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Towards the Development of Evidence-based Preventive Treatments against Cognitive Decline:

About the Effects of Learning Golf in Elderly People

Cumulative Dissertation

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(Dr. rer. medic.)

by Julia Kristin Ströhlein

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Declaration of Authorship

I hereby declare that the presented work is, to the best of my knowledge and belief, the result of my own research. Support during the research process or co-author contributions are presented for each publication. The work has not been submitted, either partly or completely, for a degree at this or another university. Ideas and formulations from other sources have been cited throughout the work.
I have read, understood and accepted the PhD regulations ("Promotionsordnung NW") from the 31st of March 2021 (AM.UNI.PB 10.21).

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Abstract

This thesis should contribute to the development of evidence-based exercise treatments for maintaining cognitive performance in elderly people in the context of prevention of Alzheimer's disease. The evidence synthesis showed that intensity of the intervention is not the sole factor for improving cognitive performance. Physical activity should therefore account for different exercise modes and should not only be interpreted as metabolically demanding training. Based on these findings, a 22-week randomized trial was developed, in which elderly people learned to play golf. The intervention was evaluated regarding the feasibility and its effects on cognitive performance by including (neuro-) biological markers (electroencephalography and kynurenine pathway).

Besides feasibility and safety of the intervention, positive effects were found for attention performance, the functional integrity of the default mode network and presumably also for regulation of the kynurenine pathway. However, findings should be considered under the limitation of the small and heterogeneous sample (n = 45) and should therefore be replicated in a larger cohort. A differentiated understanding of exercise and its combination with other domains (e.g. cognition) is necessary to move further towards the development of preventive evidence-based interventions.

Zusammenfassung

Die Thesis sollte einen Beitrag zur Entwicklung evidenzbasierter Bewegungstherapien für den Erhalt der kognitiven Leistungsfähigkeit bei älteren Menschen im Rahmen der Prävention der Demenz vom Alzheimer-Typ leisten.

Die Evidenzsynthese konnte zeigen, dass die Intensität von Bewegungsinterventionen nicht die einzige Bedingung für eine Beeinflussung der kognitiven Leistungsfähigkeit ist. Körperliche Aktivität sollte daher nicht allein als metabolisch beanspruchendes Training interpretiert werden, sondern auch weitere motorische Beanspruchungsformen berücksichtigen. Basierend auf diesen Erkenntnissen wurde eine 22-wöchige randomisierte Studie entwickelt, in der ältere Menschen das Golfspielen erlernt haben. Die Intervention wurde hinsichtlich der Machbarkeit und ihrer Effekte auf die kognitive Leistungsfähigkeit unter Einbezug (neuro-) biologischer Marker (Elektroenzephalographie und Kynureninpfad) evaluiert. Neben der Machbarkeit und Sicherheit der Intervention konnten positive Effekte auf die Aufmerksamkeit, die funktionelle Integrität des Default-Mode-Netzwerks sowie vermutlich auf die Regulation des Kynureninpfads gefunden werden. Die Ergebnisse wurden allerdings durch die kleine und heterogene Stichprobe (n = 45) eingeschränkt und sollten daher repliziert werden. Ein differenziertes Verständnis von Bewegung und ihrer Kombination mit anderen Domänen (z. B. Kognition) ist für die weitere Entwicklung präventiver evidenzbasierter Therapien notwendig.

List of Publications Considered for Thesis

1) **Ströhlein JK**, van den Bongard F, Barthel T, Reinsberger C. Dose-response-relationship between physical activity and cognition in elderly. Deutsche Zeitschrift für Sportmedizin. 2017; 68: 234-242. DOI: 10.5960/dzsm.2017.300

2) **Stroehlein JK**, Vieluf S, Zimmer S, Schenk A, Oberste M, Goelz C, van den Bongard F and Reinsberger C. Learning to play golf for elderly people with subjective memory complaints: feasibility of a single-blinded randomized pilot trial. BMC Neurology 2021; 21, 200. https://doi.org/10.1186/s12883-021-02186-9

3) **Ströhlein JK**, Vieluf S, van den Bongard F, Gölz C, Reinsberger C. Golf spielen gegen die Vergesslichkeit: Effekte des Erlernens der Sportart auf das Default Mode Netzwerk des Gehirns. Bewegungstherapie & Gesundheitssport 2020, 36:1-8. DOI: https://doi.org/10.1055/a-1120-700

4) **Stroehlein JK**, Goelz C, Vieluf S, van den Bongard F, Reinsberger C. Source Connectivity Patterns Differ Between Elderly Golf-Novices and Non-Golfers. Scientific Reports (*submitted*).

Note: Publications 1 and 3 of this thesis are not displayed in full text due to licensing agreements with the respective scientific journals. The required information for identification and access to the full text of these publications is provided in this section as well as in chapter 4.

List of Other Publications

Peer-reviewed

Goelz C, Mora K, **Stroehlein JK**, Haase FK, Dellnitz M, Reinsberger C, Vieluf S. Electrophysiological signatures of dedifferentiation differ between fit and less fit older adults. Cognitive Neurodynamics 2021. DOI: 10.1007/s11571-020-09656-9

Strote C, Gölz C, **Stroehlein JK**, Haase FK, Koester D, Reinsberger C, Vieluf S. Effects of force level and task difficulty on force control performance in elderly people. Experimental Brain Research 2020, 238, 2179-2188. DOI: https://doi.org/10.1007/s00221-020-05864-1

Non peer-reviewed

Reinsberger C, **Ströhlein JK**, Vieluf S. Die Bedeutung körperlicher Aktivität für die kognitive Gesundheit älterer Menschen. CME Beitrag. Der niedergelassene Arzt 06/2019.

Barthel T, van den Bongard F, **Ströhlein JK**, Reinsberger C. Bewegung bei neurologischen Erkrankungen. W. Banzer (Hrsg.), Körperliche Aktivität und Gesundheit, Springer-Verlag Berlin Heidelberg 2017. DOI 10.1007/978-3-662-50335-5_24

Congress abstracts

Ströhlein J, Gölz C, Vieluf S, van den Bongard F, Reinsberger C. Funktionelle Netzwerkcharakteristika des Default Mode Netzwerks bei älteren Golf-Novizen. Sports Medicine and Health Summit, Virtueller Kongress, 20. -24- April 2021. In: German Journal of Sports Medicine; 72 (3); 2021; S. 140.

van den Bongard F**, Stroehlein J**, Coenen J, Jakobsmeyer R, Reinsberger C Belastungsinduzierte Veränderungen von funktioneller Hirn-Netzwerkaktivität und peripheren autonomen Parametern bei Epilepsiepatienten.Sports Medicine and Health Summit, Virtueller Kongress, 20. -24- April 2021. In: German Journal of Sports Medicine; 72 (3); 2021; S. 145.

Gölz C., Mora K., **Stroehlein J. K**., Vieluf S., Reinsberger C. & Vieluf S. Electrophysiological signatures of brain network dynamics in elderly. 26th Annual Meeting of the Organization of Human Brain Mapping 2020, June 23 - July 3 2020 p. 58.

van den Bongard F, **Ströhlein JK**, Barthel T, Reinsberger C. Einfluss von körperlicher Aktivität auf epileptische Anfälle – Evidenz aus Tiermodellen. Deutscher Olympischer Sportärztekongress in Hamburg, 24. - 26. Mai 2018. In: Sport Orthopaedics and Traumatology; 34 (2); S 197.

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Stroehlein JK, van den Bongard F, Barthel T, Reinsberger C. Effects of a 12-week Multicomponent Exercise Intervention on Executive Functions and Episodic Memory in Healthy Elderly: A Pilot Study; 22nd annual Congress of the ECSS, 5th - 8th July 2017.

Ströhlein J, van den Bongard F, Barthel T, Reinsberger C. Körperliche Aktivität gegen kognitiven Leistungsverlust: Eine Dosis-Wirkungs-Beziehung? 47. Deutscher Sportärztekongress in Frankfurt am Main, 30. - 01. Okt. 2016. In: Dtsch Z Sportmed.; 67. Jahrgang 7-8/2016; S 181.

van den Bongard F, **Ströhlein J**, Barthel T, Reinsberger C. Einfluss körperlicher Aktivität auf die Anfallsfrequenz und Lebensqualität bei Epilepsiepatienten; 47. Deutscher Sportärztekongress in Frankfurt am Main, 30.9. - 01. Okt. 2016. In: Dtsch Z Sportmed.; 67. Jahrgang 7-8/2016; S 173.

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Figures and Tables

List of Abbreviations

6MWT	6-Minute Walk-Test
Aβ	Amyloid-beta
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive Subscale
AD	Alzheimer's Disease
ANOVA	Analysis of Variance
APOE	Apolipoprotein
BDI	Beck's Depression Inventory
BDNF	Brain-derived Neurotrophic Factor
BEM	Boundary Element Model
BMI	Body Mass Index
CRUNCH	Compensatory Recruitment Utilization of Neural Circuits
DAT	Demenz vom Alzheimer-Typ
DMN	Default Mode Network
EEG	Electroencephalography
FINGER	Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
fMRI	functional Magnetic Resonance Imaging
GRADE	Grades of Recommendation, Assessment, Development and Evaluation
HAROLD	Hemispheric Asymmetry Reduction in Older Adults
HPLC	High Performance Liquid Chromatography
ICD	International Classification of Diseases
IDO	Indoleamine-2,3-Dioxygenase
IGF-1	Insulin-like Growth Factor
INHIB	Response Inhibition Task
KAT	Kynurenine Aminotransferase
KP	Kynurenine Pathway
KYN	Kynurenine
KYNA	Kynurenic Acid
LTP	Long-Term Potentiation
MCI	Mild Cognitive Impairment
MEG	Magnetoencephalography
MET	Metabolic Equivalent

MRI	Magnetic Resonance Imaging
PASA	Posterior to Anterior Shift
PASE	Physical Activity Scale for the Elderly
PGA	Professional Golfers Association
PGC-1α	Peroxisome Proliferator-activated Receptor Gamma Coactivator 1-alpha
PET	Positron Emission Tomography
PLV	Phase Locking Value
QUINA	Quinolinic Acid
RSSG	Radiofrequency-spoiled Steady-state Acquisition Rewound Gradient Echo
SARGE	Steady-state Acquisition Rewound Gradient Echo
SMC	Subjective Memory Complaints/Impairment
STAC	Scaffolding Theory of Aging
TDO	Tryptophan 2,3-Dioxygenase
TRP	Tryptophan
VEGF	Vascular Endothelial Growth Factor
wMNE	weighted Minimum Norm Estimation

1 Introduction

*"For baby boomers, I feel like the canary in the coal mine while scientists search for a cure. I fear the day when I put my fingers on the keyboard and don't know how to write anymor*e."

Greg O'Brien, journalist and book author, diagnosed with early-onset Alzheimer's disease

Dementia is a clinical syndrome characterized by progressive loss of multiple higher order cognitive functions, which consequently affect the patient's abilities to live independently [1]. The prevalence of the disease was estimated with approximately 50 million people worldwide and is expected to triple until 2050, if effective therapies will not be developed [2]. Until now, no medical treatment can significantly prevent or fundamentally stop the progressive course of the disease [3]. Beside the high economic global burden caused by dementia, estimated to be $948 billion in 2016 [4], the disease has an enormous impact on family members and caregivers, which in turn require financial, medical, social and psychological support and resources.

One of the main risk factors for dementia, especially for the most common cause Alzheimer's disease (AD), is age. Industrialized countries experience the shift towards an older population as a consequence of the demographic change, which is characterized by increased life expectancy.
Several epidemiological studies and meta-analyses indicated that incidence and prevalence of dementia continuously increases with age [5–7]. However, not all people experience AD-related cognitive decline during aging. Besides genetic predispositions, modifiable risk factors associated with the individual's lifestyle were identified that presumably contribute to the occurrence of AD. Especially cardiovascular risk factors, such as obesity, midlife hypertension, smoking, insulin resistance and deficiency but also low engagement in cognitive activities, low social integration and interaction as well as a sedentary lifestyle were each found to increase the likelihood of developing the disease [8].
It was frequently shown that regular physical activity has a positive influence on cardiovascular risk factors, and can provide a framework to increase social interaction.

Recent studies also indicated that being physically active and fit is associated with lower AD risk and pathology [9,10]. In light of the need for effective strategies that can delay the course of the disease, regular physical activity has the potential to contribute to an active and healthy lifestyle, therefore reducing the risk of cognitive decline in the context of AD.

The current level of evidence for the effectiveness of physical activity treatments against cognitive decline was graded as moderate in one study [11] in accordance with the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system [12]. Moreover, the number of adverse events associated with supervised physical activity interventions was in general shown to be rather low, indicating the safety of these programs for elderly people [13] and patients with neurological diseases in general [14]. However, consensus about evidence-based recommendations, like training variables or combined exercise interventions, are still heterogeneous between studies [15] and need to be further developed.

To contribute to the development of evidence-based preventive treatments in the context of AD, this dissertation focuses on the role of physical activity and exercise against cognitive decline in elderly people. More specifically, the thesis will shed light on current evidence for application and design of exercise interventions in the prevention of AD, including training variables and effectiveness of the combination of exercise modes.
Based on these findings, a randomized controlled trial was designed that examined in a multimodal biomarker approach the influence of golf on cognitive performance in elderly people with subjective memory complaints. Finally, the thesis will summarize and discuss current evidence and will provide an outlook for replication of the golf trial and remaining important questions for further investigation.

2 Current State of Research

The research field of exercise and cognitive performance has gained increasing attention in the last 20 years. The number of hits when searching with the Medical Subject Headings (MeSh) “exercise AND cognition” on PubMed was 164 in 2000, and increased to 2634 hits in 2020.

One of the milestones was the detection of post-natal neurogenesis in the dentate gyrus of the hippocampus. Later findings indicated that physical activity significantly enhances the generation of new cells in this area of the hippocampus in animals. Today, neuroplasticity changes of the brain in response to a training stimulus could also be shown in humans. With the use of modern imaging methods, like magnetic resonance imaging (MRI), neuroplasticity changes were shown for taxi drivers [16], in adults that learned to juggle [17] and in elderly people after regular walking [18]. The view of a stimulus-dependent plastic human brain contributed significantly to the current understanding of the importance of an active social and cognitive lifestyle and engagement in regular physical activity to prevent cognitive decline in age. However, trials that investigated the potential of specific exercise treatments to improve cognitive performance in elderly people found mixed results. Missing consensus about most effective training variables and design of the training along with methodological limitations presumably promoted heterogeneity. This thesis will therefore contribute to the development of preventive evidence-based exercise treatments against cognitive decline due to AD.

This chapter provides background information relevant to the research aim and questions of this thesis. First, age-related non-pathological changes of cognitive decline will be explained, followed by an introduction to the continuum of AD. After that, the concept of cognitive reserve with its underlying neurobiological mechanisms known from the animal model will be described. Finally, current evidence about effects of exercise treatments against cognitive decline will be summarized and the potential of golf as a preventive treatment of AD will be introduced.

2.1 Non-pathological cognitive aging

The aging process is characterized by a functional decline of multiple physiological systems caused by a homeostatic imbalance of various underlying biological mechanisms [19]. Of note, biological aging is heterogeneous between individuals, and not necessarily equal to chronological age. However, uniform age-related changes in physiological systems consist, among others, of a decline in cognitive performance that follows different longitudinal trajectories depending on the function considered (see Figure 1). From the age of 65 years, elderly people primary tend to decrease in fluid cognitive abilities, including executive functions, processing speed, working memory and episodic memory [20–23]. Crystalline cognitive functions, on the other hand, such as general intelligence or semantic memory, remain relatively preserved [23] and emotional stability was found to improve with age [24].

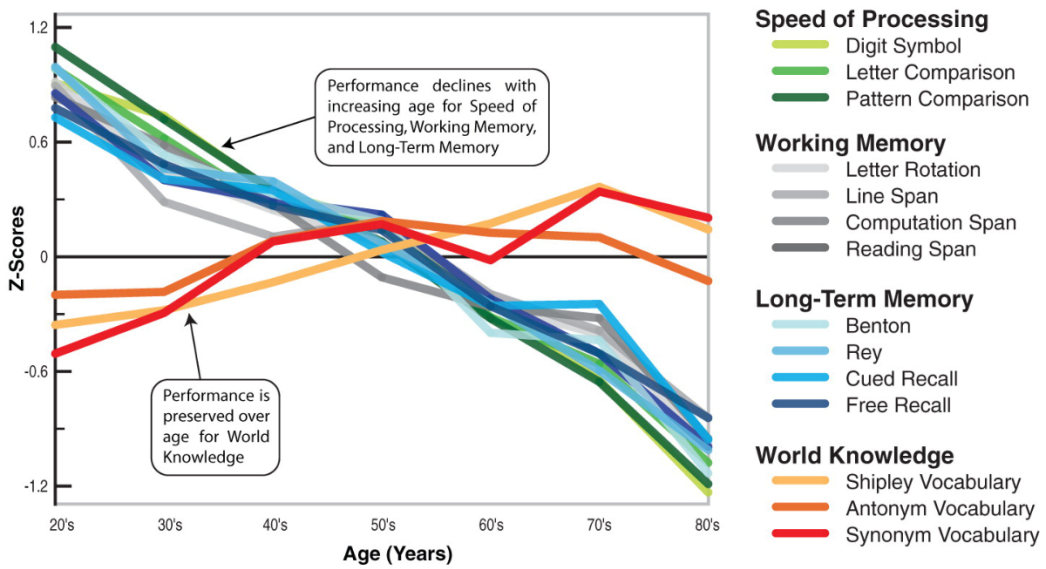

Figure 1 Age-related cognitive decline follows different longitudinal trajectories for fluid cognitive abilities (here speed of processing, working memory, long-term memory) and crystalline cognitive functions (world knowledge). Source: Park & Reuter-Lorenz [23].

Morphologically, cognitive decline mainly relates to structural and functional changes of the brain during ageing. Global atrophy of grey matter volumes and synaptic loss was observed in elderly people, which is especially pronounced in prefrontal regions and structures of the temporal lobe [25]. Moreover, white matter integrity decreases globally, but is more pronounced in prefrontal and temporal cortices as well [25]. In addition, the number of white matter hyperintensities increases [23].

The structural changes consequently affect the functional activation of brain regions and therefore presumably contribute to the decline of executive and memory functions on the behavioral level.
Functional magnetic resonance imaging studies (fMRI) indicated that the prefrontal cortex of elderly people showed an altered activation during a task with high demands on attention compared to younger adults [25]. Moreover, a trend towards a broader involvement of the prefrontal cortex (known as “posterior-anterior shift in aging, PASA”, [26] along with activation of the contralateral hemisphere (known as “hemispheric asymmetry reduction in older adults”, HAROLD [27] was observed.

The findings point to dedifferentiated activity of brain regions, which were generally interpreted as compensatory mechanisms to account for the neuronal cell loss [28]. The theoretical model propagates that alternative neural circuits are recruited during task execution to account for cognitive performance. However, once task demands increase, brain activation reaches and exceeds the highest possible degree of activation and cognitive performance decreases as a consequence [28].

Considering functional brain activations in the context of large-scale brain networks, there is some evidence that support the previous described changes. With the use of graph theory[1], characteristics of large-scale network organization during the aging process were described. In accordance with the CRUNCH approach, elderly people tend to a global functional integration of the brain [29], primarily driven by de-differentiated activity of cognitive and sensory networks [30]. At the same time, functional connectivity within networks decreases, pointing to decreased integrity presumably caused by neural cell loss [30]. The findings support the idea that the aging brain experiences functional reorganization processes of large-scale neuronal networks that are related to cognitive performance [30].

In summary, the normal aging process is accompanied by a decline in fluid cognitive functions, especially executive functions and memory. This decline relates to grey and white matter atrophy in prefrontal and temporal regions, and to a reorganization of large-scale functional networks.

[1]Graph theory is the mathematical representation of a network and can be used to describe its organizational characteristics. The basic graph consists of nodes (the brain regions) that are connected by edges (functional or structural connections).

Distinguishing non-pathological from pathological aging in the context of AD, cognitive decline due to AD was shown to correlate with volume loss especially in the medial temporal lobe along with greater memory impairment [25] and hyperactivation of the hippocampus [31,32]. The changes exceed the structural and functional alterations observed in the normal aging process.

On the behavioral level, persons in the early stage of AD show only subtle decline in neuropsychological functions, but are still able to manage activities of daily living independently. Common cognitive symptoms are progressing objective deficits in consolidation of information, in executive functions and semantic over time [8]. Some persons are able to compensate the deficits with the use of alternative strategies in daily life, which exacerbate the recognition of the disease for a long time. Retrospectively, patients with AD often changed their behavior years before clear objective symptoms of early AD occurred [8].

2.2 The continuum of Alzheimer's disease

Accordingly, current research in the field indicated that the clinical trajectory of AD moves along a continuum of (neuro-) pathological changes and clinical symptoms [33]. It incorporates a non-symptomatic preclinical phase, followed by a conversion to the prodromal phase (Mild Cognitive Impairment, MCI) with onset of clinical symptoms. Finally, the transition to AD follows, with progressive neuropathology and cognitive decline until severe stages of the disease (see Figure 2, [33]).

