on the moderators that influence the relationship between exercise and cognition, such as the temporal relationship between physical and cognitive task performance, individual characteristics of the performers, exercise characteristics (type, duration, intensity), and cognitive task characteristics (e.g., visual versus. verbal versus. motor response).

Concerning training characteristics, Tsukamoto et al. (2016), for example, investigated the effect of a high-intensity interval exercise (HIIE) on cognitive performance after cycling compared to a moderate-intensity continuous exercise (MCE). In general, MCE consists of an intensity with 40%–59% of maximum oxygen consumption (VO_2max), which is continuously in a steady-state for a duration of usually 20–60 min, while HIIE varies considerably but typically consists of a short period of exercise with alternating intervals of bouts of high intensity lasting between 60 and 240 s followed by low-intensity (Keating et al., 2017). Regardless of the type of exercise, an improvement in cognitive performance was observed immediately after exercise. In fact, methodological issues related to the type of exercise should also be considered. Lambourne and Tomporowski's (2010) meta-analysis showed that young adults' cognitive performance decreased during treadmill exercise, with cycling associated with improved cognitive function. Treadmill training may have led to a deterioration in cognitive performance because more attention had to be allocated to overall body movements than coordination when cycling (Soga et al., 2015). Therefore, intensive treadmill exercise requires more control over gait and posture and may have resulted in the deterioration of cognitive performance.

Most studies compared cognitive performance before and after exercise with single cognitive tasks when examining the temporal relationship between physical and cognitive task performance. However, skillful gait control is often required in daily life while performing secondary cognitively demanding tasks such as talking and avoiding obstacles while walking. While walking was previously often considered an automated process, it is now also known that various cognitive functions play an essential role in postural control and locomotion (Yogev-Seligmann et al., 2008). Simultaneous walking in combination with a cognitive task (i.e., dual-task, DT) may cause cognitive-motor interference leading to changes in cognitive as well as gait performance, although these changes are more pronounced with the increasing complexity of the cognitive task (Klotzbier & Schott, 2017; Li et al., 2018).

While the potential beneficial effects of exercise on cognition and brain health are well known, the mechanisms underlying this association are not fully understood. The most widely studied hypothesis explaining chronic physical activity's positive effect (several consecutive weeks of sustained performance) on cognitive performance is the so-called neurotrophic hypothesis (for a review, see Stillman et al., 2016). It is assumed that endurance training induces neuroplasticity at molecular and cellular levels. Thus, the training-induced increased central circulation of neurotrophic and growth factors (BDNF; brain-derived neurotrophic factor, insulin-like growth factor 1, vascular endothelial growth factor) leads to the upregulation of neurogenesis, synaptogenesis, gliogenesis, and angiogenesis (Schott, 2020). The effects of acute exercise (a single bout of exercise) are often explained by cerebrovascular function changes.

When our brain performs a specific task, the demand for oxygen and glucose increases so that the regional cerebral blood flow (CBF) of the brain is oversupplied to meet the increased metabolic demand. The increased CBF in response to increased neural activity is caused by neurovascular coupling (Fabiani et al., 2014; Perrey, 2008). Based on this, the oversupply in regional CBF on cerebral oxygenation level of the brain leading to increased oxygenated hemoglobin (HbO) and a decreased deoxygenated hemoglobin (HbR) can be measured by functional near-infrared spectroscopy (fNIRS) (Agbangla et al., 2017). In general, an increase in CBF has been suggested during physical exertion (Steventon et al., 2020; Thomas et al., 1989); physical exertion leads to increased cerebral neural activity and metabolism, resulting in an increase in CBF (Ogoh & Ainslie, 2009). In contrast, Moriarty et al. (2019) found that although the overall CBF of the brain stays more or less constant during acute aerobic exercise, there may be a shift in CBF from areas required for cognitive function to areas required for motor control and maintenance of vital function. Dietrich and Audiffren (2011) previously proposed the hypofrontality hypothesis of reticular activation, which states that a decrease in frontal neuronal activity responsible for reduced task performance is caused by increased activity in favor of brain regions associated with sensory and motor processes. This seems to be particularly evident during HIIE (Wang et al., 2013). Concerning the post-training effects, numerous researchers using fNIRS have argued that compared to other brain areas, posttreatment induced, the higher available cerebral oxygen supply in the prefrontal cortex can improve cognitive performance (Bediz et al., 2016; Kujach et al., 2018; Moriarty et al., 2019; Yanagisawa et al., 2010). Based on the hypofrontality hypothesis, a review by Basso and Suzuki (2017) suggests that after exercise-induced prefrontal hypoperfusion, this area can be thought of as a rebound increase in cerebral oxygenation leading to improved cognition.

In summary, there is a paucity of acute exercise studies that examine the effect on cognitive performance before and after a single exercise bout. Equally, few studies on DT's neural correlations exist, although an effect of acute exercise on the performance of a cognitive task while walking has not been investigated at all. Therefore, this study aimed to investigate the neural correlations underpinning the acute effects of HIIE versus MCE on the performance of a DT (fine motor-controlled cognitive task while walking) in healthy young adults. In the present study, we used a new digital version of the established Trail-Making Test (dTMT; (Park & Schott, 2021) and investigated behavioral and neural effects (fNIRS) before and after two different types of exercise with different intensities. First, we hypothesized that the differences in behavioral outcomes would correspond to the task difficulty of the dTMT also with respect to the cortical activation levels. Thus, the increasing task complexity (mental workload) should lead to increasing frontal brain activation, specifically in the dorsolateral prefrontal cortex (Hagen et al., 2014). Second, concerning the effect of acute exercise on DT performance while walking, an improvement in cognitive performance should occur after MCE. At the same time, a deterioration should be observed after HIIE due to the allocation of more attentional resources to postural control during walking (transient hypofrontality hypothesis: widespread neural activation of motor and sensory systems during exercise comes at the expense of prefrontal-dependent higher-order cognitions; Dietrich & Audiffren, 2011). This will be accompanied by an increase in frontal oxygenation after MCE as a basis for performance improvements as found in previous studies (Bediz et al., 2016; Kujach et al., 2018; Moriarty et al., 2019; Yanagisawa et al., 2010). In contrast, after HIIE, we expected increased neural activity in primary motor regions (M1) involved in the control of movement, with concomitant decreases in neural activity in non-motor regions (e.g., dorsolateral prefrontal cortex) of the prefrontal cortex in order to maintain gait behavior influenced by intense, exercise-induced fatigue (Loprinzi et al., 2019; Mehren et al., 2019).

2 | MATERIALS AND METHODS

2.1 | Participants

Thirty-two healthy, right-handed adult participants with normal or corrected-to-normal vision participated in this study. Inclusion criteria were a minimum of 2 hr of exercise per week and at least a fair or good fitness (43.5 ml kg^{-1} min^{-1} and above for male; 33.6 ml kg^{-1} min^{-1} and above for female), respectively (American College of Sports Medicine, 2013). Exclusion criteria were an unusual heart rate, resting pulse or blood pressure, and cardiovascular, neurological, or psychiatric diseases. Also, participants must not have any fine motor impairments that would have restricted the motor-cognitive task's performance. Injuries that would have either impaired walking on the treadmill or scalp injuries that would have affected brain activity measured using functional near-infrared spectroscopy (fNIRS) also led to exclusion from the study. Participants were recruited through the University Sports Centre, which distributed flyers both manually and by e-mail. Two participants did not reach the required fitness level and were excluded from the study after the first day of testing. Another participant had to be excluded for technical reasons (faulty recording of the fNIRS data). Therefore, 29 participants (mean age: 25.1 ± 4.04; 7 female) were included in the final analysis (baseline). However, only 25 participants were included in the analysis of the effect of exercise on cortical activation due to motor artifacts of fNIRS (pre-post-comparison; see section in fNIRS data). The study was conducted according to the Helsinki Declaration and approved by the university's local ethics committee. All participants gave written informed consent to participate in the experiment.

2.2 | Experimental design and procedure

In a randomized controlled experimental design with repeated measures in a two-armed parallel-group (between subjects), participants had to visit the laboratory on two occasions (i.e., experimental sessions one and two; see Figure 1) with at least 48 hr between visits. Each session lasted approximately 1.5–2 hr. Participants were instructed to avoid exercise 24 hr before testing, caffeine, and alcoholic drinks in the 12 hr before each visit, and to sleep for about 7 hr the night before (Pesta et al., 2013).

On the first day, participants were tested twice (with a 20 min break between trials) with the digital Trail-Making-Test (Park & Schott, 2021) while sitting at a table. At the end of the first day, the individual VO_2max of each participant was determined. On the second day, the participants were first tested with the dTMT, but this time while walking on a treadmill at a speed of 5 km/h. They were then randomly assigned to two different exercise protocols (either HIIE or MCE). After exercise, participants were tested again with the dTMT while walking on the treadmill (5 km/h), and after a 10-min rest period, a fifth dTMT measurement was taken while sitting at a table.

2.2.1 | Procedure of the experimental sessions

After the participants gave their written consent to participate on day 1, they first completed the demographic information questionnaire. Afterward, the fNIRS system was installed, and a first resting value during sitting was collected for 2 min. Then, the participants first completed Part

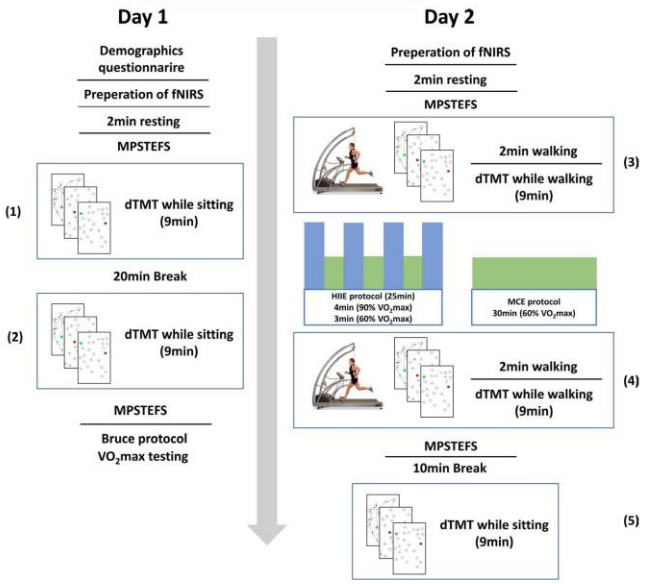

FIGURE 1 Study design and procedure. The study employed a 2 × 2 (intervention by time ([pre/post]) within-subjects randomized protocol whereby participants were randomized to either perform the HIIE or MCE intervention

II of the questionnaire on the Mental and Physical State and Trait Energy and Fatigue Scales Questionnaire (MPSTEFS; O'Connor, 2006) to determine their physical and cognitive fatigue. The first dTMT block followed this while the participants sat comfortably at a table. After a 20-min break, during which the test participants engaged in light conversation to avoid fatigue due to boredom, another 2 min of rest were measured, followed by a second dTMT block, again sitting comfortably at a table. Afterward, the participants completed the MPSTEFS a second time. The fNIRS system was removed, and the participant performed the Bruce protocol to determine the individual VO_2max.

The second day of testing began with the fNIRS system's placement, a 2 min measurement at rest during sitting, and a second response to the MPSTEFS. The participants walked on the treadmill (h/p/cosmos pulsar® 3p, Nussdorf-Traunstein, Germany) for 2 min in order to set up fNIRS before testing (incl. measurement with fNIRS); afterward, the first assessment with the dTMT while walking (5 km/h) was performed. At this time, it consisted of a total of 9 min, including alternately performing 30 s walking with dTMT and 30 s walking without dTMT (see section in Cognition, for the setting of dTMT). Next, the optodes' fiber optic cables were disconnected from the measurement system and attached to the participant to complete their exercise session undisturbed. This procedure also helped to reduce the optodes' potential movement on the head, as the cap remained on the participant's head during the entire exercise session. Subsequently, the participants completed the intervention protocol (HIIE or MCE) assigned to them. At the end of the training intervention, we recorded cerebral oxygenation using fNIRS again for 2 min without any additional task and then during the cognitive tasks (dTMT) at a walking speed of 5 km/h. During the whole time, heart rate was documented with a Polar H1 heart rate sensor (Polar Electro Europe AG). The intervention's fatigue effects were again measured with the MPSTEFS and the BORG scale (RPE, ratings of perceived exertion) (Borg, 1982). After a 10 min break, the prolonged exercise effects were evaluated by a third dTMT block, this time again sitting comfortably at a table.

2.2.2 | Focus of our research

This article focuses on comparing changes in cortical activation after two types of exercise (HIIE versus MCE) while performing a fine motor-cognitive task during walking on a treadmill. Therefore, this paper focuses on day 2, the first dTMT session before exercise, and the second dTMT session after exercise, both while our participants were walking. The comparison of dTMT performance between sitting (day 1) and walking (day 2 before exercise) will be presented in another article (Reinl et al., in preparation).

2.3 | Intervention (exercise protocols)

2.3.1 | High-intensity interval exercise

A high-intensity interval exercise (HIIE) protocol alternates high-intensity exercise blocks as load-interval with lower exercise intensity blocks as relief intervals (see Figure 1). In this study, our protocol involved 4 × 4 min running efforts with high-intensity (90% of the VO_2max) interspersed with 3 min of running with low intensity (60% of the VO_2max). The total duration of the HIIE was 25 min.

2.3.2 | Moderate-intensity continuous exercise

Since the external load (dose: intensity × duration) is an essential factor in triggering neurobiological processes that lead to neuroplastic and cognitive changes (Herold et al., 2019), it is crucial to adjust the dose in a study that focuses on the intensity of the intervention. Therefore, the MCE protocol duration was defined for the time necessary to achieve the same total work (caloric expenditure) obtained in an HIIT protocol (Magalhães et al., 2020; Tsukamoto et al., 2016). Participants randomized to moderate-intensity continuous exercise (MCE) ran for 30 min of continuous moderate training at 60% of their individual VO_2max (see Figure 1). Both training protocols were followed by a cooling phase of three minutes at 5 km/h with reattached cables of the optodes.

2.4 | Measures

2.4.1 | Cognition

The *Trail-Making-Test* (TMT; Reitan, 1955) is one of the most common neuropsychological test procedures for evaluating cognitive functions. For TMT-A (visuospatial abilities, the speed of information processing), participants must connect 25 randomly distributed encircled numbers from 1 to 25 in ascending order (i.e., 1–2–3- …). For TMT-B (cognitive flexibility, working memory, set-shifting, inhibition), individuals must connect numbers and letters in alternating, ascending order (i.e., 1-A-2-B-3-C …).

Despite being widely used, the TMT in its original, singular paper-pencil form is not suitable for repeated use, as this can lead to learning effects (Beglinger et al., 2005; Buck et al., 2008). However, the assessment of executive functions with neuroscientific methods requires a certain number of replications to obtain a suitable signal-to-noise ratio of the data (Orihuela-Espina et al., 2010). For this reason, we used the TMT in a digital version (dTMT) to overcome these shortcomings (Park & Schott, 2021). The android app-based digital TMT was designed to be similar in structure and size to the paper-and-pencil-based version as it was administered on a Samsung Galaxy Note Pro (12.2-inch diagonal LED-backlit Multi-Touch display with IPS technology; portrait alignment) with a resolution of 2,560 × 1,600. This version of the dTMT is based on the digital versions of Dahmen et al. (2017), which introduced additional measurement components (e.g., time between and inside the circles, number of lifts, distance length) and the algorithm of Zeng et al. (2017), which is based on a "divide-and-combine approach" making it possible to generate alternative versions (i.e., to avoid a possible learning effect). Also, we can run a trial with a fixed time instead of having 25 circles completed at a time. In this digital version, each condition's time records automatically from the moment the stylus touches the tablet screen and stops as soon as the last circle is reached (marked Begin and Stop, respectively). Compared to the paper version, which has to rely on the examiner, the administrator informed the participants before the test started that if a wrong circle was touched (e.g., skipped a circle, connected the wrong circles), it would change its color to red, and they must return to the last correct circle, increasing the completion time as with the ppTMT. The timing was continued even if the participant made errors (see Bowie & Harvey, 2006). In addition, we can isolate cognitive processes which Fellows et al. (2017) confirmed to be important in TMT performance using component measures such as time inside circles, time between circles, number and duration of pauses, number and duration of lifts. Most of these variables in the dTMT-A were related to visual processing speed, but more specifically for the dTMT-B, inhibition was related to the number and duration of pauses and the time between circles while working memory was predicted with the number and duration of lifts and the time inside the circles (Fellows et al., 2017). Examples of dTMT sheets are presented in Figure 2. In addition, to the dTMT-A and B, we have included the dTMT-motor (dTMT-M) as a motor speed reference test (Schott et al., 2016).

Each dTMT measurement consisted of a 9 min block in which 30 s of tasks and 30 s of rest (presentation of black fixation cross on a white background) alternated. The order of dTMT-conditions within each block was balanced pseudo-randomly so that the same condition (dTMT-M, dTMT-A, dTMT-B) was never presented twice in a row, with all conditions being presented three times each. The use of such a pseudo-randomized stimulus sequence eliminates the predictability of the conditions and thus avoids top-down effects of condition-related expectation or attention. Furthermore, we confirmed in a pilot study that learning effects do not occur before the 5th 9 min block. In addition, the participants performed a 9 min block twice on the first day, so we assumed that habituation effects were minimized to confirm the exercise effects on the second day. Within each 30 s task block, the tablet's mathematical algorithm constantly generated new dTMT-screens that never matched the previous screen. If the

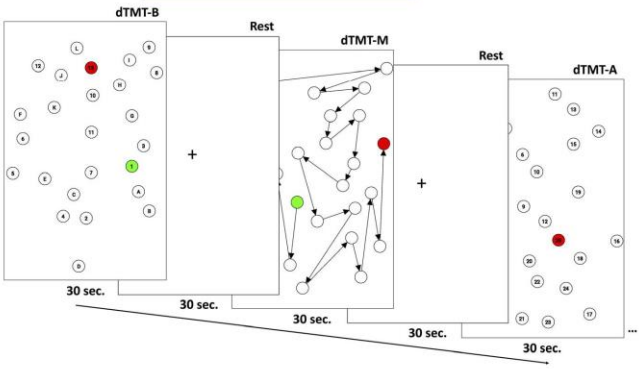

FIGURE 2 Design of the experimental task. Each version (dTMT-M, dTMT-A, dTMT-B) was presented three times leading to nine blocks of 30 s each

participant completed one screen before the end of the 30 s block, another one would appear. If the 30 s were over before the participant finished a screen, the data were still saved, and the rest block's fixation cross appeared. The instruction was to complete as many screens as possible, with additional attention being paid to error-free execution.

