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Cognitive Function and the Risk of Dementia: The Influence of Physical Fitness and Exercise in Older Adults

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Affidavits following §7 section 2 No. 4 and 5 of the doctoral regulations from the German Sport University Cologne, February 20th 2013:

Hereby I declare:

The work presented in this thesis is the original work of the author except where acknowledged in the text. This material has not been submitted either in whole or in part for a degree at this or any other institution. Those parts or single sentences, which have been taken verbatim from other sources, are identified as citations.

I further declare that I complied with the actual "guidelines of qualified scientific work" of the German Sport University Cologne.

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ABSTRACT

Cognitive impairment is one of the most common health problems among older adults and has become a major focus for healthcare providers due to the ageing of the global population [1]. The prevalence of cognitive impairment has been estimated to be around 7% among older adults aged between 60 and 65 years [2, 3], and is reported to increase to about 40% among older adults aged 80 years and over [3, 4]. Moreover, the most common mental and neurological disorders among older adults, which are Alzheimer's disease (AD) and Parkinson's disease (PD), are either defined by or associated with cognitive impairment. Cognitive impairment describes a continuum of signs ranging from subjective cognitive impairment (SCI) to mild cognitive impairment (MCI) and dementia [3, 5-7]. No cure for dementia currently exists, prompting increased efforts to understand the preclinical stages such as SCI and MCI as potential opportunities for new interventions [3, 5-7]. The current guidelines of the American Academy of Neurology (AAN) promote regular exercise for these individuals [3]. However, only two studies underpin this recommendation of the AAN, and there is a clear need for studies with larger sample sizes, standardised neuropsychological testing methods, longer intervention periods and well-defined diagnostic criteria for MCI [3]. A primary prevention strategy that delays the conversion to dementia by even two years would greatly reduce the total number of patients living with dementia, and result in important public health, economic and societal benefits [8-10]. Therefore, this thesis explored the effects of exercise on cognition in individuals at high risk for dementia to determine if targeted exercise presents an optimal primary prevention strategy. In particular, this thesis focused on different modes of exercise, while also evaluating methods to monitor exercise intensity and physical activity. In addition, this thesis investigated the efficacy of electroencephalography (EEG) markers for cognitive decline in older adults.

Physical activity, exercise capacity and cardiorespiratory fitness were compared between older adults (n= 121) across the spectrum of SCI and MCI, which was further divided into early (EMCI) and late MCI (LMCI), in **study 1**. Further, study 1 assessed the strength of the relationship between these physical characteristics and cognition. Participants with LMCI had significantly lower activity levels in both subjective ($p=0.018$) and objective ($p=0.041$) measurements. Additionally, participants with LMCI had a lower exercise capacity ($p=0.041$). Furthermore, a modest and positive relationship between cardiorespiratory fitness and cognition ($r=0.25$; $p<0.05$) was found.

These findings suggest that physical activity and exercise capacity might present a marker for the risk of further cognitive decline.

In order to determine the efficacy of EEG markers for cognitive decline, **study 2** compared auditory evoked event-related potentials (ERPs) between participants with SCI (n = 13) and MCI (n = 13). In contrast to neuropsychological tests, in which participants with MCI performed significantly worse (Trail Making Test A: p=0.001, Cohen's d=1.5; Trail Making Test B: p=0.030, Cohen's d=0.94; verbal fluency letter: p=0.001, Cohen's d=1.08; verbal fluency category: p=0.038, Cohen's d=0.86), ERPs were similar between individuals with SCI and MCI. Based on these results, neuropsychological tests may be best to discriminate between individuals with SCI and MCI and should be used in future studies.

Study 3 aimed to assess whether a target score on the subjective rating of perceived exertion (RPE) scale during light, moderate and vigorous exercise can be used to prescribe exercise intensity on an individual's heart rate (HR)-RPE relationship in older adults (n=97, 75 ± 6 years) with MCI and SCI. Even though no differences between mean target and measured HR (mean difference 1.2 bpm) were observed, this study revealed some variance between the participants, with half of them demonstrating that the HR response differed by around 10 bpm when exercise was monitored with RPE alone. Therefore, this study concludes that the RPE should only be applied with caution and, if possible, with other measurements (e.g. HR monitors) to ensure that target intensity is reached.

Study 4 investigated the validity of a commonly used wrist-worn activity monitor for tracking steps in older adults. 32 older adults (mean age 74.8 ± 5.9 years) walked for 200 meters wearing the activity monitor on the wrist of the non-dominant arm, while an operator counted steps manually. Lin's concordance correlation coefficient revealed a strong correlation (rc=0.802) between the manually counted and objectively tracked steps, and accuracy was confirmed by creating Bland-Altman plots. Therefore, the results confirmed the validity of the activity monitor to assess steps accurately.

Addressing the limitations of previous studies, the multicentre NeuroExercise study, which is **study 5** of this thesis, aimed to investigate the effects of a 12-month structured exercise program (either aerobic exercise or stretching and toning exercises) on the progression of cognitive decline in people with MCI compared to a control group. This randomized controlled trial was conducted in three European countries and a total number of 183 individuals with amnestic MCI were

randomized into three different groups. Primary ANCOVA analysis revealed no differences in cognition (Cohen's d 0.11; mean difference 0.13; 95% CI -0.02-0.28) or quality of life (Cohen's d 0.02; mean difference -1.89; 95% CI -4.59 – 1.00) between the exercise groups and the control group after 12 months. In contrast, cardiorespiratory fitness increased significantly in the exercise groups compared to the control group Cohen's d 0.40, mean difference -1.76, 95% CI -3.39 – -0.10]. Secondary analyses showed centre specific and exercise-frequency related changes. Further, differences between the two exercise groups were found regarding physical fitness with the aerobic exercise group improving significantly more than the stretching and toning group. The improved physical fitness may be an important moderator for long term disease progression for individuals with MCI but did not have a positive effect on cognition after 12 months.

It was the aim of **study 6** to systematically review the effect of different exercise modes reported in randomized controlled trials on cognition in patients suffering from PD. This systematic review included a search of five electronic databases combining keywords from three categories, which were disease, exercise, and cognition. After screening abstract, title and full texts of 2,000 studies, 11 studies met the inclusion criteria. Study quality was modest (mean 6 ± 2, range 3-8/10). In 5 trials a significant between-group effect size (ES) was identified for tests of specific cognitive domains, including a positive effect of aerobic exercise on memory (ES = 2.42) and executive function (ES = 1.54), and of combined resistance and coordination exercise on global cognitive function (ES = 1.54). Two trials found a significant ES for coordination exercise (ES = 0.84–1.88), which led to improved executive function compared with that of non-exercising control subjects. All modes of exercise are associated with improved cognitive function in individuals with PD with a tendency towards aerobic exercise leading to greatest effects.

Based on **outcomes of this thesis**, it cannot be concluded which form of exercise is best for individuals in the earliest stages of cognitive decline. Nevertheless, the results highlight the importance for considering this in future studies and the need for further direct comparisons of different exercise modes. These future studies should rely on valid methods to identify the target populations, and describe exercise interventions (e.g. exercise intensity) and their outcome parameters (e.g. steps) adequately – outcomes of this thesis will help future studies to do so. Even though a direct influence of supervised exercise on cognition was not demonstrated with this work, the relationship between cardiorespiratory fitness and cognition may indicate long-term benefits of an increased fitness for cognitively impaired individuals. As high physical fitness is a driving force

for a socially integrated and fulfilling later life – especially in individuals at risk of cognitive decline – regular exercise should become routine in older adults with and without cognitive impairment.

ABSTRACT (GERMAN)

Kognitive Störungen zählen bei älteren Erwachsenen zu den am häufigsten auftretenden gesundheitlichen Beeinträchtigungen und rücken aufgrund des demografischen Wandels weltweit zunehmend in den Fokus der Gesundheitssysteme. Die Prävalenz kognitiver Beeinträchtigungen wird bei älteren Erwachsenen zwischen 60 und 65 Jahren auf etwa 7 % geschätzt und steigt im weiteren Alterungsverlauf stetig an, so dass ungefähr 40% der Menschen über 80 Jahren unter kognitiven Beeinträchtigungen leiden [1]. Zudem werden die beiden häufigsten neurodegenerativen Erkrankungen älterer Menschen – die Alzheimer-Krankheit (AD) und die Parkinson-Krankheit (PD) - entweder durch das Auftreten kognitiver Beeinträchtigungen charakterisiert (AD) oder erhöhen das Risiko dieser signifikant (PD).

Unter dem Begriff kognitive Beeinträchtigungen wird eine Vielzahl an Konditionen subsumiert, die von subjektiven Beeinträchtigungen (SCI) über leichte kognitive Störungen (MCI) bis hin zur Demenz reichen [3, 5-7]. Da keine Heilungsmöglichkeit für an Demenz erkrankte Personen besteht, gewinnen die präklinischen Phasen wie SCI und MCI für die Etablierung neuer Interventionen, die dem weiteren Niedergang kognitiver Funktionen vorbeugen sollen, an Bedeutung[3, 5-7]. Den Patienten in den genannten präklinischen Phasen empfehlen die aktuellen Richtlinien der American Academy of Neurology (AAN) regelmäßig Sport zu treiben, um dem erhöhten Risiko an Demenz zu erkranken entgegen zu wirken [3]. Allerdings basiert diese Empfehlung auf lediglich zwei Studien. Um diese Ergebnisse zu verifizieren, sind Studien mit größeren Stichprobengrößen, standardisierten neuropsychologischen Testmethoden, längeren Interventionszeiten und klar definierten Ein- und Ausschlusskriterien für die Diagnose von MCI erforderlich [3]. Schon eine Präventionsstrategie, die das Fortscheiten der kognitiven Beeinträchtigung hin zur Demenz um nur zwei Jahre verzögern könnte, würde die Gesamtzahl der mit Demenz lebenden Patienten erheblich verringern wovon auch die Gesundheitssysteme unter ökonomischen und sozialen Aspekten entscheidend profitieren würden [8-10]. In dieser Dissertation werden die Auswirkungen von Bewegung auf die Kognition bei Personen mit einem hohen Risiko des Entstehens der Demenz erforscht, um valide Aussagen darüber treffen zu können, ob und falls ja welche gezielte Bewegungsangebote eine ideale Präventionsstrategie darstellen. Hierzu werden verschiedene Sportformen verglichen. Des Weiteren steht die Evaluation der Geeignetheit unterschiedlicher Methoden zur Überwachung der Trainingsintensität und

körperlichen Aktivität im Mittelpunkt. Darüber hinaus untersucht diese Arbeit, ob elektrokortikale Marker für die Feststellung des kognitiven Rückgangs bei älteren Erwachsenen geeignet sind.

Ziel der **1. Studie** war der Vergleich von körperlicher Aktivität und körperliche Fitness im gesamten Spektrum von SCI und MCI, welches weiter in ein frühes (EMCI) und spätes (LMCI) Stadium der Erkrankung unterteilt wurde, . Weiterhin bewertete die Studie 1 die Stärke der Beziehung zwischen diesen physischen Eigenschaften und der Kognition. Insgesamt konnten 121 Teilnehmer rekrutiert werden, die die Einschlusskriterien erfüllten. Die Teilnehmer mit LMCI hatten sowohl in subjektiven ($p=0,018$) als auch objektiven ($p=0,041$) Messungen signifikant niedrigere Aktivitätsniveaus. Zusätzlich hatten die Teilnehmer mit LMCI eine geringere körperliche Fitness als die Vergleichsgruppen ($p=0,041$). Außerdem wurde ein positiver Zusammenhang zwischen Fitness und Kognition ($r=0,25$; $p<0,05$) deutlich. Diese Ergebnisse weisen darauf hin, dass körperliche Aktivität und körperliche Leistungsfähigkeit als Indikator für das Risiko eines weiteren kognitiven Rückgangs dienen könnten.

Um die Geeignetheit von Elektroenzephalographie (EEG)-Markern für die Ermittlung des kognitiven Rückgangs zu bestimmen, verglich **Studie 2** ereigniskorrelierte Potenziale (ERPs) zwischen Teilnehmern mit SCI (n = 13) und MCI (n = 13). Im Gegensatz zu neuropsychologischen Tests, bei denen Teilnehmer mit MCI deutlich schlechter abschnitten (Trail Making Test A: $p=0,001$, Cohens $d=1,5$; Trail Making Test B: $p=0.\ 030$, Cohens $d=0,94$; Sprachkompetenz: $p=0,001$, Cohens $d=1,08$), bestanden keine Unterschiede in den ERPs von Personen mit SCI und MCI. Basierend auf diesen Ergebnissen scheinen neuropsychologische Tests am besten geeignet zu sein, um zwischen Personen mit SCI und MCI zu differenzieren und sollten bevorzugt in zukünftigen Studien verwendet werden.

Studie 3 ermittelte, ob die Trainingsintensität mithilfe der Borg Skala (RPE)) für leichtes, moderates und intensives Training bei älteren Erwachsenen (n=97, 75 ± 6 Jahre) mit MCI und SCI gesteuert werden kann. Obwohl keine Unterschiede zwischen durchschnittlicher Zielherzfrequenz und der während des mithilfe der Borg Skala gesteuerten Trainings ermittelt wurden (mittlere Differenz 1,2 Schläge pro Minute), zeigte diese Studie eine gewisse Variabilität bei der Trainingssteuerung anhand des subjektiven Belastungsempfindens. Etwa die Hälfte der Teilnehmer verfehlte ihre Zielherzfrequenz um ungefähr zehn Schläge pro Minute. Um konkrete Trainingsintensitäten zu erreichen, sollte die subjektive Trainingssteuerung mit anderen Methoden

(z. B. Herzfrequenzuhren) kombiniert werden, um sicherzustellen, dass die Zielintensität erreicht wird.

Studie 4 evaluierte die Messgenauigkeit eines am Handgelenk getragenen Aktivitätsmonitors. Hierzu gingen 32 ältere Erwachsene (Durchschnittsalter 74,8 ± 5,9 Jahre) eine Strecke von 200 Metern, nachdem der Aktivitätsmonitor am Handgelenk des nicht dominanten Arms befestigt worden war. Dieser ermittelte die Anzahl der Schritte als objektive Messgröße körperlicher Aktivität. Zeitgleich wurden die Schritte manuell gezählt. Anschließend wurden beide Werte miteinander verglichen. Lins Konkordanz-Korrelationskoeffizient zeigte eine starke Korrelation (rc=0,802) zwischen den manuell gezählten und über den Aktivitätsmonitor erhobenen Schritten. Diese Ergebnisse bestätigten die Validität des Aktivitätsmonitors, Schritte genau zu erheben.

Um Limitationen vorheriger Studien zu überwinden, zielte das multizentrische NeuroExercise Projekt, die **Studie 5** dieser Arbeit, darauf ab, die Auswirkungen eines 12-monatigen strukturierten Trainingsprogramms (entweder Ausdauer oder Stretching und Toning) auf das Fortschreiten der kognitiven Beeinträchtigungen bei Menschen mit MCI im Vergleich zu einer Kontrollgruppe zu untersuchen. Diese randomisierte kontrollierte Studie wurde in drei europäischen Ländern durchgeführt und eine Gesamtzahl von 183 Personen mit MCI wurde in drei verschiedenen Gruppen zugeteilt. Die primäre ANCOVA-Analyse ergab keine Unterschiede in der Kognition (Cohens d 0,11; mittlere Differenz 0,13; 95% CI -0,02-0,28) oder der Lebensqualität (Cohens d 0,02; mittlere Differenz -1,89; 95% CI -4,59 - 1,00) zwischen den Trainingsgruppen und der Kontrollgruppe nach 12 Monaten. Im Gegensatz dazu stieg die körperliche Fitness in den Trainingsgruppen im Vergleich zur Kontrollgruppe signifikant an (Cohen d 0,40, mittlere Differenz -1,76, 95% CI -3,39 - -0,10). Sekundäre Analysen zeigten länderspezifische Unterschiede. Weiterhin wurden Unterschiede zwischen den beiden Trainingsgruppen in Bezug auf die körperliche Fitness festgestellt, wobei sich die aerobe Trainingsgruppe signifikant stärker verbesserte als die Stretching- und Toning-Gruppe. Die verbesserte körperliche Fitness kann ein wichtiger Indikator für die langfristige Entwicklung der Erkrankung bei Personen mit MCI sein, hatte aber nach 12 Monaten keinen unmittelbaren Einfluss auf die Kognition.

Ziel der **Studie 6** war es, die Wirkung verschiedener Trainingsformen auf die Kognition bei Patienten mit Parkinson zusammen zu fassen und zu vergleichen. Hierfür wurde eine systematische Übersichtsarbeit erstellt, in der insgesamt fünf elektronische Datenbanken durchsucht wurden. In die Datenbanken wurde eine Kombination von Schlüsselwörtern aus drei Kategorien, nämlich

Krankheit, Bewegung und Kognition, eingegeben. Nach der Überprüfung von Abstract, Titel und Volltexten von 2.000 Studien erfüllten 11 Studien die definierten Einschlusskriterien. In 5 Studien wurde ein signifikanter Effekt des jeweiligen Sportprogramms auf spezielle kognitive Fähigkeiten deutlich. Ein positiver Effekt von Ausdauertraining auf das Gedächtnis (Effektstärke (ES) = 2,42) und die Exekutivfunktion (ES = 1,54), sowie von kombiniertem Kraft- und Koordinationstraining auf die globale kognitive Funktion (ES = 1,54) konnte gezeigt werden. In zwei weiteren Studien führte ein koordinatives Training zu einer verbesserten Exekutivfunktion im Vergleich zu der von nicht trainierenden Kontrollpersonen (ES = 0,84-1,88). Alle Trainingsformen zeigten das Potential domänspezifische, kognitive Funktionen zu verbessern, wobei ein Ausdauertraining mit dem größten Effekt assoziiert war.

Basierend auf den **Ergebnissen dieser Arbeit** kann nicht abschließend geklärt werden, welche Sportform am besten geeignet ist, um das Fortschreiten kognitiver Beeinträchtigungen bei älteren Personen zu verhindern. Dennoch zeigen die Ergebnisse, wie wichtig es ist, dies in zukünftigen Studien zu berücksichtigen, und dass weitere direkte Vergleiche verschiedener Trainingsformen erforderlich sind. Diese zukünftigen Studien sollten sich auf valide Methoden stützen, um Zielgruppen adäquat zu charakterisieren und Trainingsinterventionen (z. B. Trainingsintensität) und deren Ergebnisparameter (z. B. Schritte) angemessen zu beschreiben - die Ergebnisse dieser Arbeit werden zukünftigen Studien helfen, dies zu tun. Auch wenn in dieser Arbeit kein direkter Einfluss eines Sportprogramms auf die kognitiven Fähigkeiten von Personen mit MCI nachgewiesen werden konnte, kann der ermittelte Zusammenhang zwischen körperlicher Fitness und Kognition auf langfristige Vorteile einer erhöhten Fitness für kognitiv beeinträchtigte Personen hinweisen. Da eine gute körperliche Fitness die treibende Kraft für ein sozial integriertes und erfüllendes späteres Leben ist - insbesondere bei Menschen, die von kognitivem Verfall bedroht sind -, sollte regelmäßige Bewegung bei älteren Erwachsenen mit und ohne kognitive Beeinträchtigung zur Routine werden.

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LIST OF ABBREVIATIONS

Abbreviation	Title
AAN	American Academy of Neurology
Aβ	Amyloid Beta 39-43
AD	Alzheimer's Disease
AE	Aerobic Exercise
aMCI	Amnestic Mild Cognitive Impairment
ANCOVA	Analysis of covariance
BDNF	Brain-Derived Neurotrophic Factor
BMBF	Federal Ministry of Education and Research of Germany
CC	Complete Case
CE	Coordination Exercise
CG	Control Group
CI	Confidence Interval
DBP	Diastolic Blood Pressure
DemQOL	Health-Related Quality of Life for People with Dementia
ECG	Electrocardiography
EEG	Electroencephalography
EMCI	Early Mild Cognitive Impairment
ERP	Event-Related Potential
ES	Effect Size
ET	Exercise Test
f	Female
Fig	Figure
GER	Germany
GSU	German Sport University
HIIT	High-Intensity Interval Training

HR	Heart Rate
HY	Hoehn & Yahr
IGF-1	Insulin-Like Growth Factor 1
IRE	Ireland
JPND	Joint Programme – Neurodegenerative Disease Research
LAPAQ	Longitudinal Aging Study Amsterdam Physical Activity Questionnaire
LMCI	Late Mild Cognitive Impairment
LT 1	Lactate Threshold 1
LT 2	Lactate Threshold 2
MCI	Mild Cognitive Impairment
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
MoCA-MIS	Montreal Cognitive Assessment Memory Index Scale
MRI	Magnetic Resonance Imaging
NA	Not Applicable
NL	The Netherlands
NPP	Not Per-Protocl
NR	Not Reported
PA	Physical Activity
PEDro	Physiotherapy Evidence Database Scale
PICO	Population, Intervention, Comparator, Outcome
PD	Parkinson's Disease
PP	Per-Protocol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta Analyses
RCT	Randomised Controlled Trial
RE	Resistance Exercise
RPE	Rating of Perceived Exertion
SCI	Subjective Cognitive Impairment

SD	Standard Deviation
SPB	Systolic Blood Pressure
ST	Stretching and Toning Exercise
TMT A	Trail Making Test A
TMT B	Trail Making Test B
TuG	Timed up and Go
UPDRS	Unified Parkinson's Disease Rating Scale
USC	University of the Sunshine Coast
UTC	Unable to Calculate
VEGF	Vascular Endothelial Growth Factor
W	Watts
WHO	World Health Organization
y	Years

1.0. INTRODUCTION

Cognitive impairment is one of the most common health problems among older adults. The ageing of the global population has made this problem a major focus for governments and healthcare providers [1]. The prevalence of cognitive impairment is estimated at 7% among older adults aged between 60 and 65 years [2, 3]. Estimates increase to 40% among older adults aged 80 years and over [3, 4]. Moreover, the most common mental and neurological disorders among older adults, Alzheimer's disease (AD) and Parkinson's disease (PD), are respectively defined by and associated with cognitive impairment. Cognitive impairment describes a number of conditions ranging from subjective cognitive impairment (SCI) to mild cognitive impairment (MCI) and dementia [3, 5-7].

Dementia is characterised by a progressive cognitive decline that affects all cognitive domains, including memory, thinking and language. The social and economic impact of dementia places a substantial burden on health systems worldwide, but also affects relatives, caregivers and the individuals themselves because of considerable constraints on their daily function and independence [11, 12]. No cure for dementia currently exists, prompting increased efforts to understand the preclinical stages such as SCI and MCI [3, 5-7]. Individuals with SCI or MCI have an increased risk of progressing to dementia, with conversion rates from MCI to dementia of about 15% at two years after the initial diagnosis [3, 13]. A primary prevention strategy that delays conversion to dementia by even two years would greatly reduce the total number of patients living with dementia, and result in important public health, economic and societal benefits [8-10]. Therefore, current research efforts target the early states of cognitive impairment to test the efficacy of prevention and therapeutic approaches.

Although the diagnosis of both SCI and MCI includes self-report of subjectively experienced cognitive problems, the formal diagnosis of MCI requires additional objective evidence of cognitive impairment [3, 14, 15]. Research recommends extensive batteries of neuropsychological tests at multiple time points to establish the diagnosis of MCI. This process is time consuming and may cause psychological distress for the individuals being assessed [15-19]. In the search for tests that are efficient and sensitive to subclinical impairment, neuroimaging techniques such as electroencephalography are increasingly

considered to validly identify those individuals at highest risk of dementia [8, 20, 21]. Although electroencephalography has been proposed to differentiate healthy older adults from individuals with MCI and individuals with AD, less is known about the sensitivity of such measures to identify those with early-stage SCI [20].

Higher physical activity levels and high cardiorespiratory fitness may protect against cognitive decline in healthy older adults [22-26]. The relationship between physical activity, cardiorespiratory fitness and cognition has been extensively studied in healthy older adults [27-32], but less is known in those individuals with cognitive impairment who have the greatest risk of developing dementia. Nonetheless, regular physical activity and exercise have been proposed as promising treatment approaches for individuals at risk of progressing to dementia. The current guidelines of the American Academy of Neurology (AAN) promote regular exercise for these individuals [3]. However, only two studies underpin this recommendation of the AAN. One study investigated the effect of a resistance exercise intervention on the progression of MCI [33]. The other similarly investigated the effect of a 6-month multicomponent exercise intervention (consisting of resistance and aerobic exercise) [34]. These studies demonstrated a positive effect on domain-specific cognitive function (attention and episodic memory) [33, 34]. In addition, two systematic reviews both recommend aerobic exercise as the most effective form of exercise training to maintain or improve cognitive function in individuals with MCI [35, 36]. However, these reviews highlighted the need for studies with larger sample sizes, standardised neuropsychological testing methods, longer intervention periods and well-defined diagnostic criteria for MCI. Studies that address these previous research limitations will provide a better understanding of the efficacy of exercise for preventing the progression of cognitive decline to dementia.

Although exercise is recommended for individuals at risk of further progression to dementia, the type of exercise likely to provide the greatest benefit for maintaining or improving cognition is not yet established. Therefore, exercise interventions should include different exercise modes to establish which form of exercise is best. Besides exercise mode, research should investigate exercise intensity, because the effects of higher or lower intensities on cognition may differ [37]. Exercise intensity is characterised and measured in various ways, including as heart rate relative to maximum or age-predicted maximum heart rate, or as a percentage of oxygen uptake reserve [38]. A practical method of monitoring exercise

intensity is perceived effort using Borg's Rating of Perceived Exertion (RPE). This psycho-physical tool assesses the subjective perception of effort during exercise in order to rate and regulate exercise intensity [39]. However, controversy exists around the use of the RPE because both age and cognitive state may influence the rating's accuracy, and it requires testing in individuals during the early stages of cognitive decline [40-43].

1.1. Aims of this thesis

The overall aims of this research program were to develop a better understanding of the relationship between physical activity, cardiorespiratory fitness and cognitive function during the early stages of cognitive decline, and to investigate the effects of exercise on cognitive functions in older adults at high risk of developing dementia. Six primary research aims were explored:

1. (a) To compare physical activity levels, exercise capacity and cardiorespiratory fitness in older adults across the spectrum of SCI and MCI, and (b) to assess the strength of the relationship between these physical characteristics and cognitive function (reported in Chapter 3).
2. To determine the efficacy of EEG markers of cognitive decline by comparing event-related potentials in participants with SCI or MCI in response to an auditory oddball paradigm (Chapter 4).
3. To establish whether a target RPE during light, moderate and vigorous exercise can be used to achieve exercise intensity based on an individual's HR–RPE relationship (Chapter 5).
4. To assess the validity of the Polar M400© watch for measuring step-count during walking against a previously validated pedometer (Omron Walking Style©) (Chapter 6).
5. To investigate the effects of a 12-month structured exercise program, either aerobic exercise or stretching and toning exercises, on the progression of cognitive decline in people with MCI (Chapter 7).
6. To conduct a systematic review of the literature to establish what is currently known about the effects of aerobic training, resistance training, coordination training, and

combinations of exercise types on the specific cognitive impairments associated with Parkinson's disease (PD) (Chapter 8).

1.2. General Overview & Financial Support

This thesis was written as part of a joint Doctor of Philosophy program between the German Sport University Cologne, Germany (Home University), and the University of the Sunshine Coast, Australia (Visiting University).

The ethics committee of the German Sport University Cologne approved all experimental interventions in this research program. In addition, the University of the Sunshine Coast Ethics Committee approved all experimental work conducted at USC (S181196).

The present work was financially supported by the German Sport University and the University of the Sunshine Coast as defined by their joint agreement. Furthermore, this work was supported by the EU Joint Programme – Neurodegenerative Disease Research (JPND) and the Federal Ministry of Education and Research of Germany (BMBF; grant number: BMBF 01ED1510A). Additionally, some aspects of the work were supported by a scholarship of the German Academic Exchange Service awarded to Tim Stuckenschneider.

2.0. LITERATURE REVIEW

2.1. Introduction

The percentage of people around the world aged 65 years and over increased from 8% in 1950 to around 11% by 2005 and is expected to more than double by 2050 [44]. In absolute numbers, this means that by 2050 more than 2.1 billion people aged 65 years and over will live across the world [45]. This change in demographic structure is not expected to end in 2050, and will continue at least until 2100, when one-third of the global population will be 65 years or older [46]. In several regions of the world (such as Europe, Japan and Oceania), low fertility rates and longer life expectancy will change the age structure even faster, so that the one-third mark will be reached by 2020 [46, 47].

The change in age structure will clearly affect all parts of society and will present a major challenge for healthcare and social systems worldwide. At the start of 2018, the World Health Organization (WHO) acknowledged the challenge of the demographic change and called for action in five priority areas: (1) commitment to healthy ageing, (2) aligning health systems with the needs of older populations, (3) developing systems for providing long-term care, (4) creating age-friendly environments, and (5) improving measurement, monitoring and understanding. We need to start tackling these challenges now.

2.2. Healthy Ageing and Cognitive Function

Based on a comprehensive review in 2006, the mean proportion of people 'ageing successfully' will be 35.8%, which simultaneously characterizes the majority of people as ageing unsuccessfully [48-51]. As ageing is associated with – among other factors – a decline in cognitive performance, this decline might explain the low proportion of people ageing successfully [52, 53]. Cognitive functions seem to follow a similar pattern to that of physical functions throughout the lifespan: they are developed during childhood, maintained during maturity and slowly decline during old age [54] (Figure 1). This concept, however, is overly simplistic and somewhat speculative, because cognitive changes vary significantly among older adults and are subject to both intrapersonal and interpersonal experiences [55].

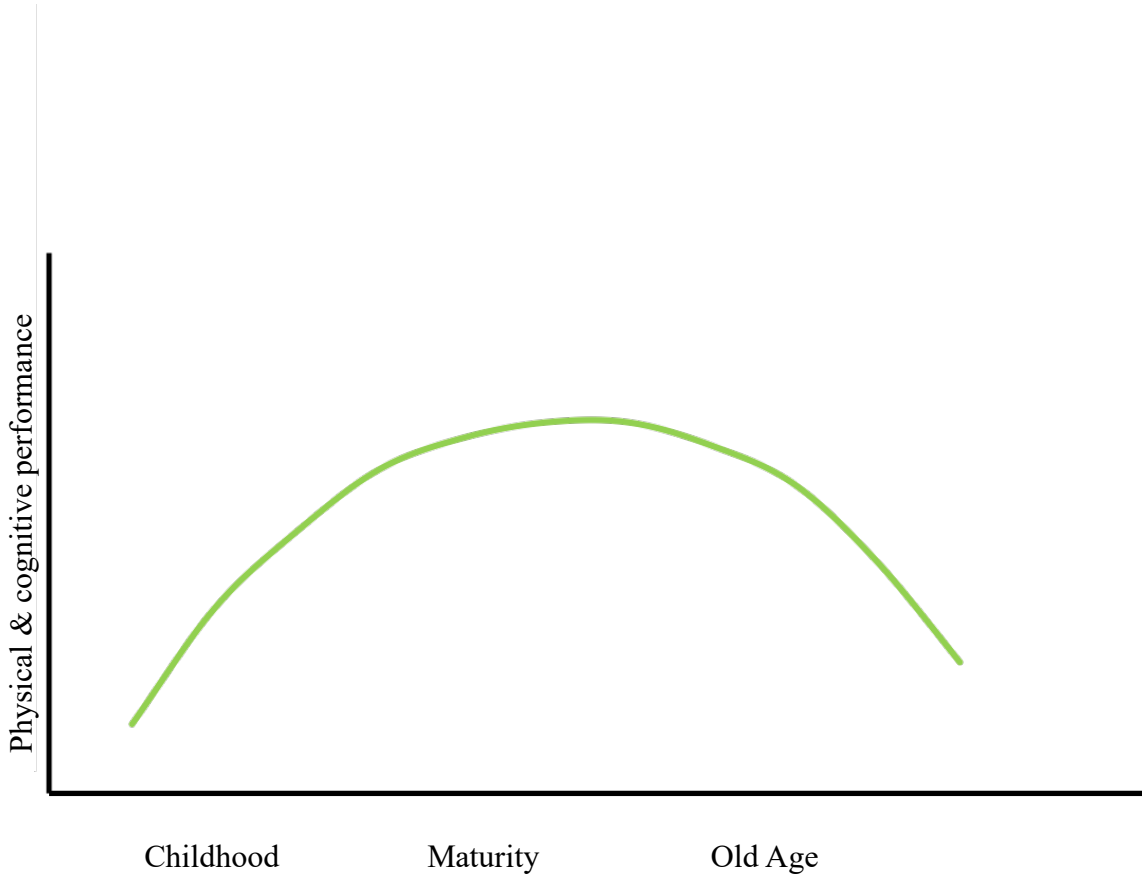

Figure 1: A speculative model of cognitive change across the lifespan (modified from Craik and Bialystok [54]).

From the early 1990s, psychologists identified different behavioural aspects of ageing: a generalized slowing of cognitive processing and a slower processing speed [56, 57], diminished inhibitory processing and distracting interference during cognitive tasks, and difficulties with attention and task switching (e.g. frequent distraction by stimuli irrelevant to the current task) [58-60]. Additionally, deficits in working memory function (e.g. decision making) [61, 62] and in episodic memory (e.g. the conscious recollection of events) were reported [63-65]. In contrast to declining cognitive functions, researchers identified that semantic memory, general knowledge [66], and emotional regulation are often maintained or even improved in healthy older adults [67, 68].

Cognitive decline with ageing is a complex phenomenon. Part of its complexity is explained by the complexity of the term cognition itself. The *Oxford Dictionary* defines cognition as ‘the mental action or process of acquiring knowledge and understanding through thought,

experience, and the senses'. However, in research, uniform definitions of cognition and cognitive functions do not exist [55, 69-71]. Most often, cognitive functions are defined by separating them into subdimensions, with terms such as attention, memory, language, visuospatial abilities, construction and executive functioning [55, 69-71].

Popular neuropsychological tests such as the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) assess multiple cognitive domains. Such tests are often called measures of *global cognitive functions* [72, 73]. The term 'global cognitive functions' does not describe a specific cognitive function but reflects an overall score for multiple cognitive domains. Most tests that assess global cognitive functions distinguish between normal ageing and cognitively impaired individuals and do not capture changes within healthy older adults. Changes in healthy adults are very subtle and may be limited to specific cognitive functions [74, 75]. Therefore, a domain-specific approach may provide a better understanding of the complex changes associated with ageing.

2.2.1. Domain-Specific Cognitive Function

Attention describes the ability to focus and concentrate on specific stimuli [75]. Subdomains of attention include selective attention, divided attention and attention switching, and sustained attention. Selective attention describes the ability to focus on one task while ignoring others that are irrelevant, whereas divided attention refers to the ability to process more than one source of information or perform more than one task at the same time. The ability to concentrate on a task over an extended period refers to sustained attention. Although these subdimensions are broadly recognized, an accepted definition of attention has not been established because attention is understood as dynamic. Researchers and theorists partition attention into many subdomains [54, 75-77].

Ageing affects more complex attentional tasks such as selective and divided attention [75-79]. A study found selective attention decreased in older adults (aged 63–74 years), who needed more time to complete selective-attention tasks than younger adults (aged 18–25 years) needed [80]. Others found similar results for divided attention, with older adults performing significantly worse than younger adults [81].

The literature uses the terms *memory* and *working memory* interchangeably and describes various memory processes such as primary memory, short-term memory, procedural

memory, episodic memory, long-term memory, semantic memory, and implicit memory [75, 82, 83]. This thesis uses short-term memory, working memory and long-term memory as umbrella terms. Short-term memory refers to the ability to, for example, repeat a number by simple rehearsal. Even though different definitions of working memory exist, they all include the active manipulation of information that is currently held available [84, 85]. In the previous example of recalling a number, we need working memory to recite a phone number backwards because this involves an active manipulation of short-term memory. Therefore, we need an intact working memory for everyday tasks (e.g. decision making, problem solving). The cognitive domain of long-term memory has received the most attention in older adults; it refers to the ability to retrieve information not maintained in an active state (e.g. childhood memories) [75, 82, 83, 85].

Healthy older adults show minimal to no deficits in short-term memory, as Nilsson found in participants across five age cohorts (35–40, 45–50, 55–60, 65–70, 75–80) who performed similarly in a short-term memory task. In contrast, age affects working memory because ageing leads to significant deficits in active manipulation, reorganization or integration of the contents of working memory [75, 82, 83, 85]. A comparison of working memory in younger (19–30 years) and older adults revealed less accuracy and slower reaction times in older adults [86]. Long-term memory clearly declines during ageing; older adults experience difficulties remembering details about remote events [55, 87, 88].

Executive functions refers to a wide range of cognitive abilities such as the ability to self-monitor, organize, reason, plan and problem-solve [89]. Researchers and psychologists agree on three core executive functions: inhibition, working memory, and cognitive flexibility [55, 89]. As explained above, working memory is often assessed alone and the term used interchangeably with memory. The terms *inhibition* and *inhibitory control* describe the ability to control one's attention, behaviour, thoughts, and emotions [55, 77, 89]. Cognitive flexibility, the third core executive function, describes the ability to change perspective, which requires the inhibition of previous perspectives to change the current perspective. Researchers often refer to cognitive flexibility as the opposite of rigidity. Cognitive flexibility closely relates to creativity and task shifting. Further, it includes the ability to appropriately adjust one's behaviour to a changing environment [55, 77, 89].

Apparently, ageing impairs inhibitory control through a processing speed deficit rather than deficits in inhibitory control per se, because updating and coordinating information takes longer in older adults [77]. However, older adults appear prone to visual and auditory distractions, which provides some evidence of a deficit in inhibitory control with ageing [75, 90-94]. We know cognitive flexibility declines with age [89, 93, 95]. For example, Wilson and colleagues analysed cognitive flexibility in 20 older (65–85 years) and 20 younger adults (18–25 years). They found a significant age effect with younger adults showing greater flexibility [96].

Speech and language describes a complex cognitive domain, which refers to vocabulary, verbal fluency, storytelling, speech comprehension, and verbal retrieval [55, 89]. Ageing does not affect speech and language. Older adults often have a more extensive vocabulary and better-structured narratives than younger people. Further, older adults use contextual information to effectively comprehend messages from others [77]. Impaired speech and language mostly occur through deficits in executive functions, particularly working memory and speed of processing [75, 97].

Visuospatial abilities enable individuals to see an object or picture and construct a replica of it [55, 77, 89]. Examples of visuospatial construction include drawing, buttoning shirts, making a bed, and putting together furniture. Visuospatial abilities allow us to locate targets and are important for navigation and orientation [55, 77, 89]. In older adults, construction and visuospatial recognition may take longer than in younger adults, which again relates to deficits in processing rather than in visuospatial abilities per se [98-100].

Age clearly affects cognition across all domains, but the degree of age-related decline varies. Variance is not only observed within (e.g. in short-term memory and long-term memory) or between (e.g. executive functions and language) cognitive domains, but also among individuals [68, 101, 102]. Studies in the 1990s showed large inter-individual variability in cognitive functions among older adults [103-105]. For example, Christensen followed up 887 individuals aged between 70 and 93 years for 8 years and reported heterogeneous changes in cognition in successfully ageing older adults [103].