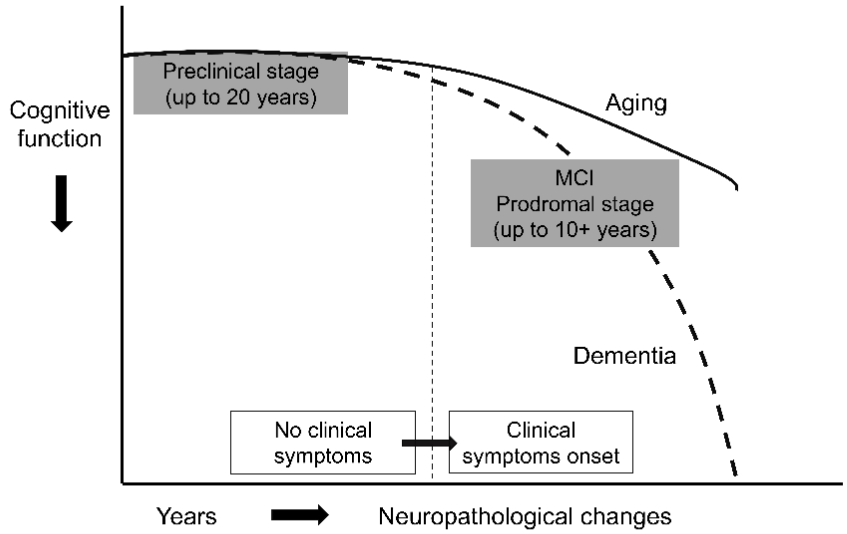

Figure 2 The Alzheimer's disease continuum of clinical symptoms (cognitive functions) and neuropathological changes. The theoretical model illustrates the clinical trajectory of AD. Source: Modified from Sperling et al. [34] and Gale et al. [35].

Of note, the proceeding of each individual on this continuum has no uniform trajectory, and not all patients with MCI convert to AD [34].

Cognitive symptoms of AD are typically objective decline in episodic memory, executive functions, orientation as well as aphasia, apraxia, and agnosia. Currently, diagnosis of AD consists of objective impairment in episodic memory (isolated or in combination with impairment in another cognitive domain), which is present for at least 6 months and continuously progresses. Further diagnosis criteria include AD-biomarker in cerebrospinal fluid [e.g. reduced amyloid-beta 42 (Aβ42) concentration and increased tau protein], positive evidence of Aβ with positron emission tomography (PET) or evidence of genetic mutation [36].

The exact etiology and pathogenesis of AD is not fully understood yet, but multifactorial in nature and influenced by various parameters, such as lifestyle, epigenetics, behavior and personality [34]. The generic neuropathological hallmarks of the disease are extracellular accumulated Aβ plaques, intracellular neuro-fibrillary tangles with tau protein and neurodegeneration. Especially oligomerization of Aβ was suggested as a key pathological mechanism that induce neurodegeneration rather than the mature plaques [8]. Other pathological mechanisms of AD include neuroinflammation, white matter atrophy, impaired glucose metabolism, reactive oxygen species and mitochondrial dysfunction [8,37,38] as well as impaired neurotransmission, such as dysfunction of the excitatory cholinergic system due to neuronal cell loss in the nucleus basalis of Meynert [8]. In the early phases of AD, Aβ plaques are predominantly distributed in neocortical regions, but affect later also subcortical brain regions, such as entorhinal regions, the basal ganglia's, the thalamus and brain stem [8].

The familial and autosomal-dominant variant of AD typically manifests at a young age (30-60 years) [39,40], and accounts for approximately 1% of all cases. Mutations in presenilin 1, 2 and the amyloid precursor protein were shown to be closely linked to this rare variant of AD [39]. Sporadic AD occurs more frequently at a higher age (> 65 years), and a specific genotype of apolipoprotein (APOE ε4 allele) was identified as a genetic risk factor [8,39]. Of note, carriers of APOE ε4 have a 12-fold increased risk for sporadic AD. However, APOE ε4 is not the sole factor or even necessary for developing the disease [39]. Other lifestyle-associated risk factors for AD were detected and comprise smoking, alcohol consumption, obesity, dyslipidemia, low education, diabetes type 2 with insulin resistance, social isolation, depression and anxiety, concussions and physical inactivity [41–44]. Cholinesterase inhibitor and memantine are frequently used in the medical treatment of the disease, but the development of new effective drugs with significant impact on disease progression failed in the last 20 years [45].

The neuropathological changes of AD, such as cortical Aβ deposition, take place before clinical symptoms occur (up to 10-20 years, see Figure 2 and Figure 3). As AD is difficult to treat once neurodegeneration and other pathological mechanisms appear, it is of great interest to identify patients in the early course of the disease, such as in preclinical or prodromal phases.

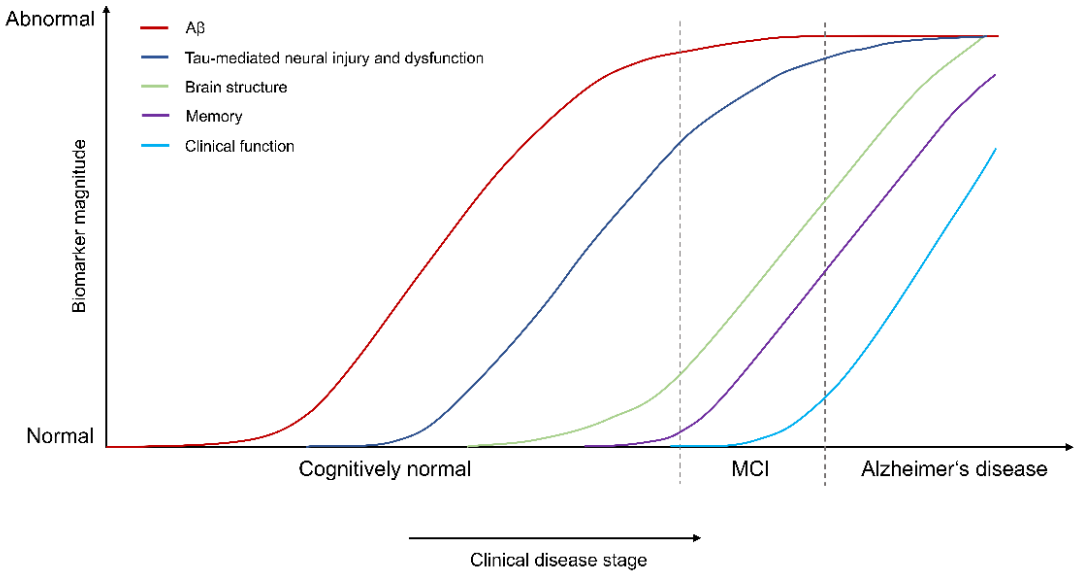

Figure 3 Magnitude of neuropathological biomarkers and clinical symptoms along the AD continuum. Aβ accumulation starts early and clinical symptoms, such as brain atrophy and memory impairment, later in the course of the disease. Source: Jack et al. [46]

The concept of MCI was suggested representing an early manifestation of dementia with onset of clinical symptoms, and was thus often referred to as “prodromal dementia” [47]. Multiple clinical subtypes were then identified and classified with different etiologies [48]. However, especially MCI with subjective and objective memory impairment (amnestic MCI, aMCI) was found to represent an early manifestation of AD [48]. In contrast to AD, general cognitive performance, social interaction and personality is mostly not affected and patients are still able to manage everyday activities. aMCI was further classified into a single-domain subtype, where only memory is impaired, and a multi-domain subtype with decline in at least one other cognitive domain [49–51]. Multi-domain aMCI was suggested to represent an advanced prodromal stage of AD, as more regions are affected by neuronal cell loss and hypometabolism [52–54].

It was estimated that 80% of all aMCI patients progress to AD in the next 5-6 years, with an annual conversion rate of 10-12% [55]. However, it was also reported that some patients (around 16% in one study) reverse to “normal aging” with minimal or without cognitive deficits [56]. Therefore, the concept of MCI is heterogeneous with multiple factors that influence the trajectory towards AD, such as genetics and epigenetics, presence of psychiatric disorders or secondary diseases [57].

From the perspective of large-scale brain networks, AD may be described very simply as a continuous “disconnection syndrome” [58]. The neuronal correlates are, among others, grey matter atrophy especially in the medial temporal lobe, hippocampus, parahippocampus, entorhinal cortex and posterior cingulate cortex [29]. These changes correlate well with clinical findings, as episodic memory is an early clinical hallmark of AD [29,59]. In multi-domain aMCI, a shrinkage of the prefrontal lobes, including the anterior cingulate cortex, was reported additionally [52].

Interestingly, the affected regions belong to the Default Mode Network (DMN)[2], a functionally and structurally connected set of brain regions that activates at wakeful rest and deactivates with external attention demands. The core regions of the DMN are vulnerable to neuropathological changes of AD, such as Aβ depositions [29,61]. Accordingly, functional and structural disruptions of the DMN correlate with cognitive impairment [62,63]. The findings for functional connectivity patterns of aMCI patients in the DMN vary between studies [64], and might be mediated by ignorance of different subtypes and genetics (APOE ε4 carrier) as well as heterogeneous diagnosis criteria of studies [64]. Hyper-connectivity, but also reduced connectivity within the DMN and its subregions were reported. Similar to the CRUNCH hypothesis observed in healthy aging, the increased functional connectivity may serve as a compensatory mechanism to maintain cognitive performance [64]. However, with disease progression, long-distance connections that integrate the networks on a global level decrease, which is related to decline in cognitive performance [65]. In accordance, especially brain regions with a key function for communication in a network (“hubs”, identified by dense connections, high vulnerability to AD pathology and high betweenness centrality), seem to be affected by the disease [58]. As a consequence, the topological organization of brain networks in AD patients tend to be more random compared to healthy elderly with less efficient information processing [58,66].

[2]The anatomical regions that were defined as the DMN are: retrosplenial cortex, inferior parietal cortex, dorsolateral frontal cortex, left inferior temporal gyrus, medial frontal regions, and hippocampal formation [60].

2.2.1 Subjective memory complaints or subjective cognitive decline

Subjective memory complaints or subjective cognitive decline (SMC)[3] refers to a perceived decline in cognitive performance in elderly people. The concept was introduced by Reisberg and colleagues in the early 80s in order to define preclinical stages of AD [68]. Objective cognitive performance is not necessarily affected compared to healthy elderly, although some studies found a link between SMC and attention, working memory, and a memory composite score [69]. Studies also found an association of SMC with neuropathology of AD, such Aβ depositions, and a predictive function for subsequent development of MCI and AD [70]. Therefore, SMC was suggested to precede MCI and might represent an early clinical indicator of AD [71], see Figure 4).

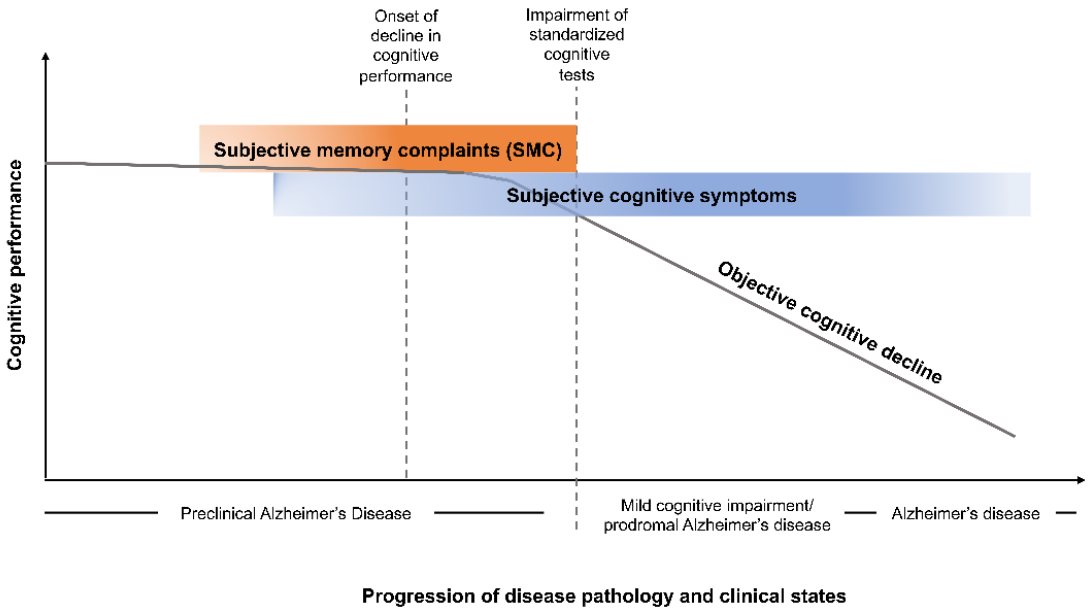

Figure 4 Theoretical model that illustrates subjective cognitive decline as a preceding stage of MCI on the AD continuum. Of note, subjective cognitive symptoms occur rather in the late stage of preclinical AD and was thus suggested to represent the transition to MCI. Modified from Rabin et al [71].

However, the concept of SMC has some limitations that exacerbates the clinical diagnosis. First, SMC may have a high sensitivity to detect MCI and AD, but a rather low

[3]The terminology across studies is heterogeneous. The terms "subjective cognitive decline", "subjective cognitive impairment", "subjective memory impairment" or "subjective cognitive complaints" are used interchangeably, but they all refer to the same underlying concept [67].

and insufficient specificity [69], raising the risk for false-positive identifications. A population-based study found that the prevalence of SMC is around 53% in elderly people, from which only a fractional part will develop MCI or AD [72]. SMC is a common symptom in old age, which can occur independent of AD [73]. Other diseases and circumstances, such as depression, anxiety, somatic complaints and sleep disturbances [74–77], can cause SMC as well. Therefore, the symptom of SMC alone may be not sufficient for clinical diagnosis of preclinical AD. Moreover, SMC are often restricted to the memory domain, but can, similar to the MCI concept, also affect other domains, such as executive functions [70,78].

To uniform and facilitate the clinical diagnosis of SMC due to AD, researchers formed a working group (Subjective Cognitive Decline Initiative, SCD-I) and published a consensus article with common identified features that increase the likelihood of SMC (the SCD-plus criteria):

> *"(a) subjective cognitive decline in memory rather than other domains, (b) onset of SMC within the last 5 years, (c) age of onset ≥ 60 years, (d) particular concerns associated with SMC, (e) the feeling of worse performance than others of the same age group, (f) confirmation of perceived cognitive decline by an informant, and (g) the presence of APOE ε4 genotype"* [79]

Of note, the criteria still need to be validated and refined in further research. For example, there is some evidence that manifestation of SMC over time represents a feature associated with an increased risk of AD [80]. In general, consensus about a common diagnostic assessment of SMC is not established yet [71].

Besides neuropathological biomarkers such as cortical Aβ deposition, morphological changes of the brain of people with SMC could be detected. The differences are only subtle compared to healthy elderly, but point to SMC as an intermediate stage between normal aging and MCI. Structural alterations were observed mainly in medial temporal lobe structures, such as the hippocampus, entorhinal cortex and amygdala [81], along with cortical thinning in medial and frontotemporal lobes [71]. Moreover, there is some evidence that functional connectivity exhibit significant alterations in a non-linear manner even before the occurrence of Aβ depositions [82]. More specifically, increases and decreases in functional connectivity have been observed in several networks of SMC

patients, including the DMN, salience network and executive control network compared to elderly control groups without the symptom [82]. Thus, there is increasing evidence for SMC as a preclinical stage of AD, which makes this group very interesting to study in the context of effective preventive treatments.

Of note, no medication exists that fundamentally delays or prevents the progressive course of the disease yet, but several lifestyle-associated behaviors were identified to reduce the risk of AD. In this context, the concept of cognitive reserve received growing interest in the research field of non-pharmacological treatments.

2.3 The concept of cognitive reserve

The concept of cognitive reserve describes the resilience of an individual's brain against neuronal damage or pathology, such as AD. The development of the assumption that the brain has additional reserve capacities originates from observations which indicated that clinical cognitive symptoms not necessarily correlate with brain pathology or damage [83]. Cognitive reserve may serve as an explanation for the long maintenance of cognitive functions in the preclinical or prodromal phase of AD. Several approaches were developed, and each contributes to the current understanding of cognitive reserve.

The first approach includes the assumption of a rather passive model of cognitive reserve. The *brain reserve* describes quantitatively the amount of neurons and synapses of a brain, the head circumference, intracranial volume as well as dendritic density that are affected by a disease (such as AD) or damage to the brain [84]. Once a critical threshold is exceeded, cognitive decline or clinical symptoms in the context of AD would occur [84].

In contrast to the passive approach of brain reserve, the *cognitive reserve* model suggests that the brain actively copes with damage or pathological changes on a functional level [83]. Not a certain threshold is crucial for the onset of clinical symptoms; but rather the ability to use existing or alternative functional neuronal networks to compensate for cell loss [83,84]. Efficiency (recruiting of fewer resources), capacity (potential to recruit additional resources) and flexibility (use of multiple networks to accomplish a task) are the key compensation mechanisms in this approach [83]. Stern et al. [85] also differentiated between *neural reserve* and *neural compensation*. The first

includes the three compensatory mechanisms, whereas the latter refers to the use of alternative networks when the original networks are damaged [85].

Both, cognitive and brain reserve have in common that they provide a capacity that compensate for the neuronal cell loss and pathological changes in the context of AD.
Of note, also other approaches exist in the context of cognitive reserve, including brain maintenance [86] and the Scaffolding theory of aging (STAC) [28]. Brain maintenance refers to the importance of the maintained neuroanatomical and neurochemical characteristics in the face of neuropathology [86], whereas STAC describes functional reorganization processes of the brain due to disrupted networks [23].

Evidence from epidemiological studies supports the concepts of cognitive reserve. Most frequently, an association of higher education with lower risk of dementia was described [87,88]. In accordance, lower engagement in cognitive stimulating activities was found to relate to a faster cognitive decline in age [89]. There is also some evidence that engaging in leisure-time activities, such as physical activity and exercise, can contribute to cognitive reserve. Higher activity levels over the lifetime were associated with reduced risk of AD and amyloid burden [10,90,91].

The findings suggest that an active and healthy lifestyle is related to cognitive health and reduced risk of dementia. A recent consensus paper[4] formulated the need to advance the theoretical concept of cognitive reserve into a concrete approach to enable the development of effective preventive interventions for dementia [45].

2.4 (Neuro-) biological mechanisms

The biological basis for cognitive reserve is the ability of the brain to undergo cellular and molecular changes in response to the environment, which is also known as neural plasticity. Angiogenesis, synaptogenesis as well as adult neurogenesis are the main mechanisms of these processes. Adult neurogenesis describes the development of physiological integration of neurons in the olfactory bulb and hippocampus originating from precursor cells [92]. For a long time, neuroscientific researchers believed that neurogenesis in the adult brain is not possible, but with advancing techniques and

[4]Working group: “International Conference on Cognitive Reserve in the Dementias and the Alzheimer’s Association Reserve, Resilience and Protective Factors Professional Interest Area”

methods, the paradigm changed. Kempermann et al. [93] were the first to describe neurogenesis in the dentate gyrus and olfactory bulb, with the use of bromodeoxyuridine (BrdU) as a marker of cell proliferation. Since then, the continuous generation of new cells in the dentate gyrus of the hippocampus was also observed in humans.

By applying mathematical methods it has been shown that approximately 700 new neurons are generated per day, with an annual turnover rate of 1.75% [94]. The functionality of these new generated cells is partially unclear. Van Praag et al. [95] found a relation of adult neurogenesis and long-term potentiation, which would support the idea of integration into existing neuronal structures.

One promising method that was found to increase neurogenesis in the dentate gyrus of the hippocampus is “enriched environment”, which describes a manipulation to the environment of rodents. The manipulations consist of toys, tunnels, nesting material and running wheels [96] with the aim to provide social, sensory and cognitive stimulation. Interestingly, van Praag et al. [97] and Fabel et al. [98] indicated that the combination of voluntary physical exercise with enriched environment provided the strongest stimulus on neurogenesis in rodents [92]. Accordingly, after 10 weeks, the combination of both lead to the highest number of new neurons in the dentate gyrus of the animals (see Figure *5*).

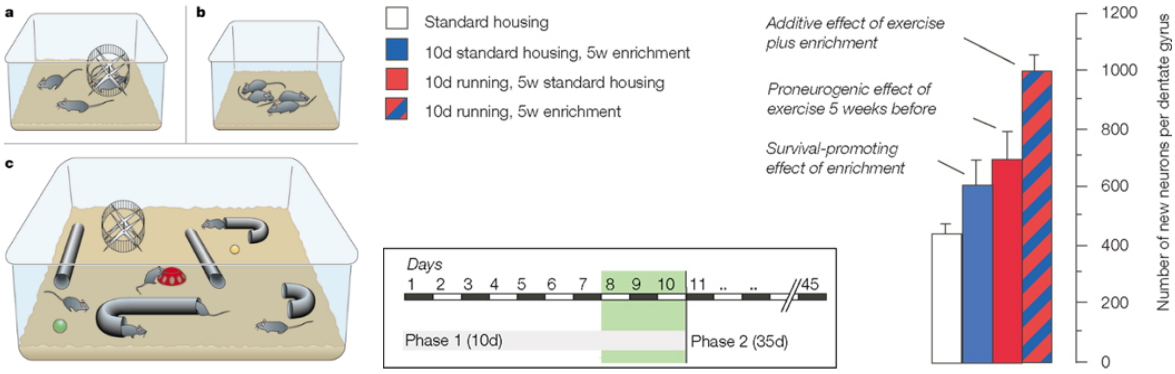

Figure 5 Left: Design of the comparison of voluntary physical exercise (a), standard laboratory housing (b), and enriched environment plus voluntary physical exercise (c) in the animal model. Source: Van Praag et al. [97]. Right: Number of new generated cells in the dentate gyrus was highest in the physical activity + exercise model compared to standard housing, enrichment or exercise alone. Sources: Kempermann et al. [92] and Fabel et al. [98].