2.4.2 | Maximum oxygen consumption test (VO_2max)

To assess participants' cardiorespiratory fitness and to define the parameters for the individualized training session, the Bruce protocol (1972) was performed on a treadmill (h/p/cosmos pulsar® 3p, Nussdorf-Traunstein, Germany) to determine cardiovascular fitness (VO_2max); heart rate (HR) was measured using a Polar H1 Heart Rate Sensor (Polar Electro Europe AG). The Bruce protocol starts with an initial speed of 2.7 km/h and a slope of 10%. Every 3 min, the incline per level increases by 2% and the speed per level by 1.3 km/h. This test protocol was aborted when (a) a participant was unable to run due to volitional exhaustion, (b) no increase in HR was observed with increasing intensity, and (c) the rating of perceived exertion (RPE) was ≥17 (Borg, 1982). Thus, an individually adapted exercise protocol was applied to all participants in the present study. Female and male participants' high cardiovascular fitness ensured that exercise intensity did not fell below the walking speed of 5 km/h for the dTMT testing.

2.4.3 | Baseline characteristics of participants

Demographic information, the type and duration of sporting activities, and the level of athletic performance (i.e., participation in competitions) were collected using a questionnaire. Also, height and weight were measured, and the body mass index (BMI, kg/m^2) was calculated to control for possible influences on training effects. Participants also completed Part II of the Mental and Physical State and Trait Energy and Fatigue Scales Questionnaire (MPSTEFS; O'Connor, 2006) several times during the experiment to detect changes in perceived feelings of energy and fatigue. This resulted in 12 separate ratings for Physical Energy, Physical Fatigue, Mental Energy, and Mental Fatigue, instructing participants to report on the question "How do you feel right now?" using a 100-mm-visual analog scale. Cronbach's α coefficients for each scale were greater than 0.85, indicating a high level of internal consistency. After the exercise session, participants completed the BORG scale (RPE, ratings of perceived exertion) (Borg, 1982) to monitor the perceived effort concerning stress intensity. This scale ranges from 6 (no exertion) to 20 (maximal exertion). The scale allows a person to subjectively evaluate the level of exertion during training or exercise tests.

2.5 | fNIRS measurement

The hemodynamic response of frontal and motor brain areas was recorded using a multichannel continuous-wave fNIRS device (NIRSport, NIRx Medical Technologies LLC) consisting of 16 light sources and 16 detectors mounted on a head cap. The sources and detectors were located over the left and right frontopolar area (FPA), the left and right dorsolateral prefrontal cortex (DLPFC), and the left and right motor cortex (M1; see Figure 3). Head cap placement was centered around Cz (10/20 international system for electrode placement), the mid-point between the nasion to inion and left to right preauricular distances, to ensure consistency between participants and sessions.

The inter-probe distance was kept at approximately 3 cm. The system collects data at a sampling rate of 7.81 Hz and emits infrared light at two wavelengths, 760 and 850 nm (Pereira et al., 2007), to measure oxygenated and deoxygenated blood

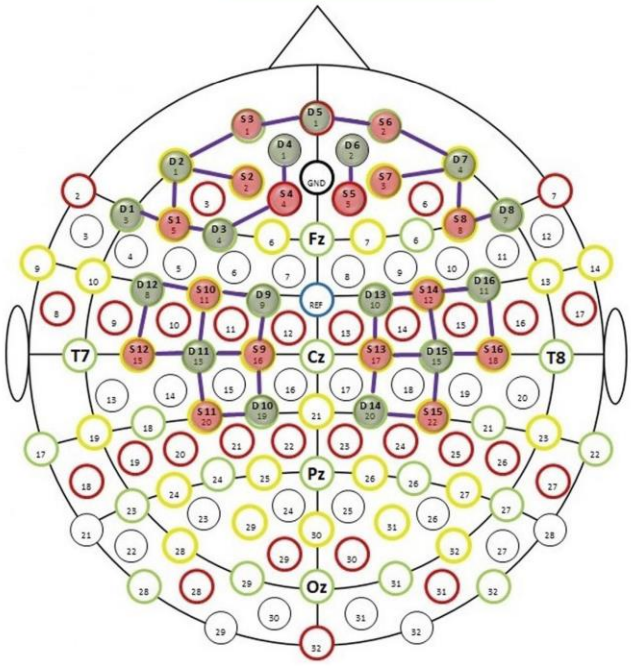

FIGURE 3 Configuration of fNIRS measurement

in the continuous-wave procedure, that is, sources that emit light with constant frequency and intensity (Scholkmann et al., 2014). Data were collected with the NIRS Star 14 Software (NIRSport, NIRx Medical Technologies LLC) on a tablet (Microsoft Surface Pro2 128GB). The trigger for each TMT and rest block was set by the NIRS Stim Software (NIRSport, NIRx Medical Technologies LLC).

2.6 | Data analysis

For this article, only part of the second day's data was analyzed to evaluate the effects of acute exercise on cognitive performance and fine motor control. We compared performance in the dTMT on a behavioral and neuronal level before and after exercise (while walking on the treadmill) between the two training groups.

Statistical analyses were performed using SPSS v.27 (SPSS). We first explored dependent variables to examine missing data points, normality of distributions (tested by Kolmogorov–Smirnov tests), and the presence of outliers. All analyses' effect sizes are indicated using partial Eta^2 (η_p^2) or Cohen's *d*. All data are presented as mean and standard deviation. Statistical significance was set a priori a $p < .05$. The classification of the partial Eta^2 also follows the conventions of Cohen (1988): 0.01 small effect; 0.06 medium effect; 0.14 strong effect.

2.6.1 | Demographic data

For the sample characteristics, possible group differences for continuous variables (e.g., age, height, weight, BMI, physical activity, VO_2max, heart rate) were tested using two-sample *t* tests. Categorical demographic variables (e.g., sex) were tested with a Chi^2 test.

2.6.2 | Objective and subjective physiological parameters

To test the effects of our training protocols, we evaluated the changes in HR using a 3 × 2 ANOVA with repeated measurements with the within-subjects factor "time" (before, during, and after exercise) and the between-subjects factor "group" (HIIE and MCE). Also, we compared subjective reports for the RPE scale using a two-sample *t* test and the MPSTEFS questionnaire using 2 × 2 ANOVAs with

repeated measurements with the within-subjects factor "exercise" (PRE-POST exercise) and the between-subjects factor "group" (HIIE and MCE) separately for each of the components (Physical Energy, Physical Fatigue, Mental Energy, and Mental Fatigue). We further calculated Pearson correlations between HR and RPE scale for each group separately.

2.6.3 | Cognition

The behavioral data of the dTMT were extracted from text files saved by the tablet via Matlab 2018b (MathWorks). We calculated the number of correctly connected circles and the time between (inhibitory control) and inside the circles (visual working memory, decision making) for each condition as the sum of all circles within one block, averaged over the three blocks of each condition. We performed $2 \times 3 \times 2$ ANOVAs with repeated measurements with the within-subjects factors "exercise" (PRE-POST exercise) and "task condition" (dTMT-M, -A, and -B) and with the between-subjects factor "group" (HIIE and MCE).

2.6.4 | fNIRS data

The neuronal data were analyzed using the +NIRS Toolbox (Santosa et al., 2018) as an open-source package implemented in Matlab 2018b (MathWorks). To estimate the quality of the data channel as signal-to-noise ratio, first, the relative coefficient of variation (CV in %) was calculated for the raw data before filtering, which is a widely used method for measuring multichannel NIRS (Schmitz et al., 2005; Schneider et al., 2011). The CV of each channel was calculated over the entire experimental duration, and CVs above 15% were rejected (Piper et al., 2014). Subsequently, data were preprocessed using a low-pass filter greater than 0.2 Hz (Scholkmann et al., 2014) to remove physiological components (e.g., heartbeats: 0.5 to 2.0 Hz, and respiration: 0.2 to 0.4 Hz) and then converted into optical density. These signals were corrected for motion artifacts by attenuating outlier fluctuations using temporal derivative distribution repair (Fishburn et al., 2019). The corrected optical density signals were then converted to oxygenated hemoglobin (HbO) as well as deoxygenated hemoglobin (HbR) concentration using the Beer-Lambert law (Santosa et al., 2018). Data were finally visually inspected for artifacts that had not been corrected by the algorithm of temporal derivative distribution repair, and such channels were rejected. Despite the correction of artifacts, a total of five HbO data sets (three participants in HIIE and two in MCE group) had to be excluded from the statistical analysis due to motion artifacts. For further analysis, channels were averaged into six different regions of interest (ROI). We evaluated activity changes in the left frontopolar area (l-FPA): S3-D2, S3-D5, the right prefrontal cortex (r-FPA): S6-D5, S6-D7, the left dorsolateral prefrontal cortex (l-DLPFC): S1-D1, S1-D2, S1-D3, S2-D2, S4-D3, S4-D4), and the right dorsolateral prefrontal cortex (r-DLPFC): S5-D6, S7-D7, S8-D7, S8-D8. The left motor area (l-M1) included all channels over the left motor cortex and the right motor area (r-M1) included all channels over right motor cortex. The average timeline of cortical activation in each ROI for 30 s was graphically presented. Each timeline was adjusted to the average resting value measured during sitting for 2 min before testing. Data preprocessing is illustrated in Figure 4.

Since HbO response is supposed a more sensitive marker of regional blood flow changes (Hoshi, 2003, 2005), we have only considered HbO changes for further analysis. For visualization of the cortical activation on a brain image, we employed the freeware MATLAB toolbox NFRI (https://www.jichi.ac.jp/brainlab/tools.html). Since the optical properties of different ROIs can vary systematically (Herold et al., 2018), the introduction of ROI as a factor in ANOVA may lead to unintentional statistical bias. Therefore, ANOVAs were performed separately for all ROIs. We corrected our alpha using the false discovery rate (FDR-corrected) for the number of ROIs to control for multiple comparisons (Glickman et al., 2014). However, due to the small number of participants in each group, we instead focused on effect sizes when assessing statistical significance (Sullivan & Feinn, 2012).

In fNIRS statistical analysis, the most common approach is to average signals across all time points of the event of interest, but the loss of time-course information limits this technique. Moreover, this averaging approach is not sensitive to detect brain activation's temporal trajectories associated with motor and/or cognitive activity (Herold et al., 2018). In other words, the relationship between motor-cognitive states and the time course of brain signals due to exercise intensity may not be revealed when using this approach. Therefore, due to the continuous execution of the dTMT over 30 s in the present study, it is also necessary to statisticallyvalidate these values that changed across the task duration. Two time windows in the range of 6 and 13 s (T1) and 25 and 32 s (T2) were used for each measured ROI to extract the time course information in the hemodynamic responses due to the effect of exercise intensity accordingly (see Figure 4). The reason for choosing the former is that the hemodynamic response lags the neuronal event by approximately 6 s for cognitive tasks (Herold et al., 2018; Pinti et al., 2020) and due to the delay of the respiratory system during exercise (Seidel et al., 2019). The second time window was chosen to reach the range of maximal concentration changes (Pinti et al., 2020). The duration of the two time windows we chose is consistent with the time duration of prior studies investigating the effects of exercise on cortical activation during the Stroop

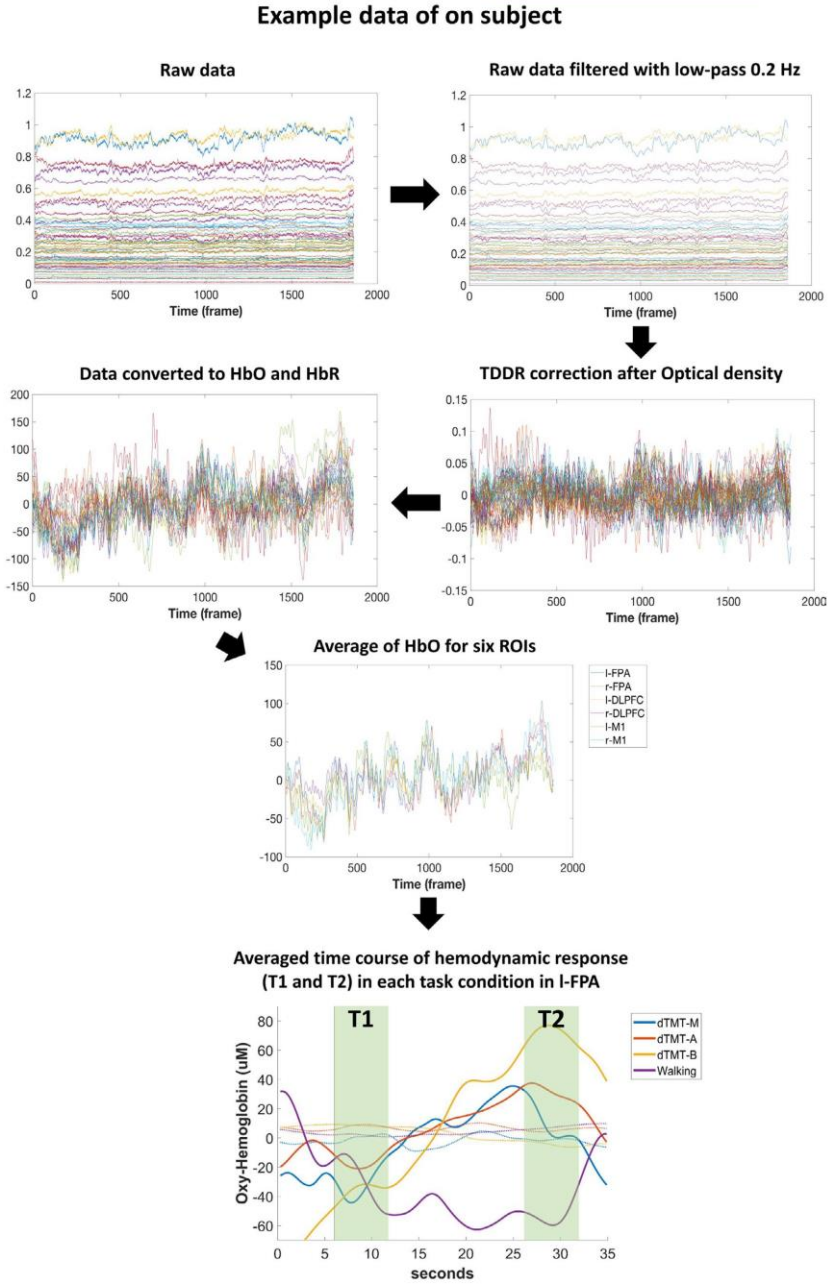

FIGURE 4 Steps of the data processing procedure

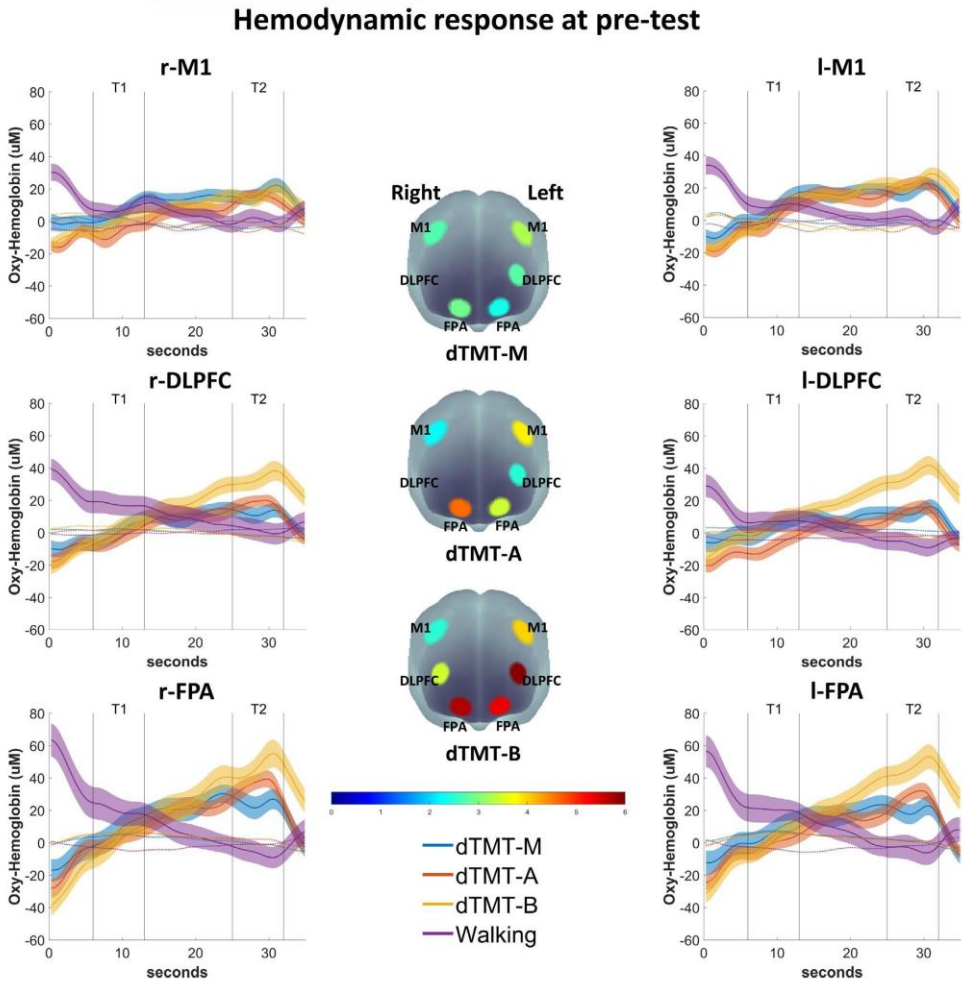

FIGURE 5 Pre-test; cortical activation patterns of all data for participants during the time course of the dTMT. The six graphs depict the mean of the timelines for oxygenated and deoxygenated hemoglobin (HbO: solid line and HbR: dotted line) signals in the prefrontal cortex, the dorsolateral prefrontal cortex, and the motor cortex. HbO and HbR signal changes are shown in arbitrary units (uM). The initial period (T1) of cortical activation for HbO and peak period (T2) are shown for all six ROIs. The timeline of HbO contains the standard error for a given time duration. The central figure is a t-map of oxy-Hb signal changes reflecting the dTMT effect. *T* values are shown according to the color bar

task (Byun et al., 2014; Kujach et al., 2018). The purpose of analyzing the two time windows was to observe walking- or exercise-induced possible differences during our continuous cognitive task over 30 s (with different characteristics of the cognitive task compared to previous studies) in acute versus sustained measured cortex activity (Hawkins et al., 2018). In addition, the same time windows for walking without task conditions were subtracted from walking with task conditions (dual-task–single-task contrast). These values were used to analyze the dual-task's cortical activation while walking to examine the difference between task difficulties and exercise effects on task difficulty.