2.2.2 Healthy Ageing and the Brain

The human brain begins to atrophy in the third decade of life, with an eventual loss of volume of about 14% in the cerebral cortex, 35% in the hippocampus and 26% in the cerebral white matter between the ages of 30 and 90 [106]. Loss of neurons in the brain stem, the cerebral cortex and the basal ganglia accompany this loss in volume [106-108]. Moreover, others have confirmed decreases in cortical grey-matter volume [109, 110] and in the volume of the cerebral hemispheres [111]. As age-related changes in the brain and cognition follow a reasonably consistent pattern, researchers have identified brain shrinkage as a major contributor to age-related cognitive decline [112-114].

For example, various studies have reported that frontal and prefrontal areas of the brain are most affected by age [106, 115-118], which accords with the 'last in, first out' hypothesis [115, 119]. This hypothesis proposes that the brain areas that are latest to develop ontogenetically are the first affected by age [115, 119]. Because frontal brain areas are associated with processing speed, executive functions and memory, structural decline may explain age-related changes in these cognitive domains [115, 120, 121]. However, Salthouse et al. reported that the relationship between brain and cognition is not unidirectional [122], which agrees with results from Persson and colleagues. These researchers followed up 90 healthy adults aged between 19 and 79 and showed that brain structure and cognition have a reciprocal influence on each other [114]. Therefore, maintenance of structural health and behavioural functions are equally important to maintain with ageing.

2.3. Cognitive Decline Beyond Normal Ageing

Many conditions associated with age increase the likelihood of cognitive decline beyond the level of healthy ageing. Among these are depression [123], sensory impairment [124], sleep disturbance [125], cerebrovascular disease [126] and cardiovascular disease [127]. Previous studies differentiated between 'normal' age-related cognitive decline and impaired cognitive functions using the core criteria of subjective complaints and/or a performance 1.5 standard deviations below the mean of the age- gender-, and education-adjusted norm on cognitive tests [128-130].

Subjective cognitive impairment (SCI) [131] and mild cognitive impairment (MCI) [6, 132] are considered the earliest stages of cognitive impairment and are referred to as preclinical

stages of dementia. Dementia is defined as a syndrome of the brain that impairs all cognitive functions [133-135] (Figure 2). Besides SCI and MCI, the two most common neurodegenerative diseases are AD) [136-138] and PD [139, 140]. The key symptom of AD is dementia. PD is also associated with various stages of cognitive decline. *Neurodegenerative disease* is an umbrella term for a number of incurable conditions that affect the neurons in the brain and result in progressive neurodegeneration [141]. Neurodegenerative diseases have diverse pathophysiology and affect both motor (e.g. ability to move) and non-motor functions (e.g. sleep) [142]. These diseases are characterized by long run-in periods, meaning that changes in the brain appear well before the onset of the disease [141]. For example, Beason-Held and colleagues reported that individuals progressing to cognitive impairment had higher cerebral blood flow in the orbitofrontal and medial frontal brain regions and lower blood flow in the parietal, temporal and thalamic regions than did individuals who remained healthy [143]. Further, brain atrophy of the affected group was significantly greater than that of healthy older adults with age-related volume loss [144, 145].

Cognitive performance as a non-motor function is often impaired in individuals affected by neurodegenerative diseases and ranges from early cognitive decline to severe dementia [119, 141]. Some researchers have suggested that the stages of cognitive decline represent a spectrum of disease progression, with subjective complaints the first stage and dementia the last [3, 5-7] (Figure 2).

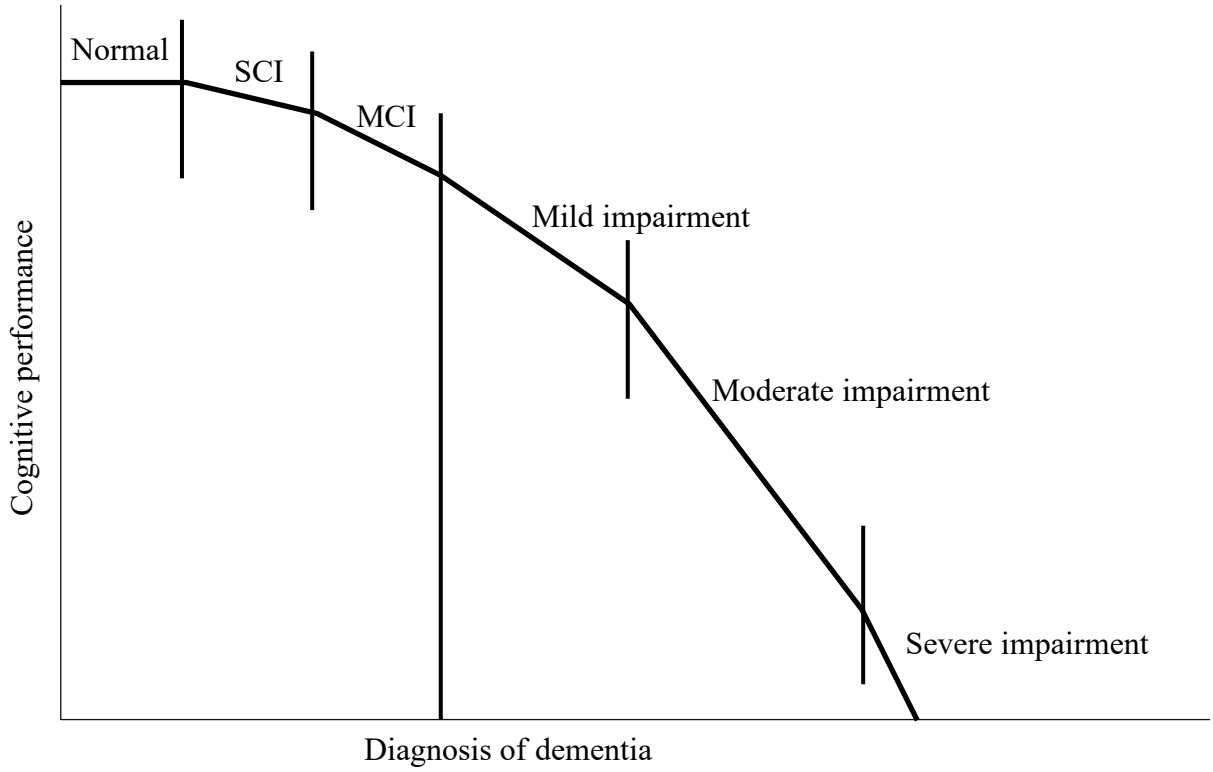

Figure 2: The spectrum of cognitive impairment (SCI = subjective cognitive impairment; MCI = mild cognitive impairment). Modified from Craik and Bialystok [146].

2.3.1. Subjective Cognitive Impairment (SCI)

SCI describes the occurrence of subjective memory complaints that do not lead to poor outcomes in neuropsychological tests [131] and cannot be explained by any specific psychiatric, neurological or medical disorder, nor by medication or substance use [129, 147]. The individual experiences cognitive deterioration, but performs within the range of standardised and normative-referenced neuropsychological measures [148]. SCI as a preclinical stage for further cognitive decline reflects the idea that the patient knows best and might be aware of a decline in cognitive function before confirmation by neuropsychological tests. Not all individuals with SCI develop further cognitive decline such as MCI or dementia [149, 150]. The mixed findings on individuals with SCI and whether they progress to MCI or dementia raised concerns that SCI is an early state of cognitive impairment. More recent research shows that individuals with SCI are at increased risk of progression to MCI and dementia, confirming it as a risk state for further cognitive decline [5, 128, 129, 151, 152].

Further, the National Institute on Aging and the Alzheimer's Association officially include SCI in their definition of the preclinical stages of AD [8, 153].

Previous studies reported that biomarkers may help to characterize SCI [8, 129, 153]. For example, Magnetic resonance imaging (MRI) studies revealed that the volume in brain regions affected by AD (e.g. medial-temporal lobe) is slightly lower in individuals with SCI than in healthy older adults [154-156]. Further, a functional MRI study showed an increase in frontal brain activity with a concurrent decrease in hippocampal activity during a memory task in those with SCI [157]. Previous research also detected loss of grey-matter volume and cerebral hypometabolism [155, 158, 159], which led to speculation that alterations in hippocampal integrity accompany SCI.

Besides MRI studies, most studies analysing cerebrospinal fluids reported amyloid deposition in individuals with SCI. These findings provide a further link to dementia because amyloid depositions play a major role in the development of dementia [148, 152, 160-162]. However, no normative or reference values have been established to validly differentiate individuals with SCI and healthy older adults. Future research should establish reliable clinical methods to differentiate between these two groups.

2.3.2. Mild Cognitive Impairment (MCI)

MCI is defined as the preclinical, or prodromal, stage of AD [6, 163] and shows several of the clinical and neuropsychological pathological features present before the onset of overt AD [164]. The prevalence of MCI in adults aged 60–64 years is about 6.7%. This figure increases to 25.2% in adults aged 80–84 years [3]. A diagnosis of MCI includes three general features: evidence of cognitive impairment measured objectively by scores lower than expected for age, gender and education level in neuropsychological tests [163]; the preservation of general cognition and functional abilities, which refers to maintaining an independent life with minimal need for assistance [165-168]; and the absence of diagnosed dementia [169].

Different subtypes of MCI exist. The most notable differentiations are amnestic and nonamnestic MCI, and single and multi-domain MCI [130]. Amnestic MCI always involves impaired memory, which is not present in the nonamnestic type. Multi-domain MCI denotes that more than one cognitive domain (e.g. memory and visuospatial function) is affected by

the disease. Because an impaired memory is the clinical hallmark of AD, differentiating between these subtypes may be important for the risk of disease progression. However, researchers debate whether the amnestic MCI subtype carries an increased risk of converting to AD because studies to date report mixed findings [170, 171]. The most recent guidelines give the risk of progression to dementia at about 10–15% within a year of the initial diagnosis for all types of MCI [3, 172, 173].

Currently, no gold standard exists for neuropsychological tests to diagnose MCI [3, 14]. Current guidelines suggest that batteries of tests should assess various cognitive functions, which include memory (e.g. immediate and delayed recall), executive function (e.g. reasoning, problem solving), visuospatial skills, language (e.g. naming, fluency, expressive speech), and attention (simple and divided attention) [14, 163]. Further, the assessment tools should be brief and validated. Section 2.5 further discusses assessing cognitive functions. The diagnosis of MCI, however, does not depend solely on a specific test score, but rather a clinical evaluation that also assesses functional status, including other comorbidities and disease history as well as instrumental and other activities of daily living [3, 14].

2.3.3. Dementia and Alzheimer's Disease (AD)

Dementia is the most common mental disorder among older adults and affects up to 10% of those aged 65 years and older [169]. Dementia is defined as 'a syndrome due to a disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions' (WHO, 2015). Dementia often results from a variety of pathological processes that are associated with and part of other diseases. These diseases include AD, cerebrovascular disease (vascular neurocognitive disorder), dementia with Lewy bodies, PD, frontotemporal lobar degeneration (fronto-temporal dementia), Huntington's disease, traumatic brain injury, HIV infection, prion disease, and other conditions (e.g. drug related) [174]. AD, the most common cause of dementia, accounts for 60–70% of all dementia cases worldwide (WHO 2015). Generally, it leads to death within 10 years of the diagnosis [174]. The core clinical criteria for all-cause dementia and for AD have been published previously and are summarized below [175].

The key symptom of dementia is a progressive cognitive decline, which affects memory, thinking, orientation, comprehension, calculation, learning capacity, language, and

judgement (WHO, 2015). Three stages of the disease are differentiated from early stage or mild dementia (e.g. forgetfulness, getting lost in familiar places) to late stage or severe dementia, in which the patients are completely dependent on others [176]. Besides the progressive cognitive impairment, dementia leads to further behavioural and psychological symptoms such as anxiety, depression, delusions and hallucinations, as well as hyperactivity and aggression – but also euphoria [177]. These symptoms combined with the disease's progressive nature and the lack of effective treatment strategies make dementia an urgent global health issue [178].

The underlying pathophysiological mechanisms of dementia are still not completely understood, but two aetiological pathways have been defined: the amyloidosis path and the tauopathy path [148]. Besides these two major proteinopathies, a general neurodegeneration might also contribute to the manifestation of dementia [179].

The amyloidosis path refers to the peptide amyloid beta 39-43 (Aβ), which is formed by cleavages of amyloid β precursor protein. The physiological function of Aβ is still unclear, but a kinase activation [180, 181], a protection against metal-induced oxidative damage [182, 183], regulation of cholesterol transport [184, 185], and formation of ion channels [186] are likely to be among the functions. In healthy individuals Aβ is a metabolite or degradation product that is released extracellularly. There, it is rapidly degraded and removed. This process is sometimes defective in older adults, which leads to an Aβ accumulation. This accumulated Aβ develops into senile plaque, which causes neurotoxicity and ultimately results in neuronal cell death and neurodegeneration [187].

Tau protein is localized on the human tau gene, which is chromosome 17. Its major physiological function is believed to be the stabilizing of microtubules [188], which are essential for intracellular transport and a number of other cellular processes. Tau expression responds to an increase in nerve growth factor [189] and is subsequently enriched in axons [190], which need this process to maintain their morphology. If tau accumulates in a hyperphosphorylated state from possible mutation, this might mark the beginning of degeneration in the brain, which ultimately causes AD [187, 191]. Because tau has been detected before Aβ accumulation [192, 193], some speculate that tau rather than Aβ is the driving mechanism in the development of cognitive decline [187]. However, this requires confirmation.

Vascular impairments such as atherosclerosis and microinfarcts often coexist with the described proteinopathies. These conditions are common in people suffering from cognitive impairment and AD. Evidence from analysing 5715 cases from the National Alzheimer's Coordinating Center revealed a strong link between vascular pathology and cardiovascular disease in AD [194]. Statement papers from the American Heart Association and the American Stroke Association acknowledge the contribution of vascular pathology to dementia [195, 196]. Therefore, decreasing vascular risk factors may be vitally important in managing cognitive impairment and dementia.

2.3.4. Parkinson's Disease (PD)

Idiopathic PD is the second most common neurodegenerative disease. Its prevalence ranges from 100 to 200 per 100 000 people [139, 197]. In PD, neurodegeneration affects several areas of the brain, such as the pigmented nuclei in the midbrain and brainstem, the olfactory tubercle and the cerebral cortex, as well as elements of the peripheral nervous system [198, 199]. The pathophysiology may start with cell loss in the substantia nigra, which is a part of the basal ganglia located in the midbrain. This cell loss leads to degeneration of dopaminergic neurons, which predominantly affects the basal ganglia that depend on such neurons [198-201]. The abnormal function of the basal ganglia leads to certain motor impairments that manifest as tremor at rest, rigidity (muscle stiffness), bradykinesia or akinesia (paucity or slowness of movement), and postural instability [198, 202]. Though PD is recognized as primarily a movement disorder, patients also display non-motor clinical signs and symptoms, prompting redefinition as a heterogeneous multisystem disorder [202].

One of PD's most common non-motor symptoms is cognitive decline. Most patients with PD develop cognitive decline and finally dementia if they live longer than 10 years after diagnosis. This decline leads to a seriously decreased quality of life, higher health-related costs and increased caregiver burden [203]. The underlying neurophysiological mechanisms of cognitive decline in PD are not completely understood [202]. However, post-mortem studies indicate a limbic and cortical Lewy body pathology, which seems to spread from the lower brainstem, the olfactory bulb or extracranial areas to the midbrain, forebrain, limbic structures and neocortical regions [204, 205]. In addition, accumulated amyloid plaques contribute to the development of dementia in individuals with PD; the role of α-synuclein

and tau proteins has not been conclusively clarified [206]. Some propose mitochondrial dysfunction, neurotransmitter changes and a synaptic pathology as causes of cognitive decline in PD [202].

The Unified Parkinson's Disease Rating Scale (UPDRS) is the most common instrument used to assess disease severity and progression in people with PD. The tool consists of four sections that assess mental activity and mood, activities of daily living, motor function, and complications of therapy for patients treated with dopaminergic medication [207]. Besides the UPDRS, various tests and wearables can assess the motor function of individuals with PD [208, 209]. Assessment tools for non-motor symptoms such as cognitive impairment are often similar to those used in people with SCI, MCI and AD. Recently, the Movement Disorder Society recommended specific tools to assess cognitive function in individuals with PD in order to improve the conformity of reporting outcomes in future studies.

2.4. Treatment Approaches for Cognitive Decline

A consensus has been reached that treatment of cognitive decline should begin as early as possible to slow, stop or reverse the pathophysiological processes that occur years before the onset of cognitive decline [3, 202, 210, 211]. Early treatment approaches may prevent or delay further cognitive decline before irreversible brain damage occurs [212]. Consequently, preventing cognitive decline has become a major healthcare topic, and prodromal stages of dementia such as SCI and MCI have become important treatment targets.

Treatment options for cognitive decline are limited despite extensive research interest. The heterogeneous aetiology and occurrence of cognitive decline in healthy older adults and people experiencing SCI or with MCI make targeting specific pathophysiological mechanisms difficult [213-215]. Fink and colleagues published a systematic review in 2018 that included 51 pharmacological trials with low to moderate risk of bias to analyse the efficacy of various pharmacologic interventions to prevent or delay cognitive decline in healthy older adults and individuals with MCI [216]. The treatments included dementia medications, antihypertensives, diabetes medications, nonsteroidal anti-inflammatory drugs, aspirin, hormones, and lipid-lowering agents. The review showed no evidence for cognitive protection or improvement [216].

The lack of an effective pharmacological treatment may explain why non-pharmacological treatment approaches play a major role in targeting cognitive decline [3, 214, 217, 218]. A systematic review and a meta-analysis investigated the effect of non-pharmacological treatment approaches such as exercise interventions and cognitive interventions for individuals with SCI [214, 217]. Both concluded that high-quality research is missing and found only small effects of group psychological interventions and cognitive interventions [214, 217]. Findings for other lifestyle interventions such as exercise were mixed. The authors concluded that more high-quality research needs to verify the effects of exercise on cognition in individuals with SCI.

The AAN recently updated its guidelines for the treatment of MCI and confirmed that pharmacological interventions lack efficacy [3]. Further, Petersen and colleagues reported that cognitive training may have an effect, but that results concerning the efficacy of exercise interventions were more promising [3]. This accords with research that identified physical inactivity and the lack of physical fitness as major risk factors in the development of cognitive decline [123, 219].

2.4.1. Physical Activity, Exercise and Cognitive Function in Healthy Ageing

The terms *physical activity* and *exercise* are often used interchangeably although they describe different concepts. Physical activity is defined as any bodily movement produced by skeletal muscles that results in quantifiable energy expenditure (e.g. kilocalories). Physical activity is often subdivided into occupational, sports, conditioning, and household or other activities. Exercise is a specific type of physical activity that is planned, structured and repetitive, with the goal of improving or maintaining fitness [220, 221].

Physical activity positively influences cognitive function throughout the lifespan [69, 222, 223]. An active lifestyle and the adoption of physical activity during mid-life (35 to 64 years) maintain or improve cognitive functions with ageing [28, 30, 224]. Therefore, engaging in physical activities is recommended throughout the whole lifespan to maintain good physical and mental health [225, 226]. Besides the evidence associated with an active lifestyle, the consequences of low levels of physical activity support the importance of living actively. Low levels of physical activity are not only associated with poorer overall health and higher incidence of disease and mortality [227, 228], but also is often described as a risk factor for

cognitive decline [229-231]. Previous studies have calculated that physical inactivity may increase the risk for dementia from AD by about 12.7% [123, 219].

Regular physical exercise promotes angiogenesis, neurogenesis and synaptic plasticity [223, 232-234]. Exercise also benefits the cardiovascular and cerebrovascular systems, which are closely associated with maintaining brain health [235]. Even the late adoption of physical activity and engaging in exercise after the age of 65 years has a positive effect on cognitive functions and reduces the risk of dementia [28]. More than 1,000 clinical trials have been designed to improve cognitive functions in healthy older adults [71], and several meta-analyses have summarized their results [70, 236-239].

Most of the meta-analyses report a beneficial effect of various forms of exercise on cognition in healthy older adults [70, 236-239]. Three meta-analyses report a modest to clear effect of aerobic exercise training, defined as cardiovascular fitness training such as walking, biking or jogging [70, 236, 239]. However, Kelly and colleagues reported mixed findings for the efficacy of aerobic exercise interventions [237]. They suggested that these contrasting results might be due to differences in participant profiles, study designs, adherence rates or outcome measures [237]. Besides aerobic exercise training, resistance training and combined resistance and aerobic training consistently improve cognition in healthy older adults [70, 236-238]. A recent meta-analysis by Northey et al. concluded that physical exercise in general can improve cognitive function in older adults [238]. This meta-analysis showed that the type of exercise – the authors analysed the efficacy of aerobic exercise, multicomponent training, resistance exercise and tai chi – is likely not decisive for improved cognitive functions. Rather, the exercise intensity (at least moderate) and exercise duration (at least 45–60 minutes on as many days of the week as possible) is the important factor. Thus, evidence supports the importance of exercise to improve cognitive functions in healthy older adults, but findings are mixed on whether all forms of exercise (resistance, aerobic, combined forms) are equally effective or one mode is superior. Further, no consensus exists on the most efficient design (exercise frequency and intensity) of exercise interventions. Therefore, future studies and reviews should directly compare different exercise modes and designs to identify the most efficient form of exercise to improve cognitive functions in healthy older adults.

2.4.2. Physical Activity, Exercise and Cognitive Function in Individuals with SCI, MCI and PD

A recent systematic review and meta-analysis analysed the effects of non-pharmacologic interventions in older adults with SCI [214]. Three of the included studies used exercise as an intervention [240-242]. These studies reported modestly improved cognition after their respective exercise interventions, which included both aerobic exercise training (i.e. walking and running activities) [241, 242] and a combination of aerobic resistance and stretching exercises [240]. The small positive effects and the limited number of studies warrant further research to verify the efficacy of exercise interventions to improve cognition in individuals with SCI [214]. This current lack of high-quality investigations mirrors the lack of information about physical activity levels of individuals with SCI. De Souto Barreto and colleagues analysed the relationship between physical activity and cognitive functions in older adults with SCI and found a wide range of activity levels among the participants [243]. They reported that leisure-time physical activity was significantly associated with cognitive functions over 3 years [243]. Evidence from previous studies suggests that exercise and physical activities help maintain cognitive functions in individuals with SCI. However, the lack of high-quality investigations merits caution when interpreting results and further investigations.

Previous cross-sectional studies show that moderate activity during mid-life lowers the risk for MCI in later life [244]. Further, Bidzan and colleagues reported that individuals with MCI and lower baseline physical activity levels had developed dementia after 7 years significantly more often than those with higher activity levels [245]. Only limited data currently exists on physical fitness and daily physical activity levels of individuals with MCI. However, early studies indicate that high physical activity levels are important for individuals with MCI to maintain cognitive functions.

The AAN recently updated practice guidelines for the treatment of MCI and noted that exercise is a promising strategy to improve cognitive function [3]. However, this recommendation was underpinned by only two studies that investigated the effect of a 6-month exercise intervention (multicomponent or resistance exercise) on the progression of MCI. The studies demonstrated a positive effect on domain-specific cognitive function (attention and episodic memory) [33, 34]. Further, two systematic reviews both recommend

aerobic exercise as the most effective training to maintain or improve cognitive function in individuals with MCI [35, 36]. Nevertheless, these reviews recommend larger sample sizes, standardised neuropsychological testing, longer intervention periods, and well-defined MCI diagnostic criteria because these methodological issues limited previous studies. Moreover, the two studies cited by the above guidelines included either women only or fewer than 100 participants, which limits their generalizability [33, 34]. Therefore, studies with longer intervention and follow-up periods are required to clarify the long-term effects of exercise, in addition to strict inclusion and exclusion criteria to guarantee the diagnosis of MCI [3].

Individuals with PD tend to have low levels of physical activity and are at a high risk of being sedentary, which might be due to the motor symptoms of the disease [246]. In people with PD, many exercise modes – aerobic training [247-249], resistance training [250-252], forced exercise training [253, 254], dance [255, 256] and balance training [257-259] – improve motor symptoms such as tremor, gait disturbances, postural instability and bradykinesia. Recently published guidelines do not recommend one specific exercise mode [260], and a combination of exercise modes might best improve motor function in individuals with PD [261].

Less is known about the effects of exercise on cognitive function in people with PD, and on the influence of specific exercise modes. Some reviews have suggested that both aerobic and resistance training, or a combination of them, might improve cognitive function [247, 250, 262]. However, others have suggested that various forms of physical activity, including aerobic, resistance and coordination exercises such as Qigong and Tai Chi, have little effect on cognitive function [263, 264]. The wide range of exercise modes used in the studies (i.e. aerobic, resistance & balance training) probably affected the findings. In addition, the exercise-induced benefits on cognitive function might be domain specific (e.g. related to attention, processing speed, executive function, memory, or working memory) [69, 70, 265].

On balance, the literature indicates that exercise benefits the cognitive functions of people with SCI, MCI or PD. Exercise may activate several mechanisms (e.g. physiological, social, mood) to exert the effects. However, high-quality randomised controlled trials with large sample sizes and strict inclusion and exclusion criteria must verify the results of previous studies, and compare the efficacy of different exercise modes. The exercise mode, frequency

and intensity that produce the best effects remain unknown. Whether disease type (e.g. MCI, PD) warrants different exercise interventions also remains unknown.

2.4.3. Mechanisms of Exercise-Induced Benefits for the Brain

2.4.3.1. Brain-Derived Neurotrophic Factor

Cognitive functions during later life apparently depend on preserved brain functions, which a physically active life and exercise support [266]. One mechanism that may explain the effects of physical activity and exercise is an increased level of brain-derived neurotrophic factor (BDNF). BDNF is a neurotrophin that plays a major role in neuronal plasticity [267]. Higher BDNF levels are associated with positive effects on cognitive domains such as spatial [268, 269], episodic [267], recognition [270], and verbal memory domains [271]. Additionally, higher levels of BDNF are associated with better hippocampal functioning [272]. Hence deficits in BDNF may contribute to the development of AD [272, 273].

Exercise induces the expression of BDNF throughout the central nervous system [274], which ultimately stimulates neuroplasticity [275, 276]. A single aerobic exercise session can increase BDNF concentration and regular exercise increases both BDNF expression and resting BDNF concentrations [272, 277]. Nascimento and colleagues compared the cognitive function and BDNF levels of both healthy older adults and individuals with early cognitive impairment with those of a non-exercising control group. After 16 weeks of multimodal exercise training, the intervention groups' cognitive function and BDNF level had increased [278]. In contrast, Maass et al. reported no change in BDNF concentration after a 3-month aerobic exercise intervention. They proposed that the low power of their study or the way they assessed BDNF caused the differences [279]. Differences in exercise protocol such as duration of the intervention may also play a role, which warrants further investigation to demonstrate whether BDNF contributes to improved cognition after exercise [70].

2.4.2.2. Growth Factors

Besides neurotrophins, increased bioavailability of growth factors such as insulin-like growth factor 1 (IGF-1) and vascular endothelial growth factor (VGEF) might stimulate neurogenesis and angiogenesis in the brain. IGF-1 is a single-chain peptide that plays a major role in homeostatic regulation and is essential for growth, development, lifespan control and

ageing [280]. The liver produces most of the body's IGF-1, but paracrine and autocrine glands can also produce it [281]. The activity and concentration of IGF-1 decrease in the process of normal ageing [282]; a greater reduction in IGF-1 level may contribute to cognitive impairment [283].

Exercise may increase IGF-1 levels in older adults [279, 284], probably through stimulating hippocampal neurogenesis [279]. However, a recent systematic review reported mixed results of exercise on both cognition and IGF-1 levels in older adults [285]. Three of the included studies reported improved cognition and higher IGF-1 levels after exercise [286-288], but another three studies reported no change in IGF-1 levels after an exercise intervention [279, 289, 290]. However, cognition did improve in two of those studies [289, 290]. Only one study referenced in the review reported lower IGF-1 levels after an exercise intervention (with no changes in cognition) [289-291]. Therefore, the role of IGF-1 in the improved brain function and cognition evoked by exercise remains unclear. Variations in exercise protocols may contribute to the uncertainty [285].

Besides IGF, VEGF is an important signalling protein involved in the angiogenic process [292, 293]. Many cell types produce VEGF, including platelets and smooth and skeletal muscle cells [294-296]. Previous studies show that exercise increases VEGF concentrations in both animals and humans, and that higher concentration is associated with better cognition [291, 297-300]. Whereas Voss et al. reported an increase in VEGF after a 1-year aerobic exercise intervention (cf. levels of a non-aerobic exercise group) [291], another study found no changes in VEGF concentration and cognition in older adults after a 3-month aerobic exercise intervention [279]. Therefore, exercise duration may play an important role and future studies should investigate the best dose-response relationship.

2.4.2.3. Vascular System Effects

Ageing alters the structure and function of the vascular system [301-304]. Structural changes cause vascular stiffness, impaired endothelial function and increased permeability of the blood-brain barrier, which increase the risk of cognitive impairment [303, 304]. Roberts et al. reported a difference in cumulative incidence of MCI between older adults with (hazard ratio of 1.77) and without cardiac disease [305]. (Cerebro)vascular impairments probably contribute to the underlying aetiology of cognitive impairment and AD [306].

Exercise may reverse or slow down vascular ageing by reducing blood pressure, arterial stiffness, oxidative stress and systemic inflammation, and by improving endothelial function [307]. Further, resting cerebral blood flow is about 17% higher in exercise-trained humans and animals than in matched sedentary controls [308-310]. Improving cerebrovascular function (e.g. increasing cerebral blood flow) might be a key mechanism to protect people from cognitive decline because better cerebrovascular functions are associated with better cognitive functions [311-313].

2.4.2.4. Effect of Exercise Mode on Physiological Mechanisms

The previous sections provided evidence on why exercise in general shows promise in preventing or delaying cognitive decline. However, which exercise mode triggers which physiological mechanisms – and therefore which, or indeed any, exercise modes are most effective – remains unclear.

In healthy older adults, aerobic and resistance exercise affect the brain in different ways. Aerobic exercise improves hippocampal volume, modulated by a higher expression of BDNF [236, 276, 314, 315]. In contrast, resistance exercise more likely produces higher concentrations of IGF-1, with a smaller or no increase in BDNF [315, 316]. Both exercise modes increase synaptic plasticity within the hippocampus after training, which is associated with improved memory [314, 317]. However, one study found that aerobic exercise training activated glutamatergic signalling proteins (e.g. N-methyl-D-aspartate and postsynaptic density protein) whereas resistance exercise training increased the expression of protein kinase C alpha, tumour necrosis factor alpha, and interleukin 1 beta [317]. In addition, animal studies have revealed that aerobic exercise produces neuronal and mitochondrial protection and increases levels of nigrostriatal neurotrophic factor [318].

Besides aerobic and resistance exercises, coordination exercises may increase the volume of the hippocampus and the basal ganglia (globus pallidus) in healthy older adults [319-321], possibly via the ‘vestibular pathway’. Coordination (e.g. balance) exercises often engage the vestibular system, which not only contributes to spatial cognition but also anatomically connects to the medial-temporal lobe (e.g. hippocampus) and to parieto-temporal cortical networks [322, 323]. This vestibular pathway may also trigger the striatum [322], which is part of the basal ganglia.

Apart from exercise mode, exercise intensity, duration and frequency, and the specific characteristics of different populations (e.g. individuals with cognitive impairment or PD), may be important. For example, previous reviews have concluded that cerebral blood flow benefits most from moderate exercise intensities rather than higher or lower ones [324, 325]. The reviews also showed that sex alters the effects of exercise on the vascular system.

Although research suggests various exercise-induced mechanisms improve cognition, direct comparisons of exercise modes are needed. We also need more insight into exercise intensity, duration and frequency in order to formulate the best treatment approaches.

2.4.2.5. Social and Mood Effects of Exercise

Besides changes in physiological mechanisms, exercise also produces environmental enrichment, particularly social enrichment, which might help prevent cognitive decline [326-328]. As many physical activities are social activities (e.g. group training), they directly increase social participation and interaction. In general, higher levels of social activities lower the risk of future cognitive decline, which may indicate a secondary beneficial effect of higher physical activity levels [329, 330]. That is, the risk of social isolation is higher in cognitively impaired individuals, which increases the risk of progression to dementia [331-333]. Previous studies have shown that higher physical fitness increases self-confidence, which in turn may increase social participation [334, 335]. Therefore, improving physical fitness may not only benefit cognitive function, but may also be a driving force for a socially integrated and fulfilling later life – especially in individuals at risk of cognitive decline.

Another hypothesis for the effect of exercise on cognitive performance is associated with mood. Depression and cognitive impairment often coexist and influence each other [336-339]. However, whether cognitive impairment swings mood toward depression, or vice versa, is unclear [340, 341]. Exercise and increased physical activity levels are evidence-based treatment approaches for depression [342, 343]. Hence, they may also contribute to improved cognitive performance.

Social and mood effects evoked by exercise and physical activity may represent two further reasons why exercise shows promise in improving cognitive function. However, the impact of these effects remains unclear.

2.5. Cognitive Function Assessment

Cognitive functions are a primary outcome measure in many intervention studies to evaluate the efficacy of treatment approaches. Previous reviews and meta-analyses to systematically review and analyse the effect of intervention studies on cognitive performance have criticised the lack of uniform assessment methods [344, 345]. For example, Young et al. reported that more than 40 different cognitive tests were used in the studies included in their review [345]. Therefore, they recommended that researchers should agree on valid assessment batteries. Similarly, the AAN recently demanded uniform reporting of study outcomes [3]. Unfortunately, a gold standard test battery to assess and diagnose subjective and mild cognitive impairment does not exist.

A wide variety of neuropsychological tests that rely on measures of task performance are used. To evaluate cognitive functions with these performance-based measures, only validated and standardised measurements with population-based normative data should be used. This allows evaluation of an individual's performance against an appropriate comparison group [89]. Even though single tests can detect subtle changes in cognitive functions, they are also prone to false positives. Approximately 20% of healthy older adults without any cognitive complaints score within the impaired range on at least one measure when tested with an extensive neuropsychological battery [20, 21, 346, 347]. To minimise false positive errors, multiple neuropsychological tests at multiple time points are recommended [15-17]. The tests can be combined into an overall score to provide a psychometrically more reliable and thus more valid construct [348].

A weakness of neuropsychological measures is that they can be influenced by interpersonal and intrapersonal factors of both the assessor and the subject (e.g. motivation, agitation or social desirability) [349, 350]. In addition, the measures are often not sensitive enough to detect subclinical impairment. In the search for sensitive, objective and reliable tests, neuroimaging techniques and laboratory tests have gained importance [8, 20, 21].

MRI, for example, functional MRI, and molecular imaging techniques such as positron emission tomography are widely recognized. These imaging techniques are often used to determine biomarkers of AD [8, 351]. Longitudinal studies also use them to assess adaptations to physical exercise [268]. Unfortunately, not all individuals are suitable for these

methods (e.g. due to pacemakers or other medical metal devices, or claustrophobia) [352]. Further, these methods have high material costs and require specially trained operators.

2.5.1. Electroencephalography

Electroencephalography (EEG) presents a valid, non-invasive and cost-effective method to record electrical activity in the brain. EEG measures fluctuations in voltage with electrodes placed along the scalp. The flow of ions in the neurons of the brain causes the voltage fluctuations [353].

EEG appears to correlate with a number of cognitive functions, which are reflected by the different frequencies recorded (delta, theta, alpha, beta and gamma) [354]. Delta oscillations are associated with inhibitory processes and attention [355], whereas theta oscillations reflect communications within the hippocampus, which is mainly associated with memory [356, 357]. In addition to delta and theta oscillations, alpha oscillations, the dominant oscillations in the human brain, also reflect memory [358] and attentional processes [359]. Also, alpha oscillations probably reflect perception. Gamma oscillations closely relate to attentive processing [360], active maintenance of memory contents [361], and conscious perception. In contrast, beta oscillations are mainly associated with motor [362] or sensorimotor [363] tasks.

Researchers have used resting-state EEG in studies of healthy elderly people, patients with AD, and patients with prodromal stages of dementia. These studies discovered participants with MCI had impaired theta, rather than alpha, band frequencies [364]. They also identified that an upper/low alpha power ratio could predict MCI due to cortical thinning and less perfusion in the temporoparietal area [365]. Previous studies showed that global cognitive functions (analysed with the MoCA) correlated with EEG signalling. The delta:theta ratio and the delta:alpha ratio correlated negatively with the scores on the MoCA. That is, higher ratios reflected poorer cognitive outcomes [366].

Besides resting-state EEG, studies often use so-called event-related potentials (ERPs) as real-time correlates of specific cognitive processes. Using ERPs enables researchers to analyse the relationship between cognitive processes and changes in electroneurophysiology [367]. Common tasks to determine cognitive functions with EEG are the Flanker Task and the Oddball Paradigm. The Flanker Task is an inhibition test, which assesses the ability to

suppress responses. During the Flanker Task participants must respond to a visual stimulus while ignoring the task-irrelevant flankers [368]. The Oddball Paradigm uses a presentation of repetitive stimuli, which are frequently interrupted by a different stimulus. Participants must react to this new stimulus and their reaction time is recorded. The Oddball Paradigm describes cognitive processing and is associated with attention [369, 370] and memory [371]. Long-latency ERPs mostly describe changes in cognitive function. For example, one study used long-latency ERPs to assess and differentiate cognitive slowing in healthy older adults and individuals with dementia. Differences between these two groups were described by specific features of the ERPs such as a delay in P300 latency [371]. A current systematic review identified the Oddball Paradigm as a promising test to differentiate between healthy older adults and individuals with MCI [20]. The authors emphasised the utility of specific components (P300 and N200) to discriminate between healthy cognitive ageing, MCI and AD. However, reference values for these groups are needed, along with comparisons between individuals with SCI and the other populations.

2.6. Summary

Cognitive decline is one of the major health challenges in coming years. Ageing and age-related diseases affect cognitive functions. Hence, the ageing population worldwide demands effective treatment approaches. Exercise interventions have gained popularity over the past decade because of promising results in healthy older adults. Exercise interventions may trigger both neurophysiological and social mechanisms. However, we currently know little about the effects of exercise in older adults at high risk for dementia, such as individuals with MCI. Unfortunately, the quality of previous research studies is only modest. For example, they often lacked statistical power because of limited sample sizes. In addition, intervention periods were often short (e.g. 6 months). Thus, the effect of exercise in this population remains under-examined. Besides the lack of quality in previous studies, we know little about the effects of different exercise modes. Previous studies lacked direct comparisons of exercise modes in individuals at high risk for cognitive decline. Therefore, we need high-quality studies that directly compare exercise modes and overcome the limitations of previous studies. Such studies would help us to better understand the effects of exercise in individuals at risk of dementia, and may help to develop effective treatments to prevent further cognitive decline.

3. CARDIORESPIRATORY FITNESS AND COGNITIVE FUNCTION ARE POSITIVELY RELATED AMONG PARTICIPANTS WITH MILD AND SUBJECTIVE COGNITIVE IMPAIRMENT

Chapter 3 includes the following manuscript:

Cardiorespiratory Fitness and Cognitive Function are Positively Related Among Participants with Mild and Subjective Cognitive Impairment

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Student contribution to work: Involved in the conception of the study, collected all data, analysed and interpreted data, was responsible for writing all drafts of the manuscript including preparation of all figures and tables, and modified drafts following co-author recommendations.