Therefore, combined physical activity and environmental enrichment may have complementary or even additive effects on neuronal cell generation in the hippocampus [92]. However, the exact physiological mechanisms remain to be elucidated and still have to be replicated in humans. An explanation might be that physical activity serves as a primer for subsequent stimulation of neurogenesis by cognitive, sensory or social stimuli [98,99]. When transferring findings into humans, it should be considered that the human brain has a more complex organization compared to rodents [99] as well as some anatomical differences, especially regarding the frontal lobes. Moreover, conduction of sports and exercise in human consists of more than wheel running, especially when considering different exercise modes [99] or the influence of positive emotions.

One of the frequently investigated possible mediators of the neuroprotective effects of exercise in humans is the release of neurotrophic factors, such as *brain-derived neurotrophic factor* (BDNF) [100]. BDNF reaches high concentrations in the hippocampus (and other brain areas) after acute and rather intense exercise [99], and is linked to synaptogenesis, synaptic plasticity, and enhanced learning and memory [100]. Further exercise-related mechanisms which have the potential to increase neurogenesis rate, synaptic plasticity and cell proliferation in the brain are (among others), the stimulation of growth factors, including *insulin-like growth factor 1* (IGF-1) and *vascular endothelial growth factor* (VEGF) [100].

Besides the frequently investigated neurotrophic factors, also the tryptophan (TRP)-consuming *kynurenine pathway* (KP) recently gained attention, as it was shown to be dysregulated in patients with AD and MCI with an accumulation of neurotoxic kynurenine metabolites, such as quinolinic acid (QUINA) [101–103]. Similarly, these metabolites were associated with poor memory performance in elderly people [104]. Findings from animal research suggested that aerobic exercise has the potential to reduce peripheral kynurenine (KYN) levels by expression of kynurenine aminotransferase (KAT), which degrades KYN to kynurenic acid (KYNA) [105]. In contrast to KYN, KYNA is poorly able to pass the blood brain barrier, which consequently leads to a reduction of central KYN levels and its downstream metabolites [106].

Moreover, the degradation of TRP to KYN is catalyzed by the isoenzymes indoleamine-2,3-dioxygenase (IDO, expressed in various cell types), and the hepatic tryptophan-2,3-dioxygenase (TDO) [101]. IDO is upregulated by pro-inflammatory stimuli, such as IL-6 or other cytokines, while TDO is stimulated by TRP and glucocorticoids [106]. Upregulation of these enzymes lead to an increased degradation of TRP to KYN, with

the consequence of an increase in kynurenine downstream metabolites, including QUINA [101]. As chronic exercise interventions were associated with anti-inflammatory characteristics [107], they may have the potential to positively impact the KP by reducing IDO activity [106].

However, currently there is a lack of studies investigating the chronic effects of exercise (especially regarding consideration of different modalities or combination with other stimuli) on the KP in elderly people with or without cognitive impairment.

2.5 Evidence-based exercise treatments targeting cognitive decline in elderly people

A number of epidemiological studies suggest a positive effect of lifelong physical exercise on the risk of AD [90,108,109] and the maintenance of cognitive performance [110]. Of note, in over 10.000 participants, no association between physical activity levels (measured by a questionnaire 7 times over 28 years) and cognitive decline or dementia risk were reported as well [111]. Interestingly, the authors observed a decline in moderate to vigorous physical activity levels in the preclinical phase of AD. Intervention trials for elderly people at risk for AD with a short follow-up (less than 10 years) therefore might be influenced by this decline, pointing to reverse causation instead of causal effects of exercise [111].

Other studies (e.g. de Souto Barreto [112] with more than 100.000 analyzed participants) suggested an inverse linear relationship between physical activity levels and AD risk – which means, the lower physical activity levels of an individual, the higher the risk of AD and vice versa. Hörder et al. [113] investigated cardiovascular fitness in a subsample of 191 women aged 38 to 60 years and examined the risk of dementia for the next 44 years. The adjusted hazard ratio for dementia in women with a high cardiovascular fitness was 0.12 (95% confidence interval 0.03 to 0.54), and 1.41 (95% confidence interval 0.72 to 2.79) among those with low cardiovascular fitness in midlife, respectively. The results suggest that physical activity, and especially cardiovascular fitness in midlife is a strong neuroprotective factor that is linearly related to dementia risk.

Findings from interventional studies focusing on cognitive performance with shorter follow-up periods (less than 10 years) are less consistent and do not necessarily support a linear dose-response relationship. Especially differences in study design, like the design of the intervention, the treatment of control groups (active vs. passive), the choice of cognitive outcomes, the sample characterization and other factors increased heterogeneity between studies and have presumably an impact on results as well. Moreover, the studies lack of double blinding, which increases the risk for overestimation (placebo) of the effect of exercise and cognition. Also psychosocial aspects, such as increased social interaction with other participants or the trainer as well as joy and motivation can positively impact at least psychological outcomes [114]. The heterogeneity between studies and uncontrolled confounders exacerbates interpretation and the development of evidence-based practical guidelines for physical activity against cognitive decline.

In the late 90s, Kramer et al. [115] found in a sample of 124 elderly sedentary subjects improved executive functions performance after 24 weeks of moderate aerobic exercise training compared to a stretching and toning control group. Using a similar design, Erickson et al. [18] demonstrated later an increase of hippocampal volume by 2% in 120 elderly people after a 1-year walking intervention along with improved spatial memory performance (see Figure 6).

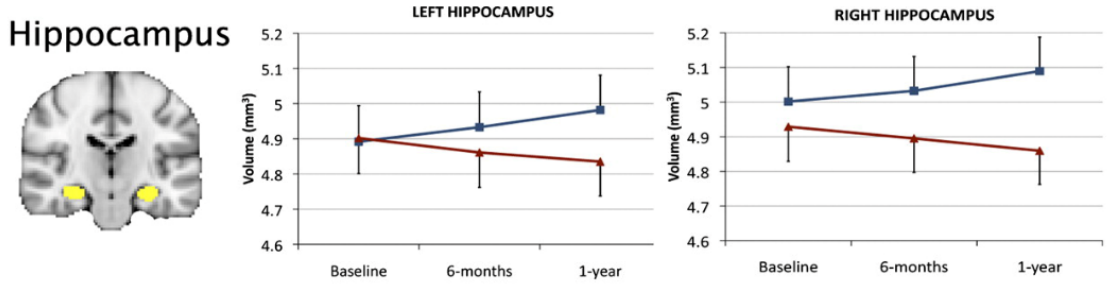

Figure 6 The figure shows the change of hippocampal volume during the 1-year intervention in both groups (blue = walking group, red = stretching and toning control group). Source: Erickson et al. [18].

After that, several randomized controlled trials investigated the influence of metabolic demanding exercise on cognitive performance in elderly people with and without cognitive impairment [116,117]. Older evidence syntheses found rather large and positive effects [118], whereas recent findings are more heterogeneous [119,120]. One reason for that might have been the divergent and restricted study selection criteria, such as the type of exercise that was applied in the interventions [11]. Following Hollmann's five forms of motor demands, exercise can be classified into the modes *endurance, strength, coordination, flexibility* and *speed* [121].

Northey et al. [11] conducted a multi-level meta-analysis to examine the effects of 36 randomized controlled exercise interventions on cognitive functions in people older than 50 years. Following Cohen's d, they found an overall small and positive effect of physical activity interventions on cognitive performance (standardized mean difference: 0.29, 95% Confidence Interval 0.17 to 0.41). They recommended especially aerobic and resistance exercise, either in combination or isolated, for at least 45 min per session at moderate to vigorous intensity. However, after 1 year follow-up, a recent randomized trial with dementia patients (n = 494) found a negative effect of 4 month combined aerobic and resistance exercise intervention on general cognitive performance measured with the Alzheimer's Disease Assessment Scale – Cognitive Subscale [122]. Of note, the

deterioration of 1.4 points does not necessarily have a clinical significance, but it raises the assumption that once patients have AD, intensive exercise treatments may not be able to significantly slow cognitive decline in the progressive course of the disease.

Besides metabolic demanding exercise, interventions consisting of low intensity, but high complexity including cognitive demands, such as coordination training, were less investigated. However, there is some evidence that coordinative exercise could be efficient to improve cognitive functions and to influence functional brain networks as well. Voelcker-Rehage et al. [123] compared the effects of a 1-year regular coordination exercise intervention with aerobic exercise and a control group on cognitive performance and task-related functional connectivity in 44 elderly people. As a main result, coordination as well as aerobic exercise both improved performance on the Flanker and Visual Search Task. Interestingly, the adaptions of functional brain networks during task execution were different after the intervention. The coordination exercise group demonstrated a higher activation of the visual-spatial network during task execution, whereas the aerobic exercise group showed a higher activation of the sensorimotor network. Similar training-related adaptions of grey matter volumes were demonstrated after juggling and learning to play golf in brain regions involved in information processing [17,124].

Therefore, intensity and metabolic demand of an intervention might be not the sole factor for improving cognitive functions in elderly people with and without cognitive impairment. Moreover, the current evidence indicates that exercise modes with low metabolic, but high cognitive demands, induce structural and functional changes in the brain and on cognitive performance as well, which is associated with the training-specific stimulus induced. Therefore, coordinative training rather has a direct effect on cognition and functional networks. Metabolic demanding exercise, with less cognitive demands, induce positive effects presumably by reducing cardiovascular risk factors, stress hormones and systemic inflammation [100,125], and by stimulation of BDNF, VEGF and IGF-1 [18,126–128].

The first hypothesis of this thesis is that metabolic demand of an intervention is not the only factor to improve cognitive performance in elderly people with or without cognitive impairment. Based on the findings from the animal model, the second hypothesis is that combining exercise modes with each other and other stimuli (such as cognitive

stimulation) may have a stronger effect on cognitive performance than each exercise mode alone. More randomized controlled trials are needed to gain a detailed understanding about the effectiveness of combined exercise (including cognitive and physical stimulation) on cognitive performance compared to single-component exercise.

2.6 The case for golf as a preventive treatment for elderly people

Golf is a leisure-time activity, which can be played at every age. For elderly people, it provides the opportunity to engage in a regular activity with social contacts, and it was found to positively influence cardiovascular risk factors and mental health [129]. The demands of golf might be similar to the enriched environment animal model, as it mainly consists of sensorimotor, cognitive and social demands. Besides low to moderate cardiovascular intensity, learning the golf swing requires good hand-eye coordination, static postural and sensorimotor control [130,131]. The cognitive demands of golf involve strategic planning, maintaining and manipulating information, adapting to changing environmental conditions, working memory, attention as well as cognitive flexibility. Golf also facilitates the establishment of social connections and increases interaction.

However, learning to play golf might be challenging, especially for people with cognitive problems. Until now, no studies investigated feasibility of learning to play golf for elderly people with SMC. Few studies investigated the effects of a golf intervention on cognitive functions, but without consideration of relevant biological surrogate markers of neuroplasticity. Shimada et al. [130] found improvements in immediate and delayed logical memory after a 24-weeks golf intervention with healthy older adults. Another research group found an increased visual imaginary ability after 20 sessions of golf training with stroke patients [132]. Of note, implementation of (neuro-) biological markers would enhance the detailed understanding of physiological mechanisms associated with the intervention, especially in light of current discussions about superiority or differential effects of exercise modes and their combination with other stimuli.

Table 1 represents a summary of the relevant biomarkers of this thesis.

Table 1 Summary of relevant (neuro-) biological markers of the thesis

	Relevance	Methods	Advantages (+) & Disadvantages (–)
Default Mode Network	▪ resting-state network vulnerable to age-related changes and AD pathology (see p. 10) ▪ hierarchically superior resting state network [133] ▪ presumably organizes and integrates information from other (resting-state) networks [133] ▪ functional integrity linked to cognitive functions in elderly people with or without AD, such as episodic memory [134] or working memory [135]	MRI ▪ investigation of various morphological characteristics [136]	+ high spatial resolution – signal sensitive to movement artifacts or several dental crowns – noisy recording – cost-intensive
		fMRI ▪ functional activation of brain regions based on oxygenated hemoglobin [136]	+ spatial resolution – temporal resolution (sec) – artifacts similar to MRI – noisy recording – cost-intensive
		EEG ▪ current changes of synchronous neuronal oscillations originating from mainly pyramid cells oriented perpendicular or parallel to the scalp [137]	+ high temporal resolution (ms, reflects direct neuronal activity) + silent recording + less cost-intensive compared to fMRI and MEG – low spatial resolution (difficult to measure activity from subcortical regions, volume conduction and inverse problem) – signal-to-noise ratio highly affected by artifacts (e.g. eye movements, heartbeat, external electric devices)
		MEG: ▪ magnetic field generated by electric fields originating from synchronous neural oscillations [137]	+ better spatial resolution than EEG, but lower compared to fMRI + signal less affected to anatomy of the head + high temporal resolution (ms, reflects direct neuronal activity) + silent recording – sensitive to dipoles with tangential orientation [138] – less sensitive to deeper and subcortical sources [137] – artifacts similar to EEG

			– limited mobility – cost-intensive
		▪ a promising approach is the combination of methods with high spatial (e.g. MRI) and high temporal resolution (e.g. EEG) to assess direct neuronal activity in brain networks [138]	
Kynurenine Pathway	▪ dysregulated in AD [101] ▪ increased peripheral KYN/TRP ratios associated with poor memory performance in elderly people [104]	CNS sample (e.g. liquor)	+ direct assessment of central KP metabolites – restricted assess in clinical trials with humans – procedure requires experienced personnel
		Peripheral sample (e.g. serum)	+ easier assess in clinical trials with humans + evidence for positive correlations between central and peripheral kynurenine concentrations (e.g. [139]) – limited significance for central levels: not all kynurenine metabolites pass the blood brain barrier [140] – limited significance for systemic changes after exercise interventions (or other stimuli)

AD: Alzheimer's disease, EEG: electroencephalography, fMRI: functional magnetic resonance imaging, CNS: central nervous system, KP: kynurenine pathway, KYN/TRP: kynurenine-to-tryptophan ratio, MEG: magnetoencephalography, MRI: magnetic resonance imaging

3 Research Aims and Questions

The overall research aim of this dissertation was to contribute to the development of evidence-based exercise treatments in the prevention of AD. More specifically, there is no consensus about the most effective training variables (such as intensity, duration or frequency) or design of exercise interventions (modes) with beneficial effects on cognitive performance in elderly people.

In addition, increasing attention has been paid to the importance of different exercise modes for improvement of cognitive functions. Animal studies suggested a superior effect of aerobic exercise combined with enriched environment, including sensorimotor, cognitive and social stimulation. The transfer of these findings into humans is still limited, but the profile of golf might have similarities to the enriched environment model. In general, less is known about the effects of such combined interventions on cognitive performance and its influence on (neuro-) biological markers, such as functional network characteristics and serum kynurenine metabolites.

Therefore, the following research questions were addressed:

1) Is there a dose-response relationship between exercise (based on randomized controlled trials) and cognitive functions in elderly people with or without cognitive impairment due to AD? (see 4.2 Research paper 1)
2) Is learning to play golf over 22 weeks feasible for elderly people with SMC? Is the intervention effective to improve cognitive functions, DMN connectivity and the kynurenine pathway (KP)? (see 4.3 Research paper 2 and 4.4 Research paper 3)
3) Is there a difference in source connectivity patterns of the DMN and cognitive functions between elderly golf-novices compared to elderly non-golfers? (see 4.5 Research paper 4)

4 Publications and Results

4 publications were considered for the thesis. Research paper 1 provides a systematic review about current evidence for preventive and rehabilitative effects of exercise for elderly people with or without AD.
The research papers 2, 3 and 4 relate to the randomized controlled trial on the effects of learning to play golf, which was conducted between April and December 2018 at Paderborn University.
In this trial, 46 elderly people with SMC were recruited and randomized to either the golf or control group. The golf group was taught how to play golf for 22 weeks; the control group received no additional treatment and continued with daily life. Different parameters of cognitive performance were investigated. The primary outcome was feasibility and cognitive performance; the secondary outcomes were (neuro-) biological markers and functional brain networks.
In research paper 2, the intervention was evaluated regarding feasibility and effectiveness on cognitive performance and the KP. In research papers 3 and 4, functional characteristics of the DMN were investigated in a small cohort of the golf group before and after the intervention (3) and in a cross-sectional comparison after the intervention only (4). The flow chart of the trial is presented in Figure 7.

Of note, the original study design was planned as a 3-group comparison of aerobic exercise (as the current “gold standard”) with golf (as the new treatment) and a control group without treatment. Sample size calculation for the primary outcome Alzheimer’s Disease Assessment Scale – Cognitive Subscale (ADAS-Cog) revealed a sample size of 69 (23 in each group) for detecting a mean effect of 1.22 with 95% statistical power in the walking group [141]. Due to problems during recruitment (of 109 assessed patients, 46 declined to participate and 17 did not meet inclusion criteria), we decided to cancel the aerobic exercise group and compared the effects of learning to play golf with the control condition to ensure an appropriate sample size within each group.

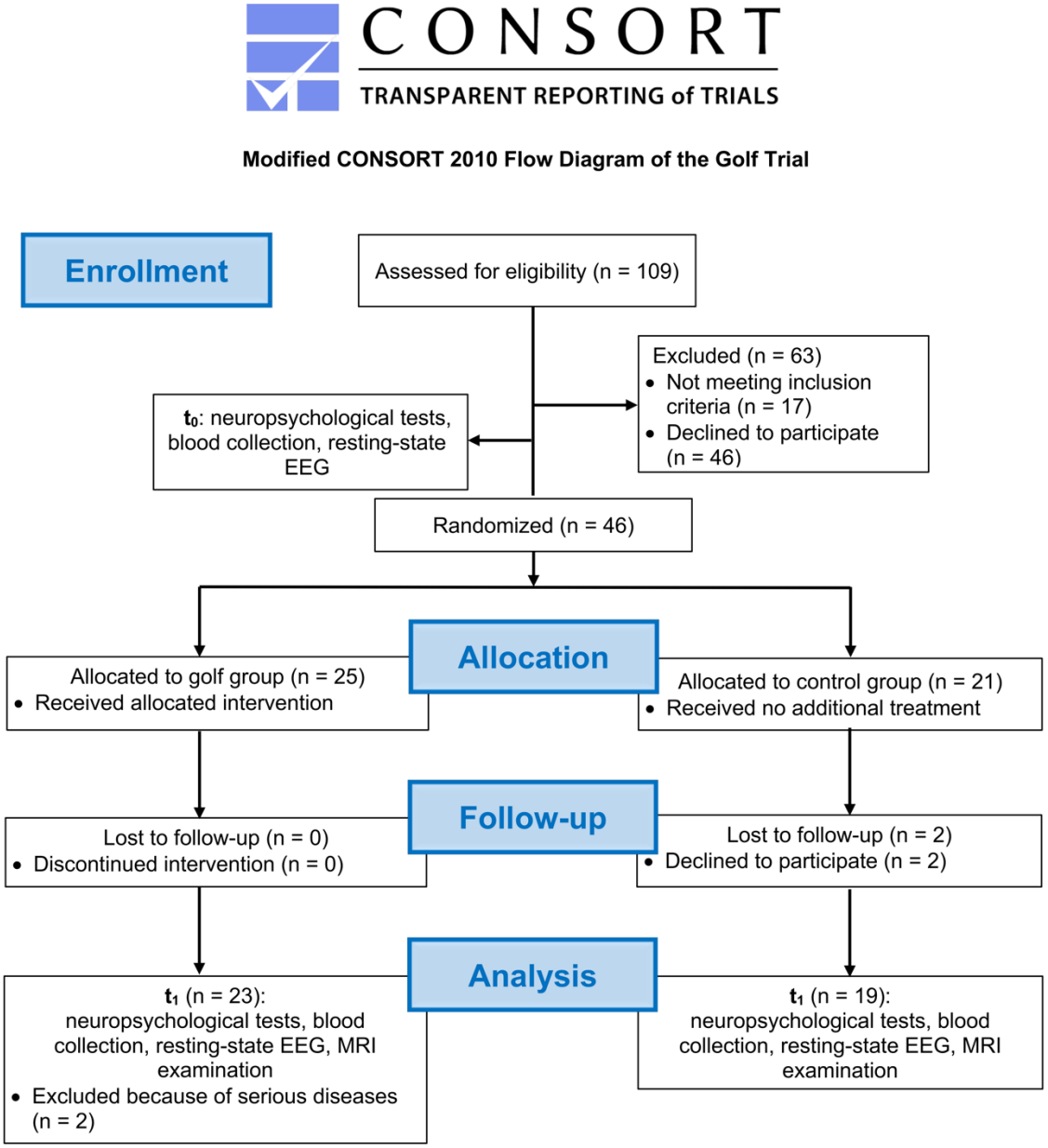

Figure 7 Modified CONSORT[5] Flow-Chart of the 22-weeks randomized controlled trial. EEG = 128-channel Electroencephalography, MRI = 1.5 Tesla T_1-weighted Magnetic Resonance Image

[5]CONSORT: Consolidated Standard of Reporting Trials [142].

4.1 Design and methods of the randomized controlled trial

4.1.1 Procedure and participants

Participants were recruited via newspapers, social media advertisements and at organizations providing leisure activities for seniors between April to June 2018. Exclusion criteria were 1) younger than 60 years, 2) answer “no” to the question: “Do you have subjective memory complaints?” 3) significant experiences in golf (i.e. proficiency certificate or handicap) 4) diagnosed neurological or mental disease or other impairment of physical abilities.

Eligible participants were scheduled for baseline data collection before randomization on two different days. At day one, the acquisition of medical history and sociodemographic data as well as the neuropsychological testing and EEG measurements took place. On the second day, participants underwent a blood sample collection and an endurance performance test.