First, we calculated the time course of the hemodynamic responses over the block duration of 30 s, separately for each ROI, before and after exercise (data preprocessing shown in Figure 4). We then calculated the mean activation pattern for each ROI for each of the two time windows (see Figure 4 below). Through our block experiment design, cortical activation patterns were averaged for all three task difficulties by performing walking with dTMT for 30 s each. Also, cortical activation patterns of walking without dTMT between each task were considered. In the first step of the analysis, we calculated a multivariate analysis of variance (MANOVA) for the hemodynamic response over time for T1 and T2 for each task condition in each ROI during the preexercise period to rule out differences between groups (HIIE and MCE). Next, we analyzed $2 \times 3 \times 2$ ANOVAs with repeated measures for each ROI with the within-subjects factors "hemodynamic response over time" (T1 and T2) and "task condition" (dTMT-M, dTMT-A, dTMT-B) and the between-subjects factor "group" (HIIE and MCE) during the preexercise period. *T* tests for T2 were calculated for a sample approaching zero to detect significant increases in each ROI's cortical activation when performing each dTMT condition before the exercise period. The T values are color-coded in Figure 5.

We then performed ROI-wise analysis separately by task conditions (dTMT-M, -A, and -B) in which all ROIs were subjected to ANCOVAs with repeated measures, controlling for the rate of change of each dTMT performance as a covariate with "exercise" (PRE-POST exercise) and "hemodynamic response time" (T1 and T2) as within-subjects factors and with "group" (HIIE, MCE) as between-subjects factors. In the final step, we calculated the rate of change for each dTMT condition (number of correctly connected circles) and the rate of change for each ROI and converted it to a positive or negative change frequency to examine the coincidences of frequency. Both frequency values (frequency of positive or negative changes in neural and behavior level in postexercise) were tested with the McNemar test, a robust nonparametric procedure, and used to study the correspondence between two incidents (Siegel & Castellan, 1988), while Chi-square tests determined between-group differences in exercise-induced behavioral and neural activation changes.

3 | RESULTS

3.1 | Characteristics of the study population

Table 1 summarizes the analyses for age, height, weight, BMI, maximum heart rate (max. HR), maximum oxygen uptake (VO_2max), and the group's duration of physical activity. There were no significant differences between the two groups regarding these variables.

3.2 | Effects of exercise on objective and subjective physiological variables

3.2.1 | HR before, during, and after exercise

Table 2 shows the mean values of HR before, during, and after exercise for both intervention groups. A 3×2 ANOVA with repeated measurement with the within-subjects factor "time" (before, during and after exercise) and the between-subjects factor "group" (HIIE and MCE) demonstrated significant effects for time ($F_{2,54} = 935$, $p < .001$, $\eta_p^2 = 0.972$) as well as an interaction effect for time by group ($F_{2,54} = 21.4$, $p < .001$, $\eta_p^2 = 0.442$). The post hoc analysis showed that HR was significantly higher in the HIIE group during ($p < .001$) and after exercise ($p = .017$) than in the MCE group. Furthermore, a significant positive correlation was found between HR during exercise and RPE ($r_{14} = 0.708$, $p = .005$) and a positive correlation towards significance between HR after exercise and RPE ($r_{14} = 0.519$, $p = .057$), but only in the HIIE group.

TABLE 1 Participants' demographics and physiological characteristics for HIIE and MCE groups

	HIIE ($n = 14$) *M* (*SD*)	MCE ($n = 15$) *M* (*SD*)	Stat. analyses
Sex (male:female)	11:3	11:4	$\chi^2_1 = 0.109$
Age (years)	26.0 (3.98)	24.2 (4.04)	$t_{27} = 1.21$, $d = 0.45$
Height (cm)	176 (9.34)	177 (9.42)	$t_{27} = 0.22$, $d = 0.02$
Weight (kg)	70.6 (10.5)	70.2 (12.0)	$t_{27} = 0.11$, $d = 0.04$
BMI (kg/m^2)	22.7 (2.29)	22.4 (2.70)	$t_{27} = 0.40$, $d = 0.12$
max. HR (bpm)	189 (6.72)	189 (5.59)	$t_{27} = 0.08$, $d = 0.46$
VO_2max (ml/kg/min)	55.2 (6.37)	56.2 (7.11)	$t_{27} = 0.41$, $d = 0.15$
Exercise duration per week (min)	175 (144)	227 (130)	$t_{27} = -1.31$, $d = 0.49$

Abbreviations: *M*: mean, *SD*: standard deviation.

3.2.2 | RPE and MPSTEFS

As expected, a *t* test for independent samples analyzing the differences in RPE in the intervention groups after training showed that the participants in the HIIE group (15.6 ± 3.37) perceived the exercise significantly more strenuous than the participants in the MCE group (12.4 ± 2.29) ($t_{27} = 2.98$, $p = .006$, $d = 1.11$).

In order to evaluate the effects of the MPSTEFS questionnaire (see Table 3), we performed a 2 × 2 ANOVA with repeated measurements with the within-subjects factor "exercise" (PRE-POST exercise) and the between-subjects factor "group" (HIIE and MCE). There were no significant effects for the four components of MPSTEFS (Physical Energy, Physical Fatigue, Mental Energy, and Mental Fatigue).

3.3 | Effects of exercise on the behavioral data of the dTMT

To test the effect of exercise on different parameters of the dTMT, we performed 2 × 3 × 2 ANOVAs with repeated measurements with the within-subjects factors "exercise" (PRE-POST exercise) and "task condition" (dTMT-M, dTMT-A, dTMT-B) and the between-subjects factor "group" (HIIE and MCE).

For the number of correctly connected circles (see Table 4), we found a main effect for exercise ($F_{1,27} = 25.9$, $p < .001$, $\eta_p^2 = 0.489$) and a significant main effect for task condition ($F_{1,27} = 243$, $p < .001$, $\eta_p^2 = 0.900$). There were no significant interaction effects for exercise by task condition. Post hoc analysis showed that the number of correctly connected circles differed significantly between all three task conditions (all $p < .001$). As the task's difficulty increased, the number of correctly connected circles decreased, resulting in the largest number for TMT-M and the smallest number for TMT-B. After exercise, the performance improved for all conditions, regardless of the type of exercise.

The ANOVA on the component measure time inside and between circles (see Table 4) revealed significant main effects for exercise (between: $F_{1,27} = 37.4$, $p < .001$, $\eta_p^2 = 0.581$; inside: $F_{1,27} = 14.0$, $p = .001$, $\eta_p^2 = 0.342$) and task condition (between: $F_{2,54} = 37.6$, $p < .001$, $\eta_p^2 = 0.582$; inside: $F_{2,54} = 145$, $p < .001$, $\eta_p^2 = 0.843$). There were no other significant interaction effects for group and exercise and/or task condition. Post hoc analysis showed that the durations for inside and between the circles were significantly shorter in the posttest compared to the pre-test ($p < .001$). In addition, all task conditions differed significantly from each ($p < .001$) with increasing durations inside and between the circles.

TABLE 2 Mean and *SD* for HR by intervention group (HIIE, MCE) before, during, and after exercise

Heart rate (bpm/min)	HIIE ($n = 14$) *M* (*SD*)	MCE ($n = 15$) *M* (*SD*)	Stat. analyses
Before	96.7 (5.69)	96.9 (9.87)	$t_{27} = -0.08$, $d = 0.03$
During	169 (9.82)	150 (14.1)	$t_{27} = 4.22^{***}$, $d = 1.55$
After	124 (9.97)	112 (14.1)	$t_{27} = 2.55^{*}$, $d = 0.98$

Abbreviations: *M*: mean, *SD*: standard deviation.
$^{*}p < .05$.; $^{***}p < .001$.

3.4 | fNIRS results

3.4.1 | Hemodynamic response at pre-test

In the first step of the analysis, the MANOVA for HbO over T1 and T2 in each task condition and all ROIs revealed no significant differences between groups during preexercise (Wilks' Lambda = 0.055, $F_{27,1} = 0.63$, $p = .780$, $\eta_p^2 = 0.945$). Subsequently, we analyzed the time course of the hemodynamic response (T1 and T2) as a function of the task conditions in each ROI (see Figure 5).

The ANOVA with repeated measurement for the six ROIs revealed that there was a significant effect of the time course of hemodynamic response (T1 to T2) in all ROIs (l-FPA: $F_{1,27} = 48.4$, $p < .001$, $\eta_p^2 = 0.642$, r-FPA: $F_{1,27} = 40.3$, $p < .001$, $\eta_p^2 = 0.599$, l-DLPFC: $F_{1,27} = 45.8$, $p < .001$,

TABLE 3 Mean and *SD* for pre- and post acute exercise MPSTEFS data by group (HIIE and MCE)

MPSTEFS dimension	Preexercise HIIE ($n = 14$) *M* (*SD*)	Preexercise MCE ($n = 15$) *M* (*SD*)	Postexercise HIIE ($n = 14$) *M* (*SD*)	Postexercise MCE ($n = 15$) *M* (*SD*)
Physical energy	301 (50.9)	298 (59.7)	307 (47.3)	297 (83.9)
Physical fatigue	151 (60.7)	134 (65.2)	176 (92.3)	149 (108)
Mental energy	299 (52.8)	313 (49.1)	309 (64.0)	289 (67.9)
Mental fatigue	154 (64.8)	108 (41.8)	160 (71.9)	156 (78.0)

Abbreviations: *M*: mean, *SD*: standard deviation.

TABLE 4 Mean and *SD* for pre- and post acute exercise dTMT data by group (HIIE and MCE)

	Preexercise		Postexercise	
	HIIE	MCE	HIIE	MCE
	(*n* = 14) *M* (*SD*)	(*n* = 15) *M* (*SD*)	(*n* = 14) *M* (*SD*)	(*n* = 15) *M* (*SD*)
Number of correctly connected circles				
dTMT-M	54.7 (12.4)	61.8 (11.4)	65.9 (9.32)	67.7 (11.8)
dTMT-A	42.2 (6.24)	43.0 (9.45)	46.9 (8.05)	48.3 (7.25)
dTMT-B	27.8 (6.44)	27.8 (7.41)	31.9 (8.86)	35.5 (8.01)
Time between circles (s)				
dTMT-M	0.24 (0.04)	0.27 (0.09)	0.21 (0.04)	0.21 (0.05)
dTMT-A	0.32 (0.07)	0.30 (0.08)	0.27 (0.06)	0.27 (0.07)
dTMT-B	0.42 (0.13)	0.37 (0.15)	0.31 (0.09)	0.32 (0.06)
Time inside circles (s)				
dTMT-M	0.18 (0.04)	0.19 (0.07)	0.16 (0.04)	0.15 (0.03)
dTMT-A	0.31 (0.06)	0.27 (0.07)	0.27 (0.10)	0.24 (0.04)
dTMT-B	0.52 (0.16)	0.48 (0.18)	0.43 (0.16)	0.41 (0.10)

Abbreviations: *M*: mean, *SD*: standard deviation.

$\eta_p^2 = 0.629$, r-DLPFC: $F_{1,27} = 41.3$, $p < .001$, $\eta_p^2 = 0.605$, l-M1 cortex: $F_{1,27} = 31.9$, $p < .001$, $\eta_p^2 = 0.542$, r-M1: $F_{1,27} = 29.5$, $p < .001$, $\eta_p^2 = 0.522$, FDR-corrected). Also, a significant of task condition was observed in l-DLPFC, $F_{2,54} = 6.03$, $p = .024$, $\eta_p^2 = 0.182$, (FDR-corrected).

Furthermore, we found a significant interaction effect between time course of hemodynamic response (T1 to T2) and task conditions in the frontal lobe (l-FPA: $F_{2,54} = 6.98$, $p = .009$, $\eta_p^2 = 0.205$, r-FPA: $F_{2,54} = 5.18$, $p = .018$, $\eta_p^2 = 0.161$, l-DLPFC: $F_{2,54} = 6.60$, $p = .009$, $\eta_p^2 = 0.196$, r-DLPFC: $F_{2,54} = 4.52$, $p = .023$, $\eta_p^2 = 0.144$, FDR-corrected), but not in the motor cortex, indicating significant increases in the HbO level for time course of hemodynamic response from T1 to T2 associated with each dTMT condition. Post hoc analysis showed that the cortical activation in T2 was significantly higher for dTMT-B than for the TMT-A (l-FPA: $p = .036$, l-DLPFC: $p = .003$, r-DLPFC: $p = .046$) and the dTMT-*M* (l-FPA: $p = .024$, l-DLPFC: $p = .004$, r-DLPFC: $p = .010$). There were no significant differences between dTMT-A and dTMT-M. The cortical activation in T2 associated with each task condition was significant in all ROIs except r-DLPFC for dTMT-M and dTMT-A (*t* test in one sample, $p < .05$, FDR-corrected; see the figure in the center of Figure 5).

3.4.2 | Changes in hemodynamic response between pre-test and posttest

Table 5 shows the main and interaction effects for cortical activation in each ROI with the statistical values controlled for the rate of change for each dTMT performance. (*F*-, *p* value, and effect size [η_p^2]). We focused on the effect size with the least moderate effects (above 0.06) because of the possibility of overcorrection for multiple comparisons in each ROI. Because the number of participants in each group tends to be small, effect sizes may be a more sensitive parameter for evaluating results (Sullivan & Feinn, 2012).

The ANCOVAs, controlled for the rate of change for each dTMT performance in each ROI, separately by task condition (dTMT-M, -A, and -B), revealed interactions with at least moderate effects sizes between exercise (PRE-POST exercise) and group (HIIE versus. MCE) in all frontal lobes, indicating higher cortical activation in the HIIE group after exercise. Moreover, we found interactions with at least moderate effects sizes between exercise, time course of hemodynamic response (T1 to T2), and group in the l-FPA (all task conditions), the l-DLPFC (dTMT-M), the r-DLPFC (dTMT-A), the l-M1 (dTMT-M and -B), and the r-M1 (dTMT-A). As indicated by the interaction effects, hemodynamic changes from T1 to T2 by exercise were greater in the HIIE than in the MCE group for the dTMT performance (see Figures 6 and 7a–f). Although there were only significant differences between groups in l-FPA ($p = .029$) and l-DLPFC ($p = .015$) during dTMT-M and in r-DLPFC ($p = .040$) and r-M1 ($p = .032$) during dTMT-B for HbO of T2 after exercise, group differences were considered to have an effect size of at least medium or greater in all task conditions of all ROIs (Cohen's *d*, greater than 0.5).

3.4.3 | Relationship between fNIRS and behavioral data

Correlational analysis revealed no associations between %Δ in hemodynamic responses in the six ROIs and %Δ in

TABLE 5 Repeated measures ANOVA results of the ROI analysis for each task condition of the dTMT with *F*, *P* value (FDR-corrected), and medium effect size (above 0.06 in bold)

Effects	l-FPA			r-FPA			l-DLPFC			r-DLPFC			l-M1			r-M1		
dTMT-M	$F_{1,21}$	*P*	η_p^2	$F_{1,21}$	*P*	η_p^2	$F_{1,21}$	*P*	η_p^2	$F_{1,21}$	*P*	η_p^2	$F_{1,21}$	*P*	η_p^2	$F_{1,21}$	*P*	η_p^2
Exercise	13.5	0.006	**0.391**	7.35	0.048	**0.259**	7.79	0.044	**0.271**	7.25	0.049	**0.257**	13.7	0.006	**0.395**	3.53	0.190	**0.144**
Exercise × Group	2.84	0.220	**0.119**	1.62	0.321	**0.072**	2.03	0.285	**0.088**	1.90	0.295	**0.083**	0.230	0.680	0.011	0.272	0.656	0.013
Time	9.23	0.029	**0.305**	11.3	0.015	**0.350**	5.85	0.079	**0.218**	7.91	0.042	**0.274**	7.20	0.049	**0.255**	8.41	0.041	**0.286**
Time × Exercise	0.634	0.502	0.030	1.76	0.311	**0.077**	2.41	0.257	**0.103**	1.14	0.370	0.051	1.90	0.421	0.041	0.099	0.778	0.005
Time × Group	1.62	0.321	**0.072**	2.99	0.214	**0.124**	2.11	0.285	**0.091**	1.43	0.341	**0.064**	2.10	0.285	**0.091**	3.46	0.193	**0.141**
Time × Exercise × Group	3.34	0.193	**0.137**	0.285	0.656	0.013	2.05	0.285	**0.089**	1.34	0.778	0.034	1.35	0.344	**0.061**	1.19	0.366	0.054
dTMT-A	$F_{1,21}$	*P*	η_p^2	$F_{1,21}$	*P*	η_p^2	$F_{1,21}$	*P*	η_p^2	$F_{1,21}$	*P*	η_p^2	$F_{1,21}$	*P*	η_p^2	$F_{1,21}$	*P*	η_p^2
Exercise	17.5	0.006	**0.455**	16.6	0.006	**0.442**	16.8	0.006	**0.444**	22.2	0.006	**0.514**	16.7	0.006	**0.443**	2.97	0.214	**0.124**
Exercise × Group	2.42	0.257	**0.103**	1.37	0.344	**0.061**	3.22	0.200	**0.133**	1.56	0.325	**0.069**	0.173	0.721	0.008	0.007	0.932	.000
Time	17.3	0.006	**0.452**	20.8	0.006	**0.497**	17.8	0.006	**0.459**	15.8	0.006	**0.429**	18.6	0.006	**0.469**	14.4	0.006	**0.407**
Time × Exercise	3.42	0.193	**0.140**	3.17	0.203	**0.131**	3.65	0.190	**0.148**	3.56	0.190	**0.145**	1.52	0.352	0.057	1.98	0.289	**0.086**
Time × Group	0.661	0.499	0.031	1.65	0.321	**0.073**	0.581	0.523	0.027	0.010	0.932	0.000	1.52	0.328	**0.067**	1.51	0.328	**0.067**
Time × Exercise × Group	2.81	0.220	**0.118**	0.103	0.778	0.005	0.380	0.612	0.018	2.39	0.257	**0.102**	0.300	0.656	0.014	1.84	0.302	**0.080**
dTMT-B	$F_{1,21}$	*P*	η_p^2	$F_{1,21}$	*P*	η_p^2	$F_{1,21}$	*P*	η_p^2	$F_{1,21}$	*P*	η_p^2	$F_{1,21}$	*P*	η_p^2	$F_{1,21}$	*P*	η_p^2
Exercise	6.68	0.057	**0.241**	11.2	0.015	**0.349**	1.31	0.350	0.059	7.64	0.046	**0.267**	14.1	0.006	**0.402**	8.28	0.041	**0.283**
Exercise × Group	2.27	0.267	**0.098**	3.36	0.193	**0.138**	3.63	0.190	**0.147**	4.38	0.143	**0.172**	1.70	0.318	**0.075**	1.09	0.378	0.049
Time	20.0	0.006	**0.488**	19.9	0.006	**0.486**	15.0	0.006	**0.417**	17.2	0.006	**0.450**	14.2	0.006	**0.403**	8.00	0.042	**0.276**
Time × Exercise	2.37	0.257	**0.102**	5.57	0.086	**0.210**	6.49	0.062	**0.236**	2.94	0.214	**0.123**	0.920	0.418	0.042	1.57	0.325	**0.069**
Time × Group	1.14	0.370	0.052	1.92	0.295	**0.084**	2.72	0.228	**0.115**	1.28	0.351	0.058	2.04	0.285	**0.089**	4.46	0.141	**0.175**
Time × Exercise × Group	3.65	0.190	**0.148**	0.275	0.656	0.013	0.045	0.851	0.002	1.07	0.381	0.048	1.37	0.344	**0.061**	0.529	0.540	0.025

Note.: Exercise: PRE-POST exercise, time: time course of hemodynamic response (T1 and T2), group: HIIE (n = 11) and MCE (n = 13).