Conceived and designed the experiment: TS, VA, TV, MOR, BL, SS

Analysed the data: TS, CDA, SS

Wrote/reviewed the paper: TS, CDA, SR, MCP, VA, TV, AK, MOR, BL, SS

3.1. Abstract

Background: By 2030 about 74 million people will be diagnosed with dementia, and many more will experience subjective (SCI) or mild cognitive impairment (MCI). As physical inactivity has been identified to be a strong modifiable risk factor for dementia, exercise and physical activity (PA) may be important parameters to predict the progression from MCI to dementia, but might also represent disease trajectory modifying strategies for SCI and MCI.

Objective: A better understanding of the relationship between activity, fitness and cognitive function across the spectrum of MCI and SCI would provide an insight into the potential utility of PA and fitness as early markers, and treatment targets to prevent cognitive.

Methods: 121 participants were stratified into three groups, late MCI (LMCI), early MCI (EMCI), and SCI based on the Montreal Cognitive Assessment (MoCA). Cognitive function assessments also included the Trail Making Test A+B, and a verbal fluency test. PA levels were evaluated with an interviewer-administered questionnaire (LAPAQ) and an activity monitor. An incremental exercise test was performed to estimate cardiorespiratory fitness and to determine exercise capacity relative to population normative data.

Results: ANCOVA revealed that LMCI subjects had the lowest PA levels (LAPAQ, $p=0.018$; activity monitor, $p=0.041$), and the lowest exercise capacity in relation to normative values ($p=0.041$). Moreover, a modest correlation between MoCA and cardiorespiratory fitness ($r=0.25$; $p<0.05$) was found.

Conclusion: These findings suggest that during the earliest stages of cognitive impairment PA and exercise capacity might present a marker for the risk of further cognitive decline. This finding warrants further investigation using longitudinal cohort studies.

3.2. Introduction

Worldwide, over 46 million people live with dementia, and this is expected to rise to about 74 million by 2030. The prevalence of mild cognitive impairment (MCI), which is a risk state for dementia [6], is about 4 % in community-dwelling older adults aged between 50 - 80 years [2]. As such, cognitive decline, dementia, and Alzheimer's disease (AD), add to the significant economic impact of an ageing population [178], and are identified as global health and healthcare priorities [1]. There is growing recognition of the importance of the early detection of cognitive decline, such as subjective cognitive impairment (SCI), which is associated with an increased risk to progress to MCI and dementia [5, 13]. There has also been a shift in research efforts to identify possibly reversible risk factors that are associated with, and present during, the stages of SCI [131] and MCI [2].

Various modifiable risk factors (e.g. physical inactivity, mid-life hypertension) have been identified as potentially contributing to the development of AD [219]. Of these, physical inactivity has been identified as the strongest independent risk factor, accounting for up to 12.7% of the risk of AD [123, 219]. Furthermore, an active lifestyle and the adoption of physical activity (PA) during mid-life (35 to 64 years) and even after the age of 65 years maintain or improve cognitive function in ageing and reduce the risk of AD [27-31]. A longitudinal study reported that participants with MCI are more likely to develop dementia after 7 years if they reported being previously inactive [245]. This indicates that differences in daily PA levels among participants with MCI might be an important parameter to predict further cognitive decline.

To date there is limited data available on the daily PA levels of participants with MCI and SCI. While cognitive impairment leads to less activity on average compared with healthy older adults, this finding does not take into account the broad range of activity levels, which ranges from no PA up to relatively high levels of PA among individuals with SCI [372] and MCI [373]. Previous studies have often been limited by the use of indirect methods of PA assessment [28, 245, 372, 373]. Furthermore, the relationship between PA and cognitive function in participants with MCI or SCI is not clear. Some studies reported no correlations between PA and cognitive function [29, 372], whereas another study reported a weak relationship between daily leisure-time PA, and cognitive function [243]. A better understanding of the relationship between activity and cognition, particularly among those

in the earliest stages of cognitive decline, is important to establish if PA might be a potential risk factor and treatment target.

Exercise training and increased levels of PA are associated with an improved cardiorespiratory fitness. Cardiorespiratory fitness may be beneficial for maintaining cognitive function in those at an increased risk for AD [26, 374]. In subjects with AD, a higher cardiorespiratory fitness might improve some aspects of cognitive function (e.g. sustained attention, visual memory [375, 376]. Recently, it has been reported that maximal exercise capacity during mid-life (mean age 59 y), which provides an estimate of cardiorespiratory physical fitness [377, 378], is associated with cognitive function in later life (mean age 77 y) [379]. To date the influence of SCI and MCI on exercise capacity and the relationship with cognitive function has not been determined.

A better understanding of the relationship between PA, cardiorespiratory fitness and cognitive function during the early stages of cognitive decline would provide an insight into the potential utility of PA and fitness as early markers, and treatment targets. Therefore, the primary aim of the present study was to compare PA levels, exercise capacity and cardiorespiratory fitness between older adults across the spectrum of SCI and MCI, and to assess the strength of the relationship between these physical characteristics and cognitive function. It is hypothesised that lower levels of PA and of exercise capacity are reflected by lower cognitive performance levels across the spectrum of SCI and MCI.

3.3. Materials and Methods

3.3.1. Participants

All participants were recruited through the NeuroExercise Project [352], a multi-centred randomized controlled trial of exercise therapy in participants with MCI across three European countries. For the purpose of the present sub-study, the participants were recruited in Germany at the German Sport University (GSU). The study was conducted in accordance with the declaration of Helsinki (1975) and approved by the research ethics committee of the GSU. Participants were recruited through newspaper advertisements and editorials. All participants provided their informed consent to the study procedures.

Participants were initially interviewed via telephone and were required to meet the following eligibility criteria, which has been published elsewhere [352]. For the purpose of this study, persons with a MOCA score >25, who reported memory impairments but did not meet the clinical criteria for MCI used in the NeuroExercise Project, were included in this substudy as participants with subjective cognitive impairment (SCI). 121 participants met the inclusion criteria and were stratified into three different groups depending on their MoCA scores. Group 1 included those with late mild cognitive impairment (LMCI), group 2 included participants with early MCI (EMCI), and group 3 included participants with SCI (SCI) (Table 1).

Table 1: Characteristics of the total sample and subgroups

Group	**LMCI (MoCA 19-21)**	**EMCI (MoCA (22 - 25)**	**SCI (MoCA > 25)**
Sample Size[#]	121	21	64	36
Age, (years) *	72.6 ± 6.3	75.0 ± 5.1	73.6 ± 5.97	69.3** ± 6.39
Sex	64 f	6 f	35 f	23 f
Education (years[+])	2.7 ± 0.58	2.7 ± 0.57	2.7 ± 0.65	2.7 ± 0.45
MoCA* (mean scores)**	24.0 ± 2.4	20.2*** ± 0.8	23.7*** ± 1.0	27.0*** ± 0.9
MoCA-MIS* (mean scores)**	7.79 ± 3.9	4.4*** ± 2.8	7.4*** ± 3.6	10.5*** ± 3.3
calculated MMSE* ***(mean scores)***	28.15*** ± 1.2	26.24*** ± 0.83	28.11*** ± 0.62	29.33*** ± 0.48

Data are mean ± SD. [+]Education level was assessed using categorical levels (1 = less than 10 years of education; 2 = between 10-13 years of education, 3= more than 13 years of education). Abbreviations: MoCA = Montreal Cognitive Assessment; calculated MMSE = Mini Mental State Examination, scores were calculated based on the individual MoCA score; f = female; * = significant difference between the groups; **= significantly younger than the other groups ($p < 0.05$); *** = significant differences between all of the groups ($p < 0.001$); LMCI = late mild cognitive impairment; EMCI = early mild cognitive impairment; SCI = subjective cognitive impairment; [#] = data for the activity monitor and the incremental exercise test could not be generated for all participants (see missing data).

3.3.2. Study overview

The participants attended two appointments for the assessment of cognitive function, exercise capacity, and daily activity levels. During their first visit the participants underwent a neuropsychological test battery. This consisted of five different tests - the Montreal Cognitive Assessment (MoCA) [73], the Trail Making Test (TMT) A and B [380], and two tests for verbal fluency [89]. The Longitudinal Aging Study Amsterdam Physical Activity Questionnaire (LAPAQ) [381] was used to assess daily PA levels. At the end of their first visit the participants were instructed to wear a watch with an activity monitor (Polar M400©, USA) for the assessment of PA over seven consecutive days. During the second visit, the participants performed an incremental exercise test on a cycle ergometer (Ergoline er900©, Bitz, Germany) for the determination of maximal exercise capacity and the estimation of cardiorespiratory fitness ($\dot{V}O_2peak$).

3.3.3. Cognitive function assessment

The MoCA is a 12-item test with scores from 0 to 30, where higher scores indicate better cognitive function. MoCA scores from 17 to 25 or from 19 to 25 have previously been used to delineate MCI [73, 382], although test sensitivity has been shown to be improved using lower cut-off scores of 22-23 [383-385]. To enable comparisons between participants across the spectrum of SCI and MCI, we adopted the lower cut-off score and stratified the sample into three groups (see *Participants*): 1) LMCI (late MCI, score 19-21) [383]; 2) EMCI (early MCI, score 22-25); 3) SCI (SCI, score > 25).

Besides MoCA total score, the MoCA memory index score (MoCA-MIS) was calculated to evaluate verbal episodic memory, which is a sensitive factor to discriminate between early and late MCI [386, 387]. The MoCA-MIS is calculated by adding the number of words in free delayed recall, category-cued recall, and multiple choice-cued recall. The number of words are multiplied by 3, 2 and 1, respectively, with a total MoCA-MIS between 0-15 [388]. Furthermore, we used the equi-percentile equating method with log-linear smoothing to calculate Mini Mental State Examination (MMSE) scores for our participants based on the individual MoCA scores [74, 382]. The MMSE is a common screening tool used by many studies with SCI and MCI. Although the MMSE lacks sensitivity and specificity to detect

MCI in comparison to the MoCA [73, 382], it is still widely used to assess cognitive function and will therefore allow further comparisons to other studies in the field of interest.

The TMT A and B are validated neuropsychological tests, which assess speed of processing and executive function [380]. In Part A, the participants were required to connect numbers in ascending order from 1 to 25. In Part B, the participants were instructed to connect numbers and letters in alternating and ascending order (e.g. 1 - A - 2 - B - 3 - C, etc.). A mistake made by the participants was immediately pointed out by the test administrator and was corrected before proceeding. Both tests were completed as fast as possible and the time taken to complete the tests was measured.

The verbal fluency test is a short test of verbal functioning, which typically consists of two tasks [89]. These tasks are letter fluency [389], and category fluency [390]. For both tasks participants were given 1 minute to produce as many unique words as possible either starting with a given letter (letter fluency) or unique words within a semantic category (category fluency). The participant's score was the number of unique correct words in each task. All cognitive function assessments were administered in-person by a trained researcher and supervised by an experienced neuropsychologist.

3.3.4. Physical activity assessment

Self-reported PA was assessed using the LAPAQ, which is a valid and reliable interview-administered questionnaire, and captures PA across six categories (walking outdoors, bicycling, gardening, light household activities, heavy household activities, and sport and exercise activities) over the preceding 14 days [381]. Mean daily activity scores, and mean time spent in sport and exercise activities were calculated by summing the reported activities in minutes and dividing those by the number of days.

Daily PA levels were also objectively assessed using the activity watch. The GPS watch is equipped with a triaxial accelerometer, which uses wrist movements to calculate distance walked per day (in km) as an objective measure of PA [391, 392]. The activity monitor was worn on the non-dominant arm for seven consecutive days to sample behavior on both week and weekend days [391]. The participants were asked to wear the activity monitor 24 hours a day. Only days with ≥10 hours of captured data, and only data-sets with ≥7 days of valid data were included for analysis [391]. Distance walked per day (in km) has been shown to be

validly measured by the activity monitor [393] and demonstrates a proxy for steps per day [392].

3.3.5. Exercise capacity and estimated cardiorespiratory fitness

An incremental exercise test was performed on an electronically braked cycle ergometer (Ergoline, type er900©, Bitz, Germany) under the supervision of a cardiologist. The progressive exercise test commenced with 3 min of unloaded cycling followed by step increments of 25 W every 2 min in accordance with clinical guidelines [394]. 12-lead electrocardiography (ECG) and heart rate (HR) were monitored throughout the test. Blood lactate levels from earlobe capillary samples, and rating of perceived exertion (RPE) [39] were assessed during the final 30 s of each stage. The participants continued to exercise until their volitional maximum and to the point where they were unable to maintain the required pedal cadence with increasing exercise intensity.

Exercise capacity was defined as the peak power (W) reached at final stage and was used to estimate cardiorespiratory fitness using the following equation ($\dot{V}O_2peak$ = (exercise capacity (W) / weight (kg)) * 10.8 + 3.5 + 3.5) [395]. To determine exercise capacity relative to population normative data, we calculated reference scores for exercise capacity using the following equation from a cross-sectional epidemiologic survey of the local population in Germany (Males: reference exercise capacity (W) = -103.512 - 1.5576 * Age + 2.2114 * Height - 0.1198 * Weight. Females: reference exercise capacity (W) = -80.628 - 0.7698 * Age + 1.4038 * Height + 0.2873 * Weight) [396, 397]. Exercise capacity was subtracted from the reference score. This parameter is referred to as relative exercise capacity.

3.3.6. Missing data

121 participants completed the neuropsychological test battery and the LAPAQ during their first visit to the GSU. Valid PA monitor data sets were collected for 84 of the 121 participants, with many participants unfortunately failing to wear the activity watch for the required daily periods. The incremental exercise test was completed sufficiently by 86 of the 121 participants. 12 participants were not given clearance by the cardiologist to undertake the test due to uncontrolled hypertension or irregularities in their resting ECG; for 7 participants, the test was terminated prior to their maximum because of adverse blood pressure, ECG or

symptomatic responses; and in 16 cases the participants did not meet the criteria for maximum effort. There were no differences in baseline characteristics and cognitive function between those with complete and incomplete data sets within each of the study subgroups, and therefore all data have been included for analysis.

3.3.7. Statistical analysis

Data were analysed using IBM SPSS Statistics 23©. Variables pertaining to cognitive function (TMT A + B, letter and category fluency), the PA assessment (LAPAQ + activity monitor), exercise capacity and estimated cardiorespiratory fitness (exercise capacity, estimated $\dot{V}O_2$peak, RPE, heart rate, blood lactate levels, and relative exercise capacity) were compared between the three groups by one-way univariate ANCOVA analysis with age and sex as covariates. Post-hoc pairwise comparisons between groups were performed using Fisher's least significant difference (LSD). Additionally, Spearman correlation was used to determine the strength of relationships between estimated $\dot{V}O_2$peak, relative exercise capacity and the MoCA, as well as its memory index score (MoCA-MIS). Furthermore, Pearson's correlation was used to assess correlations between the PA assessment, $\dot{V}O_2$peak and relative exercise capacity. Data are presented as means ± standard deviations, and p values < 0.05 were regarded as statistically significant.

3.4. Results

3.4.1. Cognitive Function

Group differences were found for category fluency ($F_{(2,119)} = 10.355$; $p < 0.001$), TMT A ($F_{(2,120)} = 11.690$; $p < 0.001$), and TMT B ($F_{(2,120)} = 14.988$; $p < 0.001$), but not for letter fluency ($F_{(2,120)} = 2.955$; $p = 0.56$). Post-hoc pairwise comparisons revealed lower cognitive function for category fluency in LMCI than EMCI and SCI. Additionally, post-hoc comparisons showed that EMCI had lower cognitive function than SCI in category fluency (Fig 3). Significant differences were also found for the TMT A and TMT B test where LMCI needed significantly longer to complete both Trail Making tests than the other two groups. Furthermore, EMCI needed significantly more time to complete the TMT A than SCI (Fig 3).

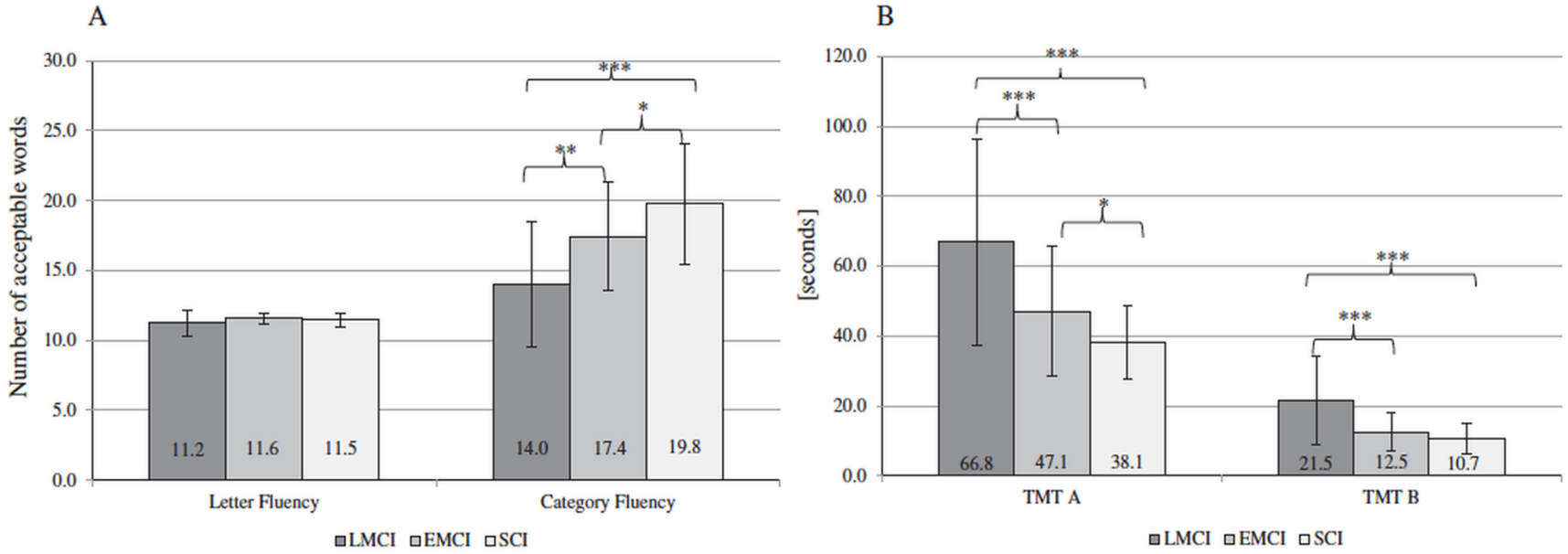

Figure 3: Results of the cognitive function assessment (* = $p < 0.05$, ** = $p < 0.01$, *** = $p< 0.001$), sMCI = severe mild cognitive impairment, mMCI = moderate mild cognitive impairment, SCI = subjective cognitive impairment); A) Verbal fluency tests (category + letter fluency; B) Results of the Trail Making Test (TMT) A + B (total means were divided by 10 for a clear depiction in this figure); * = $p < 0.05$, ** = $p < 0.01$, *** = $p< 0.001$).

3.3.2. Physical Activity Assessment

Differences between the groups were found for mean daily activity scores (LAPAQ, $F_{(2,120)} = 4.169$; $p = 0.018$), and average distance walked per day (activity monitor, $F_{(2,83)} = 3.878$; $p = 0.025$) but not for mean time spent in sports and exercise activities ($F_{(2,120)} = 2.885$; $p = 0.60$, subcategory of the LAPAQ). Post-hoc pairwise comparisons revealed that LMCI had lower mean daily activity scores (LAPAQ) than EMCI ($p = 0.006$) and SCI ($p = 0.036$). Furthermore, LMCI had a lower average distance walked per day (4.4 ± 2.4 km) in comparison to EMCI (6.4 ± 2.7 km, $p = 0.007$), but not SCI (5.9 ± 2.5 km $p = 0.089$). Means and standard deviations are presented in Table 2.

3.4.2. Exercise capacity and estimated cardiorespiratory fitness

No differences were found for exercise capacity ($F_{(2,85)} = 0.192$; $p = 0.825$), $\dot{V}O_2$peak ($F_{(2,85)} = 1.009$; $p = 0.369$), RPE ($F_{(2,85)} = 1.477$; $p = 0.236$), HR ($F_{(2,85)} = 0.117$; $p = 0.890$), and blood lactate level ($F_{(2,84)} = 0.631$; $p = 0.535$). Relative exercise capacity differed significantly between the groups ($F_{(2,85)} = 3.321$; $p = 0.041$), with post-hoc test showing LMCI to have a lower relative exercise capacity than EMCI and SCI (s. Table 2). The detailed results (means and standard deviations) can be seen in Table 2.

Table 2: Data of physical activity and physical fitness assessment

Group	**LMCI**	**EMCI**	**SCI**
Exercise capacity (W)	94.74 ± 37.8	104.02 ± 36.6	114.58 ± 44.5
Estimated $\dot{V}O_2$peak (ml kg-1 min-1**)**	20.2 ± 5.6	22.6 ± 4.8	23 ± 5.1
Rating of perceived exertion	16.5 ± 2.4	16.7 ± 2.5	17.7 ± 2.3
Heart rate (bpm)	123.4 ± 26.7	126.5 ± 24.8	134.7 ± 21.1
Blood lactate (mmol)	4 ± 1.9	4.7 ± 5.9	4.5 ± 2.0
Relative exercise capacity (W)	-46.38 *# ± 39.16	-24.18 ± 25.20	-20.9 ± 21.02
LAPAQ (min)	163.57*# ± 135.95	270.09 ± 157.09	239.78 ± 153.10
LAPAQ - Sports & Exercises (min)	12.79 ± 21.24	24.27 ± 29.78	14.42 ± 13.98
Activity monitor ***Average distance walked per day*** *(km)*	4.4* ± 2.4	6.4 ± 2.7	5.9 ± 2.5

The data presents peak data of the incremental exercise test, mean daily activity levels (LAPAQ), mean daily time spent in sports and exercises, and mean distance walked per day; * = significant difference to EMCI ($p < 0.05$); # = significant difference to SCI ($p < 0.05$); LAPAQ = Longitudinal Aging Study Amsterdam Physical Activity Questionnaire, LMCI = late mild cognitive impairment, EMCI = early mild cognitive impairment, SCI = subjective cognitive impairment; km = kilometer.

3.4.3. Correlations

Spearman correlation revealed a significant correlation between the MoCA scores and estimated $\dot{V}O_2$peak ($r = 0.245$, $p = 0.022$), as well as between the MoCA and relative exercise ($r = 0.228$, $p = 0.035$) capacity. Indicating that a higher cardiorespiratory fitness and better exercise capacity were reflected by a better cognitive performance (Fig. 4). Furthermore, a positive correlation was found between estimated $\dot{V}O_2$peak and average distance walked per day ($r = 0.266$, $p = 0.027$), but not between mean daily activity levels (LAPAQ) and $\dot{V}O_2$peak ($p = 0.600$) or between $\dot{V}O_2$peak and mean time spent in sports and exercise activities ($p = 0.545$, subcategory of the LAPAQ). Relative exercise capacity had a modest positive correlation with average distance walked per day ($r = 0.321$; $p = 0.008$), but not with the outcomes of the self-reported activity questionnaire ($p = 0.384$) or its subcategory ($p = 0.651$).

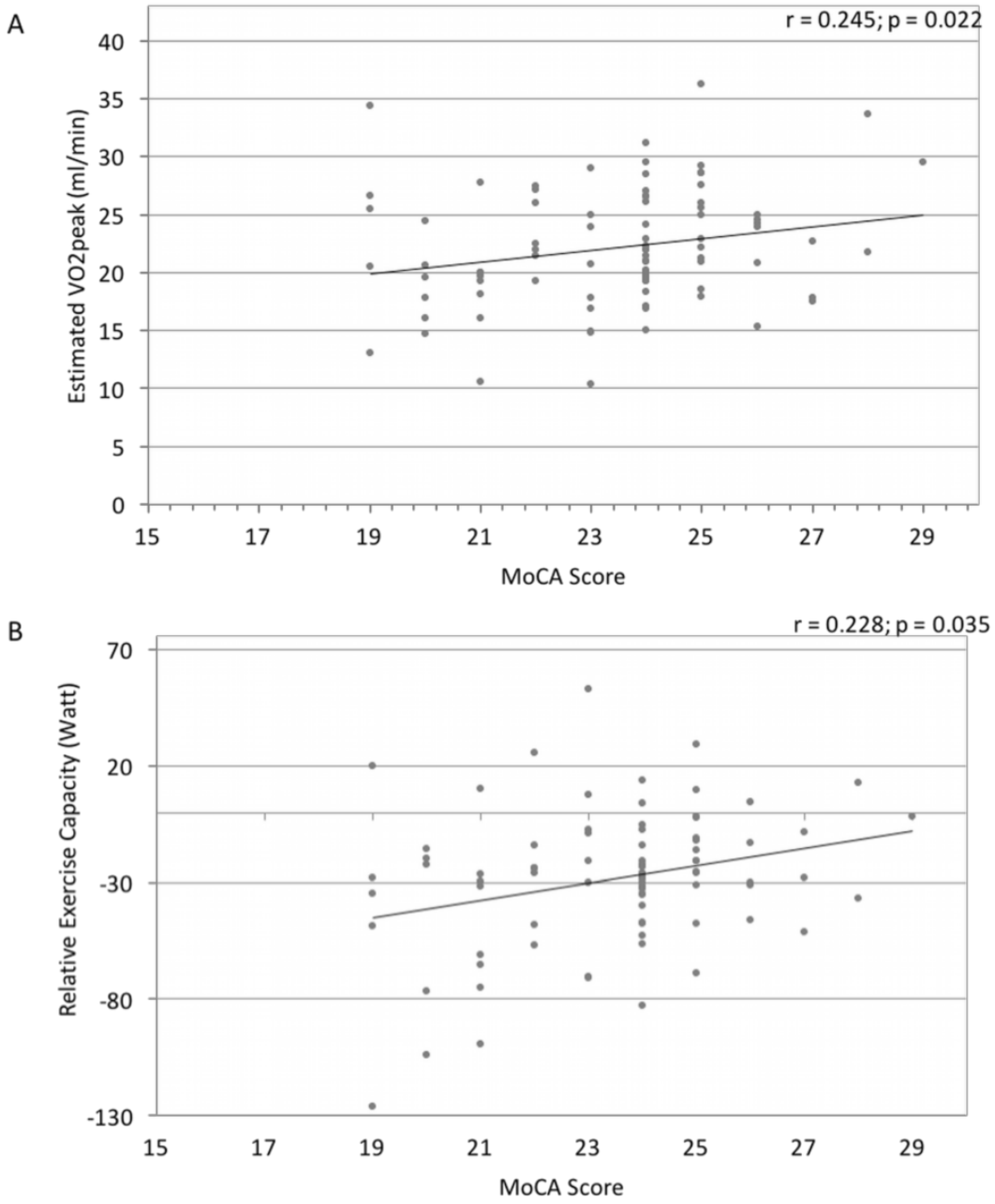

Figure 4: Correlation between estimated $\dot{V}O_2$peak and cognitive function (Montreal Cognitive Assessment (MoCA) score (A)); Correlation between relative exercise capacity and cognitive function (MoCA score) (B).

3.5. Discussion

We assessed physical activity (PA) levels and exercise capacity across a group of participants with mild cognitive impairment (MCI) and subjective cognitive impairment (SCI). The main

finding of this study was that a greater cognitive impairment (LMCI) was reflected by significantly lower PA levels and a lower exercise capacity across the spectrum of SCI and MCI. Furthermore, we observed a modest correlation between cognitive function and estimated $\dot{V}O_2$peak, as well as relative exercise capacity, but not between self-reported daily activity levels and cognitive function.

In this study, we compared three groups of participants across the spectrum of SCI and MCI. There is some inconsistency in the reported MoCA cut-off scores for MCI [73, 383], and on this basis, we applied a novel criteria to stratify participants to SCI, EMCI, or LMCI. We estimated MMSE scores, which have been previously used to describe participants with EMCI and LMCI, using every participant's individual MoCA score. The estimated MMSE scores were quite similar to the ones published by Lee et al. [398]. Furthermore, the three groups performed significantly different in the Trail Making Tests, the category fluency tests and their MoCA memory scores, which are another sensitive factor to discriminate between early and late MCI [387, 388]. As expected, LMCI demonstrated the worst cognitive function followed by EMCI and then SCI on all tests of the neuropsychological test battery. This follows the definition that participants with EMCI show milder degrees of cognitive impairment than participants with LMCI [399]. Interestingly, our verbal fluency tasks showed varying results, with significant differences among the groups in the category, but not the letter fluency task. Our results extend previous findings, which showed that even between participants with AD and healthy controls often only category fluency differs significantly[400]. We suggest, that differences across the spectrum of SCI and MCI can rather be determined by semantically demanding tasks (category fluency) than phonemic tasks (letter fluency) [401].

Our findings showed that the results of the cognitive tests were mirrored by the results of the PA assessment. LMCI had the lowest activity levels (LAPAQ and activity monitor) compared to the other two groups. This extends previous findings that activity levels are lower in people with MCI compared with healthy adults, and lower again in people with AD [373]. Gagliardi et al. reported a wide range of PA levels among individuals with MCI [373], and our findings show that this range of activity levels is related to cognitive function. It has previously been shown that low levels of engagement in PA are associated with the development of AD among people with MCI over a seven year follow up period [245]. Our

findings raise the possibility that physical inactivity might also be a contributing risk factor for the progression from subjective and mild cognitive impairment to severe MCI.

Previous studies of PA among people with MCI and healthy older adults have usually relied on self-reported activity recall questionnaires [245, 373, 402, 403]. These subjective methods are open to reporting bias, and older adults aged 65-84 years tend to overestimate PA time in comparison to objectively measured accelerometer data [404]. Aadahl et al. [405] pointed out that the so-called social desirability response bias might be responsible for this, because of the known benefits of PA and exercise in the population. Therefore, we suggest using objective measurement devices to assess PA. The use of the activity monitor was a strength of the current study, although it is acknowledged that use of an activity monitor also has the potential to positively influence activity behaviors [406].

In line with their lower activity levels, we observed that the LMCI group had a lower relative exercise capacity than the EMCI and SCI groups and tended to have a lower estimated cardiorespiratory fitness. The use of relative exercise capacity presented an opportunity to report differences in exercise capacity between the groups relative to normative values, and thereby take into account each participant's age, sex, height, and weight, which influence exercise capacity and cardiorespiratory fitness [396, 397, 407, 408]. Indeed, small differences in age and sex distribution between the groups may explain why we did not find significant differences in estimated $\dot{V}O_2$peak between the groups. Nonetheless, it is noteworthy that none of the groups in our study met the normative exercise capacity levels for healthy older adults of their age [396, 397]. This is also consistent with the low $\dot{V}O_2$peak values that ranged from 20.2 ml kg-1 min-1 (LMCI) to 23.0 ml/min (SCI), which are lower than population reference values [409, 410]. Exercise capacity and cardiorespiratory fitness are strongly influenced by exercise and PA, and indeed we found a modest correlation between the average distance walked per day (activity monitor) and estimated $\dot{V}O_2$peak ($r = 0.266$, $p = 0.027$), as well as between the distance walked per day and relative exercise capacity ($r = 0.321$; $p = 0.008$). That this relationship was not present for the self-reported daily PA levels reinforces the importance of objective PA assessment.

An important finding was the modest correlation between cognitive function (MoCA) and estimated cardiorespiratory fitness, as well as between cognitive function (MoCA) and the relative exercise capacity. This adds to previous evidence that the large differential in

cognitive function between healthy adults and those with MCI is associated with fitness [26, 374, 411, 412]. Our findings show that this relationship is also present among a cohort ranging from SCI to MCI. Observational evidence in humans associates higher levels of cardiorespiratory fitness and PA with greater brain volume, reduced brain atrophy, and the reduced risk and slower progression of dementia [28, 413-417]. An increase in cardiorespiratory fitness has also been associated with an attenuation of the effects of cerebral amyloid on cognition [26, 412]. Additionally, PA and exercise are known to improve neuroplasticity by the expression of brain derived factor [275, 276] and insulin-like growth factor [418], and increase hippocampal volume [314]. Combined with this evidence, our cross-sectional observations support the notion that cardiorespiratory fitness may be a sensitive marker of cognitive decline, and the progression from SCI to a more severe presentation of MCI. Unlike previous findings, which reported improved spatial memory after aerobic exercise [314], we did not find a correlation between the memory index of the MoCA and cardiorespiratory fitness. We suggest that spatial memory might be correlated to aerobic exercise, but that this might not be the case for verbal episodic memory (MoCA-MIS).

It is tempting to speculate that higher levels of cardiorespiratory fitness, and other factors such as improved neural connectivity [419], might underpin the association between cognitive function and PA observed in the present study. In contrast, we cannot exclude the possibility that the progression of cognitive decline leads to less engagement in PA, e.g. due to a loss of independence and/or overprotection by the individuals' families and carer [420]. Therefore, we cannot exclude a certain threshold effect due to different stages of cognitive impairment (LMCI, EMCI, SCI). Further longitudinal studies are needed to confirm these relationships, and to investigate whether prescribed changes in PA among those with SCI and MCI have positive effects on cognitive function and/or the progression of impairment.

3.5.1. Study limitations

The present study has some limitations. Firstly, the assessment period for the LAPAQ and the PA monitoring were not matched, and therefore comparisons of the two measures is somewhat compromised. However, all participants reported that they undertook their normal activities during the week where PA was assessed using the monitor. Secondly, there was a

small but significant difference in the age of group participants (Table 1) where those with SCI were younger than the other two groups. While this may have biased the results, as age affects cognitive performance and PA [421], we calculated an ANCOVA to statistically control for the effect of age. Still, this cannot completely neglect a significant influence of age. Thirdly, cardiorespiratory fitness was estimated based on the measure of exercise capacity. This was done so as to avoid the need for the collection of expired gasses during exercise, which can sometimes cause anxiety among older participants with cognitive impairment. This estimation assumes a fixed level of oxygen economy for all participants, and has been reported to overestimate $\dot{V}O_2$peak in older subjects [422, 423]. Fourthly, we assessed EMCI and LMCI with the use of the MoCA and estimated MMSE scores. In our opinion, the MoCA is the better tool to detect early cognitive impairments, because its ceiling effect is less and its sensitivity and specificity higher in the detection of mild cognitive impairment [73, 74, 385].

3.5.2. Conclusion

In conclusion, our results showed that within the spectrum of early cognitive decline, the most severely impaired participants were less engaged in PA and had a lower relative exercise capacity. Furthermore, we found a positive relationship between cardiorespiratory fitness and cognitive function across the stages of mild and subjective cognitive impairment. These findings may suggest that PA and especially cardiorespiratory fitness might be sensitive to the changes in cognitive function associated with subjective and mild cognitive impairment. However, it is also possible that people with MCI might select to be less active and are therefore less fit. This cannot be answered by our study. Further research that aims to determine the effect of changes in PA and cardiorespiratory fitness among those with SCI and MCI on cognitive function and/or the progression of impairment are warranted.

4. AUDITORY EVENT-RELATED POTENTIALS IN INDIVIDUALS WITH SUBJECTIVE AND MILD COGNITIVE IMPAIRMENT

Chapter 4 includes the following manuscript which is currently under review:

Auditory Event-Related Potentials in Individuals with Subjective and Mild Cognitive Impairment

Tim Stuckenschneider[a,b], Christopher D. Askew[b,c], Jan Weber[a], Vera Abeln[a], Stefanie Rüdiger[d], Mathew J. Summers[e] & Stefan Schneider[a,b] on behalf of the NeuroExercise study group

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Journal: Behavioural Brain Research, under revision

Author contributions:

Student contribution to work: Involved in the conception of the study, collected all data, analysed and interpreted data, was responsible for writing all drafts of the manuscript including preparation of all figures and tables, and modified drafts following co-author recommendations.

Conceived and designed the experiment: TS, VA, SS

Analysed the data: TS, JW, CDA, MJS, SS

Wrote/reviewed the paper: TS, CDA, JW, VA, MJS, SS

4.1. Abstract

Objective: The analysis of event-related potentials (ERPs) is a useful tool to differentiate between healthy older adults, and individuals with mild cognitive impairment (MCI). Less is known about the ERPs' sensitivity of differentiating between individuals with subjective cognitive impairment (SCI) and MCI, as early evidence indicates similar brain alterations between these two groups. In order, to establish tests that are sensitive to subclinical impairment, this study compared auditory evoked ERPs between individuals with SCI and MCI.

Methods: Besides assessing cognitive performance in four neuropsychological tests (Trail Making Test A + B, verbal fluency letter and category task), latency and amplitude of ERP components evoked by an auditory oddball paradigm were compared between two groups of either individuals with SCI (n=13) or MCI (n=13).

Results: While individuals with MCI performed significantly worse in all neuropsychological tests (TMT A: $p=0.001$, Cohen's $d=1.5$; TMT B: $p=0.030$, Cohen's $d=0.94$; verbal fluency letter: $p=0.0011$, Cohen's $d=1.08$; verbal fluency category: $p=0.038$; Cohen's $d=0.86$), no significant differences ($p>0.05$) were found in ERP components with small to moderate effect sizes (Cohen's d ranged between 0.11 – 0.59).

Conclusion: ERPs evoked by an auditory oddball paradigm lack sensitivity to differentiate between individuals with SCI and MCI, although significant differences in cognitive performance were detected by neuropsychological tests. Similar pathophysiological brain alterations may limit utility of ERPs as indicated by previous research and results of this study. Cognitively more challenging tasks than the auditory oddball paradigm may be considered by future investigations.

4.2. Introduction

Currently, over 46 million people are living with dementia, and its prevalence will continue to increase exponentially throughout the coming years [137]. The G8 Summit on dementia identified the significant economic impact and financial burden of dementia on healthcare systems as a major challenge into the future [1, 178]. As accurate early detection of cognitive impairment may enable the application of interventions earlier in the disease process and increase the efficacy of dementia treatment, research efforts have shifted towards the accurate diagnosis of early stages of cognitive decline [129]. It has been suggested that subjective cognitive impairment (SCI), mild cognitive impairment (MCI), and Alzheimer's disease represent different stages of the spectrum of disease progression, with SCI and MCI being the early stages of interest [3, 5-7].

Included in the diagnosis of both SCI and MCI is the self-report of subjectively experienced cognitive problems. The diagnosis of MCI requires additional objective evidence of subclinical cognitive impairment as assessed using standardised and normative-referenced neuropsychological measures; however, a gold-standard neuropsychological test that is sensitive to subclinical impairment is not currently in place [3, 14, 15]. Further, approximately 20% of healthy older adults without any cognitive complaints score within an impaired range on at least one measure when tested with an extensive, examiner-administered neuropsychological test battery [20, 21, 346, 347]. This number might be even higher for individuals with SCI, who show a subtle decline in cognitive performance with the onset of memory complaints [424]. To minimise false positive diagnoses, the use of multi-domain neuropsychological assessment across multiple time points is recommended to establish the diagnosis of MCI [15-17]. In establishing tests that are sensitive to subclinical impairment, neuroimaging techniques and laboratory assessments are increasingly being considered [8, 20, 21].