46 eligible participants with SMC were matched according to age, gender, physical activity levels (Physical Activity Scale for Elderly, PASE) and cognitive performance (ADAS-Cog) and then randomly allocated to either the golf group (n = 25) or the control group (n = 21). A researcher who was not involved in the neuropsychological tests, blood collection or golf intervention carried out the random sequence generation and group allocation. Both groups were asked to record daily activity levels with the PASE questionnaire during the intervention.

According to the BDI [143] 2 participants reported symptoms of mild depression at baseline (16 points), but were not diagnosed with depression or bipolar disorder. The other participants had no clinically relevant symptoms of depression (< 12 points). All participants of both groups reported SMC in daily life. 26 % (golf, n = 6) and 32 % (control, n = 6) reported serious worries about the complaints. The onset of memory complaints was 2.6 years ago in the golf group (± 2 years) and also in the control group (± 2.6 years). The sample was active (according to the PASE questionnaire, [144,145], physically fit (according to the 6-Minute Walk-Test, [146]) and well educated (13.5 ± 4.2 years on average). The ADAS-Cog revealed normal age-appropriate scores for the majority of the participants (n = 36, scored between 1-9 points). 10 participants scored over 10 points, which can indicate objective cognitive impairment [147,148]. 6 of them were in the golf group, and 4 in the control group.

Baseline characteristics of the participants are presented in Table 2.

Table 2 Demographic information at baseline of analyzed participants (n = 42)

	Golf group (n = 23)	**Control group** (n = 19)	**p-value**
Age (years)	68.23 ± 4.5	67.89 ± 3.9	0.99
Gender			
male	10 (43.5%)	9 (47.4%)	0.51
female	13 (56.5%)	10 (52.6%)	
Handedness			
right	22 (95.7%)	19 (100%)	0.53
left	1 (4.3%)	0 (0%)	
Formal education (years)	14.4 ± 4.5	12.26 ± 3.6	0.09
BDI (score)	4.7 ± 4.4	4.4 ± 3	0.81
ADAS-Cog (score)	7.84 ± 3.46	7.68 ± 3.41	0.77
Cardiovascular risk factors			
BMI	26.5 ± 3.5	26.3 ± 3.8	0.43
Current smoker	3 (13%)	2 (10.5%)	0.55
Heavy smoker	0 (0%)	1 (5.3%)	0.48
Diabetes mellitus type 1	2 (8.7%)	1 (5.3%)	0.54
Diabetes mellitus type 2	1 (4.3%)	1 (5.3%)	0.73
Hypertension	12 (52.2%)	7 (36.8%)	0.26
Heart disease	4 (17.4%)	3 (15.8%)	0.55
Physical outcomes			
6-min-Walk-Test (m)	651.37 ± 121.32	627.73 ± 99.67	0.48
PASE (score)	181.11 ± 59.52	153.37 ± 57.05	0.15

Quantitative variables were expressed as means ± standard deviations and categorical variables were expressed as numbers and percentage values.
Group differences were tested with Mann-Whitney U and χ^2 tests for categorical variables. BDI = Becks-Depression-Inventory, ADAS-Cog = Alzheimer's Disease Assessment Scale - Cognitive Subscale, BMI = Body Mass Index, PASE = Physical Activity Scale for Elderly, $p \leq 0.05$ = statistical significance

4.1.2 Golf intervention

The golf training was performed at Paderborn University Golf Club. The golf training sessions were planned, supervised and mostly conducted by a fully qualified professional golf trainer of the Professional Golfer Association (PGA). In addition, three other golf trainers aided and provided the training sessions. A maximum of 13

participants who were instructed by two trainers was allowed per session. The golf training consisted of three sessions per week, each lasting 60 min. Two of three sessions were supervised and instructed by trainers. The third session was not supervised, but participants were asked to practice the previously acquired skills independently at the driving range.

The supervised golf program included 18 practice sessions and 25 sessions at the driving range. All sessions started with a short warm-up (10 min), which consisted of coordination and stretching exercises. In the practice sessions (week 1 to 8), participants learned basic golf techniques, such as putting and chipping. After 5 weeks, pitching was introduced and practiced and after 7 weeks, participants learned the full golf swing. Golf trainers gave individual feedback to improve the techniques, e.g. via video recordings or verbal instructions during the sessions. At week 9, participants started to practice at the driving range. All trainers encouraged the participants to practice the golf techniques at home in front of a mirror, to learn the golf rules and to interact with the other participants.

4.1.3 Primary outcomes: Feasibility and general cognitive performance

Feasibility was assessed with a graded technical exam conducted at the end of the intervention. The exam is equivalent to the German license to play golf and included the assessment of the golf techniques putting, chipping, pitching, and the full golf swing. A score of 20 points could be achieved for each technique, resulting in a total score of 80 points. Moreover, attendance rate and safety were assessed, including adverse events and drop outs related to the golf intervention.

General cognitive performance was assessed with the ADAS-Cog. The test was conducted by trained study staff blinded to group assignment.

4.1.4 Secondary outcomes: Specific cognitive functions, (neuro-) biological markers, brain networks and endurance performance

Specific cognitive functions were assessed with the Corsi Block Tapping Task (visual-spatial working memory), the Response Inhibition Task (INHIB) and the Trail Making Test part B (as measures of executive functions). All tests were part of the automated computer-based Vienna Test System Version 6.82.000 (Schuhfried GmbH, Mödling, Austria) and conducted by study staff blinded to group assignment.

Blood samples via venipuncture were obtained during early and late morning (8-12 am) and left to clot at room temperature for 30 min. After that, samples were centrifuged for 10 min at 1800 g and frozen at -31°C until transportation (max. 2 weeks later).
High performance liquid chromatography (HPLC) and tandem mass spectrometry (MS/MS) were used to analyze serum concentrations of KP metabolites: KYN, TRP, QUINA and KYNA. Ratios of KYN to TRP as well as KYNA to QUINA were calculated to indicate changes in the degradation steps of the KP [106].

Resting-state measurements were conducted with a high-density 128-channel EEG actiCap system from Brain Products (Brain Products GmbH, Gilching, Germany). The cap was positioned according to the international 10-10 system and impedances were constantly checked and kept below 15 kΩ. The sampling rate was set to 500 Hz. The ground electrode replaced FPz, and the reference electrode replaced FCz. Participants were measured in supine position with eyes closed in an acoustically attenuated darkened room and were instructed to relax but stay awake during the 4 min recording. Individual electrode locations were registered with the BrainVision CapTrack software (Brain Products GmbH, Gilching, Germany).
Participants were additionally scanned with a 1.5-Tesla MRI Scanner (Hitachi Medical Systems, Hitachi, Japan) once during the intervention. A 3D radiofrequency-spoiled steady-state acquisition rewound gradient echo (RSSG) protocol with 170 axial slices, echo time (TE) = 2.3 ms, repetition time (TR) = 10.6, slice thickness = 1.0 mm was used.

The general preprocessing of the EEG was done with BrainVision Analyzer Version 2.1.2 (Gilching, Germany: Brain Products GmbH, www.brainproducts.com). The detailed procedure is described in research papers 3 and 4.

Endurance performance was examined with the 6MWT.

4.2 Research paper 1

Ströhlein JK, van den Bongard F, Barthel T, Reinsberger C. Dose-response-relationship between physical activity and cognition in elderly. Deutsche Zeitschrift für Sportmedizin. 2017; 68: 234-242. DOI: 10.5960/dzsm.2017.300

Consensus about the optimal dose of physical activity to improve cognitive performance in elderly with and without AD is missing. Despite regular moderate aerobic exercise, which was investigated most frequently in this field, exercise modes with low intensity, but high complexity were found to improve cognitive functions as well. The aim of this systematic review was to elucidate the existence of a dose-response relationship between exercise interventions and cognitive functions in elderly people with and without AD. Randomized controlled trials with a clear documentation of intensity (e.g. by heart rate reserve, VO_2max or 1 repetition maximum) were eligible for the study. Standardized mean differences (SMD) were calculated for each cognitive outcome. The intensity of the intervention was transferred into metabolic equivalent (MET) values in accordance with “The Compendium of Physical Activities – Tracking Guide” [149]. Risk of bias was rated with the Cochrane Collaboration tool.

After screening 18.686 studies, 13 were included in the review. In general, all included studies had a high risk for performance bias and allocation concealment was not sufficiently described in the majority of the studies as well. Moreover, half of the studies (7/13) also had a high or unclear risk for reporting and attrition bias.

As a main result, a dose-response-relationship superior to other intensities was not found for healthy elderly, MCI or AD patients (see Figure 8). The findings suggested a linear relation between MET values and standardized mean differences of executive functions in the MCI subgroup, but were based on only 3 studies with high and low risk of bias. Considerable heterogeneity of cognitive outcomes and design of studies (e.g. treatment of control group or follow-up) might had an impact on results and exacerbated comparability.
However, the results suggest that either low, moderate and high intensities are effective to improve cognitive functions in elderly people with and without AD.

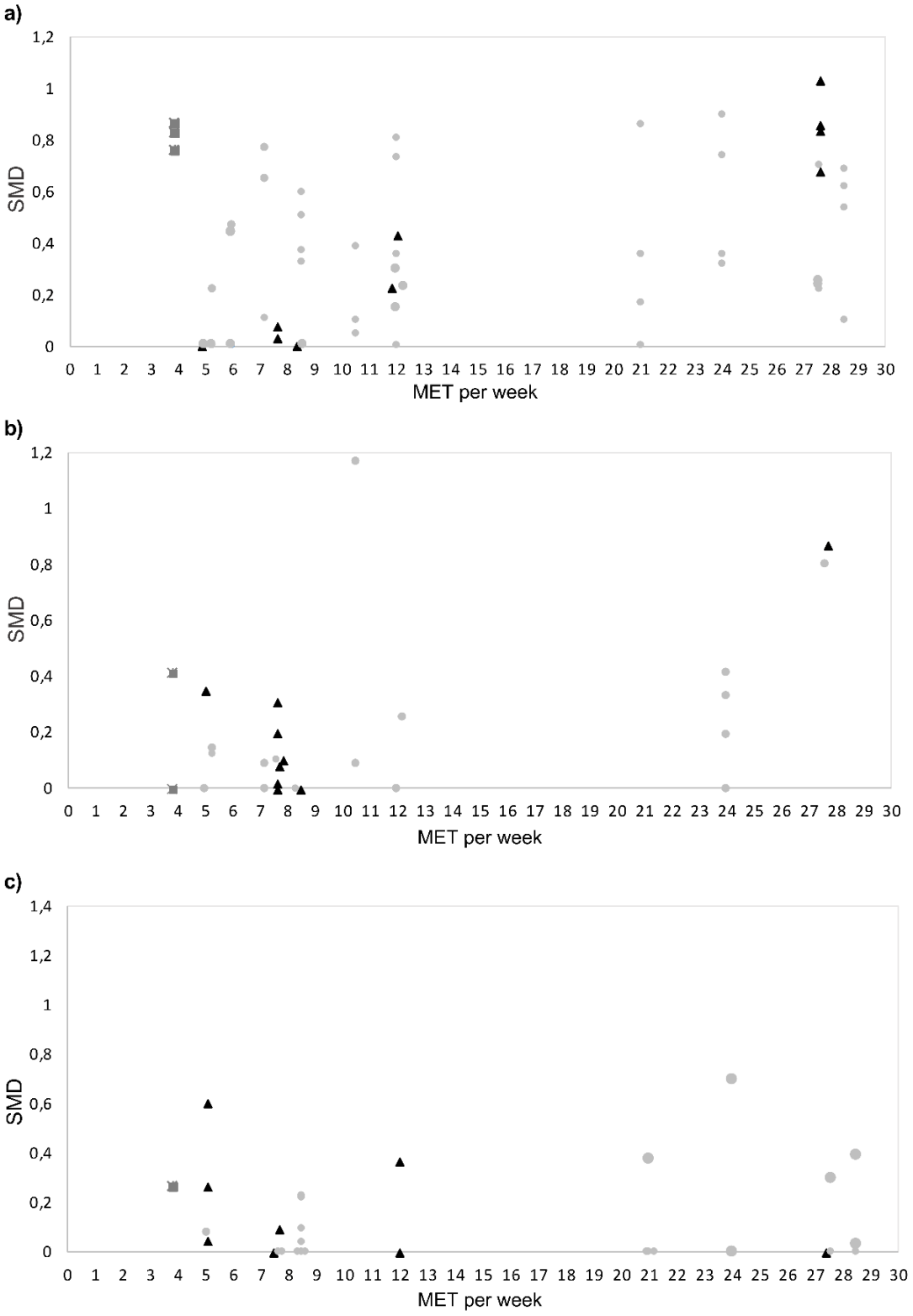

Figure 8 Dose-response relationship between metabolic equivalent (MET)-values per week and standardized mean differences (SMD) for the cognitive outcomes (a) executive functions b) processing speed and attention c) short-, long-term and verbal memory (circles: healthy elderly, triangles: MCI-patients, squares: AD-patients).

Author contributions:

Julia Kristin Ströhlein and Claus Reinsberger designed the protocol for the systematic review. Julia Kristin Ströhlein did the systematic literature research, the quality assessment and the MET calculation. She and Claus Reinsberger wrote the first draft of the manuscript. Franziska van den Bongard supported the risk of bias assessment and during the writing process. Thorsten Barthel commented on all versions. All authors agreed to the final version.

4.3 Research paper 2

Stroehlein JK, Vieluf S, Zimmer P, Schenk A, Oberste M, Goelz CJ, van den Bongard F and Reinsberger C. Learning to Play Golf for Elderly People with Subjective Memory Complaints: Feasibility of a Single-Blinded Randomized Pilot Trial. BMC Neurology 2021; 21, 200. https://doi.org/10.1186/s12883-021-02186-9

SMC in elderly people may indicate early cognitive decline in the context of AD. There is some evidence suggesting that the symptoms are accompanied by dysregulation of the tryptophan-consuming kynurenine pathway (KP). More specifically, a shift along the KP towards neurotoxic rather than neuroprotective metabolites was observed upon stimulation of inflammatory cytokines. Regular exercise was shown to influence both, cognitive performance and the KP, positively. However, because of the challenging profile, it remains to be elucidated if learning to play golf is feasible for elderly people with cognitive problems.

44 participants completed the study. 2 participants of the control group declined to participate because of group allocation and 2 participants of the golf group were excluded from analysis because of the development of severe diseases. The overall attendance rate in the golf group was 75% (48 ± 9.9 of 65 sessions) and 70% (15 ± 5.2 of 22 sessions) for the third training session only. All subjects who undertook the golf exam in the end passed (20/23) it, but three subjects were unable to attend the test due to limited time. No adverse events related to the golf intervention were observed.

Baseline-adjusted Analysis of Covariance revealed a significant time*group interaction in favor of the golf group for the number of errors on the response inhibition task ($p = 0.012$, $d = 0.89$) as well as for the QUINA/TRP ratio ($p = 0.022$, $F = 5.769$, $d = 0.84$). In accordance, only the control group showed higher values of KYN/TRP as well as QUINA/KYNA ratios after the intervention, but changes were also not significant. In the golf group, an uncorrected significant negative correlation between change of QUINA/KYNA ratios and compliance was observed ($r = -0.443$, $p = 0.039$) suggesting that the KP is sensitive to the number of training sessions. Of note, the control group had almost significant lower activity levels as indicated by mean PASE during the intervention ($p = 0.056$), which might also have contributed to the findings.

Author contributions:

Julia Kristin Stroehlein, Solveig Vieluf, Franziska van den Bongard and Claus Reinsberger contributed to the study conception and design. Julia Kristin Stroehlein, Franziska van den Bongard and Christian Goelz performed data collection. Alexander Schenk and Philipp Zimmer processed the blood data. Statistical analysis was conducted by Julia Kristin Stroehlein with support from Alexander Schenk and Philipp Zimmer. Max Oberste evaluated and advised the statistical analysis. Julia Kristin Stroehlein and Claus Reinsberger wrote the manuscript and all authors commented on previous versions. All authors read and approved the final manuscript.

4.4 Research paper 3

Ströhlein JK, Vieluf S, van den Bongard F, Gölz C, Reinsberger C. Golf spielen gegen die Vergesslichkeit: Effekte des Erlernens der Sportart auf das Default Mode Netzwerk des Gehirns. Bewegungstherapie & Gesundheitssport 2020, 36:1-8. doi: https://doi.org/10.1055/a-1120-700

The DMN is the hierarchical superior resting-state network and vulnerable to pathophysiological processes in the context of AD, which consequently influence functional network integrity. Golf is a multicomponent activity and therefore might have a positive influence on functional integrity of the DMN.

In this pilot trial, 7 participants of the golf group were analyzed, which underwent EEG resting-state measurements before and after the intervention. After pre-processing of the EEG recordings to reduce artifacts, a template MRI (FSaverage) was co-registered with the individual electrode location file to compute the forward model with the brainstorm software [150]. A cortical mesh with 642 vertices per layer (scalp, skull, brain) was computed with the Boundary Element Method (BEM) using OpenMEEG. The weighted Minimum Norm Estimate (wMNE) approach with constrained dipole orientations and current density maps as a measure was used for solving the inverse problem. An identity matrix was used for noise covariance. The reconstructed time series from 15 regions of interest (ROI), which were previously identified as DMN regions, were selected based on the Desikan-Killiany atlas and used for further analysis [151]. The phase locking value (PLV) was applied to calculate source connectivity of the DMN. The analysis focused on the beta (14-29 Hz) and theta (5-7 Hz) frequency band.

Source connectivity values were higher in 5/7 participants in the beta frequency band, and in 6/7 participants in the theta frequency band. Theta connectivity in the anterior DMN was lower in 6/7 participants. Spearman correlations revealed linear associations between percentage changes in beta ($r = 0.786$, $p = 0.036$) and anterior DMN theta connectivity ($r = –0.821$, $p = 0.023$) with compliance.
Figure 9 illustrates the increase of source connectivity in the DMN for the participant with the highest compliance.
The results suggest that golf has an influence on DMN functional integrity and organization and should be replicated in a larger cohort in comparison to a control group.

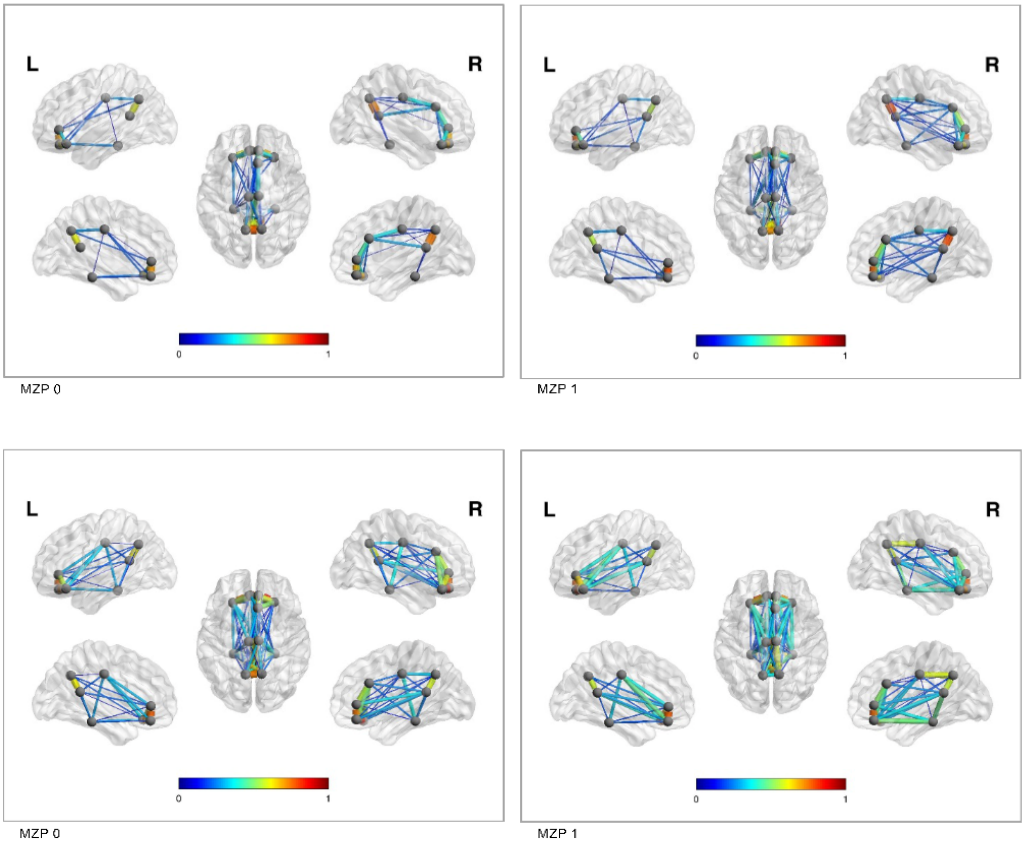

Figure 9 Source connectivity values of the DMN before (MZP0) and after the intervention (MZP1) for the participant with the highest compliance (59/65 sessions). Upper part: Functional connectivity in beta frequency band (14-29 Hz), lower part: Functional connectivity in theta frequency band (5-7 Hz).

Author contributions:

Julia Kristin Ströhlein, Solveig Vieluf, Franziska van den Bongard and Claus Reinsberger contributed to the study conception and design. Julia Kristin Ströhlein, Franziska van den Bongard and Christian Gölz performed data collection. Data analysis was conducted by Julia Kristin Ströhlein. Julia Kristin Ströhlein and Claus Reinsberger wrote the manuscript and all authors commented on previous versions. All authors read and approved the final manuscript

4.5 Research paper 4

Stroehlein JK, Goelz C, Vieluf S, van den Bongard F, Reinsberger C. Source Connectivity Patterns Differ Between Elderly Golf-Novices and Non-Golfers. Scientific Reports (submitted).