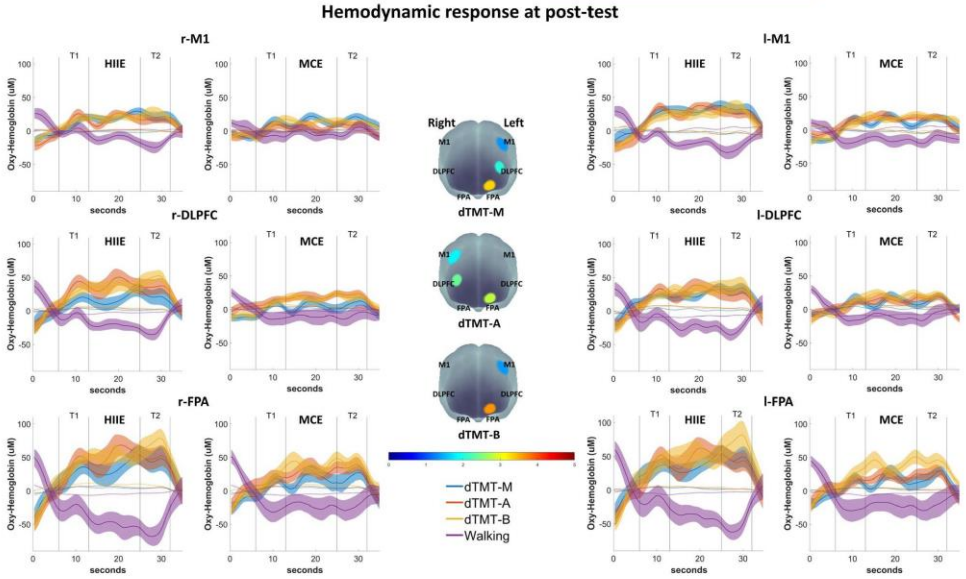

FIGURE 6 Posttest; cortical activation patterns (HIIE: $n = 11$, MCE: $n = 13$) during the time course of the dTMT. The six graphs depict the mean of the timelines for oxygenated and deoxygenated hemoglobin (HbO: solid line and HbR: dotted line) signals in the prefrontal cortex, the dorsolateral prefrontal cortex, and the motor cortex separately for HIIE and MCE. HbO and HbR signal changes are shown in arbitrary units (uM). The initial period (T1) of cortical activation for HbO and peak period (T2) are shown for all six ROIs. The timeline of HbO contains the standard error for a given time duration. The central figure is a t-map of oxy-Hb signal changes reflecting the dTMT effect. *T* values are shown according to the color bar

dTMT performance. To further examine this relationship, we applied the McNemar test, a robust nonparametric statistical procedure that allows us to assess the correspondence between two incidences (Siegel & Castellan, 1988). The contingency table (Table 6) shows that positive cognitive performance changes were associated with an increase in the hemodynamic response for almost all ROIs, especially in the HIIE group. Chi-square tests showed that groups did not differ in exercise-enhanced activation and exercise-induced improved cognitive performance.

4 | DISCUSSION

The present study aimed to explore the neural correlates underpinning the acute effects of HIIE compared to MCE on the performance of the dTMT, a fine motor-cognitive task, while walking on a treadmill. Healthy young participants performed the dTMT while walking at a fixed speed of 5 km/h before and after acute exercise, while cerebral oxygenation was recorded by fNIRS over the prefrontal and the motor cortex. Notably, this was the first study to examine such effects during exercise execution considering different training intensities compared to previous studies in which the cognitive task was performed while sitting at a table (Byun et al., 2014; Hyodo et al., 2012; Kujach et al., 2018; Yanagisawa et al., 2010). We found an overall increase in task performance at the behavioral level (dTMTM: 25.3%, dTMTA: 15.1%, dTMTB: 17.7%) independent of training intensity. Contrary to our hypothesis, this is initially surprising, as different performance effects are usually found for HIIE than MCE (Kamijo et al., 2004, 2007; Labelle et al., 2013). However, the results of a meta-analysis by Lambourne and Tomporowski (2010) also show that cognitive impairment occurs only during the first 20 min of exercise.

Similarly, the studies included in Chang et al. (2012) showed no effects during the first 10 min of exercise, an adverse effect between 11 and 20 min, and positive effects after 20 min. However, when we considered the hemodynamic changes induced by each type of exercise, we found different effects between the two groups. These results suggest that the distribution of neural resources differed according to training intensity to maintain the same task performance level.

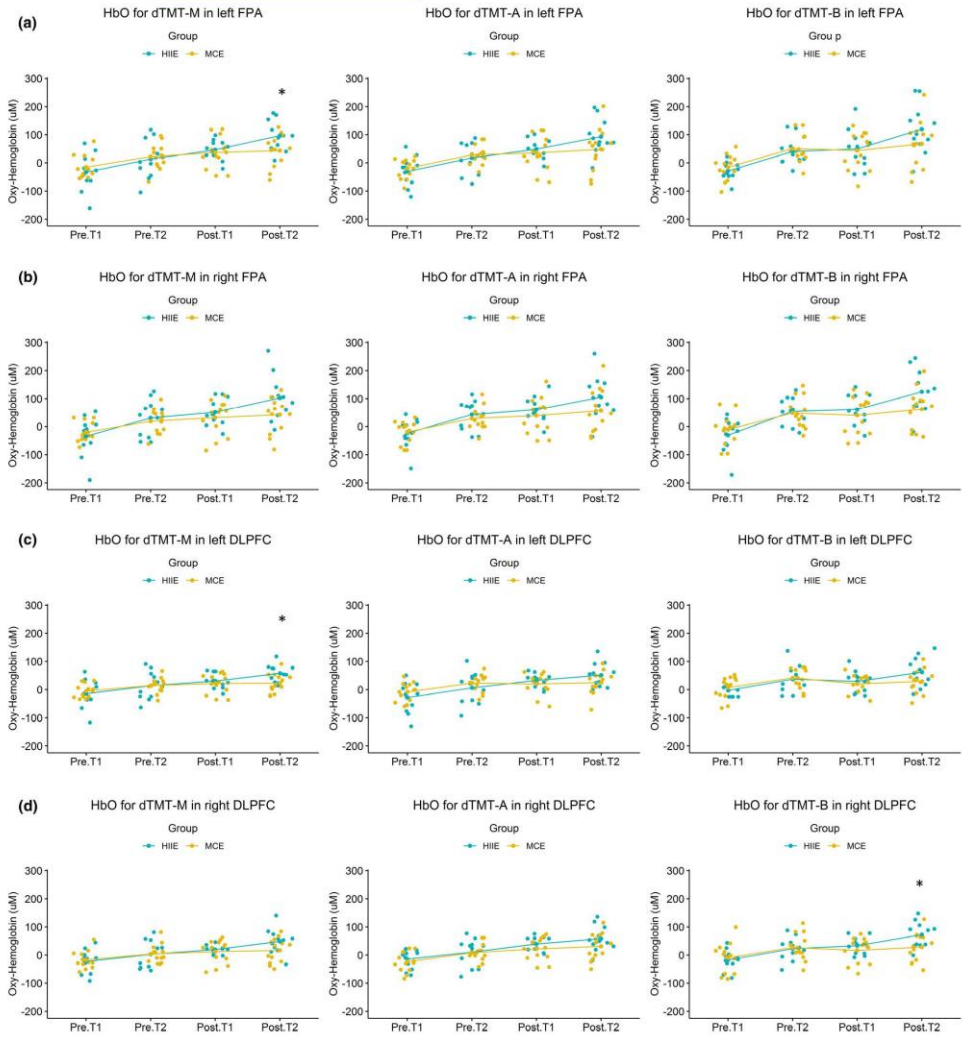

FIGURE 7 Scatterplot with a mean line for HbO in exercise (PRE-POST exercise) by time course of hemodynamic response (T1 and T2) interaction for each dTMT condition in the (A) left and (B) right FPA, (C) left, and (D) right DLPFC, and (E) left and (F) right M1 (Pre.T1: T1 in preexercise, Pre.T2: T2 in preexercise, Post.T1: T1 in postexercise, Post.T2: T2 in postexercise), $^{*}p < .05$ (Asterisk: significant difference between groups)

4.1 | Physiological effects of an acute bout of HIIE or MCE

The two types of exercise performed in this study induced different HR changes and resulted in different RPEs with higher values in the HIIE compared to the MCE group (Yanagisawa et al., 2010). HIIE protocols are generally more physically demanding than MCE protocols, and our exercise protocols effectively induced such differential exertion. Moreover, both measures, HR and RPE, were positively correlated, suggesting that objective and subjective indices of exertion are comparable. Similar effects have

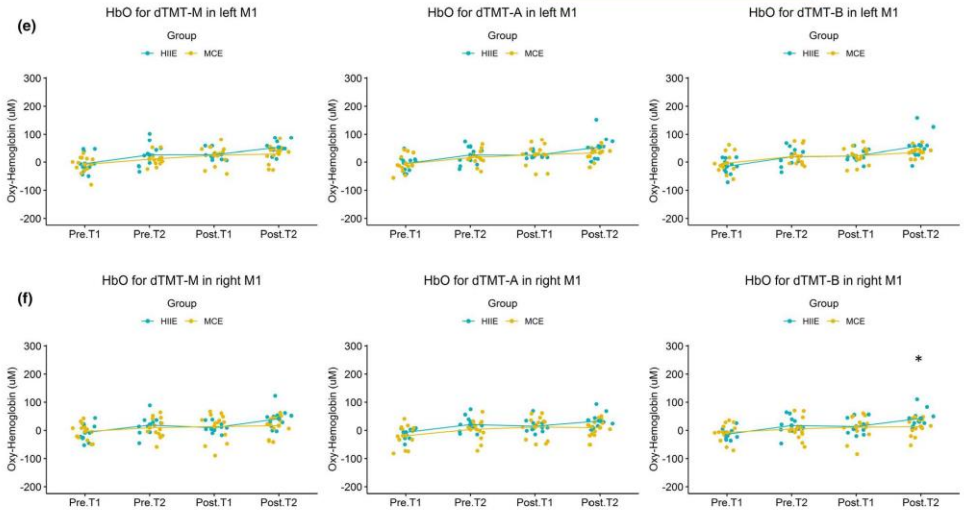

FIGURE 7 (Continued)

been found in a previous study by Green et al. (2006), in which the RPE scale was sensitively correlated with acute changes in HR during HIIE. However, the MPSTEFS did not show any effects of exercise. Because its measurement was not taken immediately after the exercise protocol, but only after the second dTMT, participants already had some time to recover (approximately 12 min in total). For this reason, it may be challenging to confirm the changes in physical and mental states before and after exercise using this scale.

4.2 | Cognitive effects of an acute bout of HIIE or MCE

To date, a large number of studies have examined the beneficial effects of acute exercise on cognitive function at the behavioral level immediately after exercise (Chang et al., 2012; Kujach et al., 2018; Lambourne & Tomporowski, 2010; Mekari et al., 2020; Moreau & Chou, 2019; Tsukamoto et al., 2016). Surprisingly, our study found that both types of exercise (intensities) had a positive effect on dTMT performance (dTMTM: 25.3%, dTMTA: 15.1%, dTMTB: 17.7%).

One of the factors that may explain the gains in cognitive performance is the timing of the cognitive tasks' performance (i.e., before, during, or immediately after exercise). Most studies measure cognitive performance before and after training, whereas fewer studies have examined what happens to cognitive performance during training, which is more relevant to sport. Only two of the previous meta-analyses (Chang et al., 2012; Lambourne & Tomporowski, 2010) described impaired cognitive performance during exercise with a small effect size. However, it was also shown that at least 20 min of training is required to observe an improvement in cognitive performance (Chang et al., 2012).

Another factor lies in the motor task itself: Our results are similar to the findings of Tsukamoto et al. (2016), who also demonstrated an improvement in cognitive performance for both types of exercise. However, unlike in our study, participants performed the protocol on a bicycle ergometer. Exercise on a treadmill was found to be more likely to impair cognitive functions, while cycling tended to enhance cognitive functions (Lambourne & Tomporowski, 2010) due to the varying degrees to which attentional resources are used to control body movements (Soga et al., 2015). A study by Penati et al. (2020) might help to explain the inconsistent effects: They compared performance on a cognitive task during overground self-paced walking to fixed-speed walking on a treadmill and demonstrated better performance when walking during fixed-speed walking. In this case, walking is an almost automatic process without external environmental changes (Wrightson & Smeeton, 2017), prioritizing a cognitive task over walking, leading to higher cognitive performance.

Another possible explanation for this observation could relate to motivational aspects underlying motor and cognitive performance. It has been shown in other research that motivation increases during endurance training due to proximity

TABLE 6 Contingency tables for the McNemar test

		Δl-FPA			Δr-FPA			Δl-DLPFC			Δr-DLPFC			Δl-M1			Δr-M1		
ΔdTMT-M		**+**	**−**	**Total**	**+**	**−**	**Total**	**+**	**−**	**Total**	**+**	**−**	**Total**	**+**	**−**	**Total**	**+**	**−**	**Total**
HIIE ($n = 11$)	−	3	0	3	3	0	3	3	0	3	1	2	3	3	0	3	1	2	3
	+	7	1	8	7	1	8	7	1	8	7	1	8	7	1	8	7	1	8
	Total	10	1	11**	10	1	11**	10	1	11**	8	3	11	10	1	11**	8	3	11
MCE ($n = 13$)	−	1	1	2	1	1	2	1	1	2	1	1	2	2	0	2	0	2	2
	+	8	3	11	9	2	11	8	3	11**	8	3	11	8	3	11	8	3	11
	Total	9	4	13**	10	3	13**	9	4	13	9	4	13**	10	3	13**	8	5	13
total ($n = 24$)	−	4	1	5	4	1	5	4	1	5	2	3	5	5	0	5	1	4	5
	+	15	4	19	16	3	19	15	4	19	15	4	19	15	4	19	15	4	19
	Total	19	5	24***	20	4	24***	19	5	24***	17	7	24**	20	4	24***	16	8	24**
ΔdTMT-A		**+**	**−**	**Total**	**+**	**−**	**Total**	**+**	**−**	**Total**	**+**	**−**	**Total**	**+**	**−**	**Total**	**+**	**−**	**Total**
HIIE ($n = 11$)	−	2	0	2	2	0	2	2	0	2	2	0	2	2	0	2	2	0	2
	+	7	2	9	8	1	9	7	2	9	7	2	9	7	2	9	5	4	9
	Total	9	2	11**	10	1	11**	9	2	11**	9	2	11**	9	2	11**	7	4	11
MCE ($n = 13$)	−	1	1	2	1	1	2	1	1	2	1	1	2	1	1	2	1	1	2
	+	6	5	11	8	3	11	4	7	11	7	4	11	6	5	11	7	4	11
	Total	7	6	13	9	4	13**	5	8	13	8	5	13	7	6	13	8	5	13
total ($n = 24$)	−	3	1	4	3	1	4	3	1	4	3	1	4	3	1	4	3	1	4
	+	13	7	20	16	4	20	11	9	20	14	6	20	13	7	20	12	8	20
	Total	16	8	24**	19	5	24***	14	10	24**	17	7	24***	16	8	24**	15	9	24**
ΔdTMT-B		**+**	**−**	**Total**	**+**	**−**	**Total**	**+**	**−**	**Total**	**+**	**−**	**Total**	**+**	**−**	**Total**	**+**	**−**	**Total**
HIIE ($n = 11$)	−	3	0	3	3	0	3	3	0	3	3	0	3	3	0	3	3	0	3
	+	7	1	8	7	1	8	6	2	8	7	1	8	6	2	8	7	1	8
	Total	10	1	11**	10	1	11**	9	2	11**	10	1	11**	9	2	11**	10	1	11**
MCE ($n = 13$)	−	1	1	2	1	1	2	1	1	2	1	1	2	2	0	2	2	0	2
	+	7	4	11	7	4	11	6	5	11	7	4	11	8	3	11	8	3	11
	Total	8	5	13	8	5	13	7	6	13	8	5	13	10	3	13**	10	3	13**
total ($n = 24$)	−	4	1	5	4	1	5	4	1	5	4	1	5	5	0	5	5	0	5
	+	14	5	19	14	5	19	12	7	19	14	5	19	14	5	19	15	4	19
	Total	18	6	24***	18	6	24***	16	8	24**	18	6	24***	19	5	24***	20	4	24***

Note.: The table shows the association between dTMT performance and cortical activation in each ROI. Frequencies of exercise-induced HbO increase in each brain area and improvement of dTMT performance (number of correctly connected circles) are summarized.

*p <.05.; **p <.01.; ***p <.001.

to the goal and progress relative to goal pursuit (Schiphof-Godart & Hettinga, 2017).