Electroencephalography (EEG) assessment, particularly the analysis of event-related potentials (ERPs), may be a useful tool in the detection of MCI [425-428]. A recent systematic review indicates that ERP components N200 and P300 have a prolonged latency in response to auditory stimuli, including the auditory oddball paradigm during active and passive tasks, may act as potential markers of MCI and AD [20]. Another study using the active auditory oddball paradigm confirmed that N200 and P300 are prolonged in individuals

with MCI compared with healthy older adults [426]. Lister et al, who used the passive auditory oddball paradigm, revealed a prolonged P1-N1-P2 complex between healthy older adults and individuals with MCI [429]. Less is known in individuals with SCI with the small number of studies to date being limited to resting state EEG assessments [430, 431]. While Babiloni and colleagues report significantly lower amplitudes in alpha 1 sources in individuals with SCI compared to individuals with MCI, López-Sanz et al. reported similar alterations in functional connectivity between SCI and MCI using magnetoencephalography [430, 432].

The aim of the present study was to compare ERPs between participants with SCI and MCI in response to an auditory oddball paradigm. It was hypothesised that individuals with MCI have prolonged N200 and P300 components during an auditory oddball paradigm in comparison to individuals with SCI. Further, differences in ERP amplitude of N200 and P300 components were expected.

4.3. Materials and Methods

4.3.1. Participants

All participants were recruited through the NeuroExercise Project [352], a multi-centred randomized controlled trial of exercise therapy in participants with MCI across three European countries (Ireland, the Netherlands, Germany). For the purpose of the present sub-study, the participants were recruited in Germany at the German Sport University (GSU). The study was conducted in accordance with the declaration of Helsinki and approved by the research ethics committee of the GSU. Participants were recruited from the community through newspaper advertisements and editorials, and from local memory clinics. All participants provided their informed consent to the study procedures.

Participants were initially interviewed via telephone and were required to meet the following eligibility criteria, which have also been published elsewhere [352]. For the purpose of this study, participants with a Montreal Cognitive Assessment (MOCA) score >25, who reported memory impairments but did not meet the clinical criteria for MCI used in the NeuroExercise Project, were classified as participants with SCI in accordance with previous studies [433-435]. A total of 26 participants meeting the inclusion criteria were stratified into groups (SCI, n = 13 and MCI, n=13) depending on their MoCA scores (Table 3). To distinguish between

amnestic and non-amnestic MCI, education adjusted cut-offs of -2 standard deviations (SD) for low education (<10 years of education), -1.5 SD for the middle education group (10–13 years of education) and -1 SD for the highly educated (>13 years of education) were obtained from the delayed recall portion of the Repeatable Battery for the Assessment of Neuropsychological Status Delayed Memory Index (Germany) [352, 436].

4.3.2. Study overview

The participants attended two appointments for the assessment of cognitive function and electrocortical activity. During their first visit the participants underwent a neuropsychological assessment battery, comprising five different tests using German-language versions: the MoCA [73], the Trail Making Test (TMT) parts A and B [380], and letter and semantic verbal fluency [89]. Furthermore, health-related quality of life was evaluated using the Health-Related Quality of Life for People with Dementia (DemQOL) questionnaire, which has good acceptability and internal reliability in patients with MCI [437, 438]. The total score of the DemQOL was calculated and used for comparisons. During the second visit, participants underwent an EEG assessment under resting conditions. Participants were asked to avoid vigorous exercise on the day of each assessment.

4.3.3. Cognitive function assessment

The MoCA is a 12-item test with scores from 0 to 30, where higher scores indicate better cognitive function. MoCA scores from 17 to 25 or from 19 to 25 have previously been used to delineate MCI [73, 388, 439]. Besides MoCA total score, the MoCA memory index score (MoCA-MIS) was calculated to evaluate verbal episodic memory [388]. The TMT A and B are validated neuropsychological tests, which assess visuomotor information processing speed and cognitive flexibility [380]. In Part A, the participants were required to connect numbers in ascending order from 1 to 25. In Part B, the participants were instructed to connect numbers and letters in alternating and ascending order (e.g. 1 - A - 2 - B - 3 - C, etc.). Any mistake made by a participant was immediately pointed out by the test administrator and was corrected before proceeding, and the time for test completion included time to correct errors. Both tests were completed as fast as possible and the time taken to complete the tests was measured. The verbal fluency test is a short test of verbal information processing speed and typically consists of two tasks [89], letter fluency [389] and category fluency [390]. For both

tasks participants were given 60 seconds to produce as many unique words as possible either starting with a given letter (letter fluency) or unique words within the semantic category "animals" (category fluency). Letter fluency consisted of 3 trials starting with the letters L, B, S. The participant's score was the mean number of unique correct words in each task. All cognitive function assessments were administered in-person by a trained researcher and supervised by an experienced neuropsychologist.

4.3.4. Event related potentials and EEG data acquisition and analysis

ERPs were elicited using an auditory oddball paradigm which is a two-tone target discrimination task. Participants were seated in a sound attenuating room, and had their eyes closed throughout the recordings to minimize any effect of eye blinks. Tones were presented binaurally via earphones in pseudo-randomised order. Participants were instructed to press a button with their dominant hand in response to the target tone as fast and as accurately as possible. The target tone was a 2000 Hz pure tone, whereas the frequency of the standard tone was a 1000 Hz pure tone. The standard tone was delivered with a probability of 80%, and the target tone with a probability of 20%. A practice session was undertaken to confirm that participants understood the requirements of the task. Accuracy (%) and reaction time were evaluated.

Electrocortical activity was continuously recorded using an electrode cap Ag/AgCl active electrodes (ActiCap EEG Active Electrode System, Brain Products GmbH, Gilching, Germany) located at 32 scalp sites based on an international 10-20 system [440]. EEG signals were analysed offline using Brain Vision Analyzer 2.1 (Brain Products, Munich, Germany). Raw data were filtered utilising a Butterworth zero phase filter including a notch filter at 50 Hz. Bandpass filter was used between 1 and 30 Hz for analyses. ERPs are a phase-locked response to specific stimuli, we identified the appearance of the task (i.e. target and standard) as the relevant stimuli. Following segmentation based on stimulus onset (-200 to 800 ms) and after visual inspection of the data, semi-automatic artefact rejection was applied on each segment (gradient <50 μV; max/min amplitude – 200 to 200 μV; lowest allowed activity in intervals 0.5 μV). Segments were marked and removed if the difference between the minimum and maximum amplitude in a single segment exceeded 100 μV. If an artefact was detected, the algorithm marked the event 200 ms before and 200 ms after the exact artefact

occurred to control for the source of noise. Additionally, Independent Component Analysis (ICA) was used to remove any eye blinks not coded by the semi-automatic artefact algorithm. The number of remaining artefact-free trials available for analysis did not differ between groups for the standard (SCI: 572 ± 24; MCI: 563 ± 65) and target tone trials (SCI: 97 ± 6; MCI: 98 ± 11).

Baseline-corrected (-200 – 0 prestimulus) data were averaged for each participant over all electrodes to determine the latency windows for the different ERP components. Specifically, P2 was defined as the largest positivity occurring between 175 – 275 ms, and N2 as the largest negativity occurring between 250 – 300 ms after the onset of the standard tone. P3 was added for the onset of the target tone as the largest positivity occurring between 350 – 700 ms. Latencies and peak amplitudes for the standard and target stimuli were evaluated at Cz, the electrode site that showed the most robust response and strongest amplitude.

4.3.5. Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics Version 25. Group (SCI, MCI) differences in sex balance was examined by Chi-Square test. Two-tailed independent samples *t* tests or Mann-Whitney U test for non-normally distributed data were employed to assess group differences in baseline characteristics, neuropsychological test performances, as well as task performance on the reaction time and accuracy components of the oddball paradigm. For statistical analysis, EEG data were resampled using the jackknife approach (leave-out one average), where latency and amplitude are determined by aggregating the estimates of each sized sub-sample [441]. Two-tailed independent samples *t* tests were used to calculate differences in latency and amplitude at Cz between the groups. Responses to target and standard tone were analysed separately. If Levene's test was significant, adjusted degrees of freedom were used and reported. *T* values were adjusted according to Ulrich & Miller $(t/(n-1))=t_{adjusted}$. Between-group effect sizes were quantified using Cohen's *d,* with 0.2 representing a small effect, 0.5 a moderate sized effect, and 0.8 representing a large magnitude effect [442, 443]. Sample size was based on previous EEG studies that reported significant differences between individuals with different cognitive functions (n = 10 – 13 [429, 444, 445]).

4.4. Results

4.4.1. Baseline characteristics

Baseline data are reported in table 3. The two groups did not differ in age, education, self-reported quality of life or the proportion of males and females. However, MoCA scores, which were utilised to stratify the two groups, and MoCA-MIS were significantly different (p. < .001).

Table 3: Demographic data

	SCI (n = 13)	**MCI (n = 13)**	***p* value**	**Effect Size (*d*)**
Age (years)	71.92 ± 6.2	73.00 ± 7.6	0.695	0.16
MoCA	28.2 ± 1.4	22.0 ± 2.4	<0.001	3.11
MoCA-MIS	14.0 ± 1.1	7.3 ± 3.6	<0.001	2.53
Sex (number of females)	9 f	6 f	(χ^2) 0.234	0.48
Education (years)	16.9 ± 4.8	13.9 ± 3.1	0.070	0.74
DemQOL (total score)	94.5 ± 6.7	88.7 ± 9.9	0.095	0.68

(presented as mean ± standard deviation; SCI = subjective cognitive impairment; MCI = mild cognitive impairment; MoCA = Montreal Cognitive Assessment; MoCA-MIS = MoCA memory index score; DemQOL = Health-Related Quality of Life for People with Dementia)

4.4.2. Neuropsychological and behavioural data from Oddball paradigm

Neuropsychological tests revealed several differences with large magnitude effect sizes between groups (Table 4). Individuals with MCI took significantly longer to complete the TMT A (p. = .001, *d = 1.5*) and B (p. = .030, *d = 0.9*) than individuals with SCI. Furthermore, they produced significantly fewer words in both letter (p. = .011, *d = 1.1*) and category fluency (p. = .038, *d = 0.86*) tests in comparison to the SCI group. In the oddball paradigm,

no significant differences were found in reaction time (p. = .104, *d = 0.7*) and accuracy (p. = .380, *d = 0.3*) between the two groups (Table 4).

Table 4: Results from neuropsychological tests

Neuropsychological Assessments	**SCI (n = 13)**	**MCI (n = 13)**	***p* value**	**Effect size *(d)***
TMT A (seconds)	36.5 ± 10.3	54.3 ± 13.6	0.001	1.48
TMT B (seconds)	94.7 ± 25.8	142.1 ± 66.5	0.030	0.94
Verbal fluency–letter score	17.9 ± 3.3	14.1 ± 3.7	0.011	1.08
Verbal fluency–category score	21.5 ± 4.8	17.5 ± 4.5	0.038	0.86
Oddball paradigm				
Oddball – reaction time (s)	0.46 ± 0.1	0.50 ± 0.1	0.104	0.66
Oddball – accuracy (%)	99.6 ± 0.7	97.0 ± 7.0	0.380	0.31

(presented as mean ± standard deviation; SCI = subjective cognitive impairment; MCI = mild cognitive impairment; TMT = Trail Making Test; total number of acceptable words are presented as verbal fluency scores)

4.4.3. Event related potentials

Independent sample *t tests* revealed no differences in ERP components between the SCI and MCI after both the standard and target tone presentations (Table 5, Fig. 5). Medium effect sizes suggested the largest differences between SCI and MCI were for P3 amplitude (p. = .142, *d = 0.6*) and latency (p. = .234, *d = 0.5*) after the target tone presentation, and for P2 amplitude (p. = .166, *d = 0.6*) after the standard tone presentation (Fig. 5).

Table 5: Mean and standard deviation of ERP components recorded at Cz after onset of standard and target tone

		Latency (ms)					Amplitude (µV)				
		SCI (n = 13)	MCI (n = 13)				SCI (n = 13)	MCI (n = 13)			
		mean ± SD	mean ± SD	*t* value	*p* value	Effect size *(d)*	mean ± SD	mean ± SD	*t* value	*p* value	Effect size *(d)*
Standard tone	**P2**	228.77 ± 1.12	247.23 ± 1.30	0.54	0.594	0.21	0.33 ± 0.03	0.85 ± 0.11	1.43	0.166	0.56
	N2	359.54 ± 2.85	392.00 ± 1.59	0.60	0.554	0.24	-0.32 ± 0.05	-0.71 ± 0.15	-0.74	0.466	0.29
Target tone	**P2**	234.31 ± 5.71	240.46 ± 2.96	0.29	0.744	0.11	0.40 ± 0.05	0.71 ± 0.13	0.65	0.522	0.25
	N2	325.23 ± 3.61	334.00 ± 1.15	0.70	0.491	0.27	-0.57 ± 0.08	-0.91 ± 0.15	-0.60	0.554	0.24
	P3	410.92 ± 3.01	429.54 ± 3.48	1.22	0.234	0.48	0.58 ± 0.10	1.60 ± 0.18	1.52	0.142	0.59

(SCI = subjective cognitive impairment, MCI = mild cognitive impairment)

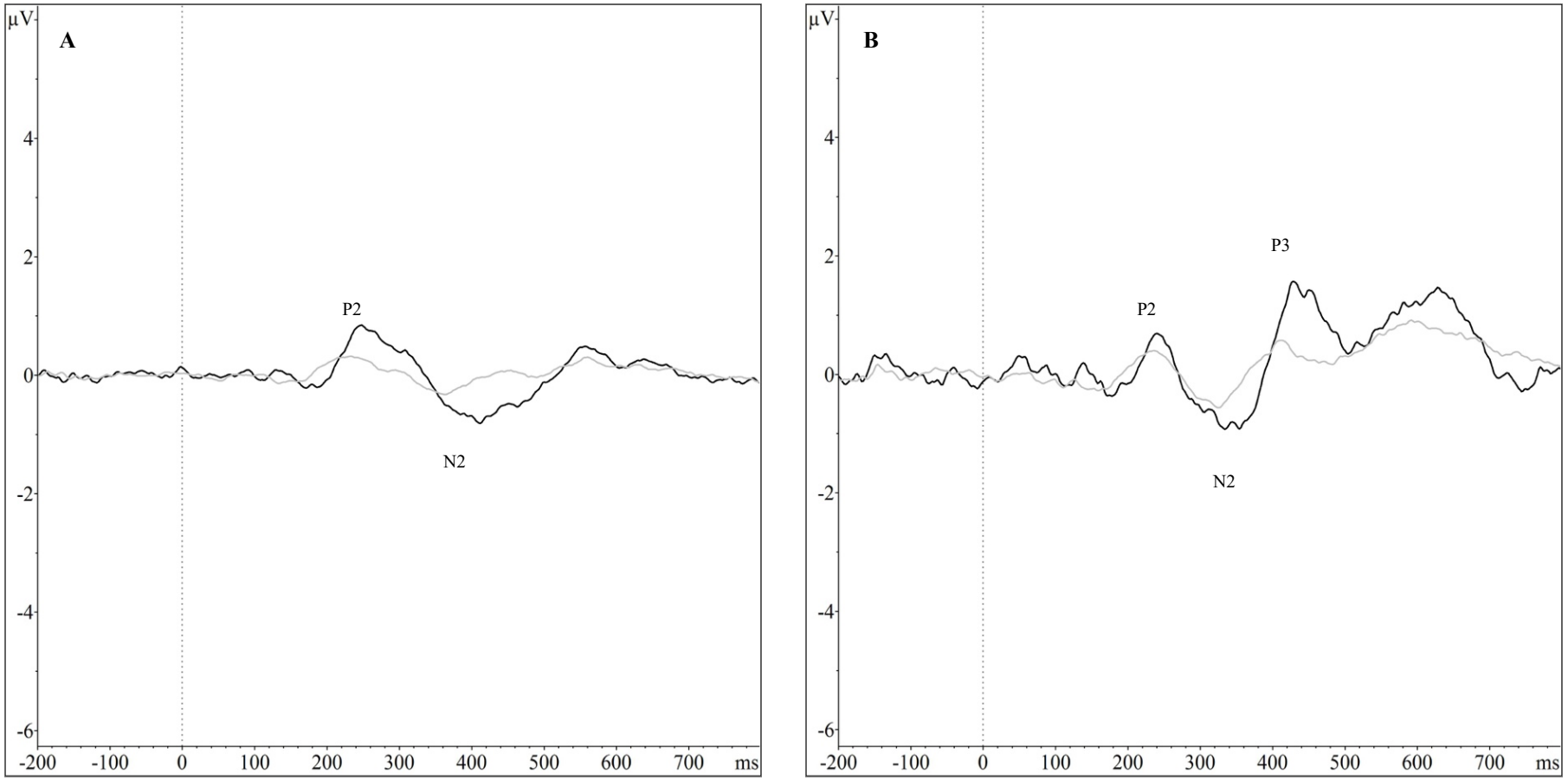

Figure 5: Averaged event related potentials for the standard (A) and target (B) conditions provoked by the oddball-task over Cz. Black lines represent individuals with MCI and grey lines represent individuals with SCI.

4.5. Discussion

With the growing prevalence of memory complaints and cognitive impairment among the elderly population, there is a need to more precisely differentiate individuals with SCI and MCI to assist in the identification of those who are at the greatest risk of further progression to dementia. The present study examined cognitive function and ERPs across individuals with SCI and MCI using the auditory oddball paradigm and selective neuropsychological tests. Individuals with MCI performed significantly worse in the neuropsychological tests; but did not differ in reaction time and accuracy on performance of the oddball paradigm. Furthermore, no differences in the magnitude or latency of the N2, P2, and P3 ERP components were detected between SCI and MCI groups.

The P2 waveform during the ERP is linked to the early stage of sensory processing and associated with short-term and working memory as well as attentional processing [446-449]. Previous research has suggested that the P2 wave differentiates between cognitively healthy older adults and those with neurological conditions (Parkinson's [450] or Alzheimer's disease [451]) but reported no differences in P2 between healthy older adults and those with MCI [452, 453]. Our results extend these previous findings, as we did not detect any differences between individuals with MCI or SCI in P2. Saunders and Summers showed previously that individuals with subjective and objective cognitive complaints were indistinguishable on complex sustained attention, divided attention, and target detection [454]. Therefore, it may be speculated that the lack of differences in the P2 wave of the ERP response between individuals with SCI and MCI reflects similar cognitive functions (e.g. attentional processing, short-term memory). There is a need to combine ERP experiments with more specific neuropsychological tests that assess short-term and working memory, as well as attentional processing, to provide further insight into this hypothesis. Besides a "behavioral" explanation (i.e. similar cognitive performance), the P2 wave is associated with frontal brain areas [455], and these structures are often affected in individuals with cognitive impairment. Previous research using MRI reported thinning of the frontal and central cortices not only in individuals with MCI, but also in those with SCI [455, 456]. Therefore, similar changes in frontal lobe integrity in both groups could further explain why no differences in P2 between individuals with MCI and SCI were found.

The N2 wave is suggested to represent selective pre-attentive stimulus evaluation, and stimulus discrimination [457, 458]. A previous review and meta-analysis reported prolonged N2 latency with more severe cognitive dysfunction when comparing healthy older adults, individuals with MCI and those with AD [20, 458]. The P3 latency is one of the most-studied ERP components and is associated with cognitive control, attention, and memory [428, 459]. Similar to N2 with 90% sensitivity and 70% specificity, P3 wave correctly discriminated (sensitivity 75%, specificity 80%) individuals with MCI, who have a significantly prolonged latency, from healthy controls [428, 457]. Based on the results of our study, N2 and P3 latency did not differ between individuals with SCI and MCI. An explanation for this result may be that individuals with SCI and MCI could have similar brain alterations, which limits the sensitivity of the EEG findings to discriminate between these two groups. Pathophysiological changes in brain function associated with AD have been reported to occur years, or even decades, before the onset of the disease and may, therefore, be present in individuals with SCI and MCI [8, 143, 144]. This hypothesis is further supported by a previous study using magnetoencephalography, which found differences in functional connectivity in individuals with SCI when comparing them to healthy older adults, but no differences in comparison to individuals with MCI [432]. As functional connectivity disruption is a consistent finding in individuals with AD, findings by López-Sanz and colleagues may further highlight that pathophysiological brain changes exist in SCI and MCI [432]. This is in line with findings of a recently published systematic review, which found a network disorganization in individuals with subjective impairment in studies using magnetic resonance imaging, position emission topography or magnetoencephalography [431]. To further investigate the hypothesis that similar brain alterations in both SCI and MCI are responsible for similar N2 and P3 components [431], ERPs should be compared across the spectrum of cognitive ageing including healthy older adults and adults with AD.

The oddball paradigm was used to elicit ERPs and it may be speculated that using a different cognitive task than the oddball paradigm while recording ERPs could provoke performance associated differences between individuals with SCI and MCI. While no differences were found between the two groups' performance in the oddball paradigm, the performance of individuals with MCI was significantly worse than those with SCI in all the neuropsychological tests used in this study. Whereas TMT A and verbal fluency tests assess

speed of processing by either stopping time until completion (TMT A) of a task or counting responses within a certain time of 60 seconds (verbal fluency), reaction time during the oddball paradigm is measured as the elapsed time between a rapid presentation and processing of a certain stimulus (i.e. high tone) [460]. Therefore, cognitive processing is likely to be different between these tasks, as indicated by previous research [460]. As both individuals with SCI and MCI had a performance accuracy of above 97% in the oddball paradigm, cognitive complexity of this task might be too low to reveal performance associated differences in ERPs. It can only be speculated that using a more cognitively demanding task may lead to changes in ERPs between the two groups, which warrants further investigations.

4.5.1. Limitations

Previous studies indicated that sex may influence ERP potentials [428, 461]. Therefore, future studies should analyse men and women separately to identify sex-related differences, which could not be done in this study because of the small sample size. Given the similar distribution of men and women in both groups of this study, sex differences are not believed to affect the data. Sample size in previous studies comparing ERPs of individuals with different cognitive functions (e.g. healthy older adults in comparison to individuals with MCI) was similar to the one used in our study [429, 444, 445]. Based on our results, however, larger sample sizes may be needed to detect any small, but potentially meaningful, differences in ERPs between individuals with SCI and MCI.

4.5.2. Conclusion

Based on results in our study, ERPs evoked by an auditory oddball paradigm do not differ between individuals with SCI and MCI. Further research is needed within the spectrum of healthy ageing towards dementia onset – including healthy older adults, individuals with SCI, MCI, and AD – to explore changes in ERPs. This may help to define objective markers, which validly discriminate between different stages of cognitive decline. Based on our findings we recommend the use of a neuropsychological test battery to discriminate between individuals with SCI and MCI. The utility of ERPs in individuals with SCI and MCI may depend on the complexity of the task used to elicit ERP components and future studies should investigate tasks other than the auditory oddball paradigm.

5. RATING OF PERCEIVED EXERTION – A VALID METHOD FOR MONITORING LIGHT TO VIGOROUS EXERCISE INTENSITY IN INDIVIDUALS WITH SUBJECTIVE AND MILD COGNITIVE IMPAIRMENT?

Chapter 5 includes the following manuscript:

Rating of perceived exertion – a valid method for monitoring light to vigorous exercise intensity in individuals with subjective and mild cognitive impairment?

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Author contributions:

Student contribution to work: Involved in the conception of the study, collected all data, analysed and interpreted data, was responsible for writing all drafts of the manuscript including preparation of all figures and tables, and modified drafts following co-author recommendations.

Conceived and designed the experiment: TS, SR

Analysed the data: TS, SR, CDA

Wrote/reviewed the paper: TS, SR, VA, CDA, VA, PW, SS

[#] = equal contribution / share first authorship

5.1. Abstract

In rehabilitation settings, exercise intensity is often monitored with Borg's rating of perceived exertion (RPE). However, previous studies showed that severe cognitive impairment may limit the usability of the RPE. The aim of this study was to assess the relationship between RPE and heart rate (HR), and to establish whether a target RPE can be used to achieve exercise intensity based on an individual's HR-RPE in people with early cognitive impairment.

97 participants (74.7±6 years) with early cognitive impairment completed an incremental exercise test. Of these, 54 were tested during a single, RPE guided exercise session. RPE and HR were monitored throughout. Correlations between HR and RPE were assessed using Spearman's correlation. Mean differences between measured HR and target HR were calculated and compared using a two-way ANOVA with factors cognition and exercise mode. Bland-Altman plots were constructed to analyze the agreement between target and measured HR.

HR and RPE correlated moderately with each other ($p<0.001;r=0.555$) and no differences between target and measured HR were observed. Bland-Altman plots revealed a mean difference of 1.2 bpm and 95% level of agreement was between 24.4 and -22.1 bpm.

No differences in rating accuracy were observed between different cognitive impairment levels nor between different exercise modes. Bland-Altman plots revealed some variance between the participants with almost half of them missing target HR by 10bpm or more. Therefore, the RPE should only be applied with caution and, if possible, with other measurements (e.g. heart rate monitors) to ensure that target intensity is reached.

5.2. Introduction

More than 46 million people live with dementia worldwide, and this number is expected to rise to about 150 million by 2050 [178]. Because mild cognitive impairment (MCI) and subjective cognitive impairment (SCI) present a risk for further cognitive decline, current research efforts target these states to test the efficacy of prevention and therapeutic approaches [3, 13]. Guidelines recently released by the AAN promote regular physical activity as the most promising strategy for preventing further cognitive decline in individuals with MCI [3]. In addition, two independent systematic reviews have reported that moderate aerobic exercise (60 - 80% of maximum heart rate [max HR]) may be the most efficient mode of exercise for increasing cognitive performance [35, 36]. An important component of exercise prescription is the intensity of exercise, which is characterised and measured in various ways including as heart rate (HR) relative to maximum or age-predicted maximum HR, or as a percentage of oxygen uptake reserve [38]. These methods require technical expertise and equipment, and often limit the translation of prescription recommendations into practice. A practical method of monitoring exercise intensity is Borg's Rating of Perceived Exertion (RPE). This psycho-physical tool assesses the subjective perception of effort during exercise in order to rate and regulate exercise intensity [39]. There is some controversy around the use of the RPE, as its accuracy may be influenced by age, cognitive state or exercise at a very high intensity (e.g. during high-intensity interval training (HIIT)) [40-43].

In rehabilitation settings, the RPE scale has been shown to provide a valid method to achieve target exercise intensity in various populations, such as patients with chronic heart failure and patients taking beta-blocker medication [462-464]. However, other studies suggest that some patient characteristics might interfere with the usefulness of the RPE scale, for example, in patients with panic disorder [465], patients with stroke, and patients with Alzheimer's disease (AD) [466-468]. Whereas people with panic disorders have difficulties in the interpretation of bodily sensations [465], accuracy of the RPE was limited by cognitive or functional impairments (e.g. leg motor impairments) in post-stroke individuals [468]. Cognitive impairments in post-stroke individuals were suggested to be a result of altered perceptions of effort. Similar limitations may occur in individuals with AD, as they are known to have problems with awareness, insight judgement, communication, and decision-making. These problems affect the validity of self-reported measures and may explain the

lack of accuracy when RPE is used to monitor exercise intensity in this population [42, 469, 470]. People with SCI and MCI are also prone to changes in self-awareness, which may affect the accuracy of the RPE scale in these individuals, however this has not yet been established [469-471]. As cognitive impairment is highly prevalent in older adults and often correlates with comorbid chronic conditions, a better understanding of the use of RPE is important not only for exercise in individuals with SCI, and MCI but also in the general aged population [472, 473].

In this study we aimed to firstly assess the relationship between RPE and heart rate (HR) during an incremental exercise test in older individuals with SCI and MCI. Secondly, we aimed to establish whether a target RPE during light, moderate and vigorous exercise can be used to achieve exercise intensity based on an individual's HR-RPE relationship. It was hypothesised that the difference between measurements of exercise intensity using the HR and the RPE scale would increase with the progression of cognitive impairment, and that this discrepancy would be influenced by the intensity of exercise.

5.3. Materials and Methods:

5.3.1. Participants

Participants for this trial were recruited through the NeuroExercise project, a multi-centred randomized controlled trial of exercise therapy on the progression of MCI across three European countries (detailed information about the NeuroExercise project have been published elsewhere [352]). Additional participants were recruited through a follow-up pilot study, which uses the same methodological approach as the NeuroExercise project and investigates the effect of HIIT on the progression of MCI. For the purpose of the present sub-study, the participants were solely recruited in Cologne, Germany. The study was conducted in accordance with the declaration of Helsinki (1975) and approved by the ethics committee of the German Sport University. Ninety-seven participants completed an incremental exercise test. Of these, 54 were also tested during one exercise session, which either consisted of light stretching and toning exercise (ST, n = 17), moderate aerobic exercise (AE, n = 17), or vigorous HIIT (n = 20).

All participants provided their informed consent to the study procedures and met the eligibility criteria, which have been published elsewhere [352]. For the purpose of this sub-

study, individuals that reported memory complaints but did not meet the clinical criteria for MCI used in the NeuroExercise project were included as participants with SCI, which is in line with previous studies [433, 434]. The participants were stratified into MCI or SCI based on their results during the baseline assessment of cognitive function [352]. Table 6 provides information on participant characteristics.

Table 6: Participant characteristics of total sample

	ET	**AE**	**ST**	**HIIT**
n	97	17	17	20
Age (years)	74.7 ± 6	70 ± 7	75 ± 6	76 ± 6
Sex (male)	45	7	10	9
Height (cm)	173	170	170	174
Weight (kg)	74	69	76	76
BMI	24.7	24.3	26.3	25.1
Resting HR (bpm)	76.3	74.9	76.9	76.2
MoCA	25.1	24.8	26.0	25.1
SCI (MoCA score; n)	27.7; n = 44	27.3; n = 9	27.8; n = 11	28; n = 7
MCI (MoCA score; n)	22.9; n = 53	22.3; n = 8	24.3; n = 6	22.3; n = 10
HR at final stage of ET (bpm)	125.9	145.2	137.3	118.4*
Resting SPB (mmHg)	128.8	128.5	128.4	129.5
Resting DBP (mmHg)	75.8	75.8	78.1	73.7

(ET = incremental exercise test) and subgroups (AE = aerobic exercise; ST= stretching and toning; HIIT = high-intensity interval training; BMI = body mass index; MoCA = Montreal Cognitive Assessment; SCI = subjective cognitive impairment; MCI = mild cognitive impairment; HR = heart rate; SBP = systolic blood pressure; DBP= diastolic blood pressure; * significantly different to the other two groups)

5.3.2. Study design

The participants attended two appointments for the assessment of cognitive function and cardiorespiratory fitness as part of the inclusion process [352]. During their first visit, the participants completed the Montreal Cognitive Assessment (MoCA) [73]. The MoCA is an 11-item test with a maximum score of 30 points and assesses global cognitive function. MoCA scores from 19 to 25 suggest MCI [73]. To enable comparisons between participants with SCI and MCI, we stratified our sample into two groups according to the aforementioned cut-offs (SCI > 25, MCI = 19 - 25).

During their second visit, the participants performed an incremental exercise test on an electronically braked cycle ergometer (Ergoline 900©, Bitz, Germany) for the determination of max HR and exercise capacity. Resting blood pressure and resting HR were measured before the start of the incremental exercise test. The progressive exercise test commenced with 3 min of unloaded cycling followed by step increments of 25W every 2 min in accordance with clinical guidelines [352, 434]. The participants continued to exercise until their volitional maximum and to the point where they were unable to maintain the required pedal cadence with increasing exercise intensity. The RPE 6 (“no exertion”) - 20 (“maximal exertion”) scale was introduced and explained to the participants before the incremental exercise test, according to ACSM guidelines [378]. Before starting the incremental exercise test, participants had the chance to ask questions, if the use of the RPE scale was still unclear. HR and RPE were assessed during the final 30 s of each stage and a HR-RPE relationship was established for each individual.

To test whether the RPE scale can be used to prescribe and monitor exercise intensity in individuals with SCI and MCI during various forms of exercise, HR and RPE were further assessed in the participant subgroups during single supervised exercise sessions. Participants were asked to exercise at a set target RPE while wearing a HR monitor, which was covered to avoid bias. The measured HR was then compared with the HR at the target RPE based on the individual HR-RPE relationship. The supervised exercise sessions were conducted as part of the NeuroExercise project or its follow-up study [352]. At the start of each of the exercise session the participants were briefly reminded of the RPE scale by referring to the lowest (6 = no effort; e.g. sitting on a couch) and highest (20 = maximal effort) value of the scale.

Furthermore, the participants were encouraged to ask questions at any time, if the use of the RPE scale was not clear.

The AE and ST classes lasted for 60 min and consisted of either walking and running exercises (AE) or light resistance, stretching and coordination exercises such as balance (ST). The AE class had a target RPE of 13, whereas the ST class aimed to not exceed an exercise intensity of RPE 10 [352]. RPE and HR were assessed three times during the exercise sessions; after 15 min, after 30 min and after 45 min. HIIT exercise was conducted on a stationary cycle ergometer for 35 minutes, and consisted of 4 x 4 min bouts [474]. Participants were instructed to exercise at a target RPE of 17 during the high-intensity intervals. RPE and HR were assessed at the last 30 s of the first and final interval, as it has been suggested that one to two minutes are required to reach target exercise intensity [475].

During exercise, HR was monitored using a Polar M400© watch and the Polar H7© chest strap [476, 477]. The participants were fitted with the watch and chest strap before the start of the exercise session and HR was continuously recorded. The HR monitor display was covered during the exercise sessions in order to decrease the risk of bias. The Borg RPE 6 - 20 scale was presented to the participants momentarily for to determine their perceived exertion on each occasion.

5.3.3. Data analysis

One-way analysis of variance (ANOVA) was performed to test for differences between the three subgroups' baseline (AE, ST, HIIT) characteristics. To determine the relationship between HR and RPE, all data pairs (HR and RPE) collected during the ET, as well as the single exercise sessions were entered in an Excel database and imported to IBM SPSS Statistics 24© [466]. Spearman's rank-order correlation was used to assess correlations between HR and RPE. The correlation analysis was performed for all data pairs, as well as sub-sets of data with the sample divided into ET and the different exercise sessions, and further divided into individuals with MCI and SCI. The strength of the correlations was defined as: 0.00 to 0.30 = negligible correlation; 0.30 to 0.50 low correlation; 0.50 to 0.70 moderate correlation; 0.70 to 0.90 high correlation; 0.90 to 1.00 very high correlation [478].

Furthermore, all participants' HR-RPE relationship was used to estimate every individual's target HR for the different exercise sessions when exercise intensity was guided by RPE (AE

= RPE 13, ST = RPE 10, HIIT = RPE 17). Mean differences between measured HR during the exercise sessions and target HR were calculated. Mean differences were compared using a two-way ANOVA with factors cognition (SCI, MCI) and exercise mode (AE, ST, HIIT). Finally, Bland-Altman plots were constructed to analyse the agreement between target HR and measured HR, where mean difference, standard deviation (SD), SD x 1.96, and upper and lower limits of agreement were calculated [479, 480]. Data will be presented as mean and SD. P-values of less than 0.05 were regarded as statistically significant. Sample size was based on previous studies, which evaluated the accuracy of the RPE and recruited between 10 – 47 participants [40, 41, 463, 464, 468]. In fact, Aamot and colleagues, whose main variable was HR, calculated that 10 participants per exercise mode were required to achieve a power of 0.8 with an alpha of 0.05 [40].

5.4. Results

5.4.1. Participant characteristics

Participants in the HIIT had a significantly lower maximum HR than the participants in the other exercise classes (AE ($p < 0.001$), ST ($p = 0.001$)). No other differences were identified (Table 6).

5.4.2. Heart rate and RPE

Overall, 542 data pairs (HR and RPE) were collected (ET = 400; AE = 51; ST = 51; HIIT = 40), which correlated positively ($p < 0.001$; $r = 0.555$) (Fig 6). The data pairs that were assessed during the different single bouts of exercise (AE, HIIT and ST exercise) had a slightly weaker correlation ($p = 0.003$; $r = 0.400$) than those during the incremental exercise test ($p < 0.001$; $r = 0.564$). When differentiated by cognitive status, Spearman's correlation revealed a moderate correlation for participants with MCI ($p < 0.001$; $r = 0.565$) and a low correlation for participants with SCI ($p < 0.001$; $r = 0.468$).

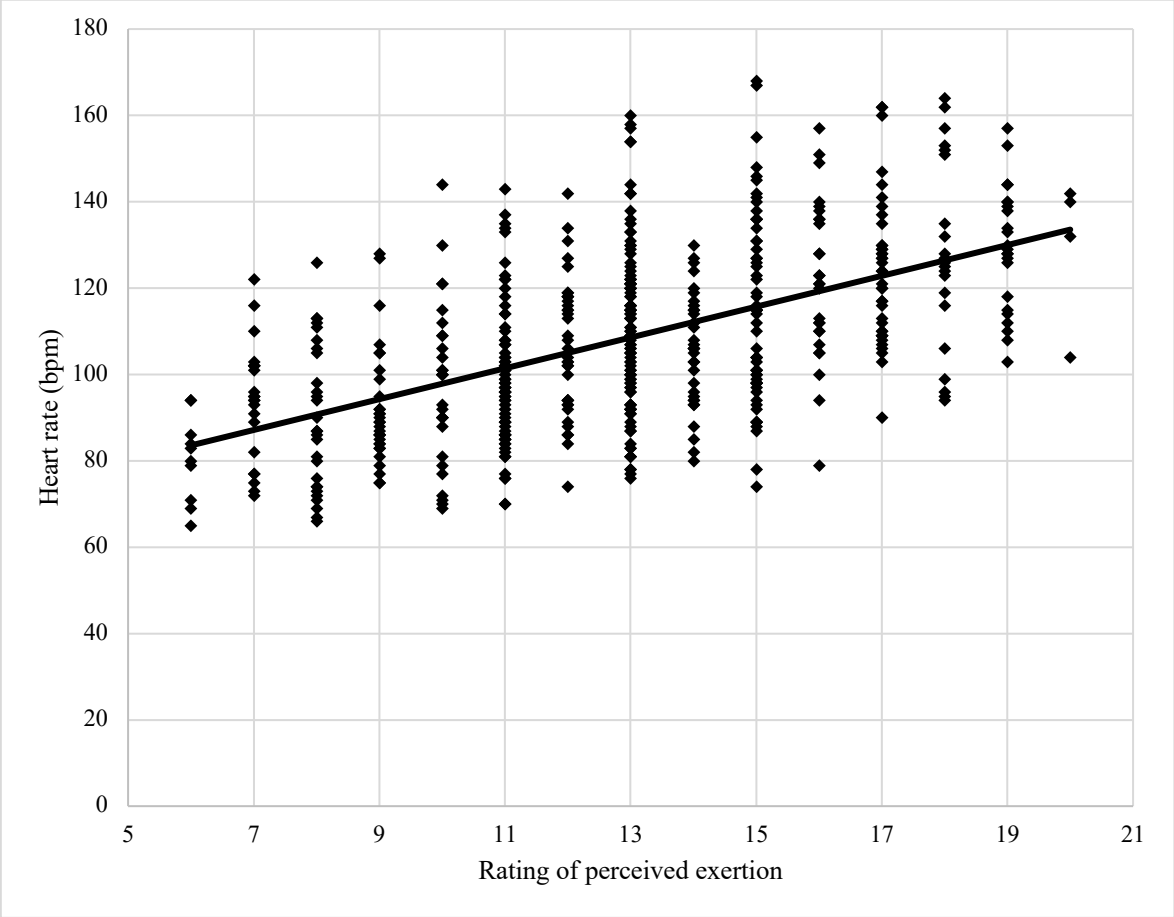

Figure 6: Correlation between Heart Rate and Rating of perceived exertion

5.4.3. Rating accuracy

A two-way ANOVA was conducted that examined the effect of cognition (SCI, MCI) and exercise mode (AE, ST, HIIT) on mean difference between target and measured HR. There was no statistically significant interaction of cognition or exercise mode on rating accuracy ($F_{(2, 48)} = 3.489$, $p = 0.163$). Additionally, simple main effects analysis showed no significant results for cognition ($p = 0.535$) or exercise mode ($p = 0.998$). Bland-Altman plots (Fig. 7) revealed a mean difference of 1.2 bpm with a standard deviation of 11.8, corresponding to a variation of ± 24 bpm when exercise intensity was guided by RPE. 95% level of agreement was between 24.4 bpm (upper level of agreement) and -22.1 bpm (lower level of agreement). Interindividual differences existed between participants in this study: about half of the participants reached a HR within ± 5 bpm of their target HR (n = 26); 22 participants had a

HR between 5 – 15 bpm above or below their target HR, and four participants had a larger (> 20 bpm) difference between the measured and target HR. Moreover, Bland-Altman plot analysis identified two outliers above the upper limit of agreement.