In this cross-sectional study, we investigated functional integrity of the DMN in elderly golf-novices (n = 12) compared to non-golfers (n = 10) with two different approaches: First, we compared source connectivity patterns in the DMN and cognitive functions between the two groups. Second, we investigated and compared associations of frontal midline theta power (an EEG-specific marker indexing external attention) and source connectivity in the DMN.

The individual MRI were pre-processed with the Freesurfer software. After that, the same procedure as described in research paper 3 was conducted in brainstorm [150], but the native MRI of each participant was used instead of a template MRI to create the head model. We additionally used the codes from the Brain Connectivity Toolbox [152] to calculate graph-theoretical parameters, including mean strength (as a measure of functional integrity) for each participant. Source connectivity and mean strength were calculated for the whole DMN as well as for portions of it (anterior, posterior and core) in the beta band (14-25 Hz) according to Kabbara et al. [151]. Frontal midline theta power was extracted via independent component analysis in the range of 4-7 Hz. Executive functions and working memory were evaluated with the Vienna test system. Mann-Whitney-U-test was applied for group comparisons and Spearman Correlations for investigating relationships. All p-values were Bonferroni corrected.

In summary, no group differences were observed regarding cognitive functions. Higher mean source connectivity values were observed in the anterior DMN in the non-golfer group (golf 0.41 ± 0.07 vs. non-golfer 0.52 ± 0.06, p = 0.002, Bonferroni-corrected p = 0.028). Similarly, mean strength of anterior DMN was significantly higher in the non-golfer group as well (golf 2.49 ± 0.41 vs. non-golfer 3.17 ± 0.39, Bonferroni-corrected p = 0.028). Uncorrected subgroup analyses in the non-golfer group revealed that higher anterior DMN source connectivity was correlated with worse performance on TMT A and B (r_s= 0.697, uncorrected p = 0.025, Bonferroni-corrected p = 0.6 and r_s= 0.770, uncorrected p = 0.009, Bonferroni-corrected p = 0.216, respectively).

Based on uncorrected findings, significant correlations between frontal midline theta power and anterior and core DMN were observed in the golf-novices group only.
Although findings should be interpreted with caution, they suggest a consistent trend across hypotheses towards age-related functional network dedifferentiation in the non-golfer group. To elucidate mechanisms induced by learning to play golf that cause network changes, findings should be replicated in a longitudinal setting.

Author contributions:
Julia Kristin Stroehlein, Christian Goelz, Solveig Vieluf, Franziska van den Bongard and Claus Reinsberger contributed to the study conception and design. Data collection was performed by Julia Kristin Stroehlein, Christian Goelz and Franziska van den Bongard. Julia Kristin Stroehlein analyzed the data and Christian Goelz supported code generation. Julia Kristin Stroehlein and Claus Reinsberger wrote the manuscript and all authors commented on previous versions. All authors read and approved the final manuscript

5 Discussion

The main objective of this thesis was to contribute to the development of evidence-based preventive exercise treatments in the context of AD. The first part of the discussion focusses on current evidence of exercise treatments to improve cognitive performance in elderly people, and emphasizes current limitations of randomized controlled trials that have to be adapted in the future in order to develop evidence-based preventive exercise guidelines of high quality.
The second part discusses the results of the 22-week randomized controlled trial that investigated the effects of golf on cognitive performance and multimodal (neuro)-biological marker in elderly people with subjective memory complaints, including recommendations for replication and consequences for further research.

5.1 Development of exercise recommendations for primary prevention of AD

The systematic literature review (see 4.2 Research paper 1) indicated that metabolic demanding activities, such as aerobic and resistance exercise, were investigated most frequently in this field. However, besides metabolic demanding exercise, other exercise modes with low intensity, but rather high complexity and inclusion of higher order cognitive functions, were found to improve certain cognitive functions as well [123]. Research paper 1 suggested in this context that intensity of an intervention was indeed not the sole factor that determined the effects of exercise on cognitive functions in elderly people, MCI or AD patients, as cognitive functions improved at low, moderate and high intensities. However, the review included only 13 studies and the analyses were carried out for healthy elderly, MCI and AD patients separately, which reduces the number of studies considered for each dose-response-relationship. Moreover, the low number of included studies also suggest that selection criteria might have been too strict. We also focused predominantly on aerobic exercise intervention, as these are most often clearly documented and therefore eligible for the review. The methodological approach in research paper 1 (calculation of MET values) lead to a focus on the training variable intensity.

In general, “dose-response-relationships” are interpreted differently by studies in the field. All have the focus on specific training variables in common, which are quantified with different methodological approaches.

Gomes-Osman et al. [153] evaluated dose-response relationship based on a variety of summarized training variables extracted from 98 studies (session duration, weekly minutes, frequency, intensity, total weeks and hours of intervention) and correlated these measures with cognitive outcomes in healthy elderly.

Similar to our results, exercise interventions influenced mostly executive functions and processing speed positively, but less visual-spatial abilities, memory processes and working memory. Interestingly, interventions of at least 52 hours length were more likely to improve cognitive functions in elderly people with and without cognitive impairment. However, similar to our results, a linear relation between the other training variables (especially intensity) was not found. The authors also emphasized that intensity was not clearly documented in the majority of studies, which lead to a small number of included studies in our review as well. Similar to our findings, intensity of the interventions was not associated with performance of any examined cognitive domain.

Northey et al. [11] applied a multi-level meta-analysis approach with exercise as a moderator variable (intensity, frequency, exercise mode, intervention length). Contrary to our findings, low intensity interventions (40-55% of heart rate maximum) were not effective to improve cognitive performance. Of note, studies that investigated regular coordination exercise were not included in the meta-analysis. Moreover, the authors suggested based on their findings that participants should train between 30-45 min of at least moderate intensity on as many days as feasible in the week. Contrary, Sanders et al. [154] did not find dose-dependent improvements of exercise interventions on cognitive functions in healthy older adults. Interestingly, for MCI patients, shorter sessions with higher frequency predicted cognitive improvement.

In summary, there is still no consensus about the most effective dose of exercise to improve cognitive performance in the research field, which might be partially caused by different methodological approaches. Consistency in the prescription of the correct dose of exercise is necessary to push the theoretical status into concrete evidence-based guidelines. However, on the other hand, although a huge number of randomized controlled trials was published in this research field in the last years, studies still have some limitations that lead to inconsistency and exacerbate the development of high-quality evidence-based exercise guidelines for prevention of AD.

First, there is an unknown risk for publication bias, which can affect validity of systematic reviews and meta-analysis. The publication of small studies, which moreover did not find significant differences between groups, is presumably more difficult compared to those that found several significant group differences. As a result, effects of exercise in systematic reviews and meta-analysis might be overestimated [155].
Second, the majority of trials examining the effects of exercise on cognitive performance in elderly people have a high risk for performance bias. In most of the trials, the participants are not blinded to group allocation or the overall research aim and background of the study. The effects of exercise on cognition could therefore also be (partly) the result of placebo effects, especially when the control group receives no additional treatment. In pharmacological trials, participants receive a placebo pill of the same look and size as the experimental pill to account for expectations associated with the treatment. In exercise trials, developing an adequate placebo is far more difficult. Although “active” control groups are favorable compared to non-active ones, even these groups cannot necessarily rule out placebo effects on cognitive performance, as expectations associated with the intervention and motivation can be different [156]. Therefore, alternatives are meant to leave participants unaware of the effectiveness of the treatment as well as to implement surveys that measures expectations associated with the treatment in each group [156].

Another argument for the implementation of active control groups is that they could provide an opportunity to account for effects caused by other factors than the intervention. For example, cognitive performance might also increase due to social interaction with other participants or with the trainer [157]. Currently, stretching and toning control groups are typically used in the majority of studies. Research paper 1 as well as Northey et al. [11] indicated that active (stretching and toning or other treatments) or social control groups have a small influence on cognitive functions as well, whereas education control treatments (computer courses, health care courses) did not significantly contribute to cognitive improvement. Therefore, consensus of a control treatment protocol to account for placebo and other factors (such as increased social interaction) would help to facilitate comparability, and reduce inconsistency of findings.

A source of inconsistency might also be caused by different characterization of the sample in each study, e.g. cognitive status, education or physical activity levels. Studies should in general clearly describe these aspects and account for them in all analyses,

for example by matching at baseline or by including covariates into their analysis. Moreover, participants should be characterized and diagnosed based on current standards, which would ensure similar selection criteria across studies. Besides, cognitive domains are tested with a variety of cognitive tests, which additionally can lead to inconsistent results between studies. Therefore, consensus for a standardized test battery is necessary as well.

Besides considerable heterogeneity between studies that might lead to inconsistent results, some of the described effects in randomized trials might not be generalizable to the whole population of elderly people. For example, sex differences regarding improvement of executive functions after a physical intervention have been described [158]. In addition, findings from healthy populations are not necessarily generalizable to diseased populations. Currently, aerobic and strength exercise were proven to be effective and are recommended for primary prevention of AD. However, a large recent randomized control trial found a slight worsening in the ADAS-Cog score of dementia patients at 6 month and 1 year follow up after 16-weeks of moderate to high aerobic and strength exercise [122]. One reason for the result might have been the design of the exercise intervention, which could have been too monotonous. In addition, the first follow-up assessment was 2 months after completion of the trial, which suggests that the effects of exercise were not sustainable for AD patients.

Current literature predominantly considered physical activity as aerobic or strength exercise only, but there is evidence that different exercise modes have different effects on cognition [123,125]. Physical activity should rather be defined as an umbrella term, which involves activities associated with daily life as well as sports and exercise, including the different motor demands (see Figure 10, [159]).

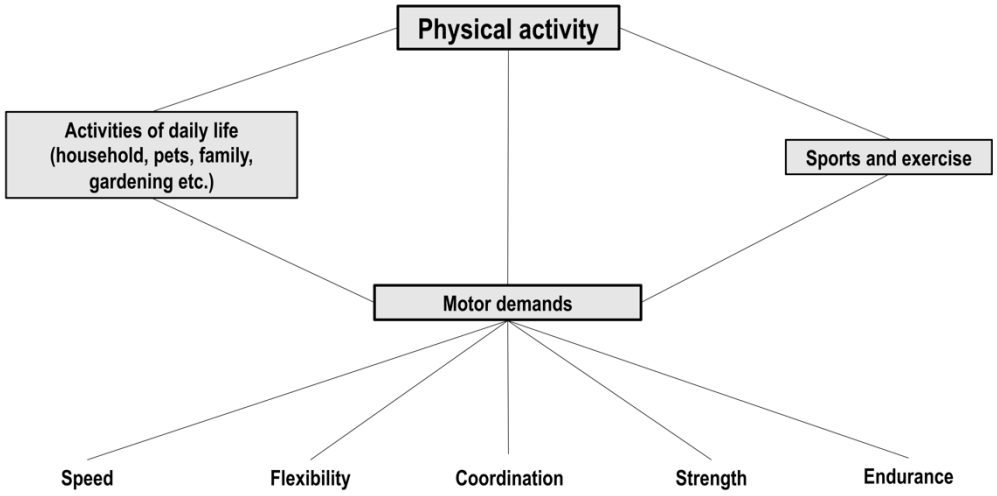

Figure 10 Definition of the umbrella term physical activity [159].

Especially the effectiveness of exercise modes with low-intensity, but high complexity (e.g. by involvement of higher order cognitive functions) in combination with aerobic exercise (similar to the enriched environment model) should be elucidated in the future [160]. Findings of the evidence synthesis also support the idea that dose-response relationships are different for each exercise mode, which is an important aspect for future research in order to design better evidence-based exercise treatments against cognitive decline.

In accordance with the concept of cognitive reserve, besides regular exercise, engaging in an active lifestyle, including diet, vascular risk reduction, social interaction and cognitive stimulation, is in general important for prevention of AD [45]. Exercise is therefore not the sole factor that determines cognitive performance in old age, which also has to be considered in the development of recommendations to prevent AD.

5.2 Learning to play golf as a primary preventive treatment for AD

Based on the findings from research paper 1, we developed a randomized controlled trial in which elderly people with subjective memory complaints learned to play golf over 22 weeks. The effects of golf on cardiovascular and mental health have been described before [129], but only few studies investigated cognitive performance [130,132].

To the best of our knowledge, no studies investigated feasibility or the effects of golf on (neuro-) biological markers such as the KP or functional brain networks.

Research paper 2 demonstrated that 20/23 participants passed the golf exam at the end, which indicates that learning to play the sport is feasible for elderly people with cognitive problems. Moreover, a small effect of the golf intervention on attention was found, indicated by a significant increased number of percentage correct responses on the response inhibition task. The golf group had a significant reduced QUINA/TRP ratio compared to the control group. Subgroup analyses revealed that delta QUINA/KYNA ratios (post-pre) were significantly correlated with compliance in the golf group (which was not significant after correction of type 1 errors).

The findings suggest that golf, as a low to moderate intensive treatment, might influence the regulation of the KP as well. However, the mechanisms that lead to the positive effects were presumably different compared to metabolic demanding exercise, such as aerobic or strength training. Acute intense exercise rather stimulates expression of the enzyme KAT, which is activated by peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α). The result is an enhanced conversion of KYN to KYNA, and the latter is poorly able to pass the blood brain barrier. By these mechanisms, it was hypothesized that central KYN levels decrease, with subsequent effects on downstream metabolites.

Interestingly, peripheral KYNA concentrations did not change due to the golf intervention, and were also not related to compliance in the golf group. This might suggest that intensity should be higher in a future intervention to enhance the positive effects on the KP. However, golf affected KP regulation presumably by other mechanisms, for example by downregulation of IDO1 activity. As the enzyme is influenced by pro-inflammatory cytokines and has a direct effect on degradation of TRP to KYN, golf might have led to a reduction of inflammatory states or stress levels [100,161]. Especially the latter mechanism raises important questions for future research, as it may also suggest a possible influence of affective factors associated with exercise (such as joy and pleasure). However, based on the combination of several components that were positively associated with cognitive performance in this intervention (exercise, cognitive stimulation, social interaction), it cannot be distinguished which was the driving factor contributing to the results or whether it was the combination itself. In addition, it would have been interesting to compare the outcomes of the trial with a group exercising with

higher metabolic demands, such as aerobic exercise, to describe differential effects associated with each exercise mode on cognitive functions and the KP.

Of note, we only measured peripheral concentrations and not central changes of the KP. Although correlations between peripheral and cerebrospinal fluid concentrations of KP metabolites have been reported [162], it is unclear how central concentrations were influenced by the intervention.

We found a positive effect of the intervention on attention performance only. Research indicates that other cognitive domains, such as memory functions, improve less consistent after a physical intervention [153]. It is of great interest to develop interventions that improve memory performance, since its influence on quality of life and activities of daily living of AD patients. In general, attention and memory performance are closely related. Attention is necessary for encoding of specific information from the environment and supports consolidation into long-term memory [163]. Therefore, an increase in attention performance might be a necessary requisite to improve (episodic) memory performance chronically. Accordingly, Mueller et al. [164] could show that attention performance improved after 6 month of a dancing intervention, whereas episodic memory improved after 12 month of regular training. Based on these findings, the golf intervention (and other physical interventions of similar length) might have been too short to increase memory performance. In accordance with the findings from Gomes-Osman et al. [153], future randomized trials should last more than 24 weeks to elucidate the full potential of exercise interventions on cognitive performance.

We also found indications that learning to play golf influenced functional integrity of the DMN. Research paper 3 indicated that mean beta functional connectivity of the DMN increased linearly to the number of training sessions in the golf group. Beta functional connectivity in resting-state was reported to be associated with better cognitive function and physical fitness [165]. However, due to the analysis in the golf group only, findings have to be interpreted with caution. A control group could have accounted for factors which were not related to golf, but which could have influenced the measurements. We also did not correlate findings with cognitive performance of the participants. Therefore, it remains unclear if the observed changes also relate to better cognitive performance, but the findings clearly indicate that the changes in beta and theta functional connectivity in the DMN are related to the amount of training the participants completed.

In a cross-sectional design, source connectivity patterns of the DMN were investigated and compared between elderly golf novices and non-golfers (see 4.5 Research paper 4). By combining high-density EEG with native MRI of each participant, we were able to measure direct neuronal activity in the DMN and found consistent trends across several parameters that suggest dedifferentiated activity in the anterior DMN of elderly non-golfers. Cognitive performance was not different between groups, but higher source connectivity values in the anterior DMN were associated with worse performance on the TMT A and B in the non-golfer group. Moreover, only the golf-novices group showed signs of functional antagonism to frontal midline theta power, a parameter indexing external attention. As learning to play golf has high demands on attention performance, the functional changes observed in the anterior DMN may result from the intervention. Interestingly, research paper 3 suggest that longitudinal changes of functional connectivity (in the theta frequency band) in the anterior DMN were indeed related to compliance to the golf intervention in a subgroup of 7 participants. However, as the analysis of research paper 4 was limited to the beta frequency band, exact mechanisms induced by learning to play golf in the DMN have to be elucidated in a longitudinal and controlled design.

The main methodological challenges in the design of the trial were the assessment of cognitive performance as well as the design of the intervention. We used the established ADAS-Cog to assess overall cognitive performance and characterize participants. However, the ADAS-Cog was recently reported to have a low ability in detecting clinically relevant changes in MCI or early AD [166]. In general, neuropsychological tests can be influenced by learning effects, especially when an adequate habituation phase was not conducted before the measurements. Moreover, a number of internal and external factors can influence performance on these tests and increase variance, although the exact impact remains partially unclear. For example, cognitive performance was shown to improve during the day, with the highest level in the afternoon and early evening [167]. Sleep quality and duration was also shown to influence cognitive performance [168] as well as stressful events [169] and emotional states of the individual [170]. Education, socio-economic status, medication, diseases, and genetic predispositions (e.g. APOE 4) are additional factors that can influence cognitive performance. Whereas some of these factors can be controlled for in the statistical analysis, others are hard to even measure. However, use of questionnaires and a comprehensive anamnesis could help to explain observed variance.

The combination of physical and cognitive stimuli in an intervention represents another challenge of this study. Until now, there is only low evidence that the combination of both is more effective than single training in humans [171]. Especially elderly people, or people with cognitive impairment, may not be able to exercise at sufficient intensity while engaging in a cognitive task. However, we were able to show in research paper 2, that elderly people with cognitive problems are still able to learn a complex sport, such as golf, but metabolic demands of the intervention have rather been low.
A recent study [164] suggested that regular dance training leads to grey matter adaptions in more regions than typical physical fitness training, but no group outperformed the other on the behavioral tests. While playing golf, physical and cognitive demands occur sequentially and simultaneously. The optimal design which induces the largest effect on cognitive performance in elderly people remains to be elucidated [160].

In summary, findings of the golf trial suggest that multimodal interventions with low metabolic demands may contribute to the prevention of cognitive decline in elderly people as well. In addition, the physiological mechanisms (indicated by the KP) and effects on functional brain organization might be different compared to metabolic demanding exercise. The effects of learning to play golf on attention performance and the functional characteristics of the anterior DMN may indicate a direct effect of golf on cognitive domains and brain network organization, whereas metabolic demanding training might rather have an unspecific effect. The findings may also suggest application of other surrogate markers of neuroplasticity than BDNF to investigate mechanisms and effects of combined and multimodal exercise interventions with rather low metabolic demands in future trials. BDNF was found to increase rather after intense exercise and has highest concentrations in the hippocampus, and therefore would presumably have not been sensitive to the effects induced by a low-intensity and complex activity as learning to play golf. The findings also encourage to consider the importance of affective factors associated with exercise, although this is difficult to measure in clinical trials yet. A differentiated view on exercise and cognitive domains is necessary in order to investigate the full potential of exercise as a preventive treatment against cognitive decline. Therefore, the following questions need to be addressed in future research:

1. What are the dose-response relationships for each exercise mode on different cognitive domains (e.g. executive functions, memory, attention etc.) in elderly people with or without cognitive impairment due to AD?

2. Is the combination of exercise modes with each other (e.g. aerobic and coordination exercise) and/or with other domains (e.g. cognition, social interaction) more effective than single-component training regarding different cognitive functions?
3. Which combination of exercise modes with other domains is most effective (e.g. aerobic exercise and cognitive stimulation)? Which other domains are mandatory to improve cognitive functions in elderly people (e.g. cognitive stimulation, social interaction)?
4. What is the optimal design to combine exercise with other domains (i.e. simultaneous or sequential stimulation) in order to improve cognitive functions in elderly people with or without cognitive impairment?

5.3 Limitations of the study and guidelines for replication

Although the design of the golf study has some strengths (such as the multimodal approach, randomization, blinding of certain primary and secondary outcomes) some aspects should be adapted when replicating the trial. First, the sample size calculation was carried out for the ADAS-Cog as the primary outcome based on Lautenschlager et al. (2008). However, the test might have not been sensitive enough to detect subtle cognitive changes in our cohort. Moreover, for secondary and tertiary outcomes, the sample size may had been too small to detect a statistically significant effect.

The control group did not receive any additional treatment, besides documentation of daily activity habits with the PASE questionnaire. The risk of placebo effects and other factors that cause cognitive improvement not related to the intervention, such as social interaction, is therefore high for cognitive and functional network outcomes. Researchers blinded to group allocation conducted the examination of cognitive functions and blood-based parameter. The processing and analysis of the EEG data was not carried out blinded. We also did not consider the 2 drop-outs in our analysis (e.g. with intention-to-treat analysis). However, an additional intention-to-treat analysis should be conducted to account for attrition bias.

A major limitation was the retrospective registration of the study protocol, which was caused by organizational problems during recruitment. Prospective registration before inclusion of participants is mandatory in a future trial.