4.3 | Exercise-enhanced hemodynamic response

We found an overall increase in HbO concentration in all ROIs after exercise. In all frontal ROIs, this effect was more robust in the HIIE group than in the MCE group. Some authors have argued that increases in CBF during physical exertion lead to this higher neuronal activity (Ogoh & Ainslie, 2009; Steventon et al., 2020; Thomas et al., 1989). Our results contradict Moriarty et al. (2019)'s findings, who suggested that the overall blood flow of the brain remains more or less constant during acute aerobic exercise. Dietrich and Audiffren (2011) proposed a shift in CBF from areas needed for cognitive function to areas needed for motor control and maintenance of vital function. We did not find a shift from frontal to motor areas but rather a general increase in hemodynamic activation. Of course, there could be a shift from other areas not involved in our task. However, because we did not measure the changes in HbO throughout the brain, we can neither confirm nor exclude this hypothesis. Furthermore, the hypofrontality hypothesis of reticular activation by Dietrich and Audiffren (2011) postulated effects during exercise and not after exercise.

Methodologically, performing the dTMT while running on a treadmill is challenging to implement. Instead, we chose to perform the dTMT during walking after the training intervention. Many studies instead examined exercise effects while sitting after exercise (Bediz et al., 2016; Byun et al., 2014; Ji et al., 2019; Kujach et al., 2018; Yanagisawa et al., 2010). Our study was the first, to our knowledge, to investigate the effects on cognition during walking after exercise interventions with different intensities. It is well known that walking is a complex process that relies on cognitive and executive functions (Schott, 2019; Sheridan & Hausdorff, 2007; Yogev-Seligmann et al., 2008). Interferences resulting from the simultaneous performance of other tasks can cause motor-cognitive interference that can impair overall performance. This effect is more substantial with the increasing complexity of motor and/or tasks (Klotzbier & Schott, 2017; Li et al., 2018; Schott, 2019; Schott et al., 2016). However, it has also been shown that DT training may benefit not only motor performance and physiological health but also cognitive functioning (Ghai et al., 2017). Therefore, studying the effects of different types of exercise protocols on motor-cognitive performance in dual- or even multi-task situations may improve performance in various situations in daily life, elderly care, or athlete's development.

Since walking, even at fixed speed on a treadmill, is an automated process leading to low prefrontal activation (Thumm et al., 2018), higher increases in HbO in frontal areas for the HIIE group can be interpreted as a higher need for resources for postural control after intensive training (González-Fernández et al., 2017). Thus, it can be surmised that the cognitive tasks can only be fully attended to if the corresponding postural responses had been initiated (or inhibited). Thus, in the context of the present study, HIIE might pose a greater threat to postural stability, resulting in poorer cognitive performance. Indeed, HIIE participants had a visibly higher effort to maintain balance while walking on the treadmill during dTMT than MCE participants. Nevertheless, participants were not impaired at the behavioral level and even improved their performance in the dTMT in the same way as the MCE group. This could be due to our participants' high cardiorespiratory fitness level, which was excellent in 41.4%, good in 37.9%, and above average in 17.2% of all cases (ACSM, 2013; Heywood, 2006). A meta-analysis by Chang et al. (2012) on the effects of acute exercise on cognitive performance pointed to the fitness level of participants as a significant mediator. Based on the neurotrophic hypothesis (Stillman et al., 2016), an increase of neuronal growth factors (BDNF, insulin-like growth factor 1, vascular endothelial growth factor) through regular exercise leads to an upregulation of neurogenesis, synaptogenesis, gliogenesis, and angiogenesis. This may lead to structural changes in the brain through improved cerebrovascular function and perfusion as a consequence of habitual physical activity (Schott, 2020). Zoladz et al. (2008) demonstrated that high resting BDNF levels occur in well-trained participants with high VO_2max compared to untrained participants with low VO_2max. Notably, Ainslie et al. (2008) also demonstrated that high cardiorespiratory fitness levels were associated with increases in CBF. Our participants' high fitness levels may have induced positive structural and functional adaptations in the brain that allowed them to perform the task without any difficulty, using improved cerebrovascular functions that respond effectively to different types of exercise. Therefore, the higher frontal activation pattern of the HIIE group when walking during dTMT performance suggests a higher recruitment of neural resources for increased demands on postural control to ensure safe walking on the treadmill.

Another explanation could be the rebound effect of cortical activation during postexercise (Basso & Suzuki, 2017; Moriarty et al., 2019). To confirm this, one would have to record brain activation not only after but also during exercise, which represents a methodological challenge when running on a treadmill, even with fNIRS, which is usually considered less sensitive to motor artifacts (Wolff, 2017). Here, exercise on a bicycle ergometer, where the upper body moves less than on a treadmill, might be more promising.

There is another major difference between our study and most other studies that use a cognitive task to measure motor-cognitive performance in DT situations: While most studies used a cognitive task that requires the participant

to respond quickly to a given stimulus (with reaction time as the dependent parameter), we used a continuous cognitive task performed in 30-s blocks during walking. This block design leads to additional motor-cognitive demands that increase over time. We examined the effects of increasing load on motor-cognitive performance by comparing the activation pattern for two time points within these 30-s blocks. We found a main effect of these time windows for all ROIs and showed that T2 exhibited higher activation than T1, indicating an increase in activation over the block duration as expected due to increasing task demands. This effect also varied for different dTMT conditions. For example, there was a main effect of task condition in the frontal cortex that showed an increase of activation from dTMT-M to dTMT-B. This can be attributed to the increasing cognitive demands and was also confirmed in previous studies (Hagen et al., 2014; Müller et al., 2014). The dTMT-B showed higher activation in frontal areas than dTMT-M and dTMT-A. This finding is related to the frontal lobe's involvement in executive functions and cognitive control processes (Shibuya-Tayoshi et al., 2007). In general, the TMT-A consists of primarily visual search and processing speed (Ríos Lago et al., 2004; Sánchez-Cubillo et al., 2009), whereas the TMT-B requires more complex cognitive abilities such as cognitive flexibility and inhibition (Arbuthnott & Frank, 2000; Kortte et al., 2002).

After the exercise interventions, we found an effect of type of exercise in all brain areas measured in the present study, with the most substantial increases irrespective of task condition at T2 for the HIIE group, resulting in significant differences between groups with effect sizes of at least medium or greater values in all task conditions of all ROIs (Cohens *d*, greater than 0.5). Among them, significant increases were found in the HIIE group compared to MCE in the frontal lobe, especially FPA and DLPFC, which play a crucial role in the cognitive control of motor behavior for the performance of the dTMT after exercise (Cieslik et al., 2013). According to Kahneman (1973), it is assumed that our brain system has limited attention resources that can be used flexibly in a given situation and influence the DT performance. Considering this, the attentional resources for performing the dTMT during a task with high demands on postural control during HIIE might be limited due to the exercise intensity. However, due to our participants' high fitness level, the increase in activation of all brain regions measured in our study was able to meet the demands of performing the fine- and the gross-motor task, which can be attributed to the provision of additional resources. Overall, the increase in cognitive performance after two types of exercise (intensity) can be considered as different resource allocation, which can be explained as a response to exercise by effective resource allocation in young adults due to the high fitness level.

One should interpret our findings in light of the study limitations. First, we did not have a control group that completed only the dTMT under walking conditions. Hence, additional possible explanations for the between-test changes could be learning effects or changes in participant motivation and stress levels following the test. However, in a pilot study in our laboratory, we were able to show that learning effects do not occur before the 6th block of testing. Therefore, we have grounds to attribute our findings to the different exercise protocols. For future studies, a relevant control condition could consist of very low exercise intensity or simply standing on the treadmill. We also acknowledge that our sample size was relatively small, although similar in size to most acute exercise studies in the literature (Chang et al., 2012; Lambourne & Tomporowski, 2010); thus, larger-scale double-blinded experiments are needed to confirm our findings. Another limitation in the present study is that since HIIE and MCE can increase body blood flow, the head surface's skin blood flow is also increased to test it. Physiological noise, such as blood flow in the extracerebral compartment (Scholkmann et al., 2014), may result in false-positive results (Tachtsidis & Scholkmann, 2016). Thus, a systematic review by Herold et al., (2018) recommended monitoring heart rate to support the interpretation of cortical hemodynamic response measured with fNIRS. In the present study, we found no significant correlation between HR and cortical hemodynamic response after exercise in both the HIIT group and the MCE group, so these two factors can be considered independently. Notably, skin blood flow may drop rapidly immediately after exercise (Endo et al., 2013), which may have been achieved in our study during 2-min walking without a task. For this reason, the interpretation of the effects of exercise with two different intensities on neural correlates during a fine motor-cognitive task seems reasonable.

5 | CONCLUSION

In conclusion, this study was a novel attempt to examine the effects of acute moderate- or high-intensity interval training on cognitive performance and the course of the hemodynamic response in young adults with high fitness levels. The results show that both types of training intensities increased cortical oxygenation during cognitive tests assessment during walking and that this response was associated with improvements in cognitive performance. Due to the small sample size, few statistically significant results suggest that the HIIE might lead to higher increased cortical oxygenation than MCE. However, the higher increases could be observed irrespective of task condition at T2 for the HIIE group, resulting in differences between groups with at least medium effect sizes in all ROIs' task conditions.

This represents a possible acute adaptation of neural processing and provides additional insight into how acute

training affects brain function. The study results are consistent with previous studies showing facilitative effects for such activities, depending on the cognitive task involved and the longer training duration (~30 min); however, this is a behavioral-level effect that is not moderated by exercise intensity. Multiple factors influence the relationship between acute training and cognition. Thus future research should be particular when examining criteria such as fitness level, training intensity (low versus. moderate versus. high), and training mode (aerobic fitness [running, cycling, swimming], strength, coordination). In addition, further research is needed examining different cognitive domains (working memory, cognitive flexibility) with sports-like testing formats, ecologically valid settings, longer training durations/types (>30 min), and trained (sport) populations at high intensities.

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CONFLICT OF INTEREST

The authors have declared that no competing interests exist.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

All relevant data supporting the study's findings are within the paper and are available from the corresponding author upon reasonable request.

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Appendix A4 – Manuscript 4

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Original Research

The Immediate and Sustained Effects of Exercise-Induced Hemodynamic Response on Executive Function During Fine Motor-Cognitive Tasks Using Functional Near-Infrared Spectroscopy

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Abstract

Background: Several studies have shown that acute exercise has a small positive effect on cognitive performance. However, it is still unclear what type of exercise has a sustained impact on cognitive performance during post-exercise recovery. Therefore, the purpose of our study was to investigate cognitive performance at the behavioral level, and their neural correlates after a 10-minute post-exercise recovery period with two different types of exercise intervention (high-intensity interval exercise (HIIE) vs. Moderate-intensity continuous exercise (MCE)). **Methods**: A total of 29 healthy young adults (7 women) between the ages of 19 and 33 with fair to good cardiovascular fitness were submitted to two different exercise protocols and a recovery session. Cognitive function was assessed using a digital Trail-Making-Test (dTMT). Cortical activity in the prefrontal and the motor cortex using functional near-infrared spectroscopy (fNIRS) was measured before, after acute exercise, and during recovery. The statistical analysis of fNIRS data was performed by comparing the slope and mean of the hemodynamic response. **Results**: High levels of hemodynamic responses were observed in the prefrontal and motor cortex on the brain during performing the dTMT while walking from pre- to post-exercise and decreased again in post-recovery, accompanied by improvement and maintenance of cognitive performance. Notably, a high hemodynamic response in the left motor area of the brain was maintained by HIIE in post-recovery compared with MCE. **Conclusions**: The high cortical activation in the left motor area from post-exercise to recovery for the HIIE group may be due to the additional availability of neural resources for fine motor and postural control by high-intensity exercise-induced fatigue. Additionally, the improved cognitive performance may have effectively utilized the available neural resources in the frontal lobe, depending on the condition (sitting and walking) and the two types of exercise protocol (HIIE and MCE).

Keywords: acute exercise; digital Trail-Making-Test; hemodynamic response; high-intensity interval exercise (HIIE); moderate-intensity continuous exercise (MCE)

1. Introduction

It is well known that *chronic* (aerobic) exercise induces a positive effect of structural and functional change in our brain, leading to enhanced cognitive performance on a behavioral level [1]. Exercise-induced increased central circulation of neurotrophic and growth factors such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF) leads to upregulation of neurogenesis, synaptogenesis, gliogenesis, and angiogenesis [2]. For example, structural changes in the brain's gray matter are found through processes of neurogenesis and synaptogenesis, especially for those repetitively active structures during exercise. These are cortical and subcortical motor areas (primary motor cortex and basal ganglia), prefrontal areas (dorsolateral, ventrolateral), limbic system (hippocampus), sensory areas (somatosensory cortex, auditory cortex, visual cortex, sensorimotor integration areas (parietal lobe), and other areas responsible for movement control (cerebellum) (see Lotze *et al.* [3] for an overview). In addition, angiogenesis may mediate the structural changes in gray and white matter volume through improved cerebrovascular function and perfusion. This is critical for neuronal growth and synapse formation, as greater blood supply is essential for providing adequate nutrients to support neuronal development [4]. These changes at the neural level are in turn associated with improvements, particularly in working memory performance (but only to a limited extent in inhibition and cognitive flexibility) in children and adolescents, and adults [5,6].

Several meta-analyses have concluded that *acute* exercise has a small positive effect on cognitive performance depending on the dose-response relationship, i.e., the intensity of exercise, the timing of the measurement and complexity of the cognitive task, and the fitness level of the participants [7–10]. Among these moderator variables, Chang *et al.* [9] revealed that the largest effect could be seen between 10 and 20 minutes after exercise and that the effect gradually disappeared after 20 minutes. However, it is

still unclear what type of exercise has an immediate or delayed effect on cognitive performance during post-exercise recovery. The acute effects of exercise on cognitive abilities also play a crucial role in neurochemical research. For example, neurotrophic factors (BDNF, IGF-1, and VEGF) stimulate the growth of new neurons and enhance synaptic plasticity and long-term potentiation, leading to improved cognitive function [11]. Specifically, acute exercise increases BDNF, leading to improved cognitive performance, and furthermore, the increase in BDNF was persistent after five weeks [12]. These neurotrophic factors may help keep cognitive performance constant during sustained tasks. Also, they may have different effects depending on the type of exercise. A study by Tsukamoto *et al.* [13] examined the acute effects of a high-intensity interval exercise (HIIE) on cognitive performance immediately after exercise and during post-exercise recovery on a cycle ergometer in comparison to a moderate-intensity continuous exercise (MCE). Immediately after exercise, both types of exercise showed enhanced cognitive performance, but the HIIE resulted in more sustained improvement during the 30 minutes post-exercise recovery [13]. This suggested that HIIE may be more effective in maintaining cognitive performance. Moreover, a recent review by Hashimoto *et al.* [14] found that the type and intensity of exercise, particularly by HIIE, induces metabolic lactate, which is associated with brain health concerning the effects of chronic exercise on brain function. Despite these results, the neural activation triggered by both types of exercise during post-exercise recovery has not been generally identified.

To date, several studies have been conducted on the effects of acute exercise on prefrontal cortex-dependent executive function using electroencephalography (EEG) or functional near-infrared spectroscopy (fNIRS) with conflicting findings [15]. Studies on the effects of acute exercise on brain activity, such as event-related potentials using EEG, demonstrate that moderate-intensity exercise induces a greater amplitude of P3b [16] or P2 [17], which are related to attentional resources and positively affect cognitive performance. In addition, Kao *et al.* [18] compared MCE and HIIE using frontal alpha event-related desynchronization and found that only HIIE was observed to enhance information processing speed and brain activation during memory retrieval. Although exercise had a positive effect on cognition, the low spatial resolution limits the ability to determine precisely which area of the brain is involved.

fNIRS studies are still relatively new in the field of cognition and motor function research. fNIRS is a non-invasive, safe, and portable optical neuroimaging method that can indirectly measure brain activity via cortical hemodynamic responses in our brain based on neurovascular coupling [19–21]. High neuronal activation occurs in specific brain regions when performing a particular, e.g., cognitive task (such as n-back or Flanker). This neuronal activity triggers changes in local brain hemodynamics (neurovascular coupling) that induce enhanced cerebral blood flow to the activated brain regions [22,23]. As the local supply of oxygen exceeds consumption, increased concentrations of oxygenated hemoglobin (oxyHb) and reduced concentrations of deoxygenated hemoglobin (deoxyHb) are observed in activated brain regions [21,24]. These neuronal activity-dependent changes in oxyHb and deoxyHb concentrations can be used as indirect indicators of local brain activation [21].

Furthermore, the use of fNIRS in the field of exercise science in conjunction with methods from cognitive psychology offers an advantage. Compared to other brain imaging devices (e.g., EEG fMRI), fNIRS generally has a high tolerance towards motion artifacts. As such, fNIRS is currently more suitable for measuring brain activation during cortical hemodynamic changes during exercise and exercise-related activities in an unrestricted environment [25]. Recent fNIRS studies with higher spatial resolution than EEG have shown that acute moderate exercise enhances cerebral neural activation in the left dorsolateral prefrontal cortex (l-DLPFC) in healthy young adults associated with improved cognitive performance [26–28]. However, in these studies, a single cognitive task was set to confirm the cortical activation induced by the acute response to one specific stimulus. Since our daily activities involve continuous cognitive demands (e.g., reading a book or solving math problems at school), it is necessary to investigate the neural activation during ongoing cognitive task performance rather than acute response. Moreover, although several studies have already examined the lasting effects of acute exercise on cognitive performance on the behavioral level [13,29–33], only a few have investigated these effects at the neural level during recovery from acute exercise [34–37]. Herold *et al.* [24] also proposed studies of sustained effects on task-related cortical activation during recovery, which may add to the knowledge of hemodynamic response during recovery. Neural mechanisms need to be identified to support the effects of acute exercise on enhanced cognitive performance. Also, the changes of neural activation during the recovery period after exercise have not yet been investigated in HIIE.

The purpose of our study was to investigate the immediate and sustained effects of two different types of exercise intervention (HIIE vs. MCE) on cognitive performance at the behavioral level, and their neural correlates after a 10-minute post-exercise recovery period. In the present study, a newly developed, accurate, and validated digital version of the Trail-Making-Test (dTMT) was used as the most commonly used neuropsychological test to measure executive function, and the cortical activation of the prefrontal and motor cortex was measured using fNIRS [38]. In addition, the performance of the dTMT was conducted in a block design (30 seconds of task performance and 30 seconds of rest). It is likely that cognitive and motor control demands increase with block duration, especially for

the dTMT-B condition, which requires more complex cognitive processes such as cognitive flexibility, set-shifting, inhibition, and working memory. For this reason, only the most demanding condition of the dTMT tasks (dTMT-B) was used for the statistical analysis in the present study. Although there is still no gold standard for fNIRS statistical analysis of changes in hemodynamic response over time, Mandrick *et al*. [39] suggested that the slope method appears suitable for identifying changes in hemodynamic response with the cognitive workload. In this regard, we also compared the mean value of the hemodynamic response over time with the slope value. In addition, the present study incorporated data from a previously published paper investigating the effects of acute exercise on fine motor-cognitive performance while walking [40]. The hemodynamic response data were reprocessed and reanalyzed along with the other data.