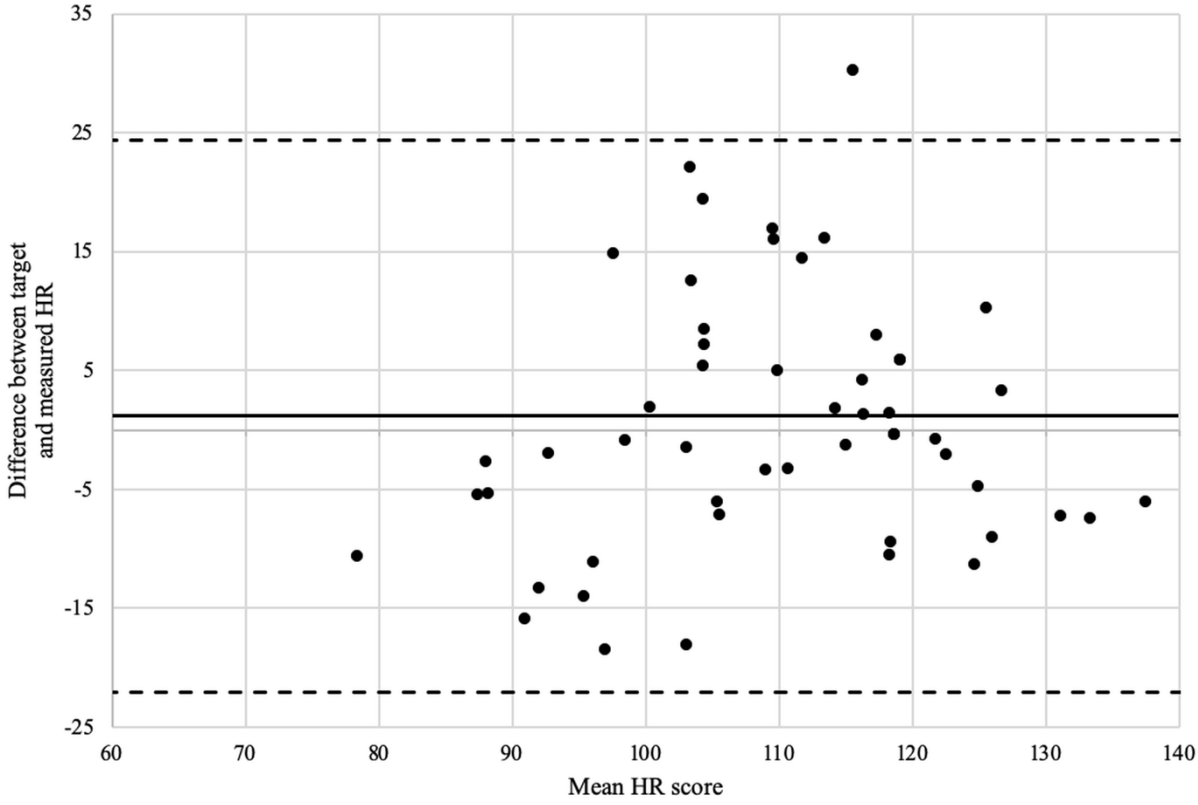

Figure 7: Bland-Altman plots showing the agreement between measured and target hear rate during single bouts of exercise of either HIIT, AE or ST exercises (AE = aerobic exercise; ST= stretching and toning; HIIT = high-intensity interval training)

5.5. Discussion:

The study revealed a moderate correlation between RPE and HR during exercise in individuals with SCI and MCI. Cognitive status did not influence rating accuracy, as no differences were observed between individuals with SCI and MCI. Furthermore, we found no differences between different exercise modes (AE, ST and HIIT). Bland-Altman plots indicated a good level of agreement with a mean difference of 1.2 bpm between target and measured HR when exercise intensity was guided by RPE. However, the variation (-22.1 – 24.4 bpm) within the limit of agreement (95%) has to be considered carefully when monitoring exercise intensity with RPE.

In comparison to Borg's initial studies with healthy middle-aged men (1973) and healthy young adult-adult men (1985), the correlation between HR and RPE was slightly lower in our study. Borg found correlations of 0.8 - 0.9 and 0.62 - 0.72 respectively, in his initial studies, which have been replicated by recent studies [41, 43]. As age affects HR and HR variability, the higher age of our participants may contribute to differences in comparison to Borg's initial studies [481]. Nevertheless, it may be speculated that the lower correlations in our study are a result of the cognitive impairment [482]. It has been reported that AD leads to an alteration of self-consciousness, which includes awareness of the body [483]. Prodromal stages such as MCI may lead to an impaired sense of self-awareness and self-experience, which are most often characterised by an unawareness of memory deficits [471, 484]. This may be the reason for a lower correlation between HR and RPE in individuals with SCI and MCI compared to healthy older adults. However, this can only be speculated based on the findings of our study and future studies should compare findings in individuals with SCI and MCI to an age matched healthy control group. As SCI and MCI may overlap in awareness scores, this might explain the lack of difference between the two groups in our study [484].

The results of the current study extend previous findings with individuals with AD, where the use of the RPE was insufficient and the correlation between HR and RPE smaller than in our study ($r = 0.38$) [466, 467]. It seems that the level of impairment observed in individuals with SCI and MCI may affect perceived exertion, but not to the same degree as in individuals with AD. Future studies should include healthy older adults and compare their rating accuracy to individuals with SCI and MCI. We recommend that future research should also

assess self-awareness and compare these scores with the accuracy of Borg's RPE. This may not only provide further insight into the relationship of self-awareness and RPE, but also present a valid method for determining the applicability of the RPE in individuals with SCI and MCI.

Interestingly, our results show that the accuracy of perceived exertion does not decrease with higher exercise intensities. This is in contrast to previous research indicating that a HIIT guided by the RPE results in lower exercise intensity than expected [40, 485]. However, these findings were reported in people in cardiac rehabilitation and it has been speculated that results were influenced by medication (e.g. beta-blockers) or that exhaustion might not only be dependent on the intensity but also on the duration of the bout [40, 485].

Bland-Altman plots revealed that half of the participants had a mean difference of 10 or more bpm, which limits the usability of the RPE. Given the age-related decline in maximal HR [486], a variation in HR by 10 or more bpm might influence exercise intensity significantly. In exercise trials with a strict target exercise intensity this variability should be considered. Given the interindividual differences identified by Bland-Altman plots, RPE may be of good use to ensure a certain intensity range is achieved but less valid for very specific intensities. For example, Scherr and colleagues identified that an RPE between 11-13 corresponds with the first lactate threshold (LT1, highest exercise intensity before lactate accumulation), whereas an RPE between 13-15 is equivalent with the individual lactate threshold (or second lactate threshold, LT2) [43]. Combining their results with our findings a target RPE of 12 or 14 may ensure exercising around LT 1 or around the anaerobic threshold, respectively. However, this is highly speculative and future studies need to validate this suggestion in older people.

The participants in this study differed in training experience as their inclusion into the project differed and some had already exercised for more than 6 months, whereas others had just started. However, previous research has stated that the rating accuracy of the RPE is independent of fitness or training experience [487, 488]. Furthermore, the time difference between the incremental exercise test and the single exercise sessions was similar (within 4 weeks). Besides differences in training experience, we did not control for caffeine intake or smoking, which may have an effect on RPE values. Future studies need to address these

limitations and control for caffeine intake and smoking, as well as add an age-matched, healthy control group.

5.5.1. Conclusion

Borg's RPE scale correlated moderately with HR in individuals with SCI and MCI and no differences in rating accuracy were observed between different cognitive impairment levels nor between different exercise modes. Nevertheless, Bland-Altman plots revealed some variance between the participants with almost half of them missing target HR by 10bpm or more. We, therefore, recommend that the RPE should only be applied with caution and, if possible, with other measurements (e.g. heart rate monitors) to ensure that target intensity is reached.

6. VALIDATION OF A WIDELY USED HEART RATE MONITOR TO TRACK STEPS IN OLDER ADULTS

Chapter 6 includes the following manuscript:

Validation of a widely used heart rate monitor to track steps in older adults

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Journal: The Journal of sports medicine and physical fitness (J Sports Med Phys Fitness)

Author contributions:

Student contribution to work: Involved in the conception of the study, collected all data, analysed and interpreted data, was responsible for writing all drafts of the manuscript including preparation of all figures and tables, and modified drafts following co-author recommendations.

Conceived and designed the experiment: TS, SR

Analysed the data: TS, SR, CDA

Wrote/reviewed the paper: TS, SR, VA, CDA, VA, PW, SS

[#] = equal contribution / share first authorship

6.1. Abstract

This study aimed to assess the validity of the Polar M400© activity tracker to count steps in older adults compared to a previously validated pedometer and observed step count. Therefore, 32 older adults (74.8±5.9 years) walked at a self-selected gait speed while wearing the activity tracker and a previously validated pedometer. Additionally, steps were counted manually. A significant difference between activity tracker and pedometer (p=0.011) was observed. Lin's concordance showed a moderate correlation between activity tracker and pedometer (rc=0.561) and between pedometer and manually counted steps (rc=0.690). A high correlation was detected between activity tracker and manually counted steps (rc=0.802). Bland Altman plots revealed good accuracy of the activity tracker. The Polar M400© activity tracker accurately assesses steps during walking. Nevertheless, a slight overestimation was observed, which should be considered when using the activity tracker for long-term tracking, or when extensive arm movements are involved.

6.2. References

Please refer to Chapter 10 for references.

7. NEUROEXERCISE: THE EFFECT OF A 12-MONTH EXERCISE INTERVENTION ON COGNITION IN MILD COGNITIVE IMPAIRMENT – A MULTICENTRE RANDOMIZED CONTROLLED TRIAL

Chapter 7 includes the following manuscript:

NeuroExercise: The effect of a 12-month exercise intervention on cognition in mild cognitive impairment – A multicentre randomized controlled trial

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Journal: Manuscript ready to submit, presubmission inquiry submitted to PLOS Medicine

Author contributions:

Student contribution to work: Involved in the conception of the study, collected all data at German site, analysed and interpreted data, was responsible for writing all drafts of the manuscript, and modified drafts following co-author recommendations.

conceptualization: SS, BL, MOR, MCP, RJS, CM, MR, BW, RM

data curation: TS, MS, KD

formal analysis: MS, RK, JA, TS

funding acquisition: SS, BL, MOR

investigation: TS, MS, KD

methodology: SS, VA, TV, TS, RK, MOR, JA, MS, BL, EG, KD

project administration: SS, BL, MOR, TS, MS, KD

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supervision: SS, BL, MOR, MCP, RJS, CM, MR, BW, RM, JC, VA, EG

validation: MS, MOR, RK, MR, SS

writing – original draft preparation: TS, MS

writing – review & editing: RK, KD, MOR, BL, SS, JA, JC, MCP, VA, EG, RJS, CM, MR, BW, RM

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7.1. Abstract

Background: The development of effective interventions to attenuate cognitive decline in individuals at high risk for Alzheimer's disease (AD) is a global priority. Exercise intervention studies in Mild Cognitive Impairment (MCI), a prodromal stage of AD, have demonstrated inconsistent yet promising results. Addressing the limitations of previous studies, the multicenter NeuroExercise study investigated the effects of a 12-month structured exercise program on the progression of cognitive decline in MCI.

Methods: A randomized controlled trial was conducted in three European countries (Ireland; Netherlands; Germany). 183 individuals with amnestic MCI were included and randomized to either an aerobic exercise program (n=60), a stretching and toning program (n=65) or to a non-exercise control group (CG; n=58). The primary outcome, cognitive performance, was determined by a neuropsychological test battery averaging six cognitive domains into a composite score. Secondary outcomes included cognitive domain scores, cardiovascular fitness ($\dot{V}O_2$peak), and quality of life measures. All outcomes were measured before and after the intervention. For the primary complete case (CC) analyses, between-group differences were analyzed with analysis of covariance under two conditions: 1) the exercise group (combined aerobic exercise, and stretching and toning groups) compared to the CG and 2) aerobic exercise compared to stretching and toning group.

Results: Primary analysis of the full cohort (n=166) revealed no between-group differences in composite cognitive score (mean difference [95% CI]), 0.12([-0.03, 0.27], p=0.13) or in any cognitive domain or quality of life. $\dot{V}O_2$peak was significantly higher in the exercise group compared to the CG after 12 months (-1.76([-3.39, -0.10], p=0.04). Comparing the two intervention groups revealed a higher ṾO2peak level in the aerobic exercise compared to the stretching and toning group, but no differences for the other outcomes.

Conclusions: A 12-month exercise intervention did not change cognitive performance in individuals with amnestic MCI in comparison to a non-exercise CG. An intervention effect on physical fitness was found, which may be an important moderator for long term disease progression and warrants long-term follow-up investigations. The large heterogeneity present in the amnestic MCI group may favor personalized intervention, based on individual responder analyses

Trial registration: ClinicalTrials.gov, NCT02913053. Registered 23 September 2016 – Retrospectively Registered, https://clinicaltrials.gov/ct2/show/NCT02913053

7.2. Introduction

Worldwide, over 46 million people are living with dementia, with the numbers expected to rise to approximately 74 million by 2030 [178]. The prevalence of mild cognitive impairment (MCI), a stage of cognitive impairment with minimal functional loss that is often, but not always, a prodromal stage of dementia [175], is 6.7 % for ages 60-64 and rises to 25.2 % for ages 80-84 [3, 168, 520]. Clinicians and researchers differentiate between amnestic MCI (aMCI), which describes the dominance of memory impairments and is most likely to transition to dementia due to Alzheimer's disease (AD), and non-anmnestic MCI, which is characterized by an impairment in other cognitive domains (e.g. language, visuospatial) [132]. Individuals with both aMCI or nonamnestic MCI have a cumulative risk of 14.9% of developing dementia within two years [3, 132, 521]. As such, cognitive decline due to dementia is a key contributor to the significant economic impact of an ageing population [178], and is identified as a global health and healthcare priority [1].

If a primary prevention strategy could delay conversion to dementia by even two years, it would reduce the total number of patients living with dementia and have substantial public health, economic and societal benefits [8-10], further highlighting the importance of early detection and treatment of cognitive decline. Currently, there is no proven treatment for people with MCI that delays progression to dementia. However, the recently updated AAN the practice guidelines for the treatment of MCI suggests that exercise is a promising non-pharmacological strategy to improve cognitive function in individuals with MCI [3]. This recommendation was underpinned by only two studies that investigated the effect of a six-month multicomponent exercise or resistance exercise intervention on the progression of MCI and demonstrated a positive effect on domain-specific cognitive function (attention and episodic memory) [33, 34]. Furthermore, the results from two systematic reviews both recommend aerobic exercise as the most effective training to maintain or improve cognitive function in individuals with MCI [35, 36]. However, these reviews recommend larger sample sizes, standardised neuropsychological testing, longer intervention periods and well-defined MCI diagnostic criteria, as these were methodological issues limiting previous studies.

Moreover, the two studies included in the AAN guideline either included only women or less than 100 participants, which limits their generalizability [33, 34].

The multicentre NeuroExercise project addressed these limitations by strictly recruiting participants with aMCI, increasing the sample size compared to previous studies, extending the intervention period, involving three different countries and bringing together experts from clinical and exercise intervention trials [352]. The aim of the NeuroExercise project was to investigate the effects of a 12-month structured exercise program (either aerobic exercise or stretching and toning exercises) on the progression of cognitive decline in MCI compared to a control group. We hypothesised that participation in an extensive exercise program, of either aerobic exercise or stretching and toning exercises, would demonstrate a slower rate of cognitive decline compared to the control group.

7.3. Methods

7.3.1. Trial overview, standard protocol approvals, and registrations

The NeuroExercise project was a randomized controlled trial performed in three centres in Europe; the German Sport University Cologne, Germany, Radboud University Medical Center, Nijmegen, the Netherlands and at St. James's Hospital and Trinity College Dublin, Ireland. Participants were randomized to either a yearlong supervised and home-based aerobic exercise program, an equivalent non-aerobic stretching and toning program or to a control group using a centrally controlled computer-generated randomization list (for each country), controlled by an independent statistician.

The ethics committee of the German Sport University, Cologne Germany, the Commisie Mensgebonden Onderzoek Arnhem-Nijmegen, Netherlands, and the Tallaght Hospital/St. James's Hospital Joint Research Ethics Committee Dublin Ireland, approved the study protocol, which has been described previously [352]. All participants provided written informed consent to participate in accordance with the provisions of the Declaration of Helsinki. Participants were recruited between October 2015 and September 2017, 183. The trial is registered at Clinicaltrials.gov, NCT02913053.

7.3.2. Participants and study procedure

Sedentary adults aged 50 years or older diagnosed with aMCI were recruited via hospital memory clinics affiliated with the three sites and from the community via advertisements in local newspapers. Eligibility criteria for inclusion were: (1) an education adjusted Montreal Cognitive Assessment (MoCA) score between 18–26; (2) stable medical condition for more than 6 months and stable medication for more than 3 months; (3) medical clearance to undergo a symptom-limited cardiopulmonary exercise test and extensive aerobic exercise training; (4) physical ability sufficient to allow performance of endurance exercise training; (5) capacity to provide written and dated informed consent form. Participants recruited from the community completed additional testing to confirm MCI status. To distinguish between amnestic and non-amnestic MCI, we applied education adjusted cut-offs of -2 standard Deviation (SD) for low education (<10 years of education), -1.5 SD for the middle group (10–13 years of education) and -1 SD for the highly educated (>13 years of education) were taken from the delayed recall portion of either the Logical Memory (story recall) subtest of the Wechsler Memory Scale IV LM (Ireland & Netherlands) or the Repeatable Battery for the Assessment of Neuropsychological Status Delayed Memory Index (Germany) [436, 522, 523].

Exclusion criteria were: (1) a diagnosis of AD or any other type of dementia; (2) any neurological disorder or other severe chronic disease; [3] engagement in moderate-intensity aerobic exercise training for more than 30 min, 3 times per week, during past the 2 years. A full list of in- and exclusion criteria has been published previously [352].

7.3.3. Interventions

In each centre participants were randomly assigned to the aerobic exercise (AE), the nonaerobic stretching and toning group (ST) or the control group (CG). Both exercise groups consisted of 3×45 min exercise sessions per week over 12 months and exercise intensity was monitored using the Borg's Rating of Perceived Exertion (RPE), which is a scale from 6 ("no exertion") to 20 ("maximal exertion") that assess subjective perception of effort during exercise [39, 435]. Participants of the AE group had a target RPE of at least 13 while exercising, whereas participants in the ST group exercised to an RPE <10 [39]. Participants attended supervised instructor led classes and completed unsupervised home exercises. Class

attendance and adherence to unsupervised home sessions were recorded for all participants. The CG received usual care and was not advised on exercise or did not attend exercise sessions [352].

7.3.4. Outcome measures

All outcomes were measured at baseline (T0) and after 12 months (T2). A neuropsychological test battery measuring six cognitive domains (verbal episodic memory, visual episodic memory, working memory, psychomotor function, executive function, attention) was administered as the primary outcome [352]. The neuropsychological test battery consisted of: a computer based CogState Battery (International Shopping List Task – immediate and delayed recall, Detection Task, Identification Task, One Back Task and One Card Learning Task), Verbal fluency, and Trail Making Test [389, 390, 524-526]. The allocation of the tests of the six cognitive domains was based on the CogState Guidelines and conventional classification of neuropsychological tests [527]. A comprehensive description of the outcome measures for each test has been published elsewhere [352] and an overview of the domain scores is presented in Table 10.

Cardiovascular fitness ($\dot{V}O_2$peak) was assessed as a secondary outcome measure using an incremental exercise test on a standard cycle ergometer. Participants at the German Sport University and Trinity College Dublin completed a maximal test in accordance with the World Health Organization Protocol [45]. In Dublin, $\dot{V}O_2$peak was based on direct spirometry (collection of expired gasses during exercise). In Cologne, $\dot{V}O_2$peak was estimated using the following equation ($\dot{V}O_2$peak = (exercise capacity (W)/weight (kg)) × 10.8 + 3.5 + 3.5) [395]. In Nijmegen, aerobic fitness was estimated from a submaximal exercise test completed according to the Astrand-Rhyming submaximal protocol. $\dot{V}O_2$peak was estimated using the average HR of minute 5 and 6 and the work load in the Astrand Nomogram [528]. $\dot{V}O_2$peak (mL/kg/min) was defined as outcome measure for cardiorespiratory fitness.

Health-related quality of life was evaluated using the Health-Related Quality of Life for People with Dementia (DemQOL) questionnaire, which has a good acceptability and internal consistency in patients with MCI [437, 438]. The total score of the DemQOL was calculated and analysed.

7.3.5. Statistical analysis

The primary analysis of this study was the comparison of cognitive functioning (primary outcome measure) before (T0) and after (T2) the one-year intervention. A composite score was calculated by averaging all six CogState domain scores into one overall cognition score. The obtained scores per test were converted into z-scores based on the standard deviation and mean of the total sample at baseline. In case of multiple tests within one domain, the average score for the domain was calculated with at least one test completed per domain (Table 10).

For the primary analysis, we included group (aerobic exercise, stretching and toning group and control group) as independent variables of an ANCOVA with dependent variable the change in composite cognitive score of T2, and as covariates baseline cognitive functioning (T0), sex and age. Between-group differences were analysed with analysis of covariance under two conditions: 1) the exercise group (combined AE, and ST groups) compared to the control group and 2) AE compared to ST.

Secondary outcome measures included six separate cognitive domain scores (verbal and visual episodic memory, working memory, psychomotor function, executive function, attention), cardiorespiratory fitness ($\dot{V}O_2$peak) and quality of life (DemQOL). Analyses for all secondary outcome parameters were carried out with similar ANCOVA analyses using the respective baseline score, age and gender as covariates. All analyses were performed as complete cases (CC) analyses including all participants independent of adherence to the intervention with baseline and follow-up data of at least one test completed per domain. Data are presented as means and 95% confidence intervals within brackets.

For further exploration of the data and to determine the effect of centre, which had a significant influence on recruitment [529], and per protocol participation on primary outcome measures, a secondary ANCOVA analysis was performed. Per-protocol (PP) participation was defined as >66% adherence in the exercise groups, which equaled an average of 2 exercise sessions per week, in line with recent recommendations from the AAN [3]. We included per protocol participation (not per protocol (NPP), per protocol (PP), control group (CG)) and centre (Ireland (IRE), the Netherlands (NEL), Germany (GER)) as independent variables of an ANCOVA with dependent variable the change in composite cognitive score

of T2, and as covariates baseline cognitive functioning (T0), sex and age. Similar secondary analyses were performed for cardiorespiratory fitness ($\dot{V}O_2$peak) and quality of life (DemQOL). In case of significant interaction effects of centre*per protocol participation, post-hoc pairwise comparisons between centres (IRE, NL, GER) and groups (PP, NPP, CG) were conducted using Bonferroni correction for multiple pairwise comparisons. SPSS 22 was used for all analyses with α set at 0.05.

7.4. Results

7.4.1. Participants

In total, 183 participants were recruited at the three centres (Germany: 79, Netherlands: 42, Ireland: 62) and randomly stratified into the three groups (AE = 60; ST = 65; CG = 58). Trial recruitment rates differed significantly between the three sites, as discussed previously [529]. Five participants dropped out in the AE group (8.6%), six participants in the ST group (9.2%), and six participants in the CG (10%). None of the dropouts were directly related to the intervention, but were due to personal or medical reasons, such as the loss of a relative or diagnosis of cancer. Participant recruitment, screening, enrollment and attrition are depicted in Figure 12.

Participant characteristics differed between the exercise group and the CG. The CG had a significantly higher proportion of women and a significantly lower hand grip strength in comparison to the exercise group (Table 7).

Table 7: Group demographics

	Exercise (AE+ST)	**AE**	**ST**	**CG**
	n=125	**n=60**	**n=65**	**n=58**
Female. n(%)	51 (40.8)*	28 (46.7)	23 (35.4)	35 (60.3)
Age. mean (SD)	71.5 (6.4)	70.6 (6.1)	72.3 (6.6)	71.6 (6.9)
Centre				
IRE	41 (32.8)	18 (30.0)	22 (33.8)	21 (36.2)
NL	32 (25.6)	14 (23.3)	18 (27.7)	10 (17.2)
GER	52 (41.6)	27 (45.0)	25 (38.5)	27 (46.6)
Education. n (%)				
Low	8 (6.4)	3 (5.2)	5 (7.7)	6 (10.0)
Middle	56 (44.8)	21 (35.0)	35 (53.8)	33 (56.9)
High	61 (48.8))	36 (60.0)	25 (38.5)	19 (32.8)
MoCA. mean (SD)	22.8 (2.4)	22.6 (2.5)	22.9 (2.2)	22.4 (2.1)
Frailty				
TuG. mean (SD)	8.26 (2.13)	8.06 (1.99)	8.44 (2.25)	8.37 (2.07)
30s. mean (SD)	13.2 (3.7)	13.5 (4.1)	13.0 (3.5)	12.5 (3.2)
Hand grip. mean (SD)	33.5 (11.0)*	32.7 (11.1)	34.3 (10.8)	29.4 (10.2)
Exercise sessions. mean (SD)	94.2 (47.0)	96.6 (45.0)	92.1 (48.9)	-
Nr of medications used. mean (SD)	2.82 (2.75)	2.05 (1.73)	3.54 (3.29)$^{\&}$	2.43 (2.17)

Exercise: both aerobic exercise (AE) and stretching and toning (ST) exercise groups together; CG: control group. IRE: Ireland; NL: Netherlands; GER: Germany; Education categories: low <10 years of education, middle 10-13 years, high >13 years; MoCA: Montreal Cognitive Assessment, education-adjusted score; One-way ANOVA analyses were used to test differences between the exercise group and the control group or the AE and ST comparison* significant difference between exercise group and CG, $p<0.05$, $^{\&}$ significant difference between AE-ST, $p<0.05$. Independent t-test was used to test differences between the number of exercise sessions in AE and ST.

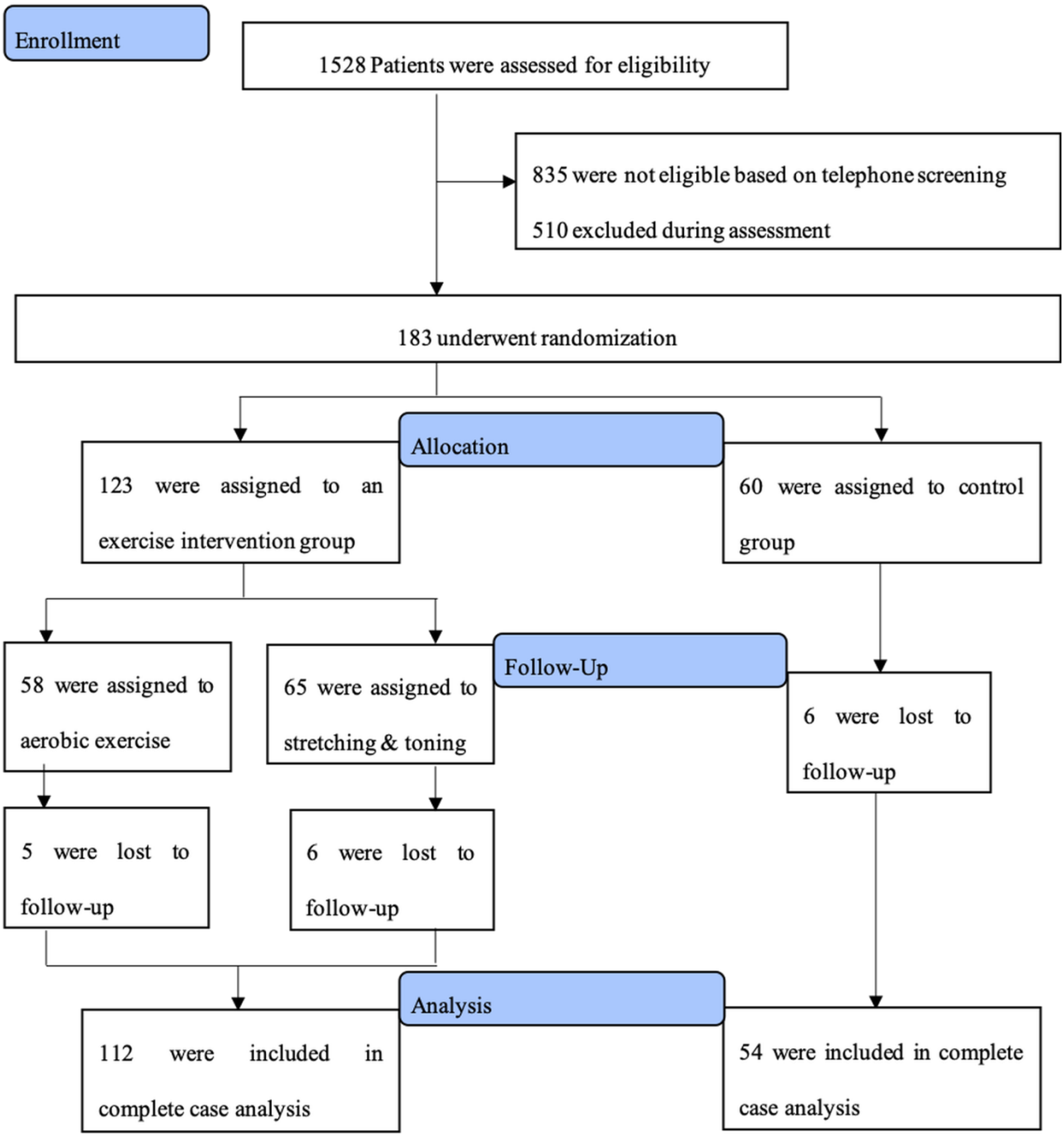

Figure 8: Trial profile

7.4.2. Complete case analysis

112 participants in the exercise group (AE = 53; ST = 59) and 54 participants in the CG were included in the CC analysis. Due to missing test results, outcomes have different numbers of cases included (Table 8). Individuals in the AE group participated in 96.6 ± 45.0 (mean ± SD) exercise sessions throughout the 12-month intervention period, while participants in the ST group exercised 92.0±49.3 times.

7.4.3. Complete case analysis – cognition & quality of life

ANCOVA did not show a significant difference in composite cognitive performance between the exercise group and the CG, nor between AE group and ST group, with effect sizes (ES) in the small range, Cohen's d 0.11 (exercise vs CG, mean difference [95% CI]), 0.12 [-0.03, 0.27]) and 0.22 (AE vs ST, 0.11 [-0.08, 0.26]) (Fig 13, Tables 8 and 9). Age ($p<0.001$), baseline cognitive functioning ($p<0.001$), but not gender ($p=0.45$) were associated with T2 cognitive composite performance. Furthermore, no significant differences were identified in any of the six cognitive domains nor quality of life between the exercise group and the CG (Tables 8 and 9). Again, baseline scores ($p<0.001$) were significantly associated with all of the T2 scores. Besides baseline scores, age had a significant association with visual memory ($p=0.007$), verbal memory ($p=0.001$), attention ($p<0.001$), executive function ($p=0.001$), and psychomotor function ($p=0.035$), but not with working memory ($p=0.054$) or quality of life ($p=0.730$). Gender was not associated with any of the aforementioned variables. ANCOVA showed a significant difference between the AE and ST groups for the domain attention ($p=0.011$ and small ES of 0.35, 0.39 [0.09, 0.67]), where the performance in the ST group was significantly higher compared to the AE group (Tables 8 and 9).

7.4.4. Complete case analysis – $\dot{V}O_2$peak

$\dot{V}O_2$peak improved significantly in the exercise group $p= 0.04$ compared to the CG and in the AE group $p=0.001$ compared to ST group, with medium ES of 0.40 (-1.76 [-3.39, -0.10] and 0.60 (-3.10 [-4.95, -1.21]). ANCOVA revealed that baseline scores were associated with $\dot{V}O_2$peak at T2 ($p<0.001$), but not age ($p=0.88$) nor gender ($p=0.45$).

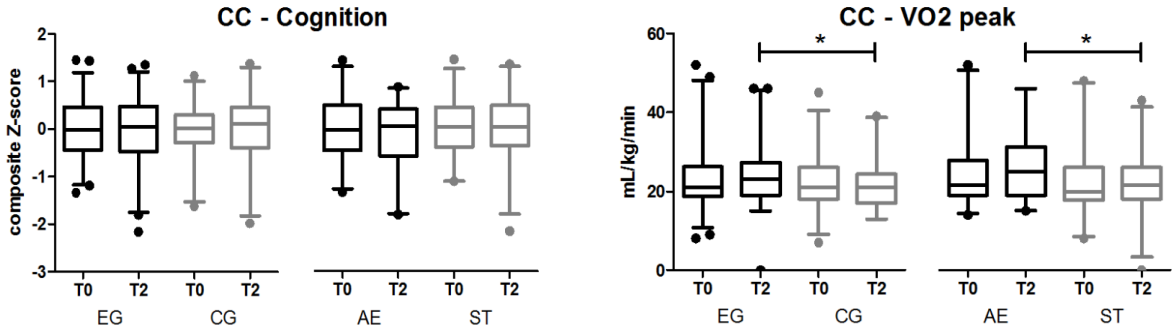

Figure 9: Results of the primary outcome: composite cognitive score for complete case (CC) analysis; results of $\dot{V}O_2$peak for complete case analysis. Boxplots of mean z-scores and 95% CI of EG: Exercise group (AE and ST together). CG: control group, AE: aerobic exercise and ST: stretching and toning exercise. No differences in the comparison between T2 results of the groupsfor cognition.: *: significant difference EG vs CG and AE vs ST, $p<0.05$ for $\dot{V}O_2$peak

7.4.5. Secondary per protocol and per centre analysis

166 participants (IRE = 56; NL = 36; GER = 74) were included in the secondary analysis. In IRE 19 participants were in the NPP group, 17 participants in the PP group, and 20 participants in the CG. In the Netherlands 8 participants were in each the NPP and the CG, and 20 participants in the PP group. 30 individuals were in the NPP group, 18 in the PP group, and 26 in the CG in Germany. Mean differences for composite cognitive score, quality of life and cardiorespiratory fitness for each group in each centre (T2 – T0) are presented in Figure 14.

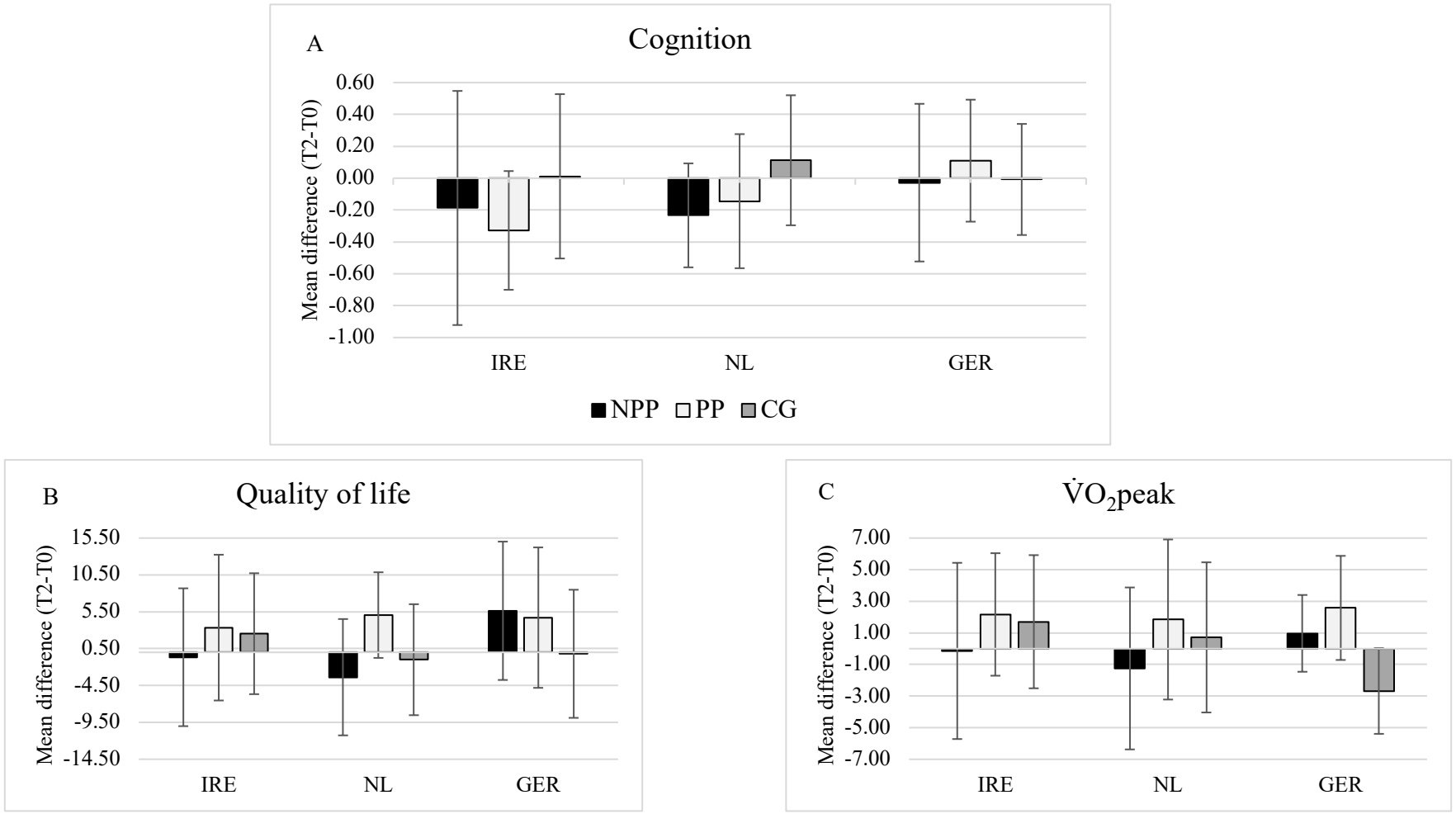

Figure 10: Mean differences for Cognition (A), Quality of Life (B), and $\dot{V}O_2$peak (C) divided by participation and centre (NPP = not per protocol; PP = per protocol; CG = control group; IRE = Ireland, NL = the Netherlands; GER = Germany)

7.4.6. Secondary analysis – cognition

Secondary ANCOVA analysis revealed no effect of group (p = 0.069) but an effect of centre (p = 0.005) on T2 cognitive composite scores. No significant interaction effect between centre and per protocol participation for cognitive composite scores (p=0.153) was found. Age (p<0.001) and cognitive functioning at baseline (p<0.001) were associated with T2 cognitive composite scores. No influence of gender (0.673) was identified.