In addition, further studies may want to adapt characterization of elderly people with SMC. The only inclusion criteria in the golf study to confirm SMC was that elderly people answer “yes” to the question “do you experience subjective memory complaints in daily life?”, and the absence of depression history. Applying criteria from the consensus paper [79] would facilitate comparability with other studies, and might increase the number of participants included which are indeed in preclinical or prodromal phases of AD. Our sample is therefore very heterogeneous considering their potential risk of AD, as we did not examine genetic risk, corresponding biomarkers or confirmed SMC by a third objective person. A larger sample would also enable subgroup analyses (e.g. patients with serious worries about SMC).

Objective measures of exercise intensity were not conducted during the golf intervention, but would have provided useful information. For example, we can only assume that intensity of the golf training might have been too low to induce strong effects on the KP in the golf group. A follow up was not conducted either, but would have provided interesting information about the sustainability of the golf induced effects on primary and secondary outcomes of the study.

6 Conclusion and Outlook

This dissertation contributed to the development of evidence-based exercise treatments in the prevention of AD. More specifically, the work indicated that intensity of exercise is not the sole factor to improve cognitive performance in elderly people with and without cognitive impairment. In accordance with findings from the animal model (enriched environment) and a growing number of studies investigating multimodal (metabolic + cognitive or sensorimotor stimulating) interventions, the thesis supports the understanding of physical activity as an umbrella term, which also includes motor demands such as coordination exercise (low intensity and involvement of higher order cognitive functions).

Second, based on the findings from the evidence synthesis, the influence of learning to play golf was investigated with different (neuro-) biological markers. Overall, results suggest that golf positively influenced specific cognitive domains (attention performance) and presumably associated network characteristics (especially the anterior DMN), as well as biomarkers associated with neurodegeneration (KP).

Regular physical activity is not the only factor that influences cognitive performance, which supports the concept of cognitive reserve. Lifestyle-related factors, including social interaction and cognitive stimulation contribute to better cognitive performance in elderly people as well [172]. A challenge for future research will be therefore to investigate
a) dose-response relationships between each exercise mode and cognitive domains,
b) the non-inferiority of combined and multimodal exercise compared to single-component exercise,
c) the most effective combinations of exercise modes with other domains,
d) the most effective design of these interventions to improve cognitive performance.
Future research should in general address placebo effects (e.g. adequate control groups), account for sex differences and increase homogeneity of study designs (consensus about treatment of control group, cognitive tests for each domain and selection criteria as well as characterization of participants) to facilitate the development of evidence based exercise guidelines as prevention of AD.

Eventually, the effects of exercise on the human brain should not be considered in analogy to that of a skeletal muscle. A differentiated view on exercise and its combination

with other domains, such as cognitive stimulation, social interaction or positive emotions on cognitive performance will be important to move further towards the development of effective evidence-based treatments against cognitive decline for elderly people.

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RESEARCH ARTICLE Open Access

Learning to play golf for elderly people with subjective memory complaints: feasibility of a single-blinded randomized pilot trial

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Abstract

Background: Subjective Memory Complaints (SMC) in elderly people due to preclinical Alzheimer's Disease may be associated with dysregulation of the Kynurenine Pathway (KP), with an increase in neurotoxic metabolites that affect cognition. Golf is a challenging sport with high demands on motor, sensory, and cognitive abilities, which might bear the potential to attenuate the pathological changes of preclinical AD. This trial investigated the feasibility of learning to play golf for elderly with cognitive problems and its effects on cognitive functions and the KP.

Methods: In a 22-week single-blinded randomized controlled trial, elderly people with SMC were allocated to the golf ($n = 25$, 180 min training/week) or control group ($n = 21$). Primary outcomes were feasibility (golf exam, adherence, adverse events) and general cognitive function (Alzheimer's Disease Assessment Scale). Secondary outcomes include specific cognitive functions (Response Inhibition, Corsi Block Tapping Test, Trail Making Test), KP metabolites and physical performance (6-Minute-Walk-Test). Baseline-adjusted Analysis-of-Covariance was conducted for each outcome.

Results: 42 participants were analyzed. All participants that underwent the golf exam after the intervention passed it (20/23). Attendance rate of the golf intervention was 75 %. No adverse events or drop-outs related to the intervention occurred. A significant time*group interaction ($p = 0.012$, $F = 7.050$, Cohen's $d = 0.89$) was found for correct responses on the Response Inhibition task, but not for ADAS-Cog. Moreover, a significant time*group interaction for Quinolinic acid to Tryptophan ratios ($p = 0.022$, $F = 5.769$, Cohen's $d = 0.84$) in favor of the golf group was observed. An uncorrected negative correlation between attendance rate and delta Quinolinic acid to Kynurenic acid ratios in the golf group ($p = 0.039$, r=-0.443) was found as well.

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Conclusions: The findings indicate that learning golf is feasible and safe for elderly people with cognitive problems. Preliminary results suggest positive effects on attention and the KP. To explore the whole potential of golfing and its effect on cognitive decline, a larger cohort should be studied over a longer period with higher cardiovascular demands.

Trial registration: The trial was retrospectively registered (2nd July 2018) at the German Clinical Trials Register (DRKS00014921).

Keywords: Golf, Subjective memory complaints, Alzheimer's Disease, Cognitive Performance, Kynurenine pathway

Introduction

Subjective Memory Complaints (SMC) are common in the elderly population and describe self-reported difficulties with cognitive functions, while objective performance remains normal [1, 2]. The heterogeneous etiology of SMC impedes a consistent characterization [3], but two distinct groups were broadly described: One, in which SMC are caused by other factors, including psychiatric diseases [4, 5], psychological distress [6] and chronic diseases [7] and the other, in which SMC represent preclinical Alzheimer's Disease (AD) [2, 8, 9]. In the latter group, SMC were associated with neuropathological changes, including amyloid-β deposition [10, 11] and diminished grey matter volumes in brain regions affected by AD [12]. A meta-analysis also reported an increased risk of developing dementia in elderly people experiencing SMC compared to those without symptoms [2]. Accordingly, SMC might be a risk factor for subsequent development of AD, thus making it a very interesting group to study with respect to prevention of AD.

There is some evidence that the Tryptophan (TRP) consuming Kynurenine Pathway (KP) is dysregulated in AD and its preclinical manifestation mild cognitive impairment [13, 14].

The isoenzymes Indoleamine-2,3-Dioxygenase 1 (IDO1) and Tryptophan 2,3-Dioxygenase (TDO) catalyze the first and rate limiting step of the essential amino acid TRP to Kynurenine (KYN) [13]. While TDO is mainly expressed in the liver, IDO1 can be expressed in various tissues upon stimulation with inflammatory cytokines, such as Interferon-γ and Interleukin-6 [15]. The result is an increase of KYN, which is further metabolized to Kynurenic acid (KYNA) or Quinolinic acid (QUINA) [13]. The latter stimulates N-methyl-D-aspartate (NMDA) receptors in the central nervous system with the potential to induce neuronal excitotoxicity, which is one of the key pathological mechanisms of AD [16]. A simplified visualization of the KP is presented in Fig. 1.

The central dysregulation of the KP also seems to manifest in the blood stream, since accumulated serum QUINA levels [17] and serum Kynurenine to Tryptophan (KYN/TRP) ratios [14] (a surrogate marker of IDO1 activity) were observed in AD patients and women with high cortical amyloid-β burden [11, 18]. In contrast, KYNA rather has a neuroprotective effect in the central nervous system by inhibiting NMDA neurotransmission [16]. Interestingly, reduced plasma KYNA levels were found in AD patients [19].

The dysregulation of the KP and its neurotoxic/neuroprotective downstream metabolites might also affect cognitive functions. In a large cross-sectional study, increased serum KYN/TRP ratios were associated with poor memory performance [20] in elderly people. In another study, higher serum QUINA levels were correlated with worse executive functions in elderly at risk of dementia [21].

Regular exercise has been found to reduce the risk of AD, maintain cognitive performance, and positively influence the KP in healthy populations [22–24]. Metabolically demanding exercise (such as aerobic and strength training) was investigated most frequently in this field. It has the potential to reduce systemic inflammation [25], which results in decreased activity of enzymes regulating the KP [26].

Interestingly, evidence from animal studies suggest a superior effect of exercise and sensory enrichment (known as enriched environment) on neuroplasticity compared to exercise alone [27, 28]. The idea is supported by recent studies in humans, which conducted multicomponent [29] or dancing interventions [30, 31]. In accordance, a recent systematic review suggested that the metabolic demands of exercise are not the sole factor to improve cognitive performance in elderly people [32]. Golf might have similarities to an enriched environment as well, because it combines physical, sensory, cognitive, and social components [33, 34]. Golf provides a low to moderate intensity profile, although walking a golf course contains periods with higher and lower intensities [33]. Besides cardiovascular activity, learning the golf swing requires high demands on hand-eye coordination, static postural as well as sensorimotor control [34, 35]. During a game, strategic planning, maintaining and manipulating information, as well as adapting to changing environmental conditions illustrate

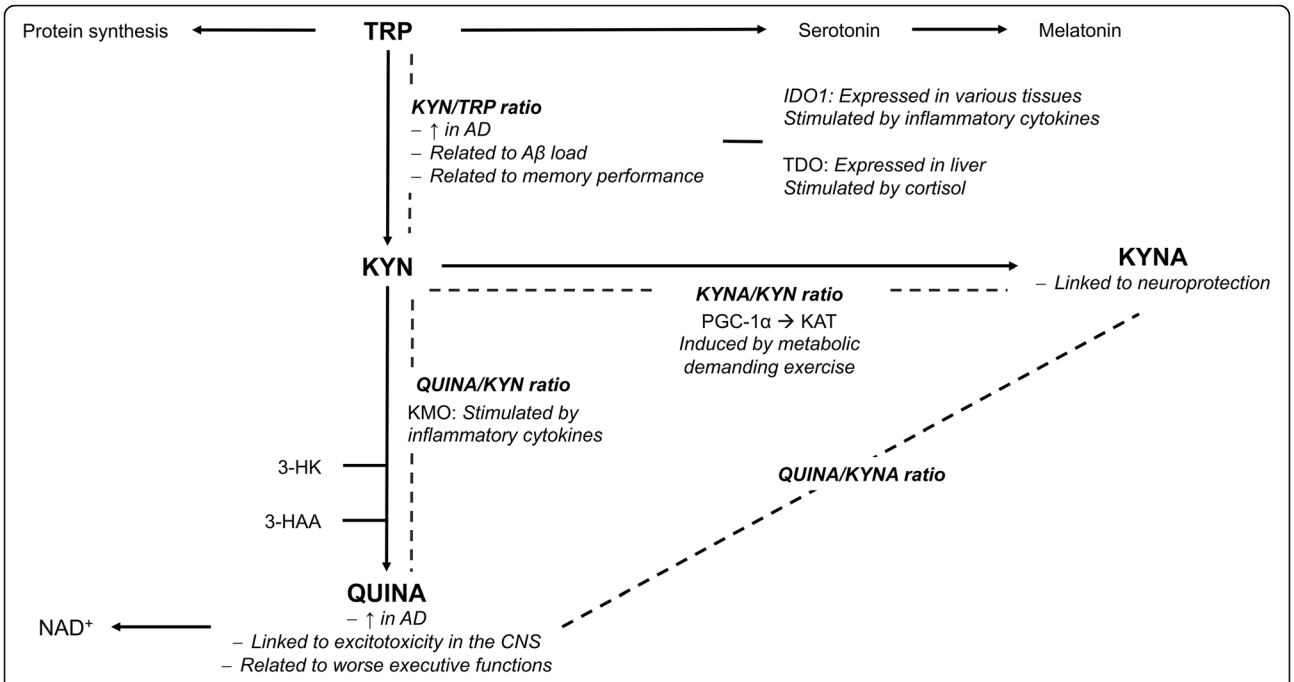

Fig. 1 Simplified visualization of the Kynurenine Pathway. TRP: Tryptophan, KYN: Kynurenine, TDO: Tryptophan 2,3-Dioxygenase, IDO: Indoleamine-2,3-Dioxygenase 1, AD: Alzheimer's Disease, PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha, KAT: Kynurenine amino transferase, KYNA: Kynurenic acid, QUINA: Quinolinic acid, KMO: Kynurenine 3-monooxygenase, 3-HK: 3-hydroxykynurenine, 3-HAA: 3-hydroxyanthranilic acid, NAD^+: Nicotinamide adenine dinucleotide (oxidized form), CNS: Central nervous system.

the cognitive demands of golf, including working memory, attention [34] as well as cognitive flexibility. In the social domain, regular golfing facilitates the establishment of social connections and relationships [33]. In sum, the multidimensional profile of learning to play golf might have the potential to positively affect SMC-related cognitive decline and biological changes in elderly people. However, because of the challenging profile, it remains unclear if elderly people with cognitive problems are able to learn the sports.

Few studies investigated the effects of learning golf on cognitive functions in elderly people. Shimada et al. (2018) [34] reported improvements in immediate and delayed logical memory after a 24-weeks golf intervention with healthy older adults from Japan. Another research group found an increased visual imaginary ability after 20 sessions of golf training in patients with stroke [36].

This study aimed to examine the feasibility of learning to play golf over 22 weeks and its effects on cognitive functions and the regulation of peripheral KP metabolites in elderly people with SMC with no experience in playing golf.

Materials and methods

The study is reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) recommendations of 2010 for pilot and feasibility trials [37].

It was designed as a 22-week randomized controlled trial and conducted between May and December 2018 at the Institute of Sports Medicine at Paderborn University. The protocol was approved by the ethics committee of the "Westfälische Wilhelms-Universität Münster". Written informed consent to participate in the study was obtained by each participant before enrollment and was in accordance with the Declaration of Helsinki. Participants were not provided any payment, but the golf group received complimentary golf training.

The trial was retrospectively registered (02/07/2018) at the German Clinical Trials Register (DRKS00014921).

Screening and eligibility

Participants were recruited locally via newspapers, social media advertisements and at organizations providing leisure activities for seniors. Exclusion criteria were (1) younger than 60 years, (2) answer "no" to the question: "Do you have subjective memory complaints?" (3) significant experiences in golf (i.e., proficiency certificate or handicap) (4) diagnosed neurological or mental disease or other impairment of physical abilities.

Procedure and randomization

After inclusion, participants were individually scheduled for baseline data collection before randomization on two

different days. At day one, the acquisition of medical history and sociodemographic data as well as the neuropsychological testing took place. On the second day, participants underwent a blood sample collection and an endurance performance test. To account for differences in physical activity habits between groups' participants were asked to fill in a questionnaire (Physical Activity Scale for Elderly, PASE, [59]) for two different weeks before randomization and during the 22-week intervention.

After baseline assessments, participants were matched according to age, gender, PASE-score, and Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog) score [38]. For the matching procedure, the method of randomly permuted blocks was applied to allocate participants with similar characteristics to the golf or control group (1:1 ratio). If a block consisted of one participant or if the number of participants in one block was uneven, the participant was allocated to the golf group. A researcher who was not involved in the neuropsychological tests, blood collection, or golf intervention (FvdB) carried out the random sequence generation and group allocation.

A CONSORT flow chart of the study is presented in Fig. 2.

Subjective memory complaints

According to current guidelines [39] a self-designed questionnaire without further formal cognitive testing was used to characterize people with SMC. It included the items memory complaints in daily life (yes/no), serious worries about memory complaints (yes/no) and the onset of the complaints (years). The presence of depressive symptoms and anxiety was evaluated with the Beck's Depression Inventory (BDI) [40].

Golf intervention

The golf training was performed at Paderborn University Golf Club. The golf training sessions were planned,

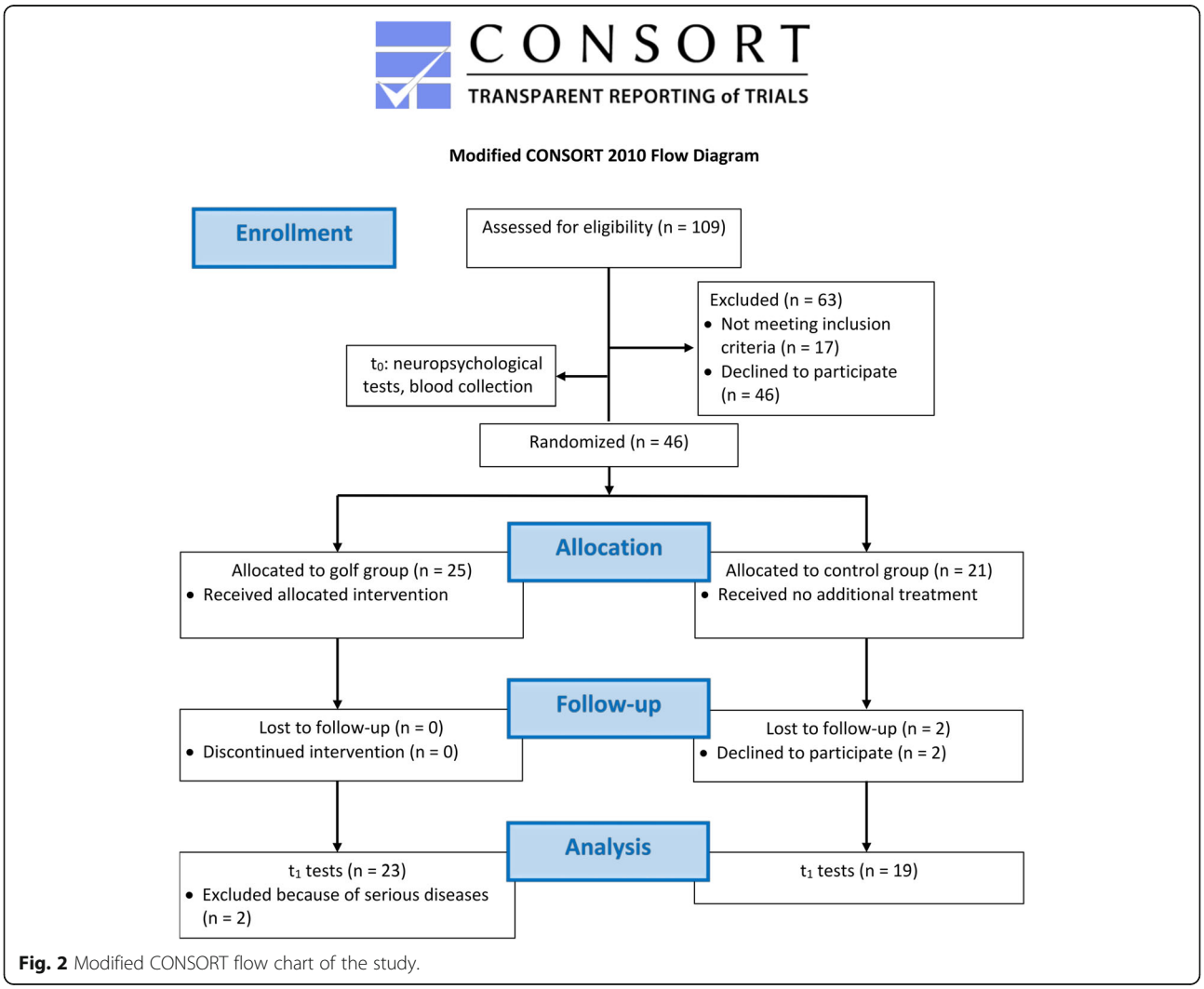

Fig. 2 Modified CONSORT flow chart of the study.

supervised, and mostly conducted by a fully qualified professional golf trainer of the Professional Golfer Association (PGA). In addition, three other golf trainers aided and provided the training sessions. A maximum of 13 participants who were instructed by two trainers was allowed per session. The golf training consisted of three sessions per week, each lasting 60 min over a period of 22 weeks. Two of three sessions were supervised and instructed by trainers. The third session was not supervised, but participants were asked to practice the previously acquired skills independently at the driving range.

The supervised golf program included 18 practice sessions and 25 sessions at the driving range. All sessions started with a short warm-up (10 min), which consisted of coordination and stretching exercises. In the practice sessions (week 1 to 8), participants learned basic golf techniques, starting with putting and chipping. After 5 weeks, pitching was introduced and practiced and after 7 weeks, participants learned the full golf swing. Golf trainers gave individual feedback to improve the techniques, e.g. via videos or verbal instructions during the sessions. At week 9, participants started to practice at the driving range. All trainers encouraged the participants to practice the golf techniques at home in front of a mirror, to learn the golf rules and to interact with the other participants.

Control group

The control group was asked to keep their lifestyle and sports activities unchanged for the course of the study. Each control subject was asked to fill out PASE questionnaires every week to monitor any changes.

Primary outcomes: Feasibility and general cognitive performance

To elucidate if learning to play golf is feasible for elderly people with cognitive problems, the golf group underwent a graded technical exam only at the end of the intervention. This exam is equivalent to the German license to play golf. It included the assessment of the golf techniques putting, chipping, pitching, and the full golf swing performed by the professional golf trainer. A score of 20 points could be achieved for each technique, resulting in a total score of 80 points. Therefore, a higher score was related to better golf performance. Attendance rate was measured by the average number of sessions which were conducted by all participants of the golf group compared to the absolute number of conducted trainings. Safety was measured by adverse events and drop-outs related to the golf intervention.

The neuropsychological tests were conducted at baseline (t_0) and after the 22-week intervention (t_1) by trained study staff not involved in the intervention and blinded to the group assignment. Blinding was ensured by asking participants not to disclose their group assignment to the outcome assessors. General cognitive functions were assessed with the ADAS-Cog [38], which was sensitive to the effects of physical activity in elderly people with SMC in another study [41].