Despite initial research on the effect of acute exercise of mostly moderate intensity, but not high-intensity, on executive control, the relationship between time course and cognitive benefits has been little studied. Therefore, we hypothesized that a single acute bout of moderate-intensity exercise would significantly improve performance on executive tasks and related changes in brain activation patterns immediately after training than would high-intensity exercise. However, we hypothesized that this effect would reverse in favor of HIIE after 10 minutes. Specifically, during post-exercise recovery, the cortical activation will decrease accordingly. This may be due to the ability to use neural resources through exercise efficiently, and this effect may persist for some time. Specifically, in HIIE, cortical activation is much greater in the motor area due to the fatigue caused by the high-intensity exercise.

2. Materials and Methods

2.1 Focus of the Present Study

The data presented here are part of a larger study of the effects of acute training on cognitive performance [40]. The focus of this article is to compare the changes in individual cortical activations during a fine motor-cognitive task (dTMT-B) in a seated position after a 10-minute post-exercise recovery period with two different types of exercise intervention. Our goal was to confirm the intervention effects of post-exercise recovery between sessions. Another previously published study examined the acute effects of two exercise protocols on hemodynamic response during dTMT while walking [40].

2.2 Sample Size Calculation

Sample size calculations were estimated using G*Power (Version 3.1.9.2) (Math.-Nat. Faculty, Düsseldorf, Nordrhein-Westfalen, Deutschland) [41] and were based on small to medium effects in prior studies of acute exercise in healthy adults [9]. A total sample size of 22 is required to detect a small to medium effect in a two-group design with a 5% risk of type 1 error (α), 80% power, and an estimated correlation of $r = 0.5$ between repeated measurements of the cognitive outcome (dTMT-B). We recruited 32 participants to account for a dropout rate of ~25%.

2.3 Participants

A total of 32 healthy young adults (7 women) between the ages of 19 and 33 participated in the present study. Inclusion criteria were right-handedness, at least 2 hours of exercise per week, and fair or good fitness (men: 43.5 mL/kg/min and above; women: 33.6 mL/kg/min and above), respectively [42]. Exclusion criteria were an abnormal resting pulse or blood pressure and cardiovascular or neurological diseases. Furthermore, participants should not have any fine motor impairments as this would hinder the performance of the cognitive task. Injuries that interfered with walking on the treadmill or scalp injuries that would interfere with measuring brain activity by fNIRS constituted another exclusion criterion. In order to recruit participants, our University Sports Club shared flyers, both manually and via e-mail, through which participation in the experiment was handled. Initially, 3 participants were excluded from the experiment, two for not reaching the required fitness level and one for the technical problem (failed recording for the fNIRS data). Thus, data from 29 participants were considered for the final analysis. The study was conducted in accordance with the Declaration of Helsinki and was approved by the university's local ethics committee. We obtained written consent to participate in the experiment from all participants.

2.4 Design and Procedure of the Experiment

As a randomized controlled trial design using repeated measures (five sessions) in a two-armed parallel-group (between subjects), two laboratory visits were required for study participants (i.e., sessions (1) and (2); see Fig. 1), with an interval of at least two days between visits. During each visit, the experiment lasted approximately 1.5–2 hours. Before the experiment, participants received several instructions: They were not to exercise for 24 hours, not consume caffeine or alcoholic beverages for the last 12 hours, and sleep for approximately 7 hours the night before [43]. Fig. 1 shows the entire study procedure.

On the first day, after the participants gave their written consent to participate in the experiment, they completed a questionnaire on demographic information. Then the fNIRS system was prepared, and sources and detectors were attached to the head cap of the participants (see 3.3 fNIRS). After preparation, an initial resting value of 2 minutes was measured in a seated position. The Mental and Physical State and Trait Energy and Fatigue Scales Questionnaire questionnaire (only Part II; MPSTEFS) was then completed to determine participants' physical and mental energy/fatigue [44]. The first dTMT session (session 1: on

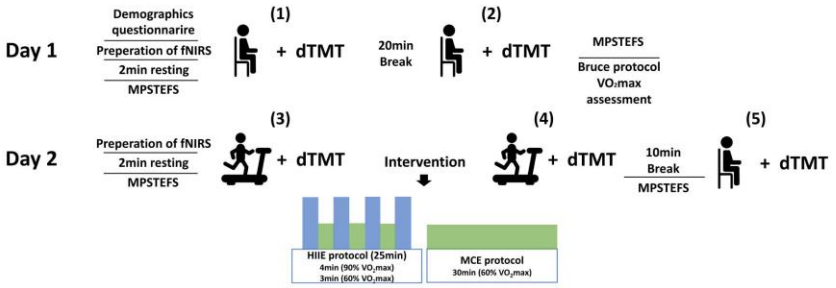

Fig. 1. Schematic illustration of the design and testing procedures consisting of two test days for the HIIE and MCE groups. Cortical hemodynamic activation was measured using functional near-infrared spectroscopy (fNIRS) while participants performed the digital Trail-Making Test (seated or during running on a treadmill).

(1) of Fig. 1) followed while participants were comfortably seated at the table. After a 20-minute rest, the second dTMT session ((2) of Fig. 1) was performed again while sitting comfortably. Participants then completed the questionnaire in the MPSTEFS Part II again. At the end of the first day, we removed the fNIRS system and determined the individual fitness level (VO_2max) by performing the Bruce protocol [45] on a treadmill (h/p/cosmos pulsar® 3p, Nussdorf-Traunstein, Germany). Participants were then randomized into one of two groups (HIIE and MCE).

On the second day, the cap with the sources and detectors of the fNIRS was placed on the head of the participants. An initial fNIRS measurement was recorded for 2 minutes at rest. Then answers to the MPSTEFS questionnaire were collected. Next, participants walked on the treadmill for 2 minutes at a speed of 5 km/h (including collecting data with fNIRS), followed by a dTMT session during walking (session 3: on (3) of Fig. 1). After completing the dTMT, the fiber optic cables of the optodes were disconnected from the fNIRS system and secured to the participants' backs to complete the remainder of their exercise sessions without interruption (HIIE or MCE). At the end of the intervention, we reconnected the cable of the optodes to the fNIRS system. Next, while walking at a speed of 5 km/h, the cortical activation was measured without additional tasks for the first 2 minutes, immediately followed by the second dTMT session (session 4: on (4) of Fig. 1). The heart rate (HR) was recorded with a Polar H1 heart rate sensor (Polar Electro Europe AG, Switzerland) before, during, and after exercise. Participants' fatigue immediately after the two types of exercise protocols was collected with the BORG scale (RPE, ratings of perceived exertion) [46]. Subsequently, participants completed the MPSTEFS questionnaire again. The third dTMT session assessed the sustained effects of each exercise protocol after a 10-minute break, but in a comfortable sitting position in this session (session 5: on (5) of Fig. 1).

2.5 Exercise Intervention Protocols

2.5.1 High-Intensity Interval Exercise (HIIE)

In the HIIE protocol, the participant is exposed to a loading interval four times over 4 minutes and an unloading interval three times over 3 minutes. The interval exercise lasted for a total of 25 minutes. The exercise intensity for the high-intensity intervals is 90% of the VO_2max, and the intensity for the relief intervals is 60% of the VO_2max.

2.5.2 Moderate-Intensity Continuous Exercise (MCE)

The external dose load, such as intensity or duration of exercise, is essential to trigger neurobiological processes leading to neuroplasticity and changes in cognitive function [47]. Therefore, it is important to adjust the dose in studies focusing on the intensity of the exercise intervention. Hence, the duration of the MCE protocol was determined as the duration required to accomplish the same total calorie consumption as the protocol of HIIE [13,48]. In the MCE protocol, the participant is subjected to 30 minutes of moderate load. This protocol's exercise intensity was consistently 60% of the previously determined VO_2max. Both exercise protocols were followed by a three-minute cool-down period at 5 km/h with optodes cables reconnected.

2.6 Measurements

2.6.1 Executive Function — Digital Trail-Making-Test (dMT)

One of the most commonly used neuropsychological tests to assess executive function is the Trail-Making-Test (TMT) [49]. Its original paper-pencil version consists of two conditions. In the TMT-A, which measures information processing speed and visuospatial abilities, 25 circles ran-

domly distributed from 1 to 25 must be connected in ascending order (i.e., 1-2-3-. . .). In the TMT-B, the most challenging condition measuring inhibitory control, cognitive flexibility, and working memory, participants must connect circles of numbers and letters in ascending, alternating order (i.e., 1-A-2-B-3-C. . .). Although the TMT is widely used, it is usually administered in its single-pencil-on-paper form (paper-pencil version). However, for this version, there are insufficiently controlled parallel versions for repeated use to rule out learning effects [50,51].

Evaluating executive function in a neuroscientific method requires enough repetitions of measurement to acquire an adequate signal-to-noise ratio of the data [52]. For this reason, we used a newly developed accurate and validated digital version of the Trail-Making-Test (dTMT) [38]. The dTMT, which was performed using a Samsung Galaxy Note Pro (12.2-inch diagonal LED-backlit Multi-Touch display with IPS technology; portrait alignment) with a resolution of 2560 $\times$ 1600, is based on an Android App. Especially in terms of design and size, this dTMT is very close to the paper-pencil version. In addition, our version of the dTMT has been optimized based on two other digital versions. One of them allows the measurement of additional variables (e.g., number and duration of lifts/pauses, time spent between and inside circles, and distance ratio of the total length) [53] and the other with a "divide-and-combine approach" that generates alternative test variations (i.e., to minimize potential learning effects) [54]. In addition, completion time and errors and all additional variables are automatically recorded when the tablet screen is touched with a stylus or finger and stopped immediately after reaching the last circle (marked as start and stop, respectively). Fellows *et al*. [53] confirmed the separation of cognitive processes as critical to TMT performance by measuring additional variables, including number and duration lifts/pauses and time spent between and inside circles. In the dTMT-A, most of these variables have been coupled with visual processing speed. In particular, in the dTMT-B, these variables relate to inhibition, such as the time spent between circles and pauses number/duration. The variables such as time spent inside a circle and lifts number/duration correlate with working memory [53]. To measure the reference for the dTMT-A and -B, we implemented a complementary trail-tracing task (dTMT-motor, dTMT-M) that assesses fine motor control [55]. Examples of the dTMT sheets are presented in Fig. 2.

Our version of the dTMT provides the option to run a block of tasks with a fixed time instead of performing the task with 25 circles completed at once. This is because enough test repetitions are required to evaluate neural correlates for the task [52]. Each dTMT assessment lasts 9 minutes, with a task block alternating 30 seconds of task completion followed by 30 seconds of rest (presentation of a black fixation cross on a white background). The task sequence of the dTMT conditions (dTMT-M, dTMT-A, dTMT-B) within every 9 minutes' block was pseudo-randomly designed such that the same condition never appeared twice in succession. All conditions were displayed three times each. Using a pseudo-randomized stimulus sequence minimizes the task condition predictability and avoids the top-down effects of condition-related expectations or attention. In order to examine the effects of exercise on behavioral-level cognitive performance, we established in a pilot study that learning effects had already decreased over the first two sessions of the experiment. Also, the program's mathematical algorithms of dTMT can continuously generate a new dTMT trial that will never match the previous sheet. Participants were instructed to complete as many circles as possible for the task performance, paying attention to error-free execution. Another was presented if they completed a sheet before the end of a 30-second block. Even if 30 seconds passed before they completed a sheet, the data was automatically saved, and the remaining blocks were displayed with a fixed cross in the center of the tablet.

2.6.2 Maximum Oxygen Consumption Test (VO_2max)

The Bruce protocol [45] was carried out on a treadmill (h/p/cosmos pulsar® 3p, Nussdorf-Traunstein, Germany), to evaluate participants' cardiorespiratory fitness (VO_2max) and to define the individualized exercise protocol. HR was measured with a Polar H1 Heart Rate Sensor (Polar Electro Europe AG, Switzerland). The starting point of the Bruce Protocol begins with an initial speed of 2.7 km/h and an incline of 10%. Every 3 minutes, the stage goes up, increasing the incline by 2% and the speed by 1.3 km/h. The testing protocol was terminated when (a) the protocol can no longer be performed due to complete exhaustion of a participant, (b) the HR increase could not be detected even when the intensity was increased, and (c) RPE was 17 or higher [46]. An individualized training protocol tailored to the participant's fitness level was used in the present study. Considering the dTMT measurement at a walking speed of 5 km/h, only the participants whose exercise intensity, that is, their running speed did not fall below 5 km/h, were included.

2.6.3 Covariates

Demographic information, type and duration of sports activities per week, and level of sports performance (i.e., their experience in participating in competitions) were obtained by questionnaire. Body mass index (BMI, kg/m^2) was calculated based on height and weight. Participants also answered Part II of the Mental and Physical State and Trait Energy and Fatigue Scales Questionnaire (MPSTEFS) a number of times throughout the experiment to monitor changes in perceived feelings of energy and fatigue (see Fig. 1) [44]. Part I of the questionnaire asks how an individual usually feels when performing physical and mental activities. Part II of the questionnaire asks how an individual currently feels and consists of 12 separate ratings for

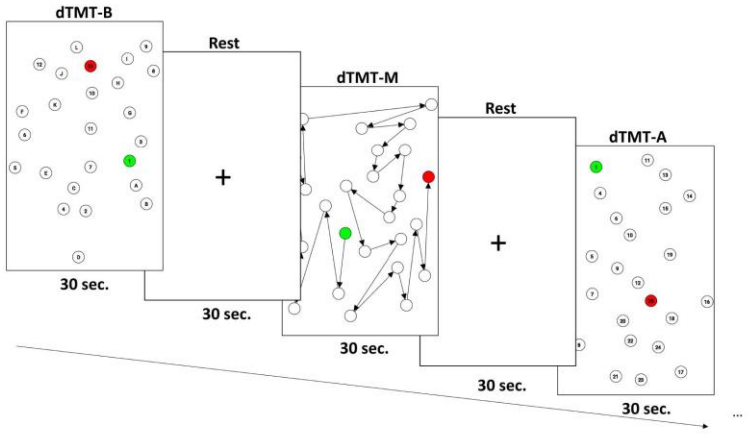

Fig. 2. The Design of experimental task for dTMT. Each condition appears randomly three times over 30 seconds, and dTMT lasts a total of 9 minutes, including a break between conditions.

physical energy, physical fatigue, mental energy, and mental fatigue. Because the questions in this study related to the effects of acute physical activity, only the components of Part II were included in this study. The questions such as "How do you feel right now?" were answered with 100 mm on a visual analog scale. High Cronbach's α coefficient already demonstrated a high internal consistency for each scale (greater than 0.85). Immediately after the exercise intervention, participants also responded to the BORG scale for RPE to monitor subjective perceived effort related to exercise intensity [46]. The range is on a scale of 6 (no exertion) to 20 (maximal exertion). This value enables to subjectively estimate the level of fatigue during or after exercise tests.

2.7 fNIRS Measurement

In the present study, concentration changes in the amount of oxygenated and deoxygenated in the right and left: frontopolar area (FPA), dorsolateral prefrontal cortex (DLPFC), and motor cortex (M1) were recorded using a portable continuous optical fNIRS system (NIRSport 88, NIRx Medical Technologies LLC, New York, NY, USA). The setup consisted of 16 light sources and 16 detectors spaced approximately 3 cm between optodes to effectively compromise depth sensitivity and signal-to-noise ratio. The center of the NIRScaps for optode placement (EASYCAP GmbH, Herrsching, Germany) was placed over the vertex (Cz) according to the international 10–20 system by marking the midpoint between the nasion and the inion and the left and right preauricular points (see Fig. 3), to ensure experiment consistency of placement between participants and experimental sessions.

The data sampling rate of this fNIRS system is 7.81 Hz and includes two wavelengths of infrared light (760 and 850 nm) [56] to measure oxygenated and deoxygenated hemoglobin (oxyHb and deoxyHb) using the continuous-wave procedure (i.e., emitting infrared light from a source with a constant intensity and frequency) [57]. Data of oxyHb and deoxyHb were recorded on a tablet (Microsoft Surface Pro2 128 GB) with the NIRS Star 14 Software (NIRSport, NIRx Medical Technologies LLC, Glen Head, NY, USA). For each 30 seconds block of alternating task and rest, triggers were set using the NIRS Stim Software (NIRSport, NIRx Medical Technologies LLC, Glen Head, NY, USA).

2.8 Data Analysis

In the present study, only the behavioral and neural data of dTMT-B condition were analyzed between the first and last session to investigate the extent to which two types of exercise affect the maintenance or improvement of cognitive performance at a behavioral and neuronal level after recovery on post-exercise (see Fig. 1). Besides, some data (e.g., demographic and physiological data, MPSTEFS, and behavioral and neural data on pre-and post-exercise) have already been reported in the work of [40]. However, behavioral and neural data were reprocessed and analyzed concerning the research question under investigation here.