7.4.7. Secondary analysis – $\dot{V}O_2$peak

Per protocol participation (p<0.001), but not centre (p=0.772) had an influence on $\dot{V}O_2$peak at T2 and ANCOVA revealed a significant interaction effect of centre*per protocol participation (p=0.021). Post-hoc pairwise comparisons showed significant differences for participants in Germany, where individuals in both the PP (p=0.001) and NPP (p=0.019) groups had a significantly higher $\dot{V}O_2$peak compared to participants in the CG. Baseline $\dot{V}O_2$peak (p<0.001), but not gender (p=0.499) or age (p=0.726) were associated with T2 $\dot{V}O_2$peak.

7.4.8. Secondary analysis – quality of life

No effect of centre (p=0.225) or per protocol participation (p=0.051) was found on quality of life. However, a significant interaction effect (centre*per protocol participation) (p=0.01) was identified. Post-hoc pairwise corrections revealed that participants in the NPP group in Germany had a significantly better quality of life in comparisons to participants in IRE (p=0.034) and the NL (p=0.01). Furthermore, in Germany the NPP group had a significantly better quality of life than the CG (p=0.023) at T2. Baseline scores (p< 0.001), but not age (p=0.245) or gender (p=0.169) were associated with quality of life after 12 months. No further differences were found in the secondary ANCOVA analysis.

7.5. Discussion

7.5.1. Main findings

This multicentre randomized controlled trial analysed the effects of a 12-month structured exercise program (aerobic exercise or stretching and toning) on the progression of cognitive decline in individuals with aMCI. We did not identify an intervention effect on cognitive performance in the primary complete case analysis. Nevertheless, an intervention effect on physical fitness was identified with a medium ES (Cohen's d 0.40).

Collaboration of three research facilities provided the opportunity to analyse aMCI populations across three different countries in North-West Europe. Furthermore, strict inclusion and exclusion criteria ensured a diagnosis of aMCI by using delayed recall scores from standardised memory tests to address limitations of previous studies. An extensive neuropsychological test battery was administered, and composite scores calculated to provide insight into both general cognitive performance and domain-specific cognitive function before and after participation.

Recently, two independent systematic reviews [35, 36] as well as the AAN [3] suggested a positive effect of exercise on cognitive function in individuals with MCI. However, the results of our study do not corroborate this, as neither the exercise groups nor the CG improved or decreased their cognitive performance over the period of 12 months. Even though it can be argued that a stable cognitive function may be positive for individuals with MCI, other studies demonstrated improvements on specific cognitive tests after an exercise intervention [33, 278, 530-532]. In contrast to previous studies, we used composite outcome measures for different cognitive domains based on standardised neuropsychological tests, which is considered the best approach to detect cognitive changes in individuals at risk of AD [348].

To date, it is unclear which people with MCI progress to dementia, remain stable, or reverse to normal cognitive function and studies report different numbers that may explain outcomes of our study. The AAN summarized findings of different studies and calculated a cumulative risk of 14.9% for the development of dementia in individuals with MCI within two years [3]. However, other studies also showed a reversion to unimpaired cognitive function on their follow-up measurements in 14.4%, 33.3%, 19%, and 38% of their respective participants

[533-536]. Individuals with aMCI are reportedly at a higher risk of progressing to dementia [168, 536-538], but over the course of 12 months stability in cognitive function may be the most frequently observed outcome [538-540]. Ganguli and colleagues reported a progression to dementia of only 1.4% for individuals with aMCI with 77.8% remaining stable and further 15.4% improving their cognitive function back to normal after twelve months [538]. Therefore, mixed outcomes in different studies may be expected in a cohort of individuals with any type of MCI.

MCI does not have one single cause (multicausality [14, 541]), which might explain the different outcomes observed in our and other studies as it is unlikely that one single treatment (e.g. exercise) will prove to be an effective intervention for all individuals. Multidomain-type (e.g. diet, exercise, cognitive training) interventions in the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) showed positive results on global cognitive function, as well as on processing speed and executive function in a sample of older individuals at risk for cognitive decline [27, 542]. However, the FINGER study showed this significant treatment benefit in a cognitively unimpaired sample of older adults at risk for future cognitive decline, but not in individuals with diagnosed MCI [27].

Despite the lack of significant differences in cognitive function, physical fitness - measured by $\dot{V}O_2$peak - increased significantly in the exercise group compared with the CG, and in the AE group compared with the ST group. These findings are in line with existing literature, as standardised exercise training increases physical fitness [543]. Even though a direct effect of an increased $\dot{V}O_2$peak on cognition was not detected, higher physical fitness might be an important outcome for future disease progression. Previous research showed that higher physical fitness during mid-life and late-life (e.g. higher $\dot{V}O_2$peak values) is positively associated with cognitive function in older adults with and without cognitive impairment [26, 374]. Individuals with MCI have an increased risk of being socially isolated, which increases the risk of future progression to dementia [331-333]. Previous studies showed that higher physical fitness leads to an increase in self-confidence, which consequently may increase social participation [334, 335]. Therefore, improving physical fitness may not only benefit cognitive function, but also may be the driving force for a socially integrated and fulfilling life during later life – especially in individuals with MCI. However, further evidence (e.g.

longer intervention periods, follow-up assessments) is required to establish the beneficial effects of an increased $\dot{V}O_2$peak on cognitive decline.

Moreover, increased fitness likely induces structural changes such as an increased hippocampal volume and an improved white matter integrity [268, 345, 379, 434, 544-546]. Findings to date are equivocal if exercise induced structural changes influence cognitive function directly or if structural changes may rather be beneficial for sustaining cognitive functions long-term [547]. To further explore this hypothesis, data from physiological measurements (e.g. MRI scans) is needed to provide insight into physiological mechanisms triggered by an increased physical fitness.

While no effective treatment currently exists for AD, a large number of mechanisms related to AD genetics and different modifiable risk factors, as well as protective factors (such as exercise) have been identified [548-550]. Given the large heterogeneity in current studies, it may be time to rethink future trials whereby personalized precision prevention may be the most appropriate approach, in which an intervention is prescribed in response to each individuals' modifiable risk factors [551]. A possible next step towards this may include a responder analysis to identify which individuals with MCI benefit most from an exercise intervention [552]. Further research is needed to better define the biomarkers or cognitive profile that best predicts different subtypes of MCI, especially those at the highest risk to progress from the preclinical stages of MCI towards dementia due to AD [8, 553].

7.5.2. Secondary analysis – effect of research setting

Participants in Germany exercising twice a week were the only participants in the exercise groups that tended to improve their cognitive function based on a positive difference between T2 and T0. Additionally, physical fitness and quality of life significantly improved in the exercise groups in comparison to the control group in Germany, whereas no significant changes for any outcome in Ireland and the Netherlands were found. Therefore, we speculate that a non-medical setting and a non-medical research community might have additional effects on improving fitness and may have additional benefits for quality of life in individuals with MCI [529]. Even though multicentre clinical studies in elderly with cognitive impairment are the backbone of evidence-based prevention, complete standardization is difficult to obtain in the different research facilities involved. Whereas the exercise classes

in Germany were all supervised, participants in Ireland and the Netherlands partly exercised on their own. Even though all participants were instructed on exercise duration and intensity [352], unsupervised exercise training may compromise treatment fidelity, which may explain findings of the secondary analysis.

7.5.3. Strength and Limitations

This study has several strengths including its large sample size, its strict inclusion of individuals with aMCI, its long intervention period (12 months) and its multicentric design. Furthermore, different cognitive tests were combined into one overall score of cognitive function (primary outcome), but also for different subdomains of cognitive function to provide a psychometrically more reliable and thus more valid construct [348]. However, subtle changes may be easier detected in single tests – even though they are also prone to false positives/ type I error.

One of the limitations of the study was that the recruitment aim of 225 individuals with aMCI (75 per centre), was not achieved. Nevertheless, recruitment numbers were sufficient regarding the power calculation for primary analysis. As numbers were significantly lower in the secondary analysis due to the differentiation by centre results of it need to be interpreted cautiously. Despite difficulties in recruitment, dropout rates were less than 10% in all groups, which shows a good acceptance of the study and the high motivation of the participants. However, only 53% of participants reached the target exercise frequency, which was defined as 100 exercise sessions (or more, at least twice a week) within the intervention period of 12 months according to recent recommendations of the AAN [3]. In comparison to previous studies the low number of participants following the per-protocol intervention may have been due to a longer intervention period (12 months) and strict and conservative target exercise frequency. The low dropout rate and more than half of the intervention group following the strict protocol is already a promising result for this inactive participant selection, which is reflected by a low baseline cardiorespiratory fitness in comparison to population reference values [409, 410]. As the best dose-response relationship of exercise on cognitive function is frequently discussed, yet still unknown [71], future exercise prevention trials should concentrate on defining the best dose-response relationship.

Different tests for $\dot{V}O_2$peak were applied, which was due to different regulations by the institutional review boards [352]. Effects of these differences were minimized by using standardised and validated $\dot{V}O_2$peak measurements at all sites. Significant differences between the groups' baseline characteristics are reported, however, these occurred rather by chance than by bias [554, 555], as a centrally controlled computer-generated randomization list (for each country), which was controlled by an independent statistician, was used. There is ongoing discussion whether to report differences in baseline characteristics or not [555]. Given the large heterogeneity observed in individuals with MCI, we presented baseline statistics to identify possible confounders. The exercise groups and CG had a different proportion of women and men with significantly more women being in the CG. While this may have biased the results, as women are at a higher risk to progress to dementia [556], we calculated an ANCOVA to statistically adjust for the effect of sex. The different proportion of women and men might also account for the differences in hand grip strength between the exercise group and the CG. As men are reportedly stronger than women, a higher value in hand grip may be expected [557].

7.5.4. Conclusion

This study does not support the recommendation from small and short-term RCTs that an exercise intervention has an effect on cognitive performance in individuals with amnestic MCI. Nevertheless, we found a reliable intervention effect on physical fitness, which may be an important outcome for disease progression. Future trials need to target long-term follow ups (up to 5 years) to evaluate the efficacy of an increased physical fitness on cognitive decline. Moreover, the heterogeneity between subjects and centres in MCI may explain different findings within the study. Therefore, future trials should consider personalized intervention approaches or multidomain interventions.

7.6. Supplementary Tables

Table 8: Results of complete case analysis

	Exercise (AE + ST)						Aerobic training						Stretching and toning training						Control group					
	T0			T2			T0			T2			T0			T2			T0			T2		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
CC results																								
Cognition composite	125	0.01	0.59	113	-0.09	0.74	60	-0.01	0.62	54	-0.15	0.74	65	0.03	0.56	59	-0.02	0.74	58	-0.01	0.53	53	-0.01	0.69
$\dot{V}O_2$peak	116	23.21	7.78	98	24.15	8.13	58	24.21	8.21	47	26.33	8.31	58	22.21	7.25	51	22.14	7.49	57	21.63	6.42	49	21.32	5.68
DEMQOL	124	89.25	11.51	111	92.59	10.97	60	88.42	12.44	54	93.19	11.29	64	90.03	10.61	57	92.02	10.72	57	91.75	10.83	52	92.06	11.79
No of exercise sessions	121	94.25	46.95				57	96.63	44.99				64	92.13	48.89									
Visual episodic memory	124	-0.02	1.03	111	-0.02	1.08	59	-0.17	1.03	54	-0.17	1.11	65	0.11	1.02	57	0.12	1.03	58	0.05	0.94	53	0.19	1.06
Verbal episodic memory	124	-0.05	0.95	112	0.04	1.08	59	-0.11	1.04	54	0.03	1.18	65	0.00	0.87	58	0.04	0.99	58	0.12	0.94	53	0.12	1.04
Working memory	124	0.02	0.98	111	0.03	1.20	59	0.06	0.96	53	-0.02	1.17	65	-0.01	1.00	58	0.08	1.23	58	-0.05	1.04	52	0.04	1.16
Attention	125	0.00	0.77	113	-0.22	1.08	60	0.02	0.78	54	-0.37	1.17	65	-0.02	0.76	59	-0.08	0.97	58	0.01	0.82	53	-0.11	0.81
Executive	125	0.01	0.77	113	0.17	0.78	60	-0.05	0.82	54	0.09	0.79	65	0.08	0.71	59	0.23	0.76	58	-0.04	0.66	53	0.11	0.66
Psychomotor	123	0.07	0.97	112	-0.45	0.98	59	0.12	1.00	54	-0.48	0.90	64	0.01	0.95	58	-0.42	1.05	58	-0.14	1.05	53	-0.38	1.06

(AE= aerobic exercise; ST = stretching and toning training; SD =standard deviation)

Table 9: Results of the ANCOVA for the complete case analysis

	Comparison between exercise (AE and ST) and CG					Comparison between AE and ST				
		Effect size		Confidence interval 95%			Effect size		Confidence interval 95%	
	p – value	Cohens-d	mean diff	lower	upper	p - value	Cohens-d	mean diff	lower	upper
Cognition composite	0.12	0.11	0.12	-0.03	0.27	0.31	0.22	0.11	-0.08	0.26
$\dot{V}O_2$peak	0.04	0.40	-1.76	-3.39	-0.10	0.01	0.60	-3.10	-4.95	-1.21
DEMQOL	0.21	0.02	-1.89	-4.59	1.00	0.31	0.11	-1.51	-4.71	1.51
Visual episodic memory	0.29	0.21	0.17	-0.14	0.47	0.53	0.31	0.16	-0.24	0.46
Verbal episodic memory	0.98	0.04	-0.01	-0.23	0.23	0.61	0.01	-0.04	-0.33	0.19
Working memory	0.82	0.02	0.04	-0.30	0.38	0.48	0.2	0.17	-0.25	0.52
Attention	0.25	0.10	0.14	-0.11	0.41	0.01	0.3	0.39	0.09	0.67
Executive	0.83	0.05	0.03	-0.14	0.18	0.74	0.2	0.03	-0.15	0.21
Psychomotor	0.13	0.07	0.24	-0.07	0.53	0.48	0.07	0.15	-0.21	0.46

(AE= aerobic exercise; ST = stretching and toning training; SD =standard deviation)

Table 10: Detailed overview of the cognitive test battery

Domain	Test	Unit	Reversed score
Verbal memory	International shopping list	Number of correct responses	-
	International shopping list delayed recall	Number of correct responses	-
Psychomotor function	Detection Task	Accuracy/Reaction time in ms	-
Executive function	Trail Making Test B/Trail Making Test A	Time in s	Yes
	Letter Fluency	Number of correct responses	-
	Category Fluency	Number of correct responses	-
Attention	Identification Task	Accuracy/Reaction time in ms	-
	Trail Making Test A	Time in s	Yes
Working memory	One Back Task	Accuracy	-
Visual memory	One Card Learning Task	Accuracy	-

The tasks international shopping list (direct and delayed recall), detection task, identification task, one back task, and one back learning task are part of a computer based CogState Battery (https://cogstate.com) [524, 525, 558] . The Trail Making Test A + B [380], as well as letter and category fluency tasks [389, 390] are paper and pencil tests. Score is reversed if a lower score = better performance

8. THE EFFECT OF DIFFERENT EXERCISE MODES ON DOMAIN-SPECIFIC COGNITIVE FUNCTION IN PATIENTS SUFFERING FROM PARKINSON'S DISEASE: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS

Chapter 8 includes the following manuscript:

The effect of different exercise modes on domain-specific cognitive function in patients suffering from Parkinson's disease: a systematic review of randomized controlled trials

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Author contributions: Student contribution to work: Involved in the conception of the study, collected all data, analysed and interpreted data, was responsible for writing all drafts of the manuscript including preparation of all figures and tables, and modified drafts following co-author recommendations.

Conceived and designed the experiment: TS, CDA, SS

Analysed the data: TS, CDA; ALM, RB, JW

Wrote/reviewed the paper: TS, CDA, ALM, RB, JW, SS

8.1. Abstract

Background: Supervised exercise training alleviates motor symptoms in people with Parkinson's disease (PD). However, the efficacy of exercise to improve nonmotor symptoms such as cognitive function is less well known.

Objective: To systematically review evidence on the efficacy of different exercise modes (coordination exercise, resistance exercise, aerobic exercise) on domain-specific cognitive function in patients with PD.

Methods: Parallel-group randomized controlled trials published before March 2018 were included. Primary outcome measures included global cognitive function and its subdomains, and the Unified Parkinson's Disease Rating Scale was included as a secondary outcome. Methodological quality was assessed using the Physiotherapy Evidence Database scale.

Results: The literature search yielded 2,000 articles, of which 11 met inclusion criteria. 508 patients (mean age 68±4 years) were included with a disease severity from 1 to 4 on the Hoehn & Yahr stage scale. Overall study quality was modest (mean 6 ± 2, range 3-8/10). In 5 trials a significant between-group effect size (ES) was identified for tests of specific cognitive domains, including a positive effect of aerobic exercise on memory (ES=2.42) and executive function (ES=1.54), and of combined resistance and coordination exercise on global cognitive function (ES=1.54). Two trials found a significant ES for coordination exercise (ES =0.84 – 1.88), which led to improved executive function compared with that of non-exercising control subjects.

Conclusion: All modes of exercise are associated with improved cognitive function in individuals with PD. Aerobic exercise tended to best improve memory; however, a clear effect of exercise mode was not identified.

8.2. Introduction

Parkinson's disease (PD) is a highly prevalent age-related condition with an average prevalence of 1601 per 100,000 population in North America, Europe and Australia [140, 559]. PD has traditionally been characterized as a movement disorder, but was recently redefined as a heterogeneous multisystem disorder [202] that includes non-motor symptoms such as hyposomnia [560, 561], mood disturbances [562-564] and, especially, cognitive decline. Up to 57% of patients suffering from PD develop mild cognitive impairment (MCI) within 5 years of their initial diagnosis [565-567], and the majority will eventually develop dementia if they survive more than 10 years [202]. The underlying neurophysiological mechanisms for cognitive decline in PD are not completely understood, but an accumulation of amyloid plaques, mitochondrial dysfunction and neurotransmitter changes are all suggested to contribute [202, 204-206].

As part of efforts to develop effective treatments and strategies to prevent cognitive decline in older adults, exercise has shown promising results. Regular physical exercise promotes angiogenesis, neurogenesis and synaptic plasticity [223, 232, 233] and has the potential to protect cognitive function with ageing [28, 71, 219]. In PD, different exercise modes (e.g. aerobic training [247-249], resistance training [250-252], forced exercise training [253, 254], dance [255, 256] and balance training [257-259]) have all been shown to improve motor symptoms such as tremor, gait disturbances, postural instability, and bradykinesia. While recently published guidelines do not recommend one specific exercise mode [260], it has been previously suggested that a combination of exercise modes might be best to improve motor function in individuals with PD [261].

Less is known about the effects of exercise on cognitive function in individuals with PD, and the influence of specific modes. Previous reviews suggested that both aerobic and resistance training, or a combination of them, might influence cognitive function positively [247, 250, 262]. However, other reviews have suggested that various forms of physical activity, including aerobic, resistance and coordination exercises such as Qigong and Tai Chi, have negligible effects on cognitive function [263, 264]. These inconsistent findings are likely influenced by the wide range of exercise modes (i.e. aerobic, resistance & balance training)

that have been used. Furthermore, there are reports that the exercise-induced benefits on cognitive function might be domain specific (e.g. related to attention, processing speed, executive function, memory, or working memory) [69, 70, 265]. For this reason, it is important to consider domain-specific neurocognitive outcomes to gain a better understanding of the effects of exercise on cognitive function in PD [69, 70, 89].

This is supported by emerging human and animal evidence that each mode of exercise training has a distinct influence on brain function [236, 238, 272, 317, 321, 322, 568]. Coordination training, but not aerobic training, is associated with improved speed of processing [319]; whereas memory is improved with aerobic training and not coordination training in healthy older adults [314]. Improvements in memory were associated with an increased hippocampal volume, while the increase in speed of processing was associated with an increased volume in the basal ganglia (globus pallidus) [314, 319]. These divergent effects on brain function suggest that different exercise modes are likely to influence cognitive function differently, but this has yet to be firmly established in individuals with PD.

Therefore, the purpose of the current study was to compare the effects of different exercise modes on various measures of cognitive function in individuals with PD by systematically reviewing previous randomized controlled trials. The primary aim was to compare the effects of aerobic training, resistance training and coordination training on cognitive function. Furthermore, the secondary aim was to identify combinations of different exercise modes (e.g. aerobic and resistance training) and evaluate their effect on cognitive function. With this approach, this study aimed to determine the most effective forms of exercise to address the specific cognitive impairments associated with PD.

8.3. Materials and Methods

This systematic review was conducted following the international guidelines established by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [569].

8.3.1. Data search

Five electronic databases were searched to identify relevant publications: PubMed, Cochrane Central Register of Controlled Trials, Scopus, LIVIVO and Web of Science. Relevant keywords from three categories – "disease", "exercise" and "cognition" – were combined with each other, and entered in the different databases. The category *disease* referred to idiopathic PD, *exercise* referred to the different exercise modes used as intervention therapies, and *cognition* refers to the different types of cognition related outcome measures. Search terms and strategies for each database are presented in Supplementary Material (Tables 22-26). Additional studies were identified through the reference lists of all retrieved articles. This review was registered in the international database of prospectively registered systematic reviews in health and social care (PROSPERO; CRD42018087575), available at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018087575. Only studies published in English were included.

Inclusion criteria according to the PICO (population, intervention, comparator, outcome) [570] format was used to select eligible studies. Only randomized controlled trials (RCTs) were included. Study populations consisted of individuals with idiopathic PD without any restriction placed on the stage of the disease or its severity. Trials targeting secondary or acquired PD were excluded. Exercise programs lasting at least 4 weeks with at least one supervised exercise session per week were considered eligible. Exercise interventions included aerobic training, resistance training, coordination training or a combination of any of these exercise modes. Studies that evaluated the combination of an exercise intervention with other treatments (e.g. drug therapy, education programs) were excluded.

The primary outcome measure was cognitive function assessed by a valid and standardised measurement (e.g. neuropsychological tests) at baseline and after the intervention. Measures of cognitive function were further stratified into different cognitive domains, similar to that used by Smith et al [70] and Engeroff et al [69]. The domains were global cognitive function, attention, executive function, speed of processing, memory and "other" (see Table 11). Outcomes related to attention were subdivided into general attention and speed of processing, whereas outcomes for working memory and memory, which are often used interchangeably [82], were combined into a single category.

The Unified Parkinson's Disease Rating Scale (UPDRS) [571] was included as a secondary outcome as it is commonly used to assess the longitudinal course of PD. The UPDRS consists of six different parts that can be assessed on their own or as a summative score.

Table 11: Domain-specific cognitive tests included in this review

Global Cognitive Function	Attention	Executive Function	Speed of processing	Memory	Other
Montreal Cognitive Assessment [597-599]	Trail Making Test A [596, 597, 600]	Stroop Color and Word test (interference condition) [591, 600]	Stroop Color and Word Test (word reading and color naming condition) [591, 596, 600]	1- and 2-back task [591]	Mental Rotation score [595]
Mini-Mental State Examination [594]	Digit-Span Forward and Backward test [591, 596, 600, 601]	Visual memory updating task [591]	0-back task [591]	Wechsler Memory Scale Logical Memory [594]	Sentence generation task [591]
Mattis Dementia Rating Scale [591]	Semantic Fluency Test [600]	Operation Span task [591]	Digit Symbol Substitution task [591]	Memory interference test [597]	Intersecting pentagons task & Benton Line orientation task [600]
	Letter Fluency Task [600]	Wisconsin Card Sorting Test [593, 594]	Phonemic Fluency Test [600]	California Verbal Learning Test (immediate and delayed recall) [600]	
	2nd letter of alphabet task [592]	Raven colored matrix [593]	Category Fluency Task [600]	Rey-Osterrieth (Rey-O) Complex Figure test [600]	
	Corsi block test [600]	Trail Making Test B [596, 597, 600]			
		Frontal Assessment Battery [595, 597]			

8.3.2. Study selection

One reviewer conducted the literature search (T.S.) and downloaded the results from all databases into bibliographic software (EndNote X8; Thompson Reuters, New York, USA). After eliminating duplicates, titles and abstracts were screened to identify eligible papers. Full texts of eligible studies were obtained and assessed. Quality of the eligible papers was assessed separately and in duplicate by three reviewers (T.S., R.B. & J.W.) using the Physiotherapy Evidence Database Scale for randomized controlled trials (PEDro) [572]. One reviewer (T.S.) extracted the data from included studies and two reviewers checked the accuracy of extracted data (R.B. & J.W.). Disagreements between reviewers were resolved by consensus or by a third reviewer when necessary.

Data extracted from each included trial consisted of (1) characteristics of trial participants, (2) characteristics of the exercise training intervention(s) (e.g. frequency, duration, mode), (3) methods used to assess primary and secondary outcomes, and (4) assessment of between-group comparative data before (baseline) and after intervention.

8.3.3. Data analysis

Trials were divided according to the different types of exercise interventions and subdivided into aerobic training, resistance training, coordination training or combined exercise modes. When trials contained two (or more) different exercise intervention groups, both were compared to the control group and to each other separately. The included studies used different neuropsychological tests to assess cognitive function (primary outcome). Due to this large variety of tests, a meta-analysis could not be conducted. Corresponding authors were contacted when data were missing or when data were not reported as mean and standard deviation (SD).

Pre-post intervention changes in mean and SD were used to calculate mean differences and between-group effect sizes (ES). Hedges' bias-correction for small sample sizes was applied and between-group ES and 95% confidence intervals (CI) were calculated as follows: between-group ES = (Δtreatment – Δcontrol)/ pooled baseline SD, where Δ describes the change between pre- and post-measurements. In cases where the required data for ES

calculations were not reported and could not be obtained from the corresponding authors, the mean and SD were estimated where possible using Hozo's equation [573]. To correct for differences in the direction of the scale of tests within a cognitive domain, we followed the Cochrane handbook for systematic reviews and multiplied the mean values by -1 [574]. ES were classified as 'trivial' (<0.20), 'small' (≥0.20 to <0.50), 'moderate' (≥0.50 to <0.80), and 'large' (≥0.80) [442]. ES and 95% CIs are shown as forest plots. The between-group ES did not reach a level of statistical significance ($p<0.05$) when the CI crossed the vertical midline (zero) [575].

8.4. Results

A total of 2,000 citations were retrieved through the search strategy. After duplicates were excluded (n = 797), another 1,203 studies were discarded based on the abstract and title. Twenty-seven studies were retrieved for full-text examination; however, sixteen of these studies did not meet inclusion criteria and were subsequently excluded. Reasons for exclusion were: (1) non-randomized controlled trials (n = 9) [576-584], (2) control group performing exercise or cognitive training (n = 5) [585-589], (3) exercise intervention was not adequately described (n = 1) [590], or (4) duplicate data (n = 1). Thus, eleven studies were included in the systematic review (Figure 15) [591-601].

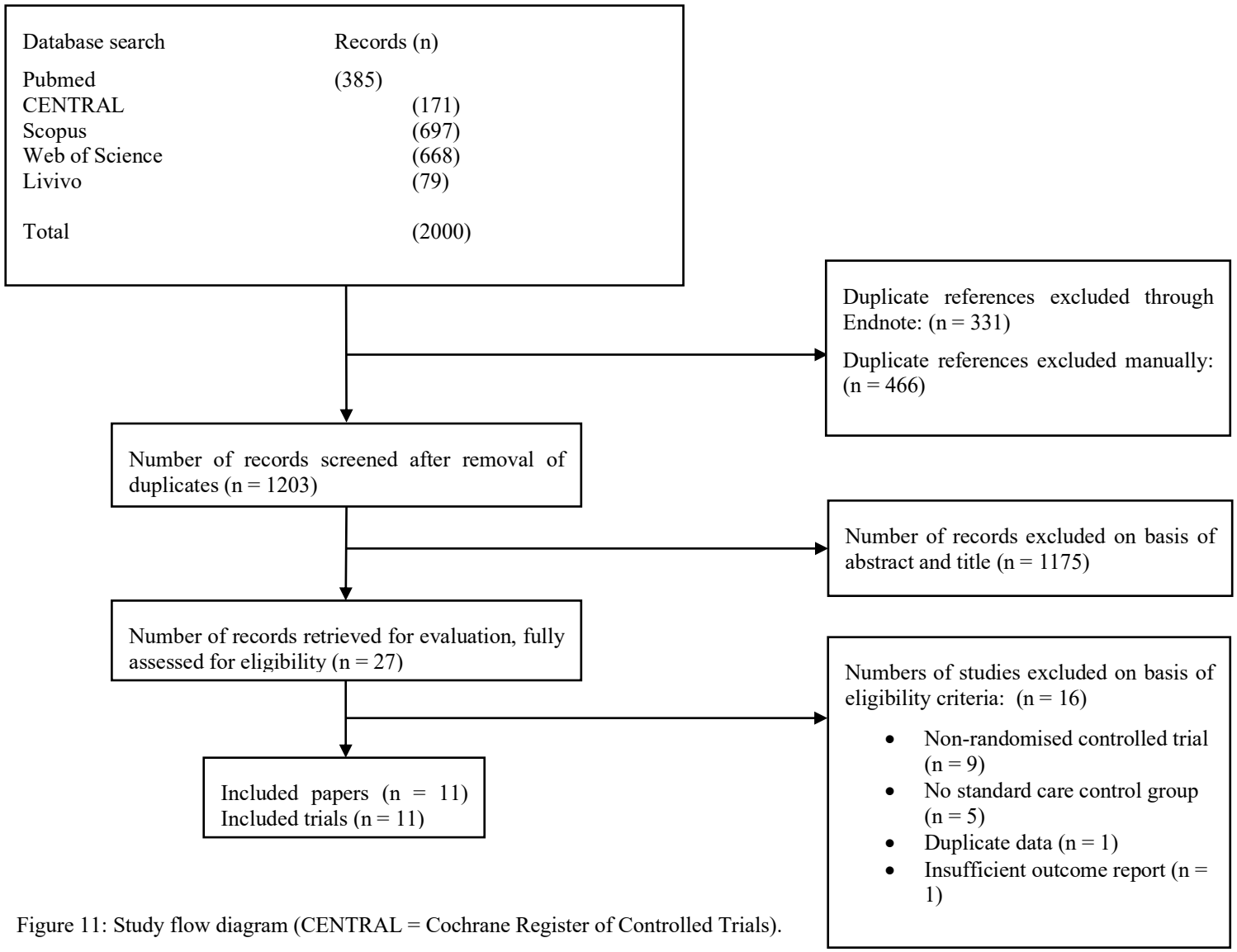


Figure 11: Study flow diagram (CENTRAL = Cochrane Register of Controlled Trials).

8.4.1. Results – Quality Assessment

The included studies had a modest overall quality based on the average PEDro score (mean ± SD 6 ± 2, range 3-8/10, Table 12). The participants in all included studies were randomly allocated to their respective group and baseline characteristics only differed significantly in one study, where the control group had more years of education [600]. Eligibility criteria was reported in seven of the eleven trials [592, 593, 595, 597-600], but none of the included studies reported blinding of the exercise intervention therapists or participants. However, this is somewhat common and difficult to avoid in trials that evaluate the effects of an exercise intervention. Apart from two studies [598, 600], all trials used blinded assessors, but only three studies presented sufficient information about concealed allocation [592, 595, 597]. Four studies had a greater drop-out rate than 15%, which might have had an effect on the outcomes of these studies [591, 594, 595, 600]. Most of the studies reported point measures and measures of variability (91%) as well as between group statistics (100%), but only three studies specifically stated that all participants received the originally allocated treatment (intention-to-treat analysis) [597, 598, 601].

Table 12: Quality assessment of the included studies (PEDro scale)

Study	Eligibility criteria specified[a]	Random allocation	Concealed allocation	Baseline similarity	Blinding of participants	Blinding of therapists	Blinding of assessors	Dropout <15 %	Intention-to-treat analysis	Between group statistics	Point measures and measures of variability	Final score (/10)
Hashimoto et al., 2015# [595]	YES	YES	YES	YES	NO	NO	YES	NO	NO	YES	YES	6
Rios Romenets et al. 2015# [598]	YES	YES	NO	YES	NO	NO	NO	YES	YES	YES	YES	6
Gobbi et al. 2013 [594]	NO	YES	NO	YES	NO	NO	YES	NO	NO	YES	YES	5
Altman et al. 2016 [591]	NO	YES	NO	YES	NO	NO	YES	NO	NO	YES	YES	5
Conradsson et al. 2015 [592]	YES	YES	YES	YES	NO	NO	YES	YES	NO	YES	YES	7
De Oliveira et al., 2017# [593]	YES	YES	NO	YES	NO	NO	YES	YES	NO	YES	YES	6
Silva-Batista et al., 2016# [599]	YES	YES	NO	YES	NO	NO	YES	YES	NO	YES	YES	6
Silveira et al., 2018 [600]	YES	YES	NO	NO	NO	NO	NO	NO	NO	YES	YES	3
Nocera et al., 2013 # [596]	NO	YES	NO	YES	NO	NO	YES	YES	NO	YES	NO	5
Picelli et al., 2016 # [597]	YES	YES	YES	YES	NO	NO	YES	YES	YES	YES	YES	8
Yen et al., 2011 # [601]	NO	YES	NO	YES	NO	NO	YES	YES	YES	YES	YES	7

[a] Item does not contribute to total score; # = scores are available at PEDro database (https://www.pedro.org.au/) [54]

8.4.2. Study Characteristics

The study and patient characteristics are presented in Table 13. In total 904 participants were screened for eligibility and 508 participants were included in the different trials. Idiopathic PD was an inclusion criterion for all trials, and all but one trial [600] excluded participants with early signs of cognitive impairment. Most of the studies used a specific cut-off score of the Mini Mental State Examination to detect cognitive impairment (cut-off scores differed between 23 and 26). Most of the studies defined any other major comorbidities (such as cardiac diseases, other neurological disorders) as an exclusion criterion. Further, the studies that did not specifically exclude participants with depression or apathy, did not include participants with severe symptoms of these disorders according to the studies' different baseline scores [597, 598, 600]. A mean age of 68 ± 4 years was reported across the studies and the included participants' PD severity ranged from 1 to 4 on the Hoehn & Yahr stage scale [602].

Different exercise interventions were used by the included studies and a summary of the characteristics of the interventions is presented in Table 14. The intervention periods differed between four [597] and twenty-six [593] weeks, with an exercise frequency between once [595] and three times [591, 592, 596, 597, 600] a week. Five studies analysed the effects of aerobic exercises [591, 595, 597, 598, 600], one study the effects of resistance exercises [599], and five further studies the effects of coordination exercises [591-593, 596, 601]. In addition, three studies investigated the effects of combined resistance and coordination exercises [594, 595, 599]. In three of the included trials the control group met regularly to control for the effect of social interaction [594, 597, 599] and in one further study the control group was provided with information about the benefits of exercise [598]. In the other trials, the control group consisted of standard care and did not receive additional treatment [591-593, 595, 596, 600, 601].