Secondary outcomes: Specific cognitive functions, physical evaluation and the KP

In addition, three different tests of specific cognitive functions were conducted and consisted of visual-spatial working memory (assessed with Corsi Block Tapping Task), and executive functions (assessed with INHIB Response Inhibition and the Trail Making Test part B, respectively). Except for the ADAS-Cog, all tests were part of the automated computer-based Vienna Test System Version 6.82.000 (Schuhfried GmbH, Mödling, Austria).

To assess endurance performance, the 6-Minute-Walk-Test (6MWT) was conducted [42].

Blood samples via venipuncture were obtained during early and late morning (8–12 am) to investigate the KP and IL-6. Participants were asked to avoid physically demanding activities on the same morning before the blood sample collection. The serum samples were left to clot at room temperature for 30 min. After that, samples were centrifuged for 10 min at 1800 g and frozen at -31 °C until transportation (max. 2 weeks later).

Blood samples were processed and analyzed as described in detail in Joisten et al. 2020 [43]. High performance liquid chromatography (HPLC) and tandem mass spectrometry (MS/MS) were used to analyze serum concentrations of KP metabolites (KYN, TRP, QUINA, KYNA). Ratios of KYN to TRP, QUINA to KYNA, QUINA to TRP and QUINA to KYN were calculated to indicate changes in the degradation steps of the KP.

IL-6 was measured using the Quantikine high sensitive IL-6 Enzyme-linked Immunosorbent Assay (ELISA, R&D Systems, Minneapolis, USA) according to the manufacturers protocol.

Statistical analysis

The sample size calculation was conducted with G*Power [44] and was based on the randomized controlled trial of Lautenschlager et al. (2008) [41]. The standardized mean difference for ADAS-Cog was – 1.22. The drop-out rate was set to 20 %. We estimated that a sample size of 46 participants (23 in each group) would provide 95 % power for detecting a significant group difference.

All statistical analyses were conducted per protocol and with the statistical software SPSS version 23 for Windows (IBM, Armonk, NY, United States). Baseline differences between groups regarding anthropometric data, the prevalence of risk factors and physical performance were checked with either independent t-test,

Mann-Whitney-U-test or χ^2-test for categorical variables. Data were z-transformed and statistical outliers (defined as ± 3 SD from the mean) were excluded for each variable. Normal distribution was checked with the Shapiro-Wilk test ($p > 0.05$), and homoscedasticity with Levene's test ($p > 0.05$). Baseline-adjusted Analyses of Covariance (ANCOVAs) were conducted to determine significant group differences for cognitive and blood biomarkers, with group (golf, control) and time (baseline, post) as the main factors. The specific baseline values as well as age were used as covariates for all analyses. Additionally, the change score of BMI (t_1-t_0) was used as a covariate for the analysis of the KP, since visceral fat mass is known to induce systemic low-grade inflammation [23]. Significant time*group interactions were post-hoc analyzed with pairwise Bonferroni-adjusted tests. Due to the explorative character and the small sample size, a larger p-value spectrum was considered for the KP data only [45]. Of note, not all parameters fulfilled the criteria for parametric tests (not normal distributed, heteroscedasticity). ANOVA was shown to be robust against violation of normal distribution, especially when group sizes were over 10 [46]. Transformation of variables to achieve assumptions for parametric tests was also performed, but not associated with different results.

An effect size between Cohen's $d \leq 0.2$ was considered a small effect, Cohen's d 0.2 to 0.5 a medium effect and Cohen's $d > 0.8$ a large effect [47]. To explore the association between compliance (overall number of sessions, number of attended third unsupervised training sessions only) and biological markers (IL-6, KP metabolites), Spearman-rank correlations were calculated, with a significance level of $p < 0.05$. The obtained p-values from the correlation analysis were corrected with the False Discovery Rate (FDR) procedure [48]. Due to the explorative character of the study, corrected and uncorrected p-values of the correlation analysis were reported.

Results

Baseline characteristics

No statistically significant baseline differences between groups regarding age, gender, education, BDI-score, ADAS-Cog-Score, as well as cardiovascular risk factors and physical outcomes were detected. According to the BDI [40], two participants reported symptoms of mild

Table 1 Demographic information at baseline of analyzed participants ($n = 42$)

	Golf group ($n = 23$)	Control group ($n = 19$)	*p*-value	Cohen's d
Age (years)	67.87 ± 4.7	67.89 ± 3.9	0.95	0.05
Gender				
male	10 (43.5 %)	9 (47.4 %)	0.51	
female	13 (56.5 %)	10 (52.6 %)		
Handedness				
right	22 (95.7 %)	19 (100 %)	0.53	
left	1 (4.3 %)	0		
Formal education (years)	14.4 ± 4.5	12.26 ± 3.6	0.13	0.59
BDI (score)	4.7 ± 4.4	4.4 ± 3	0.93	0.10
ADAS-Cog (score)	8 ± 3.55	7.68 ± 3.41	0.71	0.09
Cardiovascular risk factors				
BMI	26.3 ± 3.4	26.2 ± 3.9	0.44	0.02
Current smoker	3 (13 %)	2 (10.5 %)	0.55	
Heavy smoker	0 (0 %)	1 (5.3 %)	0.48	
Diabetes mellitus type 1	2 (8.7 %)	1 (5.3 %)	0.54	
Diabetes mellitus type 2	1 (4.3 %)	1 (5.3 %)	0.73	
Hypertension	12 (52.2 %)	7 (36.8 %)	0.26	
Heart disease	4 (17.4 %)	3 (15.8 %)	0.55	
Physical outcomes				
6-min-Walk-Test (m)	651.37 ± 121.32	627.73 ± 99.67	0.48	0.24
PASE (score)	181.11 ± 59.52	153.37 ± 57.05	0.15	0.48

Quantitative variables were expressed as means ± standard deviations and categorical variables were expressed as numbers and percentage values
Group differences were tested with Mann-Whitney-U for ordinal scaled variables, with independent t-test for metric variables, and with χ^2 tests for categorical variables. *BDI* Becks-Depression-Inventory; *ADAS-Cog* Alzheimer's Disease Assessment Scale - Cognitive Subscale, *BMI* Body Mass Index; *PASE* Physical Activity Scale for Elderly, $p \leq 0.05$ = statistical significance

depression at baseline (16 points), but were not diagnosed with depression or bipolar disorder. The other participants had no clinically relevant symptoms of depression (< 12 points). An overview of baseline characteristics is presented in Table 1.

Subjective memory complaints

All participants of both groups reported SMC in daily life. 26 % (golf, $n = 6$) and 32 % (control, $n = 6$) reported serious worries about the complaints. The onset of memory complaints was 2.6 years ago in the golf group (± 2 years) and also in the control group (± 2.6 years). After the intervention, 35 % ($n = 8$) of the golf group reported an improvement of these symptoms, while no improvement was reported in the control group. 5.3 % ($n = 1$) of the control group and no one in the golf group reported a worsening during the 22 weeks. 65 % ($n = 15$) of the golf group and 95 % (n = 18) of the control group reported unchanged symptoms.

Primary outcomes: Feasibility and general cognitive performance

A CONSORT Flow Diagram of the study is presented in Fig. 2. All participants (n = 25) of the golf group and 19 participants of the control group took part in the assessments at both time points. Two participants of the control group dropped out without provided reasons. The development of serious diseases during the intervention (brain tumor and motor neuron disease), which were not related to the study, required the exclusion of two participants of the golf group from all analyses. There were no adverse events related to the golf intervention during the study. The overall attendance rate in the golf group was 75 % (48 ± 9.9 of 65 sessions) and 70 % (15 ± 5.2 of 22 sessions) for the third training session only. All subjects who undertook the golf exam in the end passed (20/23) it, but three subjects were unable to attend the test due to limited time. 69 % of all PASE questionnaires were filled out during the observation period in both groups. Self-reported activity levels during the study are presented in Fig. 3.

No significant time or time*group interactions were found for ADAS-Cog ($p = 0.613$, F = 0.260, Cohen's d = 0.17). An overview of the statistical results as well as means and standard deviations at t_0 and t_1 is presented in Table 2.

Secondary outcomes: Specific cognitive functions, KP metabolites, and physical performance

No significant time or time*group interactions were found for TMT B or INHIB reaction time. Significant time effects were found for Corsi forward ($p = 0.033$, F = 4.888, Cohen's d = 0.16) and Corsi backwards ($p = 0.023$, F = 5.620, Cohen's d = 0). However, after Bonferroni-adjusted pairwise post-hoc analysis no significant changes in both groups for these parameters remained. A significant time*group interaction was found for INHIB correct responses ($p = 0.012$, F = 7.050, Cohen's d = 0.89), while reaction time remained stable in both groups. Bonferroni post-hoc analysis revealed a significant increase in INHIB correct responses in the golf group compared to the control group ($p = 0.012$, 95 % CI 0.653, 4.834).

No significant time or time*group interactions were found for KYN, TRP, KYNA, QUINA, KYNA/KYN, QUINA/KYNA or QUINA/KYN ratio, IL-6 and for the 6-Min-Walk-Test, but for QUINA/TRP ($p = 0.022$, F = 5.769, Cohen's d = 0.84) in favor of the golf group ($p = 0.022$, 95 % CI 0, 0.001).

A trend towards a significant time*group interaction was found for KYN/TRP ratios ($p = 0.087$, F = 3.108, Cohen's d = 0.61). Another almost significant

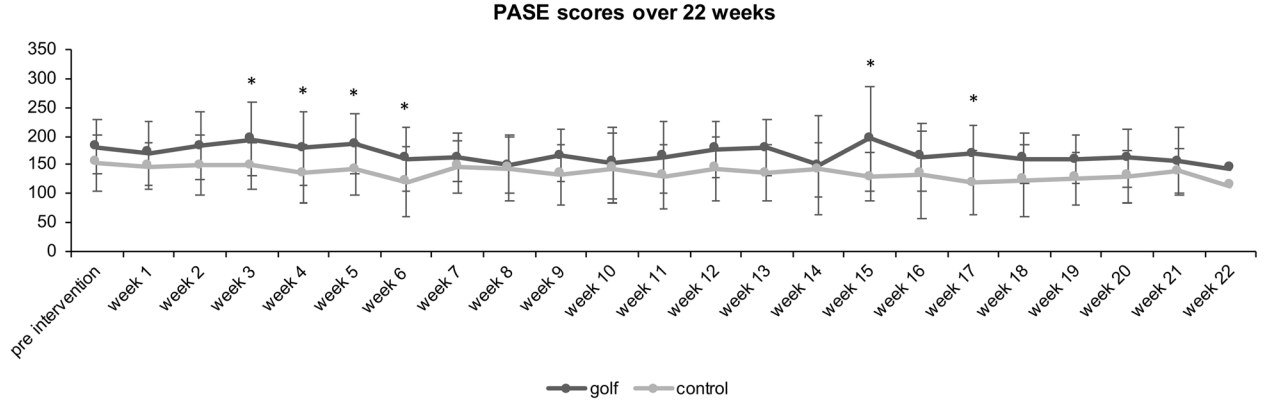

Fig. 3 Mean ± Standard Deviation (SD) Physical Activity Scale for Elderly (PASE) scores before the intervention and for every week in each group during the intervention. * indicate significant group differences at $p < 0.05$. 69 % of all PASE questionnaires were filled out in both groups. The lowest number of returned PASE questionnaires was at week 20 (n = 20), the highest number at weeks 1 and 4 ($n = 35$).

Table 2 Descriptive data indicated as mean and standard deviation (SD) at baseline (t_0) and after the intervention (t_1)

outcome	group	n	t_0 (mean, SD)	t_1 (mean, SD)	ANCOVA time*group (p, F, Cohen's d)	post-hoc analysis (p, 95 % CI)
ADAS-Cog[1] (score)	golf	22	7.45 (2.46)	6.82 (2.67)	0.613, 0.260, 0.17	
	control	19	7.68 (3.40)	6.58 (2.97)		
Corsi forward[1] (no. of sequences)	golf	22	7.91 (1.31)	7.77 (2.02)	0.641, 0.221, 0.16	
	control	19	6.74 (2.13)	7.16 (2.43)		
Corsi backwards[1] (no. of sequences)	golf	23	6.48 (2.35)	6.65 (2.77)	0.921, 0.010, 0	
	control	19	6.26 (2.96)	6.42 (3.15)		
TMT B time[1] (s)	golf	22	49.44 (18.87)	47.58 (12.57)	0.305, 1.085, 0.35	
	control	18	49.81 (22.25)	52.66 (29.03)		
INHIB reaction time[1] (ms)	golf	22	0.37 (0.05)	0.36 (0.05)	0.975, 0.000, 0	
	control	19	0.35 (0.04)	0.35 (0.05)		
INHIB correct responses[1] (%)	golf	22	91.36 (6.84)	95.27 (3.24)	**0.012***, 7.050, 0.89	**0.000***, (2.075, 4.884)
	control	18	92.87 (4.27)	93.07 (4.41)		0.349, (− 0.827, 2.280)
KYN[2] (μmol/L)	golf	22	1.69 (0.55)	1.84 (0.74)	0.418, 0.671, 0.28	
	control	17	2.04 (0.99)	2.19 (0.85)		
TRP[2] (μmol/L)	golf	22	127.48 (25.68)	129.67 (16.39)	0.464, 0.548, 0.26	
	control	17	129.67 (20.90)	126.56 (21.13)		
KYN/TRP ratio[2]	golf	22	0.014 (0.005)	0.014 (0.005)	0.087, 3.108, 0.61	
	control	17	0.016 (0.006)	0.017 (0.006)		
KYNA (μmol/L)[2]	golf	22	0.093 (0.023)	0.095 (0.031)	0.926, 0.009, 0	
	control	17	0.105 (0.048)	0.105 (0.039)		
KYNA/KYN ratio[2]	golf	22	0.058 (0.02)	0.057 (0.02)	0.598, 0.284, 0.18	
	control	17	0.057 (0.02)	0.054 (0.03)		
QUINA (μmol/L)[2]	golf	21	0.72 (0.24)	0.67 (0.22)	0.224, 1.537, 0.43	
	control	17	0.71 (0.24)	0.73 (0.19)		
QUINA/KYNA ratio[2]	golf	21	8.20 (2.32)	7.38 (1.69)	0.227, 1.513, 0.43	
	control	17	7.43 (2.65)	7.64 (2.92)		
QUINA/TRP	golf	21	0.0058 (0.002)	0.0051 (0.001)	**0.022***, 5.769, 0.84	**0.022***, (0, 0.001)
	control	17	0.0057 (0.002)	0.0059 (0.002)		0.527, (-0.001, 0)
QUINA/KYN	golf	21	0.456 (0.145)	0.406 (0.154)	0.869, 0.028, 0.06	
	control	17	0.394 (0.141)	0.364 (0.107		
IL-6 (pg/ml)[2]	golf	22	1.54 (0.59)	1.82 (0.97)	0.607, 0.270, 0.18	
	control	15	2.05 (1.17)	2.16 (1.33)		
6-Min-Walk-Test[1] (m)	golf	23	651.65 (115.75)	653.58 (153.82)	0.439, 0.613, 0.26	
	control	16	646.21 (91.12)	673.78 (106.33)		
PASE (score)[1]	golf	21	180.86 (59.02)	171.05 (45.72)	0.056, 3.888, 0.66	
	control	19	153.37 (57.05)	137.50 (37.91)		

Results of baseline-adjusted ANCOVA are presented (time, time*group) with Bonferroni-corrected pairwise post-hoc analysis for each parameter. * indicate statistical significant changes or differences at $p < 0.05$. *ADAS-Cog* Alzheimer's Disease Assessment Scale - Cognitive Subscale, *TMT* Trail Making Test, *INHIB* Response Inhibition, *KYN* Kynurenine, *TRP* Tryptophan, *KYNA* Kynurenic acid, *QUINA* Quinolinic acid, *IL-6* Interleukin 6, *PASE* Physical Activity Scale for Elderly, *FDR* False Discovery Rate (Benjamini Hochberg Procedure) [1]adjusted for age, [2] adjusted for age and mean change of BMI (t_1-t_0)

group*time interaction was found for PASE ($p = 0.056$, F = 3.888, Cohen's d = 0.66). Significant interaction effects as well as trends within the KP are visualized in Fig. 4.

Exploratory Spearman correlation analysis showed a significant negative correlation of delta QUINA/KYNA ratio (t_1-t_0) with adherence to the third training session in the golf group ($p = 0.039$, r_s = -0.443). Of note, the

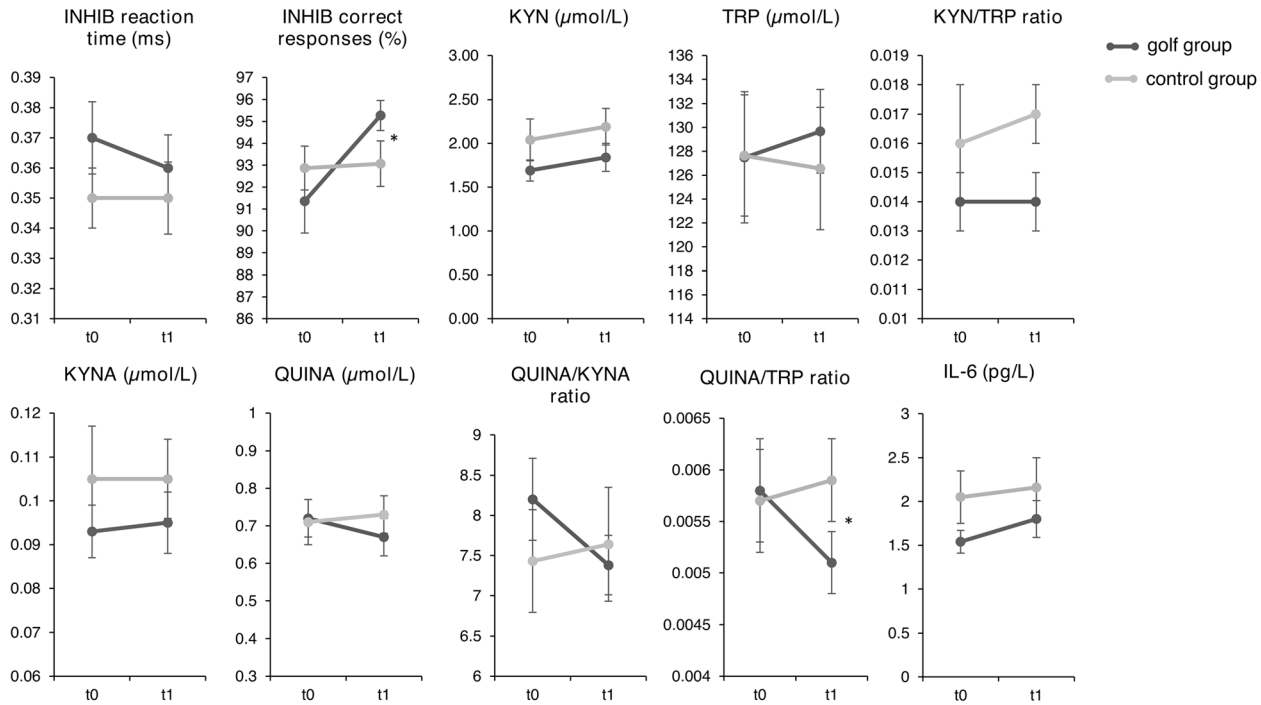

Fig. 4 Raw data (means) with standard error (SE) in both groups at t_0 and t_1. * indicate statistical significant time*group interactions at $p < 0.05$. KYN: Kynurenine, TRP: Tryptophan, QUINA: Quinolinic acid, KYNA: Kynurenic acid, INHIB: Response Inhibition task, BDNF: Brain-derived neurotrophic factor, IL-6: Interleukin-6.

correlation was not significant after FDR correction. An association between the achieved points of the golf exam and the KP was not found. Results of the correlation analyses are presented in Fig. 5.

Discussion

The aim of this study was to elucidate the feasibility of a 22-weeks golf intervention on the driving range and its effects on cognitive functions and the KP in elderly people with SMC without prior golf experience. We could show that elderly people with cognitive problems were able to learn golf, although it is a complex and difficult sport to learn. No adverse events related to the golf intervention were reported, and no participant in the golf group dropped out. Overall adherence to the golf training was 75 %, which can be considered as acceptable. Two participants of the control group dropped out, as they made their participation contingent on allocation into the golf group. Of note, this might have

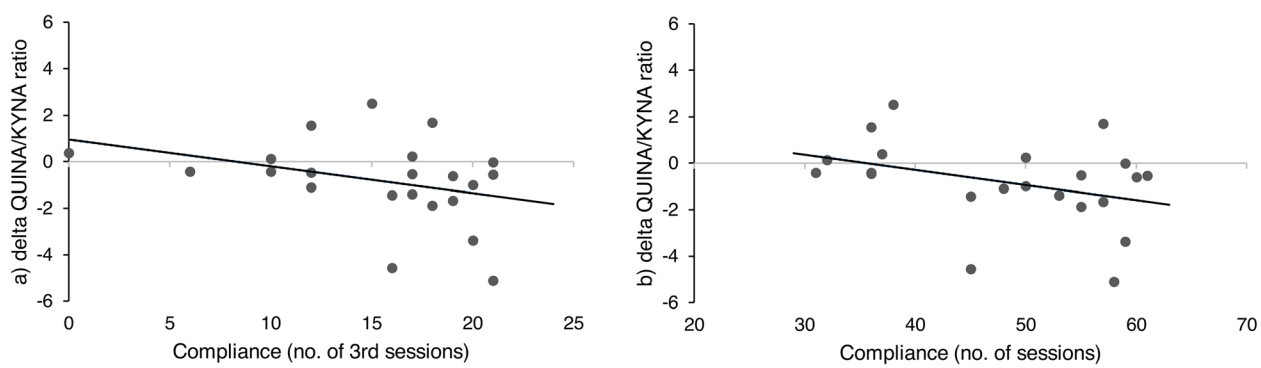

Fig. 5 Results of Spearman correlation analyses. **a** + **b**: Association of compliance (number of attended sessions) with delta Quinolinic acid to kynurenic acid ratios (QUINA/KYNA ratios, t1 - t0). **a**: only number of third sessions attended) and delta QUINA/KYNA ratios, **b** number of all attended sessions and delta QUINA/KYNA ratios. **a** $r_s = -0.443$, $p = 0.039$, **b** r_s= -0.400, $p = 0.065$. Of note, the correlation between compliance (no. of 3rd sessions) and delta QUINA/KYNA ratios was not significant after correcting for type 1 errors ($p = 0.039 > 0.005$

influenced comparability of both groups, e.g. regarding physical activity levels (PASE). Three participants were not able to attend the golf exam due to organizational reasons. All other participants passed it (20/23). Therefore, for people with cognitive problems, findings support the idea that learning to play golf is feasible and safe.