Statistical analyses were performed using SPSS v. 27 (IBM Corp., Armonk, NY, USA). First, we explored the dependent variables for missing data points, normality of distributions (tested by Kolmogorov–Smirnov tests), and the presence of outliers. The effect sizes for all analyses are expressed using partial Eta^2 ($\eta_p{}^2$) or Cohen's *d*. For all sta-

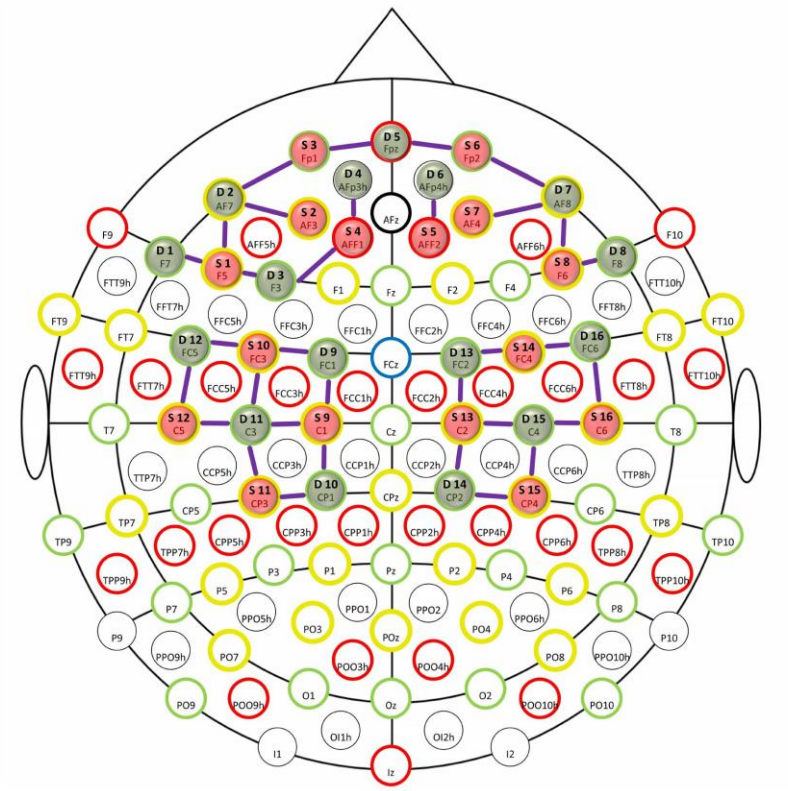

Fig. 3. Configuration for fNIRS Measurement.

tistical tests, an alpha level was set a priori $p < 0.05$. The classification of the partial Eta^2 also followed the conventions of Cohen [58]: 0.01 small effect; 0.06 medium effect; 0.14 strong effect. Sphericity issues were addressed with the Greenhouse Geisser correction for repeated measurements ANOVA. The statistically significant values in ANOVA lead to post-comparison using Bonferroni correction.

2.8.1 Demographic and Physiological Data

For the demographic variables, continuous variables (e.g., age, height, weight, BMI, exercise duration, VO_2max, heart rate) were calculated using two-sample *t*-tests to observe possible group differences. In addition, categorical demographic variables (e.g., sex, participation in competitions) were tested with a Chi^2 test.

2.8.2 Subjective Physiological/Psychological Parameters

We compared the subjective fatigue parameters of the MPSTEFS questionnaire using 3 × 2 × 2 ANOVAs with repeated measurements with the with-in-subjects factor "session" (before session 1, before session 3, and before session 5) and "energy/fatigue" (physical and mental energy/fatigue) and the between-subjects factor "group" (HIIE and MCE) separately for two components (Physical and Mental Energy or Physical and Mental Fatigue) between before task beginning on the first day and before task beginning on pre-and post-exercise on the second day (see Fig. 1 before (1), (3) and (5)). This is to investigate the comparison between the state of the first day and the second day and the state between pre-and post-exercise (pre-recovery).

2.8.3 Executive Function

First, the data from dTMT had to be extracted from a text file stored on the tablet via Matlab 2018b (MathWorks,

Natick MA USA). Then, we selected three variables (number of connected circles, time spent inside circle [working memory], and speed between circles [inhibitory control]) from the data of dTMT for the behavioral analysis, and we averaged three blocks of three selected variables in each condition. In particular, the variable "number of correctly connected circles" was used as an indicator of the dTMT-B in the present study because the task had to be performed continuously for a given duration of 30 seconds. As mentioned earlier, we statistically analyzed only the dTMTB condition, the most challenging task. In the statistical analysis step at the behavioral level, we obtained a comparison between all sessions using 5 × 2 ANOVAs with repeated measurements on the number of correctly connected circles, the time spent inside and speed between circles as the dependent variables with the within-subjects factors "session" (from first to last session) and with the between-subjects factor "group" (HIIE and MCE).

2.8.4 fNIRS Data

The analysis of the neural data was conducted with the NIRS Toolbox [59], an open-source program installed in Matlab 2021a (MathWorks, Natick, MA, USA). The relative coefficient of variation (CV in %) was first estimated with unfiltered raw data to check the data quality as a signal-to-noise ratio, a data processing method commonly used in NIRS measurements using multi-channel [60,61]. CVs above 15% for each channel computed during each experimental session were excluded for the subsequent analysis [62]. After removing poor channels, data were processed using a low-pass filter with 0.2 Hz [57] to remove physiological components (e.g., heartbeats: 0.5 to 2.0 Hz, and respiration: 0.2 to 0.4 Hz). From these data, they could be converted to optical density. The converted data were then corrected for motion artifacts by attenuating outlier variations using temporal derivative distribution repair (TDDR) [63]. These preprocessed optical densities were finally converted into oxygenated hemoglobin (oxyHb) as well as deoxygenated hemoglobin (deoxyHb) concentration using the modified Beer-Lambert law [59]. The data of all channels were processed into time-series data by calculating the inter-trial mean of each dTMT condition. Each time-series data was corrected using the baseline period's average value for two seconds before the onset of a task block (baseline correction). Furthermore, task contrast was performed by subtracting the time-series data for the resting conditions between task conditions from task conditions. Changes in hemodynamic responses for each condition were plotted as topographic on brain image over time during 30 seconds of task execution. Each channel of source-detector was averaged over six different regions of interest (ROI) in a further step for statistical analysis. The areas divided into six ROI consisted of the left frontopolar area (l-FPA) with source-detector pairs (S3-D2, S3-D5), the right frontopolar area (r-FPA) with source-detector pairs (S6-D5, S6-D7), the left dorsolateral prefrontal cortex (l-DLPFC) with source-detector pairs (S1-D1, S1-D2, S1-D3, S2-D2, S4-D3, S4-D4), and the right dorsolateral prefrontal cortex (r-DLPFC) with source-detector pairs (S5-D6, S7-D7, S8-D7, S8-D8), the left motor area (l-M1) containing all channels above the left motor cortex, and the right motor area (r-M1) containing all channels above the right motor cortex. We employed the freeware MNE-NIRS (v. 0.1.2; https://mne.tools/mne-nirs/) [64] from the MNE toolbox (v. 0.24.0; mne.tools) in Python [65] and MATLAB based toolbox NFRI (https://www.jichi.ac.jp/brainlab/tools.html) to visualize the topographic on a brain image [66]. It is believed that the oxyHb response can be used as a more sensitive indicator of changes in regional blood flow [67,68]. For this reason, we used only changes of oxyHb levels for further statistical analysis. The use of ROIs as a factor in ANOVAs may lead to unintended statistical bias because the optical properties may differ systematically between ROIs [24]. Therefore, for statistical analysis, ANOVAs were performed separately for each ROI. To account for this, alpha values were corrected for the number of ROIs using the false discovery rate (FDR-corrected) to perform multiple comparisons [69]. The emphasis was also placed on the effect sizes when evaluating statistical significance due to the small number of participants in each group in the present study [70].

The parameters extracted from the fNIRS statistical analysis were the mean parameter and the slope over time (from onset to 32 sec) of the conditional block (see Fig. 4). The time of 32 sec was chosen to account for the fact that the maximum range of concentration changes is reached within a few seconds after the end of the task. According to the systematic review by Herold *et al*. [24], the methods used for statistical analysis of fNIRS data are very diverse (mean value, area under the curve, slope or GLM analysis, etc.). Therefore, for comparing the two parameters (slope and mean) in the present study, we followed the study of [39], which suggests that the slope method seems to be suitable for detecting changes in hemodynamic response over time with the cognitive workload.

In the statistical analysis, we analyzed 5 × 2 ANCOVAs with repeated measures for each oxyHb in ROI while adjusting for the rate of change in behavioral data (dTMT-B) as a covariate with the within-subjects factors " session" (from first to last session) and the between-subjects factors "group" (HIIE and MCE), to test the effects of post-exercise recovery on changes of hemodynamic response over session. Also, we further calculated Pearson correlations between behavioral data and neural data in each session for each group separately.

3. Results

3.1 Demographic and Physiological Data

Table 1 shows the demographic and physiological characteristics. No significant differences between the two

Table 1. Demographic and physiological characteristics of participants by group.

	HIIE (n = 14) *M* (*SD*)	MCE (n = 15) *M* (*SD*)	statistical analysis
Age (years)	26.0 (3.98)	24.2 (4.04)	$t_{27} = 1.21, p = 0.238, d = 0.45$
Sex	m: 11; w: 3	m: 11; w: 4	$\chi^2{}_1 = 0.109, p = 0.742$
Height (cm)	176 (9.34)	177 (9.42)	$t_{27} = 0.222, p = 0.826, d = 0.02$
Weight (kg)	70.6 (10.5)	70.2 (12.0)	$t_{27} = 0.105, p = 0.917, d = 0.04$
BMI (kg/m^2)	22.7 (2.29)	22.4 (2.70)	$t_{27} = 0.396, p = 0.695, d = 0.12$
max. HR (bpm)	189.1 (6.72)	189.3 (5.59)	$t_{27} = 0.083, p = 0.952, d = 0.46$
VO_2max (mL/kg/min)	55.2 (6.37)	56.2 (7.11)	$t_{27} = 0.405, p = 0.695, d = 0.15$
Exercise duration (min per week)	175 (144)	227 (130)	$t_{27} = -1.31, p = 0.201, d = 0.49$
Participation in competitions	International: 0% National: 7.1% Regional: 21.4% Local: 42.9% No: 28.6%	International: 13.3% National: 20% Regional: 20% Local: 26.7% No: 20%	$\chi^2{}_4 = 3.513, p = 0.476$

Note. M, mean; SD, standard deviation.

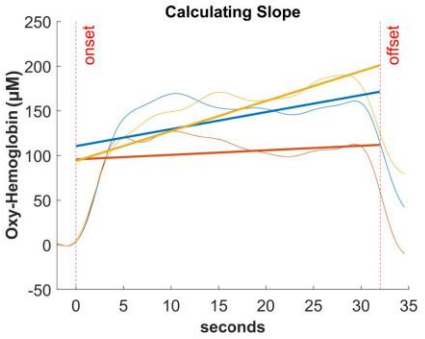

Fig. 4. Example for calculating slope for oxyHb while performing the dTMT over time.

exercise groups were found in the statistical analysis. Besides, the types of sports that subjects participate generally varied, including team sports (e.g., Basketball, Volleyball), endurance (e.g., rowing, track athletics, cycle, swim), individual sports (e.g., apparatus gymnastics, boxing, taekwondo), racket sports (e.g., tennis, table tennis).

3.2 Subjective Physiological/Psychological Parameters (MPSTEFS)

Table 2 shows the physical/mental energy/fatigue components using a visual analog scale that yielded 12 separate ratings for Physical Energy, Physical Fatigue, Mental Energy, and Mental Fatigue before and after exercise. A 3 ("session": before (1), before (3), and before (5)) × 2 ("energy or fatigue": physical and mental energy/fatigue) × 2 ("group": HIIE and MCE) showed a significant effect of session only for physical and mental fatigue, F (1.49, 40.2) = 3.38, $p = 0.041$, $\eta_p{}^2 = 0.111$, indicating an overall increasing physical and mental fatigue in post-exercise (before (5)) regardless of the group.

3.3 Executive Function (dTMT)

First, we performed 5 × 2 ANOVAs with repeated measurements on the number of connected circles, time spent inside circle, and speed between circles as a dependent dTMT-B variable with the within-subjects factors "session" from first to last session and with the between-subjects factor "group" (HIIE and MCE) to examine the change in cognitive performance over session. A significant effect of session was found for the variables "number of connected circles" F (2.92, 78.8) = 16.7, $p < 0.001$, $\eta_p{}^2 = 0.383$, "time spent inside circle", F (4, 108) = 8.78, $p < 0.001$, $\eta_p{}^2 = 0.245$, and "speed spent between circles", F (2.61, 70.4) = 8.57, $p < 0.001$, $\eta_p{}^2 = 0.241$. However, no interaction effect between session and group was observed for any of these variables. A post hoc analysis of the factor session is shown in Fig. 5. No significant difference was found for the other variables, except for the speed between circles between the second session on the first day (during sitting) and the third session in pre-exercise (during walking). For the number of connected circles, we found a significant increase in cognitive performance between pre-and post-exercise, but there was no significant improvement between post-exercise (during walking) and -recovery (during sitting). When comparisons were made between the same conditions (during sitting), a significant difference was found between the second session on the first day and post-recovery.

In summary, for the behavioral data of the dTMT, task speed performance (speed between circles) increased during walking. Still, overall task performance (number of

Table 2. MPSTEFS data (mean and standard deviation) for before (1), (3), and (5) session by group (HIIE and MCE).

MPSTEFS components	Before (1)		Before (3)		Before (5)	
	HIIE	MCE	HIIE	MCE	HIIE	MCE
	(n = 14)	(n = 15)	(n = 14)	(n = 15)	(n = 14)	(n = 15)
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
Physical Energy	286 (49.7)	286 (45.3)	301 (50.9)	297 (59.7)	307 (47.3)	297 (83.9)
Physical Fatigue	127 (39.1)	115 (72.6)	151 (60.7)	133 (65.2)	176 (92.3)	149 (108)
Mental Energy	301 (45.7)	298 (50.5)	299 (52.8)	313 (49.1)	309 (64.0)	289 (67.9)
Mental Fatigue	138 (66.2)	111 (66.7)	154 (64.8)	108 (41.8)	160 (71.9)	156 (78.0)

Note. *M*, mean; *SD*, standard deviation.

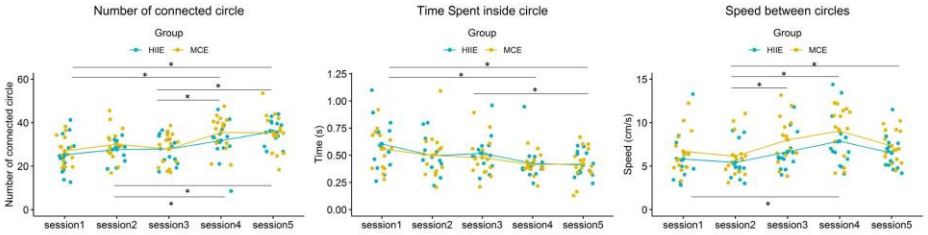

Fig. 5. Behavioral data extracted from the dTMT-B by group. * $p < 0.05$.

connected circles) remained unchanged between sitting and walking. Overall, cognitive performance improved significantly in both groups in post-exercise and was maintained in post-recovery.

3.4 Neural Correlates (fNIRS)

Fig. 6 shows the hemodynamic responses during the performance of the dTMT for 30 seconds over a session. As shown in Fig. 6, for each condition (during sitting and walking), changes in oxyHb levels can be observed across sessions (from first to fifth session) during task performance. High cortical activation can be found after HIIE, and compared to MCE, high cortical activation was maintained to some extent after recovery.

Table 3 shows the statistical results for the hemodynamic response over session with the ANCOVA with repeated measures for slope and mean of oxyHb in each ROI. The slope and mean value parameter over the entire session in all ROIs are shown in Fig. 7. The slope parameter showed a significant effect of the session in all ROIs, but the mean parameter showed a significant effect with a medium effect size in r-FPA, l-DLPFC, r-DLPFC, l-M1, and r-M1. An interaction effect with a medium effect size between session and group was observed for both parameters only in the l-M1 (see Fig. 8A), indicating a significant difference with an above medium effect size between groups (Fig. 7 (1-e and 2-e)) for slope value in post-exercise while walking ($p = 0.073$, $d = 0.694$) and post-recovery while sitting ($p = 0.027$, $d = 0.871$), and a significant difference between groups for mean value in post-exercise ($p = 0.024$, $d = 0.886$) and post-recovery ($p = 0.026$, $d = 0.873$). In summary, high hemodynamic responses were observed in all ROIs during performing the dTMT while walking in pre-and post-exercise and decreased again in post-recovery. Notably, a high hemodynamic response in l-M1 was maintained by HIIE in post-recovery compared with MCE.

4. Discussion

The present study investigated the immediate and sustained effects of acute exercise with different exercise intensity on neural correlates underpinning cognitive performance in the post-recovery period. In our previous study [40], two different exercise intensities resulted in increased activation in task-related areas (FPA and M1). Accordingly, cognitive performance was improved by using the available neural resources effectively. The main focus of this present study was on the oxyHb changes related to cognitive performance (dTMT-B) during recovery in post-exercise. Since we already confirmed the differences in oxyHb levels between task conditions in pre-exercise [40], in the present study, we only investigated the dTMT-B, which is mainly used to test complex cognitive functions such as working memory set-switching over the entire session.

4.1 Demographic and Physiological State and MPSTEFS

Demographic data were reported in our previous study [40]. Among them, there were no significant differences between groups. Also, no differences were found for

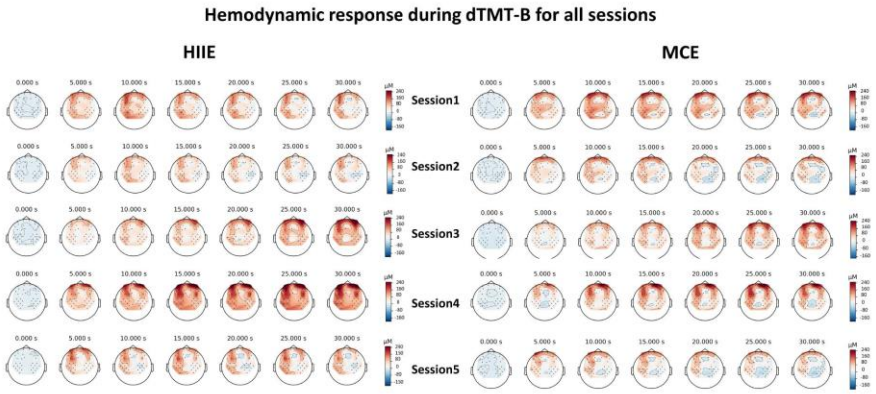

Fig. 6. Change of OxyHb for 30 seconds over session by group.

Table 3. ANCOVA with repeated measures for Slope and Mean of oxyHbO in each ROI with *F*-, *p*-value (FDR-corrected), and effect size.