Table 13: Study characteristics

Study	Country	Patients inclusion criteria	Group	N	Gender (%) male	Age (years)	BMI (kg/m^2)	Education years	Cognitive function assessment	Years living with the disease
Altmann et al. [591]	USA	HY 1 – 3 stable medication MMSE score of 25 or above	AE	11	NR	63 ± 9	NR	20 ± 4.	29.5 ± 1.0 MMSE	NR
			CE	9		63 ± 7		16 ± 4	29.4 ± 0.9 MMSE	
			CG	10		68 ± 10		17 ± 4	29.2 ± 1.0 MMSE	
Conradsson et al. [592]	Sweden	HY 2 – 3 stable medication MMSE score of 24 or above	CE	47	60	73 ± 6	22.1	NR	NR	6 ± 5
			CG	44	51	74 ± 5	22.3			6 ± 5
de Oliveira et al. [593]	Brazil	HY 1 – 3 absence of dementia (MMSE scores)	CE	7	57	75 ± 5	NR	4 ± 2	25.1 ± 2.8 MMSE	4 ± 3
			CE	8	75	75 ± 9		5 ± 5	26.3 ± 2.9 MMSE	4 ± 2
			CG	8	38	68 ± 6		4 ± 5	24.9 ± 2.4 MMSE	4 ± 1
Gobbi et al. [594]	Brazil	HY 1 – 3 stable medication no cognitive impairment (MMSE scores)	RE + CE	11	55	69 ± 11	NR	NR	27.2 ± 2.8 MMSE	NR
			RE + CE	10	40	68 ± 8			27.7 ± 2.2 MMSE	
			CG	13	46	67 ± 9			27.2 ± 2.7	
Hashimoto et al. [595]	Japan	HY 2 – 4	AE	15	25	68 ± 7	NR	NR	28.2 ± 2.0 MMSE	6 ± 5
			RE + CE	17	12	63 ± 15			28.5 ± 2.0 MMSE	8 ± 6
			CG	14	50	70 ± 4			28.3 ± 2.0 MMSE	7 ± 4
Nocera et al. [596]	USA	HY 2 – 3 stable medication	CE	15	47	66 ± 11	27.4	16 ± 3	27.5 ± 2.2 MMSE	8 ± 5
			CG	6	67	65 ± 7	25.4	15 ± 2	28.2 ± 2.3	7 ± 2

		MMSE scores of 26 or above							MMSE	
Picelli et al. [597]	Italy	HY 3 stable medication MMSE score greater than 24	AE CG	9 8	56 50	71 ± 9 72 ± 7	NR	NR	22.7 ± 5.3 MoCA 22.8 ± 4.6 MoCA	11± 6 11 ± 4
Rios Romenets et al. [598]	Canada	HY 1 – 3 stable medication absence of dementia	AE CG	18 15	67 47	63 ± 10 64 ± 8	NR	NR	27.0 ± 2.4 MoCA 26.7 ± 26.1 MoCA	6 ± 4 8 ± 5
Silva-Batista et al. [599]	Brazil	HY 2 – 3 stable medication absence of severe cognitive impairment (MMSE <23)	RE RE + CE CG	13 13 13	69 77 77	64 ± 9 64 ± 11 64 ± 8	25.5 25.0 24.3	9 ± 3 8 ± 3 9 ± 2	28.5 ± 1.9 MMSE 21.8 ± 4.3 MoCA 28.8 ± ± 1.7 MMSE 20.8 ± 3.2 MoCA 28.5 ± 1.8 MMSE 22.7 ± 5.7 MoCA	10 ± 4 11 ± 4 11 ± 6
Silveira et al. [600]	Canada	idiopathic PD cognitively normal & mild cognitive impairment	AE CE CG	22 21 15	82 57 73	71 ± 9 70 ± 8 68 ± 8	NR	15 ± 3 14 ± 3 17 ± 2	25.2 ± 4.5 MoCA 24.6 ± 4.0 MoCA 25.8 ± 5.0 MoCA	6 ± 5 6 ± 4 6 ± 6
Yen et al. [601]	Taiwan	HY 2 – 3 stable medication MMSE score greater than 24	CE CE CG	14 14 14	86 86 64	70 ± 7 70 ± 7 72 ± 6	22.9 22.9 23.0	NR	28.5 ± 1.6 MMSE 28.5 ± 1.2 MMSE 28.1 ± 0.8 MMSE	6 ± 3 6 ± 3 8 ± 4

(Values are mean ± SD; NR = not reported; AE = aerobic exercise; RE = resistance exercise; CE = coordination exercise; CG = control group; MoCA = Montreal Cognitive Assessment; MMSE = Mini-Mental State Examination; HY = Hoehn & Yahr)

Table 14: Characteristics of the exercise interventions

Study	Groups	Length (weeks)	Frequency (days/ week)	Duration (min/ session)	Modality	Intensity	Supervision/ settings
Altmann et al. [591]	AE	16	3	progressed from 20 to 45 minutes	Aerobic exercises + warm-up stretching	Intensity increased by 5% each week from 50% to 75% of maxHR	Supervised group sessions at university
	CE		3	NR	Stretching exercises (mostly seated) + balance tasks on a force platform	NR	
	CG		0	NA	Usual care without additional treatment	NA	NA
Conradsson et al. [592]	CE	10	3	60	Balance training including motor agility, stability limits and sensory integration	NR	Supervised group session at university hospital
	CG		0	NA	Usual care without additional treatment	NA	NA
de Oliveira et al. [593]	CE	26	2	60	10 minutes warm up, 25 minutes of strengthening and 25 minutes of balance and gait training	Borg scale 11 – 14	Supervised, individualized sessions
	CE		2	60			Supervised group sessions
	CG		0	NA	Usual care without additional treatment		NA
Gobbi et al. [594]	RE + CE	17	2	60	Multimodal exercise included resistance, motor coordination (rhythmic activities) and balance training	Heart rate monitor, heart rate remained between 60% and 595% of maxHR (220 – age)	Supervised group session
	RE + CE				Multimodal exercise (as described above) with additional emphasis on exercises for posture and gait		
	CG				Psychosocial interaction through non-motor activities (such as crafts, artistic and intellectual competencies)	NA	
Hashimoto et al. [595]	AE	12	1	60	Dance exercises (seated or standing) 20 minutes warm up, 35 minutes main lesson, 5 minutes relaxation	Heart rate monitor recorded an intensity	Supervised group sessions

	RE + CE				Multimodal exercises included light resistance exercises, gait training, flexibility and stretching	between 50 – 70% of maxHR	
	CG		0	NA	Usual care without additional treatment	NA	NA
Nocera et al. [596]	CE	16	3	60	Tai Chi was performed after a specific warm up with focus on kinaesthetic awareness	NR	Supervised group sessions
	CG		0	NA	Usual care without additional treatment	NA	NA
Picelli et al. [597]	AE	4	3	45	Treadmill training with differing speed (1.0 km/h, 1.5 km/h, 2.0 km/h)	NR	NR
	CG				Social interactions in group meetings without physical training	NA	
Rios Romenets et al. [598]	AE	12	2	60	Argentine tango was performed with a partner (mostly spouses or friends)	NR	Supervised group sessions
	CG		0	NA	No contact control group was provided with a pamphlet about exercise		NA
Silva-Batista et al. [599]	RE	12	2	50	Resistance training included a 10 minute warm up on a cycle ergometer followed by five resistance exercises, which load was progressively increased	NR	Supervised exercise sessions at a gym
	RE + CE				Followed same protocol as the other group with concurrent degree of instability in the exercises (e.g. balance pad)		
	CG		1	60	Control group included bingo games and education through lectures	NA	Group meetings
Silveira et al. [600]	AE	12	3	60	Training on a cycle ergometer; 5 min warm up followed by 30-40 min of aerobic training (by week four all participants exercised for 40 minutes) and 2 min cool down	40-50% of heart rate reserve was increased to 60-70% of heart rate reserve by week 4 using Karvonen formula	Supervised exercise sessions
	CE				20 – 30 minutes of non-aerobic gait exercises (focus on body coordination) and non-progressive muscle-toning exercises using resistance bands and own body weight	NR	Supervised exercise sessions
	CG		0	NA	Usual care without additional treatments	NA	

Yen et al. [601]	CE	6	2	30	Virtual-reality augmented balance training included a 10 minute warm up (stretching exercises), and 20 minutes of balance training on a virtual reality balance board. Exercises were 10 minutes of a 3 D ball-rolling game and 10 minutes of indoor-outdoor virtual activities	NR	Supervised exercise sessions
	CE				Balance training included a 10 minute warm up (stretching exercises) and a 20 minute balance training performed standing on pieces of foam under three conditions (static stance, dynamic weight shifting, and external perturbations)		
	CG		0	NA	Usual care without additional treatments	NA	NA

(AE = aerobic exercise; RE = resistance exercise; CE = coordination exercise; CG = control group; NR = not reported; NA = not applicable; HR = heart rate)

8.4.3. Outcome measures

Executive function was the most commonly assessed (n = 7) [591, 593-597, 600] cognitive domain followed by attention (n = 6) [591, 595-597, 600, 601]. Global cognitive function was analysed by five studies [591, 594, 597-599, 601]. Speed of processing (n = 3) [591, 596, 600, 601] and memory (n = 5) were also measured in multiple studies [591, 594, 597, 600, 601]. Furthermore, language [591], motor imagery [595], and visuospatial skills [600] were only assessed by a single study, respectively, and effect sizes for these measures are shown in the supplementary material (Table 27).

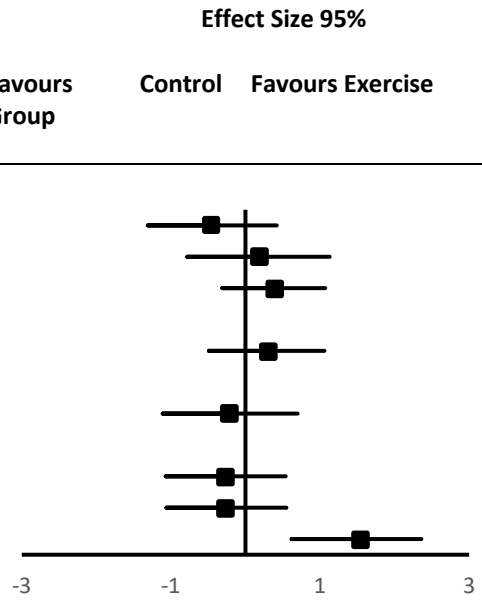
The neuropsychological tests most often used were the Montreal Cognitive Assessment score [597-599], the Trail Making Test A + B [596, 597, 600], the digit span forward and backwards [591, 596, 600], and the Stroop colors task [591, 596, 600].

8.4.4. Primary outcome – global cognitive function

Of the five studies assessing global cognitive function (Table 15) two performed an aerobic exercise intervention [597, 598] and one other study included an aerobic exercise intervention as well as a coordination exercise intervention [591]. One intervention consisted of resistance exercise and a combination of resistance exercise and coordination exercise intervention [599]. The fifth study analysed the effects of a combined resistance and coordination exercise intervention [594]. The between-group ES were trivial for aerobic exercises (0.04; range -0.46 – 0.39) and small for resistance exercises (ES=0.30) or the combined resistance and coordination exercises (0.33; range -0.27 – 1.54. The average between-group ES for coordination exercises was small and negative (ES=-0.22). Only one of the estimated ES reached the level of significance and was in favor of combined resistance and coordination exercises in comparison to the control group (ES=1.54; $p < 0.001$) [599].

Table 15: Effect size calculations for global cognitive function

Study	Control group Δ Mean ± SD	N	Exercise group Δ Mean ± SD	N	Mean difference [95% CI]
Aerobic exercise					
Altmann et al. [a] [591]	0.1 ± 4	10	-1.3 ± 1.7	11	-1.40 (-4.16 to 1.36)
Picelli et al. [b] [597]	0.6 ± 4.6	8	1.6 ± 5.3	9	0.93 (-4.25 to 6.11)
Rios Romenets et al. [b] [598]	-0.6 ± 2.8	15	0.4 ± 2.4	18	1.00 (-0.85 to 2.85)
Resistance exercise					
Silva Batista et al. [b] [599]	-1.1 ± 5.7	13	0.4 ± 4.3	13	1.5 (-2.59 to 5.59)
Coordination exercise					
Altmann et al. [a] [591]	0.1 ± 4	10	-0.6 ± 2.1	9	-0.70 (-3.85 to 2.45)
Resistance exercise + coordination exercise					
Gobbi et al. [c] [594]	0.8 ± 2.7	10	0.02 ± 2.8	13	-0.75 (-3.08 to 1.58)
Gobbi et al. [c] [594]	0.8 ± 2.7	10	0.1 ± 2.8	11	-0.67 (-2.88 to 1.54)
Silva Batista et al. [b] [599]	-1.1 ± 5.7	13	6 ± 3.2	13	7.10 (3.36 to 10.84)



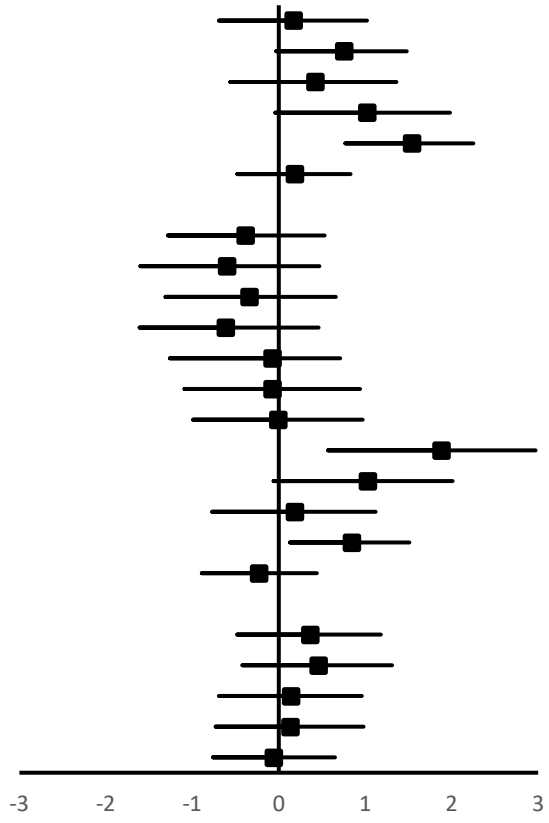
(forest plot detailing between-group effect size and 95% confidence intervals for each outcome in each trial; [a] = Mattis Dementia Rating Scale; [b] = Montreal Cognitive Assessment (MoCA); [c] = Mini-Mental State Examination (MMSE))

8.4.5. Primary outcome – executive function

A broad variety of neuropsychological tests were used to assess executive function, which contributes to the large range of mean differences (Table 16). The average between-group ES for aerobic exercise interventions was moderate (mean ES=0.68; range 0.17 – 1.54), whereas the average between-group ES for coordination exercise interventions (mean ES=0.13; range -0.62 – 1.88) and for combined resistance and coordination exercise interventions was trivial (ES=0.13; range -0.06 – 0.46. Significant improvements in executive function ($p < 0.05$) were found in three of the trial groups, which showed large ES and favored aerobic exercise [600] and coordination exercise interventions [593, 600] over the control group.

Table 16: Effect size calculations for executive function

Study	Control group Δ Mean ± SD	N	Exercise group Δ Mean ± SD	N	Mean difference [95% CI]
Aerobic exercise					
Altmann et al. [a] [591]	0.3 ± 1.0	10	0.4 ± 0.8	11	0.15 (-0.63 to 0.93)
Hashimoto et al [d] [595]	1.1 ± 1.8	14	3.1 ± 3.3	15	2.00 (-0.05 to 4.05)
Picelli et al. [e] [597]	14.1 ± 93.9	8	50.4 ± 80.2	9	36.32 (-53.65 to 126.29)
Picelli et al. [d] [597]	0 ± 2.1	8	2.6 ± 2.8	9	2.56 (-0.03 to 5.14)
Silveira et al. [e] [600]	-72.7 ± 70.5	15	17.3 ± 48.9	22	90.03 (50.26 to 129.80)
Silveira et al. [f] [600]	0.4 ± 11.5	15	2.68 ± 13.6	22	2.28 (-6.4 to 10.96)
Coordination exercise					
Altmann et al. [a] [591]	0.3 ± 1.0	10	-0.08 ± 0.8	11	-0.34 (-1.18 to 0.46)
de Oliveira et al [g] [593]	2.1 ± 17.2	8	-6.1 ± 7.6	7	-8.20 (-23.45 to 7.05)
de Oliveira et al [g] [593]	2.1 ± 17.2	8	-3.1 ± 12.7	8	-5.20 (-21.41 to 11.01)
de Oliveira et al [h] [593]	6.4 ± 20.7	8	-3.5 ± 16.1	7	-9.90 (-27.89 to 8.09)
de Oliveira et al [h] [593]	6.4 ± 20.7	8	1.1 ± 15.6	8	-5.30 (-24.96 to 14.36)
de Oliveira et al [k] [593]	4.3 ± 27.7	8	2.6 ± 12.2	7	-1.70 (-26.24 to 8.09)
de Oliveira et al [k] [593]	4.3 ± 27.7	8	4.1 ± 15.6	8	-0.20 (-26.33 to 25.93)
de Oliveira et al [l] [593]	-2.1 ± 2.6	8	2.4 ± 2.6	7	4.50 (1.82 to 7.18)
de Oliveira et al [l] [593]	-2.1 ± 2.6	8	1.3 ± 4.1	8	3.40 (-0.13 to 0.98)
Nocera et al [e] [596]	7.8 ± 23.1	6	15.4 ± 46.8	15	7.60 (-34.75 to 49.95)
Silveira et al. [e] [600]	-72.7 ± 70.5	15	-12.2 ± 72.8	21	60.55 (11.17 to 109.93)
Silveira et al. [f] [600]	0.4 ± 11.5	15	-1.9 ± 8.7	21	-2.26 (-9.11 to 4.59)
Resistance exercise + coordination exercise					
Gobbi et al [b] [594]	-0.8 ± 6.7	10	1.7 ± 7.1	13	2.52 (-3.57 to 8.61)
Gobbi et al [b] [594]	-0.8 ± 6.7	10	1.9 ± 5.1	11	2.72 (-2.68 to 8.12)
Gobbi et al [c] [594]	0.01 ± 1.9	10	0.2 ± 1.3	13	0.49 (-1.17 to 1.61)
Gobbi et al [c] [594]	0.01 ± 1.9	10	0.2 ± 0.7	11	0.19 (-1.12 to 1.50)
Hashimoto et al [d] [595]	1.1 ± 1.8	14	1.0 ± 1.7	17	-0.10 (-1.39 to 1.19)



(forest plot detailing between-group effect size and 95% confidence intervals for each outcome in each trial; [a] = composite z scores; [b] = Wisconsin Card Sorting Test (WCST) - perseverative errors; [c] =WCTS categories completed; [d] = Frontal Assessment Battery (FAB); [e] = Trail Making Test (TMT) B; [f] = Stroop Word & Color Interference; [g] = WCST – number of trials; [h] = WCST – correct answers; [k] =WCST - number of errors; [l] = Raven colored matrix)

8.4.6. Primary outcome – attention

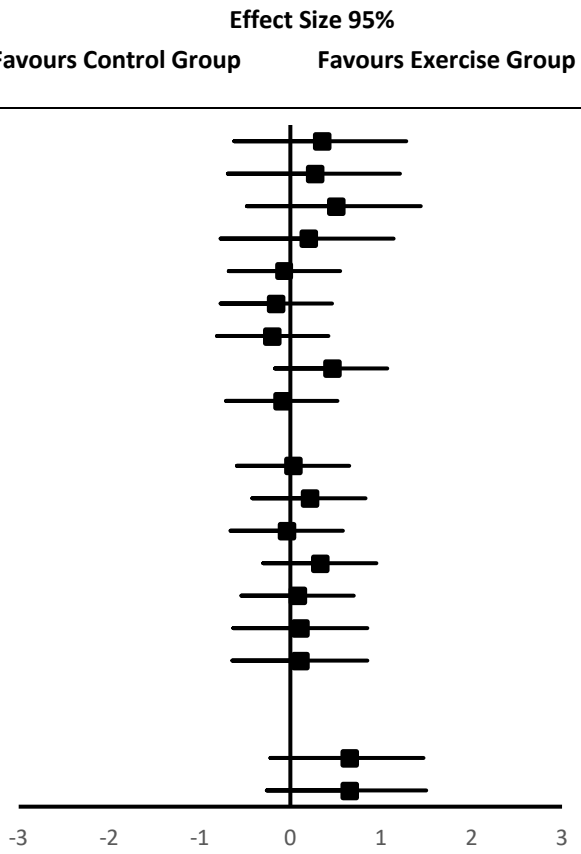
No significant ES were found for attention (Table 17). The average between-group ES were trivial for aerobic exercise interventions (mean ES= 0.02; range -0.2 – 0.46), small for coordination exercise interventions (mean ES= 0.20; range -0.04 – 0.35), and moderate for combined resistance and coordination exercise interventions (mean ES= 0.65).

8.4.7. Primary outcome – speed of processing

None of the included studies had a significant between-group ES for speed of processing (Table 18). The two studies [591, 600] that included aerobic exercise intervention (ES=-0.18; range -0.54 – 0.01) as well as the three studies with a coordination exercise intervention (ES=-0.03; range -0.40 – 0.38) had a trivial average between-group ES.

Table 17: Effect size calculations for attention

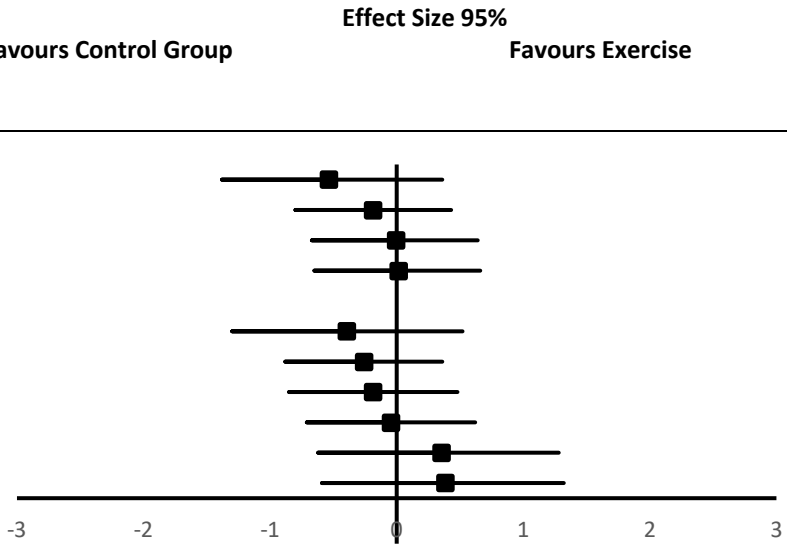
Study	Control group Δ Mean ± SD	N	Exercise group Δ Mean ± SD	N	Mean difference [95% CI]
Aerobic exercise					
Nocera et al. [b] [596]	0.2 ± 7.9	6	11.5 ± 32.7	15	11.30 (-21.76 to 44.36)
Nocera et al. [c] [596]	-1.4 ± 9.6	6	2.4 ± 15.7	15	3.80 (-10.38 to 17.98)
Nocera et al. [d] [596]	0 ± 2	6	1 ± 2	15	1.00 (-1.02 to 3.02)
Picelli et al. [e] [597]	-1.3 ± 101.3	8	20.3 ± 114.0	9	21.58 (-90.53 to 133.7)
Silveira et al. [f] [600]	-0.2 ± 2.3	15	-0.4 ± 2.5	22	-0.16 (-1.68 to 1.36)
Silveira et al. [g] [600]	0 ± 2.2	15	-0.4 ± 2.3	22	-0.36 (-1.81 to 1.09)
Silveira et al. [h] [600]	-0.1 ± 1.2	15	-0.3 ± 1.3	22	-0.25 (-1.06 to 0.56)
Silveira et al. [i] [600]	-3.6 ± 34.1	15	8.2 ± 14.6	22	11.73 (-4.45 to 27.9)
Silveira et al. [j] [600]	0.9 ± 4.5	15	0.6 ± 3.8	22	-0.35 (-2.73 to 2.03)
Coordination exercise					
Silveira et al. [f] [600]	-0.2 ± 2.3	15	-0.14 ± 2	21	0.06 (-1.30 to 1.42)
Silveira et al. [g] [600]	0 ± 2.2	15	0.4 ± 1.9	21	0.43 (-0.88 to 1.74)
Silveira et al. [h] [600]	-0.06 ± 1.2	15	-0.1 ± 0.9	21	-0.04 (-0.71 to 0.63)
Silveira et al. [i] [600]	-3.6 ± 34.1	15	6.1 ± 24.6	21	9.68 (-9.23 to 28.59)
Silveira et al. [j] [600]	0.9 ± 4.5	15	1.3 ± 4.8	21	0.39 (-2.59 to 3.37)
Yen et al [k] [601]	-22.3 ± 523.5	14	20.5 ± 195.1	14	42.80 (-264.1 to 349.7)
Yen et al [k] [601]	-22.3 ± 523.5	14	31.4 ± 422.4	14	53.70 (-315.83 to 423.2)
Conradsson et al [592]	UTC		UTC		UTC
Resistance exercise + coordination exercise					
Gobbi et al [a] [594]	-0.6 ± 1.8	10	0.61 ± 1.8	13	1.16 (-0.41 to 2.73)
Gobbi et al [a] [594]	-0.6 ± 1.8	10	0.3 ± 0.5	11	0.85 (-0.35 to 2.05)



(forest plot detailing between-group effect size and 95% confidence intervals for each outcome in each trial; [a] = Wisconsin Card Sorting Test (WCST) – failure to maintain set; [b] = Trail Making Test (TMT) A; [c] = letter fluency; [d] = digit backward; [e] = TMTA; [f] = digit forward; [g] = digit backward; [h] = Corsi block test; [i] = TMT A; [j] = letter fluency; [k] = digit backward; UTC = unable to calculate)

Table 18: Effect size calculations for speed of processing

Study	Control group Δ Mean ± SD	N	Exercise group Δ Mean ± SD	N	Mean difference [95% CI]
Aerobic exercise					
Altmann et al. [a] [591]	0.39 ± 0.92	10	-0.04 ± 0.69	11	-0.43 (-1.17 to 0.30)
Silveira et al. [b] [600]	-5.0 ± 6.8	15	-7.1 ± 4.9	22	-1.11 (-4.82 to 2.60)
Silveira et al. [c] [600]	-0.5 ± 19.8	15	-0.8 ± 21.7	22	-0.29 (-14.54 to 13.96)
Silveira et al. [d] [600]	-0.06 ± 16.3	15	0.09 ± 17.5	22	0.15 (-11.43 to 11.73)
Coordination exercise					
Altmann et al. [a] [591]	0.39 ± 0.92	10	0.05 ± 0.76	9	-0.34 (-1.16 to 0.48)
Silveira et al. [b] [600]	-5.0 ± 6.8	15	-6.8 ± 6.9	21	-1.80 (-6.18 to 2.58)
Silveira et al. [c] [600]	-0.5 ± 19.8	15	-4.1 ± 18.4	21	-3.52 (-16.57 to 9.53)
Silveira et al. [d] [600]	-0.06 ± 16.3	15	-0.72 ± 12.0	21	-0.66 (-10.25 to 8.93)
Nocera et al. [d] [596]	0.9 ± 3.8	6	3.8 ± 9.5	15	2.9 (-5.58 to 11.38)
Nocera et al. [b] [596]	-0.5 ± 4.6	6	1.8 ± 6.5	15	2.3 (-3.82 to 8.42)



(forest plot detailing between-group effect size and 95% confidence intervals for each outcome in each trial; [a] = composite z scores; [b] = category fluency; [c] = Stroop Word; [d] = Stroop Color)

8.4.8. Primary outcome – memory

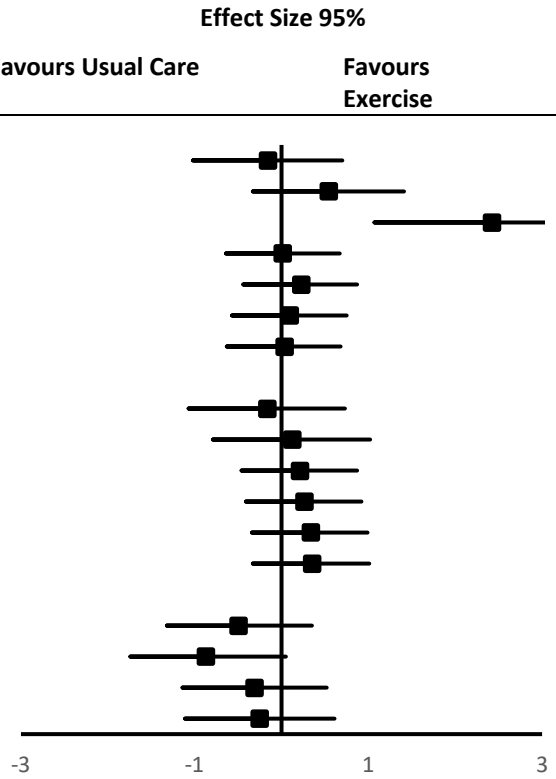
Four studies used different neuropsychological tests to assess memory (Table 19). Two of them investigated the effects of aerobic and a coordination exercise interventions [600], whereas the other two investigated the effects of aerobic exercise [597], and combined resistance and coordination exercise [594]. Average between-group ES was trivial for coordination exercise interventions (ES=0.18; range -0.17 – 0.35) and small for both aerobic exercise interventions (ES=0.45; 0.01 – 2.42) and combined resistance and coordination exercises (ES=-0.49; range -0.88 - -0.26). One trial demonstrated a significant ES in favor of the aerobic exercise intervention (ES= 2.42; $p<0.001$) [597].

8.4.9. Aerobic vs. coordination exercise

Besides comparing the outcomes to a control group, one study compared an aerobic exercise intervention with a combined resistance and coordination exercise intervention (ES=0.79) [595] and two other studies compared the effects of an aerobic exercise intervention with a coordination exercise program [600]. Table 20 shows the between-group ES for these studies across several cognitive domains. The average between-group ES for the comparison of aerobic exercise and coordination exercise interventions was trivial (ES=-0.04; range -0.6 – 1.09). However, two trials revealed a significant ES, and both favored aerobic exercise with a large ES (1.09) for memory [591] and a moderate ES (0.79) for executive function [595], in each study respectively.

Table 19: Effect size calculations for memory

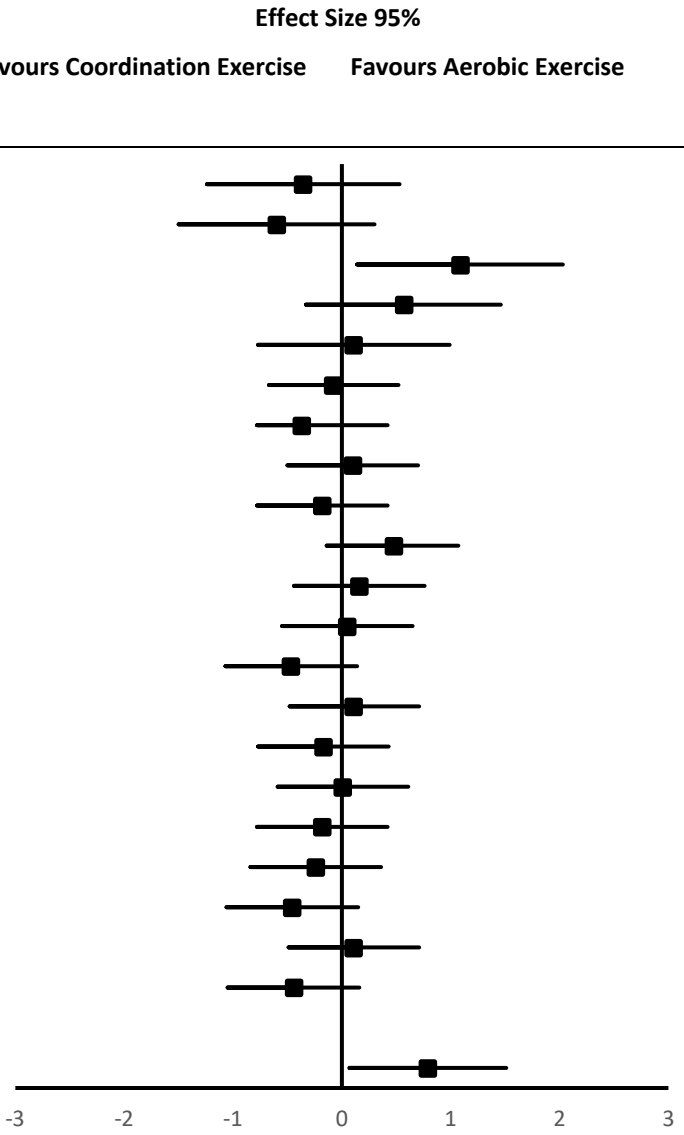
Study	Control group Δ Mean ± SD	N	Exercise group Δ Mean ± SD	N	Mean difference [95% CI]
Aerobic exercise					
Altmann et al [h] [591]	0.09 ± 0.14	10	0.06 ± 0.14	11	-0.02 (-0.57 to 0.39)
Altmann et al [i] [591]	-0.07 ± 0.23	10	0.06 ± 0.23	11	0.13 (-0.08 to 0.34)
Picelli et al. [c] [597]	-0.31 ± 1.57	8	3.0 ± 1.18	9	3.31 (1.89 to 4.73)
Silveira et al. [d] [600]	0.06 ± 1.95	15	0.09 ± 2.12	22	0.03 (-1.41 to 1.47)
Silveira et al. [e] [600]	-0.06 ± 2.19	15	0.5 ± 2.79	22	0.56 (-1.18 to 2.30)
Silveira et al. [f] [600]	1.07 ± 6.52	15	1.79 ± 8.53	22	0.72 (-4.57 to 6.01)
Silveira et al. [g] [600]	1.2 ± 5.86	15	1.41 ± 8.6	22	0.21 (-4.95 to 5.37)
Coordination exercise					
Altmann et al [h] [591]	0.09 ± 0.14	10	0 ± 0.5	9	-0.09 (-0.57 to 0.39)
Altmann et al [i] [591]	-0.07 ± 0.23	10	-0.06 ± 0.12	9	0.01 (-0.10 to 0.13)
Silveira et al. [d] [600]	0.06 ± 1.95	15	0.42 ± 1.47	21	0.36 (-0.80 to 1.52)
Silveira et al. [e] [600]	-0.06 ± 2.19	15	0.47 ± 1.97	21	0.53 (-0.89 to 1.95)
Silveira et al. [f] [600]	1.07 ± 6.52	15	3.19 ± 6.2	21	2.12 (-2.23 to 6.47)
Silveira et al. [g] [600]	1.2 ± 5.86	15	3.22 ± 5.7	21	2.02 (-1.95 to 5.99)
Resistance exercise + coordination exercise					
Gobbi et al [a] [594]	5.09 ± 8.7	10	0.61 ± 8.6	13	0.69 (-12.05 to 3.25)
Gobbi et al [a] [594]	5.09 ± 8.7	10	-2.4 ± 7.99	11	-7.49 (-15.23 to 0.25)
Gobbi et al [b] [594]	3.45 ± 9.04	10	0.55 ± 9.02	13	-2.90 (-10.80 to 5.00)
Gobbi et al [b] [594]	3.45 ± 9.04	10	1.1 ± 9.14	11	-2.35 (-10.67 to 5.97)



(forest plot detailing between-group effect size and 95% confidence intervals for each outcome in each trial; [a] = Wechsler Memory Scale I; [b] = Wechsler Memory Scale II; [c] = memory with interference test; [d] = California Verbal Learning Test (CVLT) short; [e] = CVLT long; [f] = Rey-Osterrieth Complex Figure Test (Rey-O) - short; [g] = Rey-O – long; [h] = 1-back task; [i] = 2-back task)

Table 20: Effect size calculations between different exercise modes

Study	Motor fitness Δ Mean ± SD	N	Physical fitness Δ Mean ± SD	N	Mean difference [95% CI]
Aerobic exercise vs. coordination exercise					
Altmann et al [a] [591]	-0.6 ± 2.1	9	-1.3 ± 1.7	11	-0.70 (-2.48 to 1.08)
Altmann et al [b] [591]	0.05 ± 0.8	9	-0.4 ± 0.7	11	-0.45 (-1.13 to 0.23)
Altmann et al [c] [591]	-0.6 ± 0.5	9	0.3 ± 0.9	11	0.86 (0.14 to 1.58)
Altmann et al [d] [591]	-0.08 ± 0.9	9	0.4 ± 0.8	11	-0.49 (-0.29 to 1.26)
Altmann et al [e] [591]	-0.04 ± 0.2	9	-0.01 ± 0.32	11	0.03 (-0.24 to 0.30)
Silveira et al [g] [600]	-0.1 ± 2.0	21	-0.4 ± 3.5	22	-0.22 (-1.97 to 1.53)
Silveira et al [h] [600]	0.4 ± 1.9	21	-0.4 ± 2.3	22	-0.79 (-2.09 to 0.51)
Silveira et al [i] [600]	-0.1 ± 0.9	21	-0.3 ± 1.3	22	-0.21 (-0.9 to 0.48)
Silveira et al [j] [600]	6.1 ± 24.6	21	8.2 ± 14.6	22	2.05 (-10.36 to 14.46)
Silveira et al [k] [600]	-12.2 ± 72.8	21	17.3 ± 48.9	22	29.48 (-8.55 to 67.51)
Silveira et al [l] [600]	-4.1 ± 18.4	21	-0.8 ± 21.7	22	3.23 (-9.19 to 15.65)
Silveira et al [m] [600]	-0.7 ± 12.0	21	0.09 ± 17.5	22	0.81 (-8.48 to 10.10)
Silveira et al [n] [600]	8.1 ± 8.7	21	2.7 ± 13.6	22	-5.46 (-12.52 to 1.60)
Silveira et al [o] [600]	0.4 ± 1.5	21	0.09 ± 2.2	22	-0.33 (-1.50 to 0.84)
Silveira et al [p] [600]	0.5 ± 2.0	21	0.5 ± 2.8	22	0.03 (-1.46 to 1.52)
Silveira et al [q] [600]	3.2 ± 6.2	21	1.8 ± 8.5	22	-1.40 (-6.01 to 3.2)
Silveira et al [r] [600]	3.2 ± 5.7	21	1.4 ± 8.6	22	-1.81 (-6.32 to 2.7)
Silveira et al [s] [600]	1.3 ± 4.8	21	0.6 ± 3.1	22	-0.74 (-3.21 to 1.73)
Silveira et al [t] [600]	-6.8 ± 6.8	21	-6.1 ± 4.9	22	0.69 (-2.96 to 4.34)
Silveira et al [u] [600]	0.8 ± 2.0	21	-0.04 ± 1.7	22	-0.85 (-1.98 to 0.28)
Silveira et al [v] [600]	-0.4 ± 1.7	21	-0.2 ± 1.8	22	0.20 (-0.87 to 1.27)
Silveira et al [w] [600]	4.5 ± 11.4	21	0 ± 8.3	22	-4.50 (-10.62 to 1.62)
Aerobic exercise vs. resistance exercise + coordination exercise					
Hashimoto et al [f] [595]	1 ± 1.7	17	3.1 ± 3.3	15	2.10 (0.23 to 3.97)



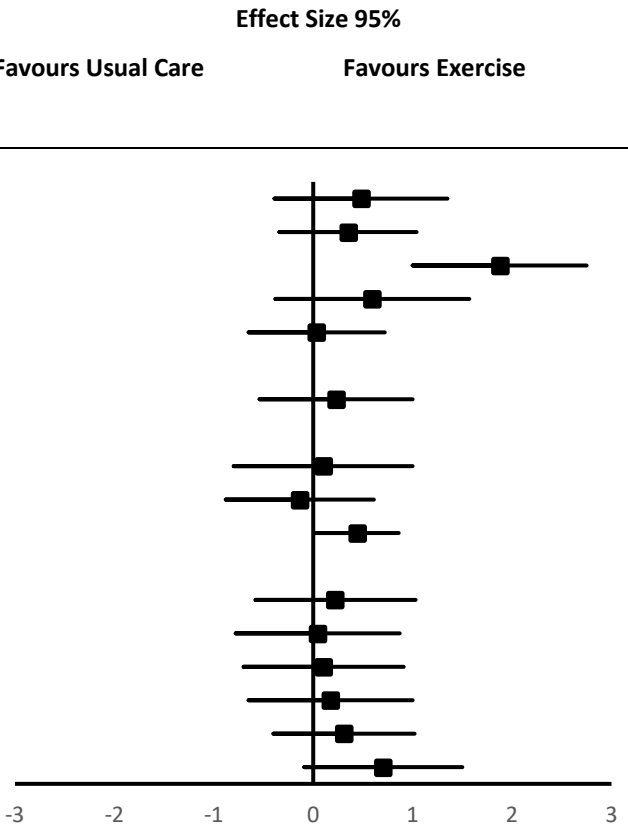
(forest plot detailing between-group effect size and 95% confidence intervals for each outcome; [a] = global cognitive function – Mattis Dementia Rating Scale; [b] = composite z scores - speed of processing; [c] = composite z scores – memory; [d] = composite z scores – executive function; [e] = composite z scores – language; [f] = executive function (Frontal Assessment Battery); [g] = attention (digit span forward); [h] =attention (digit span backward); [i] = attention (Corsi block test); [j] = attention (Trail Making Test A); [k] = executive function (Trail Making Test B); [l] = speed of processing (Stroop Color); [m] = speed of processing (Stroop Word); [n] = executive function (Stroop Color Word interference); [o] = memory (California Verbal Learning Test (CVLT) short); [p] = memory (CVLT long); [q] = memory (Rey-Osterrieth Complex Figure Test (Rey-O) – short); [r] = memory (Rey-O long); [s] = speed of processing (phonemic fluency); [t] = attention (verbal fluency); [u] = language (Boston Naming Test); [v] = visuospatial function (Intersecting Pentagons); [w] = visuospatial function (Benton Line Orientation Test))

8.4.10. Secondary outcome – Unified Parkinson's Disease Rating Scale

Seven of the included studies used the UPDRS to evaluate the overall health status of their participants [591, 592, 594, 595, 597-599] (Table 21). Two of these studies reported the total score of the UPDRS as well as the subscore of the motor evaluation [591, 594]. Furthermore, two studies reported either the total scores [595, 597] or the scores of the motor evaluation [598, 599] and one of the included studies reported the subcategory activities of daily living [592] (Table 21). Besides one negative between-group ES in the coordination exercise interventions (ES=-.014), all other ES tended to be in favor of the exercise interventions. The average between-group ES was trivial for coordination exercise interventions (ES=0.13; -0.14 – 0.44), small for combined resistance and coordination exercise interventions (ES=0.26; range 0.1 – 0.7), and moderate for aerobic exercise interventions (ES=0.67; range 0.03 – 1.88). Two of the trials demonstrated significant improvements in the UPDRS with aerobic exercise ($p<0.001$) [595] and coordination exercise ($p=0.04$) [592] compared with control.