Results of this pilot study revealed no significant effects of learning to play golf on general cognitive performance, working memory or other measures of executive functions compared to the control group. Only the number of correct responses on the INHIB task increased significantly in the golf group compared to the control group, while the reaction time remained unchanged. For the INHIB task, participants should only react when a certain stimulus is presented (Go/NoGo). Golfers therefore made less omission (missing reaction) and commission errors (wrong reaction) compared to the control group throughout the task. These findings suggest a small effect on sustained attention.

Shimada et al. (2018) [34] found an improvement in logical memory after 24 weeks golf intervention, which was not an outcome in this study. Learning to play golf requires high demands on motor and cognitive abilities [35] and less on cardiovascular abilities (compared to endurance training). In addition, the golf training consisted mostly of whole-body-coordination exercises at the driving range, which is also indicated by an unchanged endurance performance in the golf group. The findings are in accordance with Voelcker-Rehage et al. (2011) [49], who found a higher accuracy during a Flanker and a Visual Search task in a coordination exercise group. Thus, our results might not reflect the multidimensionality of playing golf, which also includes cardiovascular demands that is induced by walking over the fairway [33]. Evidence from studies investigating the effects of dancing (which is possibly comparable to golf because of its multidimensionality) revealed increases in attention only at 6 months of dance training, whereas episodic memory performance increased after 18 months of training [30]. Improvements in cognitive functions were reportedly not linear [30], and the positive effects of a multidimensional activity on cognitive functions might not be present at 22 weeks of practice. In this study, only data from the 22-week observation is available, which impedes the long-term investigation of all demands of golf on cognitive functions.

On a biological level, learning to play golf showed a positive, but non-significant influence on peripheral KP regulation, which could be of interest for future studies. A significant group*time interaction was only found for QUINA/TRP ratios in favor of the golf group. Descriptive data indicated that KYN levels as well as KYN/TRP ratios remained stable during the intervention in the golf group, but increased almost significant in the control group, suggesting enhanced IDO1 activity. Of note, KYN/TRP ratios could also increase by cortisol due to higher stress levels in the control group, which in turn influences the expression of TDO [23, 50]. Interestingly, the KYN/TRP ratios observed in this study are lower compared to findings from cross-sectional studies, e.g. in elderly people (median KYN/TRP ratio 0.025, interquartile range 0.006, [20]) and in AD patients (median KYN/TRP ratio 0.034, interquartile range 0.008, [17]). Besides substantially increased KYN/TRP ratios that have been described in neurodegenerative diseases [51], the participants in Solvang et al. [20] were on average 10 years older compared to this sample, which might be one explanation for the higher values. To the best of our knowledge, no cut-off value exists yet that indicates an increased risk for future cognitive decline or AD.

The non-significant increase of KYN/TRP ratios could also be the result of decreased habitual physical activity in the control group during the observation period, as indicated by PASE scores (see Fig. 2). The activity associated with regular golf training therefore might have the potential to counteract age or AD-related changes of IDO1 activity. This is supported by the non-significant decrease of serum QUINA levels as well as serum QUINA/KYNA ratios golf group only, which might indicate a reduction of Kynurenine 3-monooxygenase (KMO) activity [50, 52]. IDO1 and KMO activity are both driven by inflammatory states [13, 53]. Of note, the findings did not reach statistical significance, and should therefore be replicated in a larger sample. In addition, it cannot be ruled out that the results are affected by other enzymes of the KP, such as Kynureninase or Kynurenine aminotransferase (KAT).

We also found a negative association between delta QUINA/KYNA ratios and the number of golf training sessions, indicating a positive influence of training frequency on the KP. Of note, the correlation was not significant after Benjamini Hochberg-correction of type 1 error and should also be interpreted carefully.

One randomized controlled trial exists which investigated the effects of a multicomponent exercise intervention (endurance, coordination, balance, flexibility, strength) in elderly at risk of dementia. Küster et al. [21] did not find effects of a 10-week multicomponent exercise intervention on KP metabolites either. Similar to our intervention, the metabolic demands might have been too low to trigger mechanisms that were described regarding the positive effects of exercise on the KP [23], as KYN remained unchanged in the golf group. The positive effects of learning to play golf on the KP might be rather mediated by reduced systemic inflammation, stress or other mechanisms, which are reported effects of physical activity [25, 54].

Our study has some limitations, which should be considered when interpreting the results. First, the sensitivity of the ADAS-Cog might have been too low to detect cognitive changes in this cohort. However, this test was chosen as the primary outcome to allow comparability to previous studies with similar cohorts (e.g. [55–57]). Second, the sample was active (according to the PASE questionnaire, [58, 59]), physically fit (according to the 6MWT, [42]) and well educated (13.5 ± 4.2 years on average), which indicates a selection bias that may affect the generalizability of the results. Of note, it would be of great interest to motivate sedentary elderly people, which are not already physically active, to take part in such a program. In recent years, accessibility of golf was increased by modifying rules of the game, the golf course as well as the equipment for people with various impairments [60]. Moreover, playing golf can facilitate establishment of social relationships, which in turn increases motivation to continue with the sports.

Third, self-reported and cognitive outcomes in this study might be prone to reflect placebo effects or other factors related to the intervention, such as an increased social interaction, because blinding of the participants was not possible and there was no adequate treatment in the control group. The results should therefore be interpreted carefully.

Accordingly, we did not achieve the calculated sample size because many of the screened subjects made their participation in the study contingent on a randomization into the golf group and therefore had to be excluded. The study is therefore underpowered, which might have led to the absence of the effects of golf on neuropsychological outcomes and the KP. Thus, our findings should be replicated in a larger, more representative sample and rather be interpreted as preliminary results. Subgroup analyses of the effects of golf on cognitive functions and the KP accounting for particular concerns and gender differences would have also been useful [4]. In this context, it was recently shown that elderly women with high cortical amyloid-β burden also had higher serum KYN levels and KYN/TRP ratios [11]. Serious concerns about SMC were further associated with quantitative amyloid-β deposition [10] and it was suggested, that the decline in estrogen levels after menopause might increase the vulnerability to KP activity and AD [11]. In our study IL-6 was used as a surrogate marker for inflammatory processes that may influence KP regulation via upregulation of IDO or TDO. However, further studies should include a broader variability of markers of neurodegeneration, neuroinflammation and neuroplasticity.

People with SMC were diagnosed according to guidelines published in [39]. There is some evidence that self-reported SMC can predict future cognitive decline [61], but findings are controversial [62]. Thus, it remains unclear if the study population is relevant for AD or if SMC had other etiologies.

Participants were not scheduled at the exact same time of the day at baseline and after the intervention for the blood sample collection and chronobiological effects might not be fully excluded. However, moderate to strong correlations of t_0 and t_1 IL-6 and KP parameters do not support relevant effects. Participants were not fasted during blood sample collection, which might have influenced the outcome measures as well. Therefore, future studies should conduct measurements with standardized conditions.

In general, causality of central changes of the KP by the golf intervention cannot be assumed, but has to be elucidated in further studies [21].

Since the aim of this study was to assess effects of a complex multicomponent activity in analogy to the enriched environment animal model, we are limited in concluding which stimulation (cognitive, social, sensory, motor) had the largest effects on cognitive outcomes and the KP or whether the combination of all the above is most effective. However, the current literature supports positive effects of recreational and physical activities in natural green environments on mental health in elderly people [63] and attention performance [64].

Conclusions

The findings of this randomized trial support the idea that learning the challenging sports golf with a multidimensional profile is feasible and safe for people with SMC. Preliminary results revealed improved attention performance and a trend towards a positive influence on the regulation of the KP in the golf group. To elucidate the effects of long-term golf training and the potential to reduce cognitive decline and associated changes in the KP, studies should replicate the findings in a larger and less active sample of elderly people with SMC over a longer period, including higher metabolic demands by playing on the golf course.

Abbreviations

AD: Alzheimer's Disease; ADAS-Cog: Alzheimer's Disease Assessment Scale – Cognitive Subscale; ANCOVA: Analysis of Covariance; ANOVA: Analysis of Variance; BDI: Beck's Depression Inventory; BMI: Body-Mass-Index; CNS: Central nervous system; CONSORT: Consolidated Standards of Reporting Trials; ELISA: Enzyme-linked Immunosorbent Assay; FDR: False Discovery Rate; HPLC: High performance liquid chromatography; IDO1: Indoleamine-2,3-Dioxygenase 1; IL-6: Interleukin-6; INHIB: Response Inhibition Task; KAT: Kynurenine Amino Transferase; KMO: Kynurenine 3-monooxygenase; KP: Kynurenine Pathway; KYN: Kynurenine; KYNA: Kynurenic Acid; NAD+: Nicotinamide adenine dinucleotide (oxidized form); PASE: Physical Activity Scale for Elderly; PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PGA: Professional Golfers Association; QUINA: Quinolinic Acid; SD: Standard Deviation; SMC: Subjective Memory Complaints; TDO: Tryptophan 2,3-Dioxygenase; TMT: Trail Making Test; TRP: Tryptophan; 6MWT: 6-Minute Walk Test; 3-HK: 3-hydroxykynurenine; 3-HAA: 3-hydroxyanthranilic acid

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Authors' contributions
JKS, SV, FvdB and CR contributed to the study conception and design. JKS, FvdB and CG performed data collection. AS and PZ processed the blood data. Data analysis was conducted by JKS with support from AS and PZ. MO reviewed the statistical methods and analyses. JKS and CR wrote the manuscript and all authors commented on previous versions. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The protocol was approved by the ethics committee of the "Westfälische Wilhelms-Universität Münster". Written informed consent to participate in the study was obtained by each participant before enrollment and was in accordance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The golf training was financially supported by the Heinz Nixdorf Westfalian foundation.
The authors declare no competing interests.

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Publisher's Note

Source Connectivity Patterns in the Default Mode Network Differ Between Elderly Golf-Novices and Non-Golfers

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Abstract

Learning to play golf requires specific activation of task-relevant brain networks with high demands on attention and may counteract age-related changes of functional brain networks. This cross-sectional study compared source connectivity in the Default Mode Network (DMN) between elderly golf novices and non-golfers.

Four-minute resting-state electroencephalography (128 channels) from 22 participants (mean age 67 ± 4.3 years, 55% females) were recorded after a 22-week randomized trial in which elderly people learned to play golf or continued with normal life. Source connectivity was assessed after co-registration of EEG data with native MRI within pre-defined portions of the DMN in the beta band (14-25 Hz).

Non-golfers showed significantly higher source connectivity values in the anterior DMN. Correlation analyses might indicate that those values were associated with worse executive functions. Correlations between a marker of external attention with functional connectivity and strength of the anterior DMN were present in the golf group only, but failed to keep significant values after Bonferroni correction.

Therefore, the observed network changes within the DMN may provide a tool to further investigate if and how learning golf may have an impact on age-related cognitive decline. Findings should be replicated in a longitudinal design with a larger sample.

Key words: Golf, Default Mode Network, Functional Network Characteristics, Elderly people, EEG

Introduction

Aging is accompanied by structural and functional changes of the brain. Besides grey and white matter atrophy [1–3], pathological mechanisms in the context of Alzheimer's disease (AD) such as cerebral hypometabolism [4,5] as well as amyloid-ß and tau deposits [6] have the potential to impair functional network organization [7,8].

Pathological mechanisms related to AD were also found in elderly people experiencing subjective memory complaints (SMC) [9,10]. It was further associated with an increased risk for AD compared to elderly people without SMC [11]. The etiology of SMC, however, is heterogeneous, and can also be caused by other factors not related to AD, such as psychiatric or chronic diseases or psychological distress [12]. Nevertheless, SMC due to preclinical AD were shown to be associated with impaired functional network organization[13].
As a consequence of an alteration of functional networks, dedifferentiated activity especially of sensorimotor, visual, and dorsal attention networks were described, leading to functional integration of the whole brain and lower within-network connectivity (functional segregation) in elderly people [14].

The Default Mode Network (DMN), as the hierarchically superior resting state network, may also be affected by functional reorganization processes in the context of aging and AD. A reduced ability to deactivate the DMN during external attention demanding tasks was observed in elderly people and AD patients, which points to a stronger de-differentiated involvement of DMN hubs (grey matter regions of high significance in a network) in other sensory (sensorimotor, visual) or cognitive networks (dorsal attention, visual-spatial) [15,16]. Vice versa, increases in connectivity to regions outside the DMN could be observed, which was interpreted as lower network integrity [17,18].

Task related demands on external attention is often assessed by oscillatory activity in the theta frequency band (4-7 Hz) at frontal electrodes (frontal midline theta) derived from electroencephalography (EEG) [19]. Evidence from simultaneous resting-state EEG and functional magnetic resonance imaging (fMRI) studies indicated a negative association between frontal midline theta power and the blood-oxygen-level-dependent (BOLD) signal of DMN regions [20,21]. It was therefore suggested that frontal midline theta power may index functional antagonism to the DMN in resting-state [21]. Presumably, the inverse relation between frontal midline theta power and the DMN is also affected by the reorganization processes of functional networks due to age or by early preclinical neurodegenerative processes of AD, but this has not been described yet specifically.

Evidence from epidemiological studies suggest that regular physical activity has the potential to counteract age and AD-related changes by reducing amyloid burden [22] and prevent cerebral atrophy [23–25]. Especially cardiovascular fitness and aerobic exercise interventions were investigated most frequently in this context, with positive effects on cognitive performance [26,27] and functional integrity of the DMN [28–30].

Besides aerobic exercise, however, functional networks also adapt in response to complex training, which involves higher order cognitive functions. Binder and colleagues [31] found task-specific increased functional connectivity and efficiency in networks, which were stimulated by multi-domain cognitive training in elderly people even 1 year after the intervention. Similar practice-related structural and functional adaptations of networks were also found for musicians [32,33], meditation practice [34] and middle-aged golf novices [35].

Golf is a popular leisure time activity in the elderly population with high demands on cognitive and motor functions. Learning to play golf mainly consists of different swings (full swing, pitch, chip, put) and golf-specific rules. Executing the different swings requires specific activation and switching between sensorimotor [36] and visual-spatial networks. It might therefore be hypothesized that these requirements on attention performance are associated with stronger functional deactivation of DMN hubs. Consequently, learning to play golf might have an influence on source connectivity patterns in the DMN of elderly people.

We therefore compared DMN source connectivity patterns and cognitive performance in elderly people with a history of 22-week golf training to a control group without golf-experience that continued with daily life. In an explorative and hypothesis-generating approach we further investigated a potentially reverse relationship between frontal theta as a neurophysiological marker of external attention and DMN source connectivity in both groups to provide the basis for further studies investigating mechanisms of dedifferentiation (of the DMN).

Results

In this study, we analyzed data from 22 participants, from which 12 were golf novices, who completed a golf training 3 times per week over 22-weeks, and 10 non-golfers, which served as a control group. All participants reported subjective memory complaints, but had no diagnosed mental or neurological disease (e.g. depression, AD, Parkinson's Disease). The Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog, [37] revealed normal age-appropriate scores for the majority of the participants (n = 23, scored between 1-9 points).

Four participants scored between 10-13 points, which possibly indicates mild cognitive impairment [38,39]. Two of them were in the golf-novices group, and two in the non-golfer group. In general, both groups were comparable regarding age, gender, education, and ADAS-Cog score, cardiovascular fitness and daily activity habits indicated by the Physical Activity Scale for Elderly (PASE). Baseline characteristics are presented in table 1.

>> insert table 1 around here <<

Four-minute high-density resting-state EEG recordings were collected from each participant and frontal midline theta power was extracted via independent component analysis. The data was further co-registered with native MRI of each participant, and DMN activity was assessed by EEG source connectivity [40]. Functional connectivity of DMN hubs was calculated in the beta frequency band (14-25 Hz) based on Kabbara et al. [40]. Mean connectivity values of the whole DMN and DMN portions (anterior DMN, posterior DMN and core DMN) were used for correlation analyses with frontal midline theta power as well as for the group comparisons. Bonferroni-corrected as well as uncorrected p-values were reported due to the explorative character of the study.

Group differences in the DMN and for cognitive performance

Significant group differences were found for anterior DMN mean functional connectivity (golf 0.41 ± 0.07 vs. control 0.52 ± 0.06, p = 0.002, Bonferroni-corrected p = 0.028). Similarly, mean strength of anterior DMN was significantly higher in the control group (golf 2.49 ± 0.41 vs. control 3.17 ± 0.39, Bonferroni-corrected p = 0.028). No significant differences were found for other connectivity and graph measures of the DMN as well as for cognitive functions.
An overview of the results is presented in table 2.

>> insert table 2 around here <<

Subgroup analyses revealed that higher mean functional connectivity of anterior DMN was associated with worse performance on TMT A (r_s= 0.697, uncorrected p = 0.025, Bonferroni-corrected p = 0.6), and TMT B (r_s= 0.770, uncorrected p = 0.009, Bonferroni-corrected p = 0.216) in the control group. Similar results were obtained for higher mean strength in the anterior DMN and worse performance on TMT A (r_s= 0.685, uncorrected p = 0.029, Bonferroni-corrected p = 0.696), TMT B (r_s= 0.794, uncorrected p = 0.006, Bonferroni-corrected p = 0.144).

Interestingly, higher mean connectivity in the anterior DMN was associated with a faster reaction time in the golf group (r_s= -0.578, uncorrected p = 0.045, Bonferroni-corrected p = 1), similar to mean strength (r_s= -0.594, uncorrected p = 0.042, Bonferroni-corrected p = 1).

Frontal midline theta power and the DMN

The dipole of the average independent theta components (n= 22) was localized in Brodmann area 24 (MNI coordinates: X=4.2 Y=7.9 Z=30.8), with a goodness-of-fit of 93%. Brodmann area 24 is defined as the anterior cingulate cortex (see figure 1).

>> insert figure 1 around here <<

Frontal midline theta power was not significantly different between groups (golf: 0.04 ± 0.06 vs. control: 0.02 ± 0.02, p = 0.628).

Uncorrected significant negative correlations for anterior DMN mean connectivity and mean strength with power were only observed in the golf group (r_s= -0.699, p = 0.011, Bonferroni-corrected p = 0.176; r_s= -0.678, p = 0.015, Bonferroni-corrected p = 0.240). No significant correlations were found between functional connectivity of the whole or posterior DMN and frontal midline theta power in either group. Uncorrected inverse relationships were also again found in the golf group only for core DMN connectivity (r_s= -0.650, p = 0.022, Bonferroni-corrected p = 0.240).

An overview of the results is presented in table 3.

>> insert table 3 around here <<

Discussion

In this study, an EEG source connectivity approach with native MRI was used to explore network changes in the DMN of elderly people that learned to play golf compared to elderly non-golfers. A significantly higher mean functional connectivity and strength in the anterior DMN was observed in the group of non-golfers compared to the golfers. An interpretation based on findings not corrected for multiple testing furthermore may suggest stronger functional antagonism between anterior DMN mean source connectivity and frontal midline theta in elderly golf novices, as no significant correlations were observed in the non-golfer group. Because of the high number of conducted tests, no p-value remained significant, but similar to our uncorrected results, the observed inverse associations between frontal midline theta and the DMN have been described in healthy young adults in a previous study [21]. Exploratory subgroup analyses may indicate that higher values of functional connectivity and strength within the anterior DMN were associated with worse performance of executive functions and working memory in the control group, but due to the high number of correlations, no p-value remained significant after Bonferroni correction for this hypothesis as well.

Although findings should be interpret with caution, they suggest a consisted trend towards age-related neuronal adaptation to decreased functional specialization of brain areas across groups, which is in line with previous observations from fMRI studies [41]. The resulting compensatory involvement of further resting-state networks in elderly people was recently shown to be driven by de-differentiated activity of sensorimotor, visual and cognitive networks, leading to a higher functional integration of the whole brain [14]. Functional connectivity between DMN hubs identified in the beta frequency range may further support this interpretation because it has been shown to be associated with multisensory integration of information in long range connections [42].

Learning to play golf was shown to be associated with regional structural adaptations of the brain [35]. Interestingly, significant anatomical differences were only observed between golf-novices and professional golf players in the literature, but not in comparison to moderately skilled players [36]. In general, patterns of functional brain networks might differ when learning a new motor skill compared to training of rather automated movements. Learning a new motor skill, like golf, was found to be associated with higher activation in brain regions defined as the Dorsal Attention Network (DAN), a network involved in task-related attention and cognitive control [43] that is functionally anti-correlated with the DMN [44]. Interestingly, this activation in the DAN decreased with automatization of movements, presumably indicating less cognitive control and attention [43]. Considering a