Effects	l-FPA			r-FPA			l-DLPFC			r-DLPFC			l-M1			r-M1		
Slope	$F_{4,104}$	p	η_p^2	$F_{1,21}$	p	η_p^2	$F_{1,21}$	p	η_p^2	$F_{1,21}$	p	η_p^2	$F_{1,21}$	p	η_p^2	$F_{1,21}$	p	η_p^2
Session	2.83	0.028	**0.098**	4.49	0.002	**0.147**	3.85	0.006	**0.129**	5.12	0.001	**0.164**	4.11	0.004	**0.136**	7.77	0.001	**0.230**
Session × Group	1.07	0.377	0.039	1.38	0.245	0.050	0.398	0.810	0.015	0.919	0.456	0.034	1.90	0.116	0.068	1.36	0.254	0.050
Mean	$F_{1,21}$	p	η_p^2	$F_{1,21}$	p	η_p^2	$F_{1,21}$	p	η_p^2	$F_{1,21}$	p	η_p^2	$F_{1,21}$	p	η_p^2	$F_{1,21}$	p	η_p^2
Session	1.27	0.285	0.047	2.60	0.040	**0.091**	1.92	0.113	**0.069**	3.16	0.017	**0.108**	1.68	0.161	**0.061**	4.37	0.003	**0.144**
Session × Group	0.966	0.430	0.036	1.54	0.197	0.056	0.470	0.757	0.018	0.892	0.471	0.033	2.68	0.057	**0.094**	1.36	0.253	0.050

Note. Session: from first to fifth session; group: HIIE and MCE; Slope: slope of hemodynamic response between onset and 32 sec; Mean: mean of hemodynamic response for last 7 sec of task end. Bold: Above a medium effect size 0.06 in bold.

VO_2max at baseline, so that the group classification was already established before the intervention. As subjective variables, the fatigue of physical and mental parameters increased from pre- to post-exercise, but fatigue did not correlate with cognitive task performance and task-related cortical activation. Since these parameters were measured after the post-test and not immediately after exercise, they could not sensitively reflect physical and mental changes in energy/fatigue. However, as an objective variable, the change of heart rate induced by the exercise intervention during acute exercise and post-test led to a difference between groups [40]. This implies that the two different types of exercise-induced different intensities.

4.2 Change of dTMT-B Performance at the Behavioral Level Over Session

First, we conducted two sessions on the first day to effectively control for learning effects. No significant difference in cognitive performance for our three reported variables (see Fig. 5) was found between the first and second sessions. Recent studies have shown that individuals with high fitness levels show little or no improvement with acute exercise [71,72]. However, due to the training regime we chose, the participants had to have at least an intermediate fitness level to perform the full extent of the training. In addition, it was possible to effectively control the learning effect by integrating a divide-and-combine approach [54], creating alternative sheets of the TMT task from the newly developed dTMT. Despite different conditions, there was no significant difference between the second and third sessions (between sitting and walking). In general, cognitive performance seems to be impaired during a dual-task while walking in children, adolescents, and older adults [73,74]. However, this was not the case in our study. In comparing sitting and walking, the cognitive performance for the number of connected circles did not decrease due to the automation of gait in the treadmill task performance [75]. Notably, cognitive performance increased in the post-exercise period, which is supported by a study by Penati *et al*. [76] that showed better cognitive performance in fixed-speed walking on a treadmill than over-ground walking. Above all, the increased activation of the frontal lobe induced by exercise may have amplified the posture-second strategy [77] to fo-

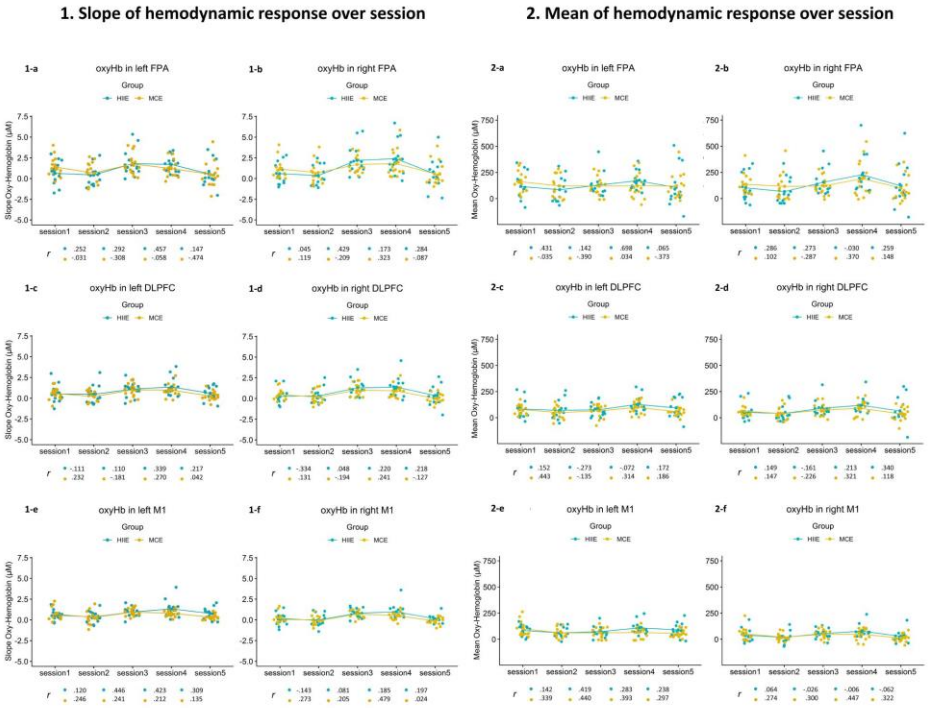

Fig. 7. Slope (1) and Mean (2) of OxyHb related to dTMT-B performance over session by group. Individual slope and mean oxyHb changes related to dTMT-B performance over the whole session are shown in all ROIs. Below each graph is the correlation coefficient between the rate of behavioral data (number of corrected circles) and the rate of neural data (slope and mean) between each session (e.g., Δ session 2 – session 1, Δ session 3 – session 2, Δ session 4 – session 3, and Δ session 5 – session 4).

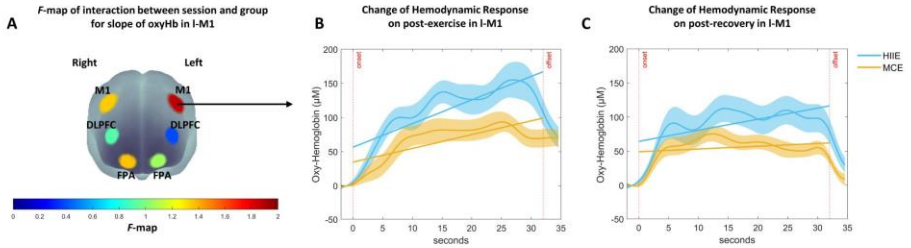

Fig. 8. Change of OxyHb related to dTMT-B performance for 30 seconds over session by group. (A) F-map of oxyHb signal changes of slope reflecting the interaction between session and group for the dTMT-B performance. Among the six regions of interest, an interaction with a medium effect size can be seen in the left motor cortex (l-M1) (FDR-corrected). F-value is displayed according to color bars. (B) Time course of oxyHb changes in response to dTMT-B performance in the l-M1 in post-exercise while walking between HIIE and MCE. (C) Time course of oxyHb changes in response to dTMT-B performance in the l-M1in post-recovery while sitting between HIIE and MCE. Error bars indicate standard error.

cus more on cognitive tasks due to the automatized walking on the treadmill. As the posture-second strategy, dual-tasks while walking on a treadmill could enable resource allocation toward cognitive tasks while performing automatized walking naturally, contributing to improved motor and cognitive function. In this regard, dual-task performance on the treadmill may be a suitable alternative to improve motor and cognitive functions in clinical or rehabilitation fields.

However, significant cognitive performance increases were no longer observed post-recovery, but the performance was maintained. This sustained performance in the post-recovery period was significantly different, especially compared with the first and second session as baseline under the same condition (during sitting). According to the meta-analysis by Chang *et al.* [9], the greatest positive effect on cognitive performance was found after 10–20 minutes in post-exercise. This effect gradually decreased when it lasted longer than 20 minutes. In the present study, the increase and maintenance of cognitive performance in post-exercise and -recovery were independent of the intervention group. In the study by Tsukamoto *et al.* [13], the cognitive performance was also maintained for 20 minutes. In the case of HIIE, the performance was maintained up to 30 minutes longer than in MCE. However, in our study, only a 10-minute recovery was given, and thus a follow-up study on the post-exercise maintenance of cognitive performance should be conducted. Notwithstanding the limitations associated with the short recovery period, in the present study, in which exercise-induced changes of neural correlates related to task performance were additionally investigated using fNIRS, the comparisons between the two types of exercise should also be observed at the neural level.

4.3 Change of oxyHb Levels at the Neural Level Over Session

To date, the effect of acute exercise on cognitive task-related neural correlates has been studied extensively using fNIRS (for a systematic review, see Herold *et al.* [24]). However, studies on the neural correlates of the maintenance of cognitive performance in post-exercise are still lacking. Furthermore, only few studies have investigated the sustained effects of exercise on task-related neural correlates [34–37]. In general, acute exercise plays a role in increasing cortical activation concerning enhanced cognitive performance. Prefrontal cortical activation in post-exercise positively affects cognitive task performance [14]. In a recent study on the effects of exercise on cognitive performance in post-recovery, the cortical neural activation in the prefrontal area depends on age. At the behavioral level, inhibitory control for young and older adults improved immediately after 15-minutes of moderate exercise with 40-60% heart rate rebound, and, notably, was maintained even 30-minutes after recovery [34]. However, the cortical activation at the neural level appears to differ between young and older adults. In young adults, the cortical activation gradually decreased from baseline to post-exercise and -recovery periods. In contrast, in the elderly, it increased in the middle frontal lobe post-exercise and returned to pre-exercise levels in post-recovery again. In children aged 8–10 years, the cortical activation of the frontal lobe also increased in post-exercise (continuous and intermittent moderate-intensity exercise). However, it decreased steadily post-recovery, maintaining cognitive performance for 30 minutes [36].

The present study investigated the effects of exercise on various brain areas by additional measurement of the motor area, unlike other studies that are generally limited to frontal lobe measurements. Also, performing task conditions (during sitting and walking), type of cognitive task (dTMT-B), and exercise types (HIIE and MCE) should be considered when interpreting the results of the present study compared with other studies. Furthermore, from the point of view of statistical analysis, the simultaneous analysis and comparison of the mean and the slope value could be an appropriate alternative solution for the fNIRS analysis methods, for which there is no golden standard yet.

The performance of the 1st and 2nd sessions serves as a baseline to control the learning effect of the task. The results for oxyHb between the 1st and 2nd session showed decreased cortical activation only in the l-FPA with no change in cognitive performance. This appears to have been effectively utilized by reducing the neural resources due to the learning effect [78]. In comparing performance conditions, higher cortical activation in all ROIs was shown during the fine motor-cognitive task for 30 seconds while walking than sitting. In this regard, the higher cortical activation during walking compared with sitting might be due to allocating more neural resources to postural control and task performance while walking, which is why cognitive performance may have been maintained even during the dual-task condition. In particular, the slope of exercise-induced cortical activation was increased or maintained in post-exercise, which seems different between the two types of exercise. Notably, considering the mean value, there was a significant increase in the r-FPA and l-DLPFC from pre- to post-exercise, regardless of the intervention group, which is consistent with other studies showing exercise-induced increased cortical activation in the l-DLPFC [27,79]. However, compared with these studies, more neural resources may need to be recruited in other areas due to type of exercise (intensity or duration), performing condition (sitting or walking), and type of cognitive task (Stroop task or fine-motor cognitive task) to maintain task performance in post-exercise. Thus, further studies should be conducted considering the factors mentioned above.

More importantly, depending on the characteristics of the fine-motor cognitive task, the motor area may have been significantly differently affected by the two types of exercise. After HIIE, the cortical activation was increased in both M1 areas, whereas it decreased after MCE. Notably, the rate of change for oxyHb (both parameters for slope

and mean) between pre-and post-exercise (adjusting rate of change for dTMT performance as a covariate) showed a significant difference between groups. The increased activation of M1 in the HIIE group, along with an increase in the frontal lobe, could be explained by the need for more neural resources for postural control and fine-motor control, along with smooth task performance while walking on the treadmill [40]. According to the conceptual model of mechanisms of physical activity [1,80], regular exercise induces changes in cellular and molecules such as brain growth factors, which in turn lead to structural and functional changes in the brain, leading to an increase in cognitive performance. In addition, the upregulation of VEGF by exercise in animal models increased cerebral blood flow [81,82]. Moreover, the increased cerebral blood flow velocity is related to fitness level and healthy human aging [83]. Given the physical fitness level of the subjects participating in the regular exercise in the present study, the increase in cerebral blood flow to the frontal lobe in post-exercise, which plays an essential role in the executive function, seems reasonable. A further increase in M1 caused by HIIE could also be explained. Therefore, other studies are needed to determine whether HIIE induces high cortical activation and enhanced cognitive performance when used in different age groups (children and the elderly) or groups with varying levels of fitness (high and low) [71].

Moreover, cortical activation had returned to baseline levels (1st and 2nd sessions) in all ROIs after recovery, even when both variables for the slope and mean parameters were accounted for. Notably, interaction with the above medium effect size for both slope and mean parameters was found only for l-M1, indicating that the higher cortical activation in the l-M1 appeared to be maintained in HIIE than MCE. In addition, in oxyHb, there was no difference between groups in the rate of change between post-exercise and -recovery periods. However, the exercise-induced increased cortical activation from post-exercise was maintained until the post-recovery period, resulting in a significant difference between groups ($p = 0.027$, $d = 0.871$). In a previous study that applied moderate-intensity exercise [84], the cortical activation of the frontal lobe tended to decrease in post-recovery. Still, the cognitive performance was maintained for up to 30 minutes. In the present study, decreased cortical activation was also observed in the frontal lobe. An additional measurement of the motor cortex also revealed decreased oxyHb in the left and right M1. In particular, the left M1 was more affected by HIIE. This can be interpreted as the effect of exercise intensity. Although it was necessary to mobilize a large amount of neural resources to process the fine-motor cognitive task simultaneously with walking in post-exercise, a general downregulation of cortical activation occurred during sitting in the post-recovery period. HIIE, which may have led to fatigue due to high intensity, could affect the upregulation of the left M1 in processing the fine motor task.

Also, the change in behavioral data was already considered by performing ANCOVA with repeated measurements between sessions and groups for oxyHb, adjusting the Δ of the first and last sessions for dTMT performance. As for any correlation between the Δ in hemodynamic responses and the Δ in dTMT performance (number of correct connected circles) (see Fig. 7 under each graph), except for strong correlations with behavioral data and hemodynamic response (mean parameter) of the left frontal lobe for HIIE group between pre-and post-exercise ($r = 0.698$, $p = 0.006$), no significant correlation was found between sessions. HIIE exercise resulted in an increase in the left frontal lobe and improved cognitive performance. In contrast, in the MCE group, behavioral data and cortical activation increased simultaneously, although there was no significant correlation. Overall, the absence of significant correlations could result from the proper allocation and effective use of neural resources depending on the execution and task conditions in the experimental design. In addition, the Δ of cortical activation decreased without any difference between groups in all ROIs from post-exercise to -recovery. In contrast, the Δ of the behavioral data resulted in a difference with small to medium effect size ($p = 0.202$, $d = 0.486$) between HIIE ($12.3 \pm 27.2\%$) and MCE ($1.6 \pm 24.2\%$). For this reason, in the present study involving healthy young adults with a high fitness level according to normative data for VO_2max (at least a fair or good fitness for VO_2max from Heywood [85]), there was an increase in cognitive performance from pre-exercise to post-exercise and maintenance occurred in post-recovery, resulting in different cortical activations adapted to the two types of exercise.

4.4 Limitation of the Present Study

Although the present study has provided novel attempts and interesting findings, some limitations are worth noting. First, the sample size in our study was small, which may indicate high inter-individual variability in exercise-induced cortical activation. Therefore, in statistical analysis, emphasis was placed on the effect size to compensate for this. Nevertheless, a large number of participants is required for generalization. Second, although various moderator parameters between acute exercise and cognition are involved, it is necessary to observe the acute and sustained effects of cortical activation induced by exercise on cognitive function through studies that consider various fitness levels (age group or high/low fitness). For this reason, given the participants' high fitness levels, we probably did not observe any differences in cognitive performance at the behavioral level due to the effective use of neural resources by the two types of exercise. Finally, our study's recovery duration was very short compared to studies investigating the sustained effect of acute exercise-induced neural correlates on cognitive function. Since the regular accumulation of acute exercise results from chronic exercise, the sustained effect of acute exercise by prolonging

the recovery duration could be a bridge to show the effect of chronic exercise.

5. Conclusions

In the present study, a novel comparison was attempted between two types of exercise with different intensities from pre-exercise over post-exercise to post-recovery. The results showed increased cortical activation in all ROIs from pre- to post-exercise and a decrease in the post-recovery period along with the increase and maintenance of cognitive performance. Also, on the behavioral level, no difference was found between groups. HIIE, however, showed an increase and maintenance of cortical activation in the left motor area from post-exercise to -recovery, likely due to an additional availability of neural resources for the fine motor and postural control due to the high intensity of exercise. Furthermore, it appears that the available neural resources of the frontal lobe were effectively utilized to increase or maintain cognitive performance depending on the conditions (sitting and walking) and the two types of exercise (HIIE and MCE). Further studies are needed to complement the limitations mentioned above in future studies. From the perspective of fNIRS statistical analysis, two variables (slope and mean) were considered to interpret the hemodynamic response data. This is a step towards exploring the advantages and limitations of both parameters and a proposal for a new alternative to fNIRS analysis.

Abbreviations

BDNF, Brain-derived neurotrophic factor; deoxyHb, Deoxygenated hemoglobin; DLPFC, Dorsolateral prefrontal cortex; dTMT, Digital Trail-Making-Test; EEG, Electroencephalography; FDR, False discovery rate; fNIRS, Functional near-infrared spectroscopy; FPA, Frontopolar area; HIIE, High-intensity interval exercise; HR, Heart rate; IGF-1, Insulin-like growth factor-1; M1, Motor cortex; MCE, Moderate-intensity continuous exercise; MPSTEFS, Mental and Physical State and Trait Energy and Fatigue Scales; oxyHb, Oxygenated hemoglobin; ROI, Regions of interest; RPE, Rating of perceived exertion; TMT, Trail-Making-Test; VEGF, Vascular endothelial growth factor; VO_2max, Maximum oxygen consumption.

Author Contributions

NS designed the research study. SYP performed the research. NS provided help and advice on the analysis. SYP and NS analyzed the data. SYP and NS wrote the manuscript. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

The study was conducted according to the Helsinki Declaration and approved by the university's local ethics committee. All participants gave written informed consent to participate in the experiment.

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Conflict of Interest

The authors declare no conflict of interest.

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Author contributions

All authors listed on the publication list hereby certify that

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I hereby declare that this dissertation is solely my own work except where otherwise indicated. Passages and ideas from other sources have been identified as such and properly acknowledged.

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