Table 21: Effect size calculations for the Unified Parkinson's disease rating scale

Study	Control group Δ Mean ± SD	N	Exercise group Δ Mean ± SD	N	Mean difference [95% CI]
Aerobic exercise					
Altmann et al [a] [591]	-4.8 ± 11.3	10	1.2 ± 12.5	11	6.00 (-4.93 to 16.93)
Altmann et al [b] [591]	-2.1 ± 7.7	10	0.9 ± 8.7	11	3.00 (-2.89 to 8.89)
Hashimoto et al [a] [595]	-3.9 ± 14.2	14	23.2 ± 13.9	15	27.10 (16.39 to 37.81)
Picelli et al [a] [597]	0.9 ± 3.0	8	2.9 ± 3.5	9	2.00 (-1.30 to 5.30)
Rios-Romenets [b] [598]	1.2 ± 14.5	15	1.6 ± 12.3	18	0.40 (-8.36 to 9.16)
Resistance Exercise					
Silva Batista et al [b] [599]	-1.6 ± 8.6	13	1.1 ± 13.4	13	2.70 (-6.41 to 11.81)
Coordination exercise					
Altmann et al [a] [591]	-4.8 ± 11.3	10	-3.7 ± 10.1	11	1.10 (-9.32 to 11.52)
Altmann et al [b] [591]	-2.1 ± 7.7	10	-3.1 ± 6.4	11	-1.00 (-6.55 to 4.55)
Conradsson et al. [c] [592]	-0.4 ± 4.6	44	1.7 ± 4.8	47	2.10 (0.13 to 4.07)
Resistance exercise + coordination exercise					
Gobbi et al. [a] [594]	-0.08 ± 8.7	13	3.3 ± 19.6	11	3.39 (-9.07 to 15.85)
Gobbi et al. [a] [594]	-0.08 ± 8.7	13	0.4 ± 11.4	10	0.48 (-9.48 to 10.44)
Gobbi et al. [b] [594]	0 ± 6.7	13	1.1 ± 13.2	11	1.09 (-7.57 to 9.75)
Gobbi et al. [b] [594]	0 ± 6.7	13	1.4 ± 9.0	10	1.40 (-5.41 to 8.21)
Hashimoto et al [a] [595]	-3.9 ± 14.2	14	0.9 ± 15.8	17	4.80 (-6.35 to 15.95)
Silva Batista et al [b] [599]	-1.6 ± 8.6	13	4.5 ± 8.2	13	6.10 (-0.7 to 12.9)



(forest plot detailing between-group effect size and 95% confidence intervals for each outcome in each trial; [a] = Unified Parkinson's Disease Rating Scale (UPDRS) – total score; [b] = UPDRS – motor score; [c] = UPDRS – activities of daily living)

8.5. Discussion

This review included eleven RCTs that analysed the effect of different exercise modes (aerobic exercise, resistance exercise, coordination exercise, and combined resistance and coordination exercise) on at least one cognitive domain in individuals suffering from PD. Executive function, attention and memory tended to improve after each form of exercise in comparison to these cognitive functions in the non-exercise control group. However, we did not observe this trend for speed of processing. Global cognitive function tended to improve after aerobic, resistance, and combined resistance and coordination exercises, but not after coordination exercises. The average between-mode ES ranged from small to moderate, but often lacked statistical significance, and therefore this review was unable to identify a clear effect of exercise mode on the cognitive domains. However, in five trials a significant between-group ES in favor of the exercise group over the non-exercising control group was identified for tests of specific cognitive domains. These significant between-group ES included a positive effect of aerobic exercise on memory and executive function, and of combined resistance and coordination exercise on global cognitive function. Two trials found a significant ES for coordination exercise, which led to improved executive function compared with that of non-exercising control subjects.

8.5.1. Global cognitive function

We identified one significant between-group ES, which favored combined resistance and coordination exercises over the non-exercise control group [599]. The other exercise modes did not lead to any significant changes, suggesting that combined resistance and coordination exercises could be best to improve global cognitive function in individuals with PD. However, another study that investigated the effect of combined resistance and coordination exercises did not replicate the above findings. These conflicting results may be due to methodological differences or differences in participant characteristics [594]. The MoCA was most commonly used (3 of 5 studies [597-599]) to assess global cognitive function, which is consistent with current recommendations for PD [603]. This instrument is possibly

more sensitive for detecting early cognitive decline in individuals with PD than are the other instruments used in the studies (MMSE, Mattis-Dementia Rating Scale (MDR)) [73, 604-606]. This sensitivity difference could explain the conflicting outcomes of these two studies, because the MoCA scores changed significantly, but not the MMSE or MDR scores.

The only significant between-group ES was found for the intervention group with the lowest reported baseline MoCA scores (mean score 20.8) [599]. Participants with a MoCA score of 20.8 probably had MCI: MCI produces MoCA scores from 19 to 25, and scores from 19 to 21 can indicate late-stage MCI [73, 434]. Accordingly, multimodal exercise training may only increase global cognitive function in individuals with both PD and MCI, which concurs with recent recommendations of the AAN for the treatment of MCI [3]. Future research should focus on assessments sensitive to early and subtle changes in global cognitive function. Based on the findings of our review, combined resistance and coordination exercises might be best to improve global cognitive function. However, given the aforementioned differences in participant characteristics, these findings require confirmation.

8.5.2. Executive function

The transition from normal cognition to MCI is often characterized by impaired executive function in individuals with PD [93, 607-609]. Exercise has a stronger effect on executive function than on any other cognitive domain in healthy older adults [236, 266]. However, we identified only three instances of a significant ES, where either aerobic or coordination exercises were superior to control [593, 600]. A recent study in healthy older adults suggests that exercise mode does not specifically affect executive function [71]. In contrast, another study that compared aerobic exercise to combined resistance and coordination exercises found a significant effect for aerobic exercise [595].

According to previous studies, the apparent effect of exercise can vary with different neuropsychological tests and may relate to selective deficits in executive function (e.g. control of interference, cognitive flexibility, and planning). This factor may partially explain the results of our review [69, 93, 610]: only the TMT B, which assesses cognitive flexibility, and the ‘Raven colored matrix’ task, which uses a problem-solving task associated with visuospatial dimensions, revealed significant changes [611, 612]. In the same studies, we

observed no changes in other neuropsychological tests that assess planning and control of interference (e.g. Wisconsin card sorting task, Stroop test) [593, 600]. Hence, exercise may improve specific deficits in individuals with PD.

The TMT B was used by Silveira et al. [600] and by two other studies that investigated the efficacy of either aerobic or coordination exercises. These two studies observed a positive tendency for exercise [596, 597]. The lack of significance might be explained by the smaller sample sizes and the participant characteristics in these studies. Silveira et al. included participants with MCI; their sub-analysis revealed that the performance of only the cognitively impaired participants changed significantly after the exercise intervention [600]. These combined findings suggest exercise is effective in improving executive function in individuals with PD who experience MCI, which agrees with our findings for global cognitive function. Future studies should concentrate on selective deficits in executive function and use larger sample sizes in order to provide further insight into the efficacy of different exercise modes.

8.5.3. Attention and speed of processing

We did not identify significant effects of any exercise mode on attention or speed of processing, although many of the neuropsychological tests used in the review studies meet recent recommendations of how to assess these functions in individuals with PD [97, 103, 104]. Our results contrast with findings of a recent systematic review in healthy older adults and in individuals with MCI and with dementia. The review identified attention and speed of processing among the cognitive domains most consistently improved by exercise [71]. However, the authors stated that at least 52 sessions of about 60 minutes may be needed to improve cognitive performance [71]. No exercise intervention in our review included this many sessions, which may explain why we found no significant effects. Additionally, simple attention tasks might not be complex enough to detect changes in cognitive performance in small sample sizes [69, 266]. Ideally, future research should use longer intervention periods with more exercise sessions and batteries of complex cognitive tests in order to detect small, but important, changes in these functions.

8.5.4. Memory

Individuals with PD often suffer from deficits in short-term and long-term memory, which can be present before the onset of other cognitive complaints [613]. However, we identified only four studies that assessed the effect of an exercise intervention on memory. Of these, one found a significant between-group ES favoring the aerobic exercise intervention over the control group [597]. This study used the auditory consonant trigram test, which is a short-term memory retention task [614, 615]. The findings of this study agree with those of previous research in healthy older adults and individuals with MCI that showed aerobic exercise was associated with improved memory [35, 314]. Another of the studies compared aerobic exercise and coordination exercise regimens, finding the aerobic mode superior in improving memory [591]. Therefore, we speculate that aerobic exercise has a superior effect on improving memory in individuals with PD, because no other exercise mode (coordination exercise, combined coordination and resistance exercise) led to significant changes. This would support previous findings that proposed the superior role of aerobic exercise for slowing disease progression in PD [616].

Another study in our review used aerobic exercise training but found no significant improvement in memory [600]. In the studies in which aerobic exercise did improve memory, participants exercised on a treadmill, whereas the participants in this study exercised on stationary bikes. Together, these findings suggest that treadmill training could be superior to cycling on a stationary bike for improving memory. The unique associations between memory and distinct aspects of postural control and gait in individuals with PD could explain the differences between cycling on a stationary bike and walking on a treadmill [108]. Treadmill training improves postural instability and gait disturbances, so this form of exercise might address the clinical signs of parkinsonism better than cycling [507, 617, 618]. Therefore, future research should be encouraged to directly compare these exercise modalities. As memory is likely to worsen in individuals with PD, and an impaired memory decreases quality of life, validated treatment options are urgently required [619].

8.5.5. Secondary outcomes – Unified Parkinson's Disease Rating Scale (UPDRS)

The UPDRS instrument is commonly used to assess individuals with PD. Using the UPDRS results as an outcome, our finding that in general exercise tended to improve symptoms of PD agrees with that of previous reviews [256, 620]. We did not find a significant effect of mode: the two studies with significant improvements after the intervention (cf. non-exercise control group) employed either aerobic or coordination exercises [592, 595]. Overall, our findings suggest that clinicians and researchers should be encouraged to prescribe exercise in individuals with PD; however further evidence is required to confirm the optimal form of exercise.

8.5.6. Insights into possible physiological mechanisms

We identified that various exercise modes have the potential to improve both global cognitive function and executive function in individuals with PD, but that aerobic exercise may be best for improving memory. In addition, one study reported that aerobic exercise was superior to combined resistance and coordination exercises in improving executive function. These findings indicate that a particular exercise mode could be more effective than other modes in improving certain cognitive domains. This difference in effect could result from different mechanisms within the brain that are triggered by specific exercise modes.

In healthy older adults, aerobic and resistance exercise affect the brain in different ways. Aerobic exercise improves hippocampal volume, modulated by a higher expression of brain-derived neurotrophic factor (BDNF) [236, 276, 314, 315], whereas resistance exercise more likely produces higher concentrations of insulin-like growth factor 1 (IGF-1), with a smaller, or no, increase in BDNF [315, 316]. Both exercise modes increase synaptic plasticity within the hippocampus after training, which is associated with an improved memory [314, 317]. However, one study found that aerobic exercise training activated glutamatergic signaling proteins (e.g. N-methyl-D-aspartate and postsynaptic density protein) while resistance exercise training increased the expression of protein kinase C alpha, tumor necrosis factor alpha, and interleukin 1 beta [317]. Because altered glutamatergic neurotransmission and neuronal metabolic dysfunction are part of the pathophysiology in PD, we speculate that an activation of glutamatergic signaling proteins might have a greater effect in individuals with

PD [621, 622]. The potential of glutamatergic signaling proteins in improving cognitive function, especially memory, has been discussed in previous research with humans and animals and may explain why aerobic exercise better improves memory, as we identified in the current review [622-625]. However, this remains speculative and needs further proof.

In addition, animal studies have revealed that aerobic exercise produces neuronal and mitochondrial protection and increases nigrostriatal neurotrophic factor levels in parkinsonian mice [626]. Mitochondrial dysfunction is seen in both PD and Alzheimer's disease, further supporting the role of aerobic exercise in improving cognition, especially memory, in individuals with PD [318]. However, more research is needed to completely understand the physiological mechanisms behind the effects of aerobic exercise in individuals with PD.

Besides aerobic and resistance exercises, coordination exercises are suggested to increase the volume of the hippocampus and the basal ganglia (globus pallidus) in healthy older adults [319-321], possibly via the 'vestibular pathway'. Coordination (e.g. balance) exercises often engage the vestibular system, which not only contributes to spatial cognition but is also anatomically connected to the medial-temporal lobe (e.g. hippocampus) and to parieto-temporal cortical networks [322, 323]. This vestibular pathway may also trigger the striatum [322], which is part of the basal ganglia – the brain area affected by PD. This pathway could explain the potential of coordination exercises to improve cognitive performance and general disease severity in individuals with PD, which we found in our review [593, 600].

Evidence exists that different physiological responses to specific exercise modes accompany increased cognitive performance. However, the role of each pathway in individuals with PD is not fully understood. Assessing physiological mechanisms and cognitive function to identify the pathways that are responsible for behavioral changes is recommended to provide further insight into the efficacy of different exercise modes. Such information would help to identify efficient treatment strategies.

8.5.7. Social interaction

Besides changes in physiological mechanisms, another benefit of group exercises is environmental enrichment, particularly social enrichment, which might also prevent cognitive decline [326]. However, the results of our review do not support this notion. Three of the included RCTs compared the effects of group exercises to a control group, which met regularly to control for the effect of social interactions [594, 597, 599]. Whereas significant results were found for executive function [597] and global cognitive function [599] following the exercise interventions in two studies, the control groups did not improve in any of the studies. Furthermore, one study investigated the effect of a group or an individual exercise class and only the participants of the individual exercise class improved their cognitive performance significantly [593], suggesting that exercise-induced changes are more important for improving cognitive performance than any effects of social interaction. Nevertheless, we should not underestimate the power of social interactions during exercise classes as part of a holistic treatment of PD because of the potential benefits for quality of life and mood [627-629].

8.5.8. Strength and limitations

To prescribe exercise interventions for maintaining or improving cognitive function, we need a better understanding of the specific effects of different exercise modes in individuals with PD. Therefore, our review systematically analysed the effect of aerobic, resistance and coordination exercises on domain-specific cognitive function, which provides further insight into previous findings [250, 262-264]. Additionally, we strictly followed the PRISMA guidelines, only included RCTs, and calculated between-group ES using the mean difference between pre-tests and post-tests to address limitations of previous studies [262-264].

The large number of neuropsychological tests used in the studies, coupled with differences in outcome parameters and the small number of trials within each cognitive domain, prevented us undertaking a meta-analysis. We excluded conference abstracts and other non-peer-reviewed publications from the current review, although we cannot exclude the possibility of publication bias completely. Average between-group ES does not take the grade

of evidence for each outcome or differences in study sample sizes into account, as does the overall (weighted) ES of a meta-analysis.

Further, the included studies used a wide range of exercises, which made it difficult to categorize and compare them. For example, we cannot exclude the possibility that different forms of exercises such as treadmill training or stationary bike training lead to different adaptations, although both are considered aerobic exercise. Nevertheless, given the current lack of RCTs, analyzing the efficacy of different exercise modes is an important first step before comparing different training forms within a mode. Also, some studies did not sufficiently report how they monitored exercise intensity during the exercise classes, particularly during coordination exercises [591, 592, 596-601]. To provide further insight into the role of intensity, future study designs should include measuring exercise intensities in convenient ways (e.g. heart rate monitors, subjective rating of perceived exertion). Besides the range of exercises and the lack of monitoring intensity, the intervention periods in the included studies differed between 4 to 26 weeks. Further, average sessions per week as well as length of the exercise classes ranged between once to three times a week and 30 to 60 minutes per session, which marks a high heterogeneity of the different study designs. As a previous review discussed a dose-response effect of exercise in healthy older adults and recommended a minimum of 52 sessions lasting 60 minutes to improve cognition, it is possible that the different study designs may have influenced the results of this review [71]. However, we identified significant between group-effects in studies with an intervention period of 4, 12, 16, and 26 weeks, as well as an average participation per week of two to three times with exercise classes lasting between 45 and 60 minutes [591, 593, 596-601]. Therefore, we were not able to identify a specific effect of exercise volume (intervention period, length of exercise classes, average exercise sessions per week), but recommend that future studies should aim to identify the best dose-response relationship.

Previous sample size calculations for the effects of exercise interventions on disease severity in individuals with PD (n = 36) and of exercise on cognitive performance in individuals with MCI (n = 210) identified the need for larger sample sizes than those used in the included studies [352, 630]. This lack of power could partly explain the small number of significant

between-group ES that we identified, and highlights the need for larger sample sizes in future studies.

8.5.9. Conclusion

This systematic review found no clear effect of exercise mode on domain-specific cognitive function in individuals with PD, but that aerobic exercise tended to best improve memory in individuals with PD. Further, exercise in general appears to be associated with improved cognitive function in individuals with PD. However, improvements might be limited to certain cognitive domains (global cognitive function, executive function or memory). Besides cognitive function, exercise, regardless of mode, tended to slow disease progression in individuals with PD. The currently limited number of high-quality RCTs makes it difficult to draw further conclusions, but emphasises the need for more quality investigations.

8.6. Supplementary Tables

Table 22: Search strategy for CENTRAL in The Cochrane Library

#1	MeSH descriptor: [Parkinson Disease] explode all trees
#2	MeSH descriptor: [Exercise] explode all trees
#3	MeSH descriptor: [Cognition] explode all trees
#4	#1 and #2 and #3
#5	danc*:ti,ab,kw (Word variations have been searched)
#6	training:ti,ab,kw (Word variations have been searched)
#7	“physical activity”:ti,ab,kw (Word variations have been searched)
#8	balance:ti,ab,kw (Word variations have been searched)
#9	resistance:ti,ab,kw (Word variations have been searched)
#10	aerobic:ti,ab,kw (Word variations have been searched)
#11	"executive function":ti,ab,kw (Word variations have been searched)
#12	memory:ti,ab,kw (Word variations have been searched)
#13	"verbal fluency":ti,ab,kw (Word variations have been searched)
#14	visuospatial :ti,ab,kw (Word variations have been searched)
#15	attention:ti,ab,kw (Word variations have been searched)
#16	"cognitive function":ti,ab,kw (Word variations have been searched)
#17	"neuropsychological test":ti,ab,kw (Word variations have been searched)
#18	“Parkinson* disease”:ti,ab,kw (Word variations have been searched)
#19	cognition:ti,ab,kw (Word variations have been searched)
#20	exercise:ti,ab,kw (Word variations have been searched)
#21	#5 or #6 or #7 or #8 or #9 or #10 or #20
#22	#11 or #12 or #13 or #14 or #15 #16 or #17 or #19
#23	#4 or #18 and #19 and #15
Filters	Trials

(171 records identified – last searched 17th April 2018)

Table 23: Search strategy for PubMed

#1	cognition [MeSH Terms]
#2	exercise [MeSH Terms]
#3	Parkinson disease [MeSH Terms]
#4	#1 and #2 and #3
#5	Parkinson disease [TIAB]
#6	Parkinson's disease [TIAB]
#7	cognition [TIAB]
#8	"cognitive function*" [TIAB]
#9	"executive function*" [TIAB]
#10	memory [TIAB]
#11	"verbal fluency" [TIAB]
#12	"neuropsychological test" [TIAB]
#13	visuospatial [TIAB]
#14	attention [TIAB]
#15	exercise [TIAB]
#16	"physical activity" [TIAB]
#17	danc* [TIAB]
#18	training [TIAB]
#19	balance [TIAB]
#20	resistance [TIAB]
#21	aerobic [TIAB]
#22	#5 or # 6
#23	#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#24	#15 or #16 or #17 or #18 or #19 or #20 or#21

(385 records identified – last searched 17th April 2018)

Table 24: Search strategy for Scopus

#1	Parkinson disease
#2	Parkinson's disease
#3	#1 or #2
#4	exercise
#5	training
#6	"physical activity"
#7	aerobic
#8	resistance
#9	balance
#10	danc*
#11	cognition
#12	"cognitive function"
#13	"executive function*"
#14	memory
#15	attention
#16	"neuropsychological test"
#17	visuospatial
#18	"verbal fluency"
#19	#4 or #5 or #6 or #7 or #8 or #9 or #10
#20	#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
#21	#3 and #19 and #20
Filters	Document type: Articles
	Keywords: Human
	Keywords: Humans

(697 records identified – last searched 17th April 2018)

Table 25: Search strategy for Web of Science

#1	TS=(Parkinson* disease)
#2	TS=(exercise)
#3	TS=(training)
#4	TS=("physical activity")
#5	TS=(danc*)
#6	TS=(training)
#7	TS=(aerobic)
#8	TS=(balance)
#9	TS=(resistance)
#10	#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#11	TS=(cognition)
#12	TS=("cognitive function")
#13	TS=("executive function")
#14	TS=(memory)
#15	TS=(attention)
#16	TS=("verbal fluency")
#17	TS=("neuropsychological test)
#18	#11 or #12 or #13 or #14 or #15 or #16 or #17
#19	#1 and #10 and #18
#20	TI=(endoluminal)
#21	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
Filters	Document types: Article
	Indexes=SCI-EXPANDED, SSCI

SCI-EXPANDED – Science Citation Index Expanded (1900 to present); SSCI – Social Sciences Citation Index (1900 to present), (668 records identified – last searched 17th April 2018)

Table 26: Search strategy for LIVIVO

#1	TI=(Parkinson disease)
#2	TI=(Parkinson's disease)
#3	#1 or #2
#4	TI=(exercise)
#5	TI=(training)
#6	TI=("physical activity")
#7	TI=(danc*)
#8	TI=(training)
#9	TI=(aerobic)
#10	TI=(balance)
#11	TI=(resistance)
#12	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
#13	TI=("executive function")
#14	TI=(memory)
#15	TI=(attention)
#16	TI=("verbal fluency")
#17	TI=("neuropsychological test)
#18	TI=(cognition)
#19	TI=("cognitive function")
#20	#13 or #14 or #15 or #16 or #17 or #18 or #19
#21	MESH=(Parkinson disease)
#22	MESH=(exercise)
#23	MESH=(cognition)
#24	#21 and #22 and #23
#25	#24 or #1 and #12 and #20
Filters	English
	Document types: Article

(61 records identified – last searched 17th April 2018)

Table 27: Effect size calculations for language measures

Study	Control group Δ Mean ± SD	N	Exercise group Δ Mean ± SD	N	Mean difference [95% CI]	Effect Size (95% CI)
Aerobic exercise						
Altmann et al. [a] [591]	0.1 ± 0.2	10	0.1 ± 0.2	11	-0.02 (-0.28 to 0.27)	-0.10 (-0.96-0.76)
Altmann et al. [b] [591]	0.2 ± 0.3	10	0.1 ± 0.3	11	-0.08 (-0.35 to 0.19)	-0.27 (-1.13-0.59)
Altmann et al. [c] [591]	0.04 ± 0.3	10	-0.01 ± 0.3	11	-0.05 (-0.31 to 0.21)	-0.17 (-1.03-0.69)
Coordination exercise						
Altmann et al. [a] [591]	0.1 ± 0.2	10	-0.02 ± 0.16	9	-0.11 (-0.28 to 0.05)	-0.64 (-1.56-0.28)
Altmann et al. [b] [591]	0.2 ± 0.3	10	0.06 ± 0.2	9	-0.15 (-0.40 to 0.11)	-0.53 (-1.45-0.38)
Altmann et al. [c] [591]	0.04 ± 0.3	10	-0.04 ± 0.24	9	-0.08 (-0.32 to 0.15)	-0.33 (-1.24-0.58)

(CI = confidence interval, SD = standard deviation)

9. GENERAL DISCUSSION

The main aim of this thesis was to assess the effects of exercise on cognitive functions in older adults at high risk of developing dementia. This thesis had six primary research aims:

1. (a) To compare physical activity levels, exercise capacity and cardiorespiratory fitness in older adults across the spectrum of SCI and MCI, and (b) to assess the strength of the relationship between these physical characteristics and cognitive function (Chapter 3).
2. To determine the efficacy of EEG markers of cognitive decline by comparing event-related potentials in participants with SCI or MCI in response to an auditory oddball paradigm (Chapter 4).
3. To establish whether a target RPE during light, moderate and vigorous exercise can be used to achieve exercise intensity based on an individual's HR–RPE relationship (Chapter 5).
4. To assess the validity of the Polar M400© watch for measuring step-count during walking against a previously validated pedometer (Omron Walking Style©) (Chapter 6).
5. To investigate the effects of a 12-month structured exercise program, either aerobic exercise or stretching and toning exercises, on the progression of cognitive decline in people with MCI (Chapter 7).
6. To conduct a systematic review of the literature to establish what is currently known about the effects of aerobic training, resistance training, coordination training, and combinations of exercise types on the specific cognitive impairments associated with PD (Chapter 8).

9.1. Cardiorespiratory Fitness and Cognition in Individuals with Cognitive Impairment

Chapter 3 reported the investigation of the relationship between cardiorespiratory fitness and cognition in individuals with SCI and MCI. This study revealed that within the spectrum of early cognitive decline cognition was positively related to cardiorespiratory fitness and that the most severely impaired participants were less engaged in physical activity and had a lower exercise capacity. These findings extend previous research, which has established a positive association between cardiorespiratory fitness and cognition throughout the lifespan. However, the relationship had not been shown in individuals at a high risk of further cognitive decline [27-30]. Nevertheless, this cross-sectional study could not establish a causal relationship between cognition and cardiorespiratory fitness. Thus further longitudinal investigations were warranted.

Chapter 7 presented results of a longitudinal study that investigated the effects of a 12-month exercise intervention on cognitive functions in individuals with MCI. The study revealed no changes in cognition in either of the exercise groups (performing aerobic or stretching and toning exercises) or in the control group. While the lack of an intervention effect on cognition contrasts with the findings of previous research [3, 35, 36], this study addressed major limitations of many previous studies. The collaboration of three research facilities in three countries in North-West Europe allowed the recruitment of a large participant cohort. Further, the long intervention period, strict inclusion and exclusion criteria, and the use of an extensive neuropsychological test battery ensured the high quality of the study and its current uniqueness.

Although cognition did not change within the exercise intervention study reported in Chapter 7, the results revealed that cardiorespiratory fitness ($\dot{V}O_2peak$) significantly improved in the exercise groups compared with fitness of the control group. Improved cardiorespiratory fitness may play an important role in future progression of disease. Increased fitness likely induces structural changes in the brain such as increased hippocampal volume and improved white matter integrity [268, 345, 379, 544-546]. Therefore, previous researchers have speculated that higher physical fitness preserves cognitive function in those at increased risk

for AD and helps prevent further cognitive decline [26, 374]. The results of the secondary analysis in this study may further emphasise the importance of improved cardiorespiratory fitness. The secondary analysis revealed a significantly increased cardiorespiratory fitness only for the exercise group in Germany, which was also the only group showing a positive trend for cognition. Therefore, we could speculate that an increase in fitness is needed to improve cognition, which has been confirmed by mediation analyses in studies with healthy older adults [631, 632]. Further, this finding aligns with the positive association between cognition and fitness reported in Chapter 3 of this thesis. Establishing the effects of improved cardiorespiratory fitness in individuals with MCI requires longer intervention periods and follow-up assessments. Mediator analyses may also provide additional insight into the acute effect of changes in cardiorespiratory fitness.

9.2. Research Setting

Previous studies reported differences in study outcomes (e.g. success in recruitment) between clinical settings such as the memory clinics in Ireland and the Netherlands and more lifestyle-oriented research settings such as the nonmedical sport university in Germany [529]. To explore the influence of research settings, a secondary analysis was conducted in the Chapter 7 study. Although exercise intensity and frequency were standardised across the three sites, the results indicate that a lifestyle-oriented setting might have contributed to additional and more beneficial effects (e.g. positive trend for cognition, significantly increased cardiorespiratory fitness). This hypothesis is supported by the results for quality of life presented in Chapter 7, where again participants in the exercise groups in Germany were the only ones to report significantly improved quality of life significantly after the intervention.

Stigma associated with diagnostic labels of cognitive impairment, which may be greater in existing Alzheimer centres and memory clinics such as those in Ireland and the Netherlands, could contribute to the different results for these settings in the secondary analysis [529, 633, 634]. Apart from stigma, previous research has found that individuals aware of their diagnosis and their increased risk for subsequent dementia have poorer study outcomes and a lower quality of life [635, 636]. Again, we could speculate that this awareness caused subtle but important differences among the three research centres because participants in memory

clinics may be more aware of their risk, which could affect research outcomes [634]. Future studies need to address the stigma surrounding cognitive impairment and create welcoming and positive research settings for individuals experiencing the first signs of cognitive decline. Comparisons between different research settings (e.g. clinical vs lifestyle-oriented) are also needed to analyse the influence of the research setting on trial outcomes.

9.3. MCI and the Conversion to Dementia

The longitudinal exercise intervention study reported in Chapter 7 did not reveal any changes in cognition in either the exercise groups or the control group. Although MCI is regarded as a preclinical stage of dementia, studies to date report different findings on disease progression. For example, the AAN calculated a cumulative risk of 14.9% for the development of dementia within 2 years in individuals diagnosed with MCI [3]. However, Ganguli and colleagues reported a progression to dementia of only 1.4% in individuals with MCI, with 77.8% remaining stable and a further 15.4% returning to normal cognitive function after 12 months [538]. Therefore, stability of cognitive functions might be the most common outcome in interventions lasting 12 months.

The conflicting results on disease progression may arise in part from heterogenous populations. AD-related brain damage is suggested as the most common etiology of MCI, especially of aMCI [541, 637, 638]. However, MCI does not have a single cause (multicausality [14, 541]) and several risk factors, such as psychiatric symptoms of anxiety or the presence of specific genetic markers for Alzheimer-type dementia, may influence conversion to dementia [639]. Although strict inclusion and exclusion criteria were applied in the study reported in Chapter 7, heterogeneity of the population may have contributed to the mixed outcomes of this longitudinal study. Future investigations should consider the heterogeneity of previous studies and aim to better define the biomarkers or cognitive profile that best predicts subtypes of MCI, especially those at highest risk of progress towards dementia [8, 553]. Given the heterogeneity in individuals with cognitive impairment, it may be time to rethink future trials; personalised, precise prevention may be the most appropriate approach [551].

9.4. Exercise Mode, Frequency and Intensity

A 2018 systematic review by Gomes-Osman and colleagues of more than 1000 clinical trials, 174 systematic reviews, and 50 meta-analyses examined the effects of exercise on cognitive function in older adults [71]. Findings appear consistently positive [71, 236, 237, 345, 640], but practical guidelines are often superficial, recommending exercise without specifying mode, frequency and intensity. For example, the AAN recommends exercise twice weekly for individuals with MCI but does not specify the type of exercise [3]. The review by Gomes-Osman et al. concluded that at least 52 hours of accumulated exercise are associated with improved cognitive performance in individuals with and without cognitive impairment, but did not define exercise frequency (e.g. average exercise sessions per week) [71]. Northey and colleagues examined exercise frequency in their systematic review and recommended exercise on as many days as possible in order to improve cognitive function [238]. Further research is warranted to establish the most effective exercise frequency.

Chapter 8 reported a systematic review of the effects of different exercise modes on cognitive performance in individuals with PD, who have a high risk of cognitive decline [202]. The results of the systematic review agree with those of previous research: all modes of exercise were associated with improved cognitive function [71]. To define optimal and specific training programs, the effects of different exercise modes on cognitive performance should be directly compared. The study reported in Chapter 7 takes a first step towards comparing different exercise modes, but the prescription of goal-oriented exercise programs to improve cognitive performance requires more research.

The need to compare exercise modes directly with each other also arises from previous research on physiological mechanisms underlying the effect of exercise on the brain. Studies in animals and humans show that specific exercise modes trigger different physiological mechanisms in the brain. These mechanisms range from a higher expression of neurotrophins such as BDNF and the expression of growth factors such as IGF-1 to activating the vestibular pathway [238, 315, 322]. We can hypothesise that different physiological mechanisms affect individuals differently. Therefore, future studies should not only compare different exercise

modes, but also aim to assess underlying physiological mechanisms in order to completely understand the effect of exercise on the brain.

9.5. Monitoring Exercise Intensity and Physical Activity

Chapter 8 discusses the need for more consistent reporting of exercise intensity, mode and frequency, because many studies included in the systematic review did not sufficiently describe the exercise intervention. Most often, studies lacked sufficient reporting of exercise intensity, which was also observed by Gomes-Osman and colleagues in their systematic review [71]. To provide insight into the role of intensity, future study designs need to establish and include feasible (convenient) methods of monitoring exercise intensity (e.g. heart rate monitors) in order to define the best dose-response relationship between exercise and cognition. In addition, studies should directly compare the efficacy of different exercise intensities [37].

Exercise intensity is an important component of exercise prescription and can be described in various ways such as heart rate relative to maximum or age-predicted maximum HR [38]. Chapter 5 reported the investigation into using Borg's RPE scale for guiding exercise intensity in individuals with SCI and MCI. The scale is a practical method that assesses subjective perception of effort during exercise in order to rate and regulate exercise [39]. The study found no differences between different cognitive impairment levels or between different exercise modes in the accuracy of exercise intensity guided by Borg's RPE scale, which suggested good usability of the RPE scale. However, the study revealed some variations in HR, with half of the participants differing from target HR by 10 bpm. Therefore, exercise intensity should be better monitored using objective measurements (e.g. HR measured by a validated HR monitor) if a strict exercise intensity is wanted. For rough estimates, which may be sufficient in rehabilitation settings, the RPE scale can be used as a cost-effective method to monitor exercise intensity [463, 464].

The recommendation given in Chapter 5 to use objective rather than subjective monitors might be especially important in older adults, in whom cognitive decline is highly prevalent. Individuals with cognitive decline may suffer changes in self-awareness [469-471]. This factor may also explain the outcomes of the study reported in Chapter 3. In this study,

objective, but not subjective, measures of daily physical activity correlated with physical fitness. Higher levels of physical activity are associated with better physical fitness; hence, these results may indicate the superiority of objective measures. This finding agrees with that of a previous study that reported that older adults (65–84 years) tend to overestimate physical activity time with subjective methods compared with the time objectively measured with an accelerometer data [404].

As research studies are often subject to financial restrictions, the need for methods to objectively measure exercise intensity and physical activity presents a challenge to researchers. Therefore, the study reported in Chapter 6 evaluated the use of a validated HR monitor to also track steps accurately. The study yielded promising results: the accuracy of the activity tracker was good and correlated highly with manually counted steps. Devices that can both track activity levels and monitor exercise intensity may present an ideal and cost-effective solution for researchers and should be considered for use in future studies.

9.6. The Use of Neuropsychological Tests to Diagnose Cognitive Impairment and Assess Cognitive Function

Participants in the studies reported in chapters 3, 4 and 5 were defined as having subjective or mild cognitive impairment, which marks them as individuals at high risk of future progression to dementia. To minimise false positive diagnoses of these risk states, the use of multi-domain neuropsychological assessment at multiple time points is recommended [15-17]. In the search for tests that are sensitive to subclinical impairment, neuroimaging techniques and laboratory tests are gaining importance [8, 20, 21]. Therefore, the study reported in Chapter 4 investigated the potential of EEG, specifically ERPs evoked by an auditory oddball paradigm, as a non-invasive and objective method to differentiate between individuals with SCI and MCI.

This study found no differences in ERPs between participants with MCI and those with SCI, but neuropsychological tests did reveal differences in performance: participants with MCI performed significantly worse in all neuropsychological tests. Several reasons may explain why neuropsychological tests, but not ERPs, differed between the participant groups. Possibly the cognitive complexity of the auditory oddball task chosen to evoke ERPs was too

low, meaning that both groups performed at ceiling. On the other hand, evidence from neuropathological and biochemical studies shows that pathophysiological changes in brain function associated with dementia occur years or even decades before the onset of the disease [8, 143, 144]. Hence structural and functional brain alterations may exist in both SCI and MCI, which may limit the diagnostic accuracy of the EEG. To further explore the potential of EEG measurements, future studies should use different tasks for recording ERPs. Studies should also compare ERPs across the spectrum of cognitive ageing from healthy older adults to adults with dementia to gain more insight into the underlying functional and behavioural changes that occur with SCI and MCI.

The results presented in Chapter 4 suggest that neuropsychological tests best differentiate between individuals with MCI and those with other risk states. Besides their use for diagnosis, researchers commonly use neuropsychological tests to evaluate cognitive function. Often a single neuropsychological test is used to describe the efficacy of a treatment. However, the most reliable approach to detect cognitive changes over time in individuals with MCI is to transform several neuropsychological tests into an overall score [348, 641]. The study reported in Chapter 7 used a composite score to follow this recommendation. Previous research in this area often demonstrated changes in cognition with specific tests only, which are prone to false positives, rather than with composite scores [33, 278, 530-532]. This difference may present an additional reason why no changes were detected in the current study. Future studies should assess changes in cognition using an extensive neuropsychological test battery and calculate composite scores to provide a psychometrically more reliable and thus more valid construct.

9.7. Methodological Considerations and Research Limitations

The findings reported in this thesis can be applied to older adults experiencing the first signs of cognitive impairment. Due to strict inclusion and exclusion criteria, common comorbidities correlating with cognitive impairment, such as depression and anxiety, were not examined within this research. Therefore, the effect of exercise in older adults suffering not only from cognitive impairment but also from anxiety or depression could not be established. Further, only participants cleared to undergo an exercise intervention were

included in the studies. This criterion may have prevented very frail older adults from participating in the research. Future studies could investigate opportunities for exercise participation in frail older people, especially given their high risk of suffering from cognitive impairment and eventually developing dementia [642].

While the physiological mechanisms of the effects of exercise on the brain have been frequently discussed throughout this thesis, they were not analysed directly. Especially in the study of the longitudinal effects of exercise on the progression of MCI (Chapter 7), adding physiological measurements (e.g. with MRI) could uncover differences between the exercise and control groups on a structural level. Although assessing physiological mechanisms did not form part of this doctoral research, MRI measurements and epigenetic analyses were conducted as part of the NeuroExercise study protocol. The findings of these assessments, which remain outstanding, may be an important addition to the results presented in this thesis.

9.8. Outlook

This thesis identifies future research aims that the scientific community should address. Direct comparisons of different exercise modes are warranted to establish the most effective mode of exercise for maintaining or improving cognitive function with ageing. Besides exercise mode, future research should also aim to establish the effect of different exercise intensities, frequencies, and duration. Exercise appears to benefit both cognition and fitness in older adults, so future studies must refine the prescription of exercise to promote the greatest benefits. Additionally, researchers need to investigate the effects of exercise in different cohorts because disease-specific characteristics (e.g. pathophysiology related to PD or AD) might affect results demonstrated in healthy older adults. Moreover, underlying physiological mechanisms must be assessed to provide insight into key mechanisms that might accompany changes in cognition triggered by different forms of exercise. Finally, exercise intervention periods and follow-up periods require extension to determine the long-term effects of exercise.

9.9. Summary of findings

This thesis provides new knowledge regarding the effects of exercise on cognitive function in individuals suffering from early cognitive impairment. The research findings did not demonstrate a direct effect of 12 months of exercise on cognition, but participation in an exercise class for 12 months improved cardiorespiratory fitness significantly. Site-specific differences in findings between clinical and lifestyle-oriented settings were detected, which indicates the importance of a welcoming, non-stigmatising research setting. The relationship between cardiorespiratory fitness and cognition may indicate long-term benefits of increased fitness for cognitively impaired individuals. This research did not establish which form of exercise is best for individuals in the earliest stages of cognitive decline. Nevertheless, the results highlight the importance of considering the form of exercise in future studies. Researchers should rely on valid methods to identify target populations correctly and should adequately describe exercise interventions (e.g. exercise intensity) and their outcome parameters (e.g. steps). The findings presented in this thesis will help them to do so.

10. REFERENCES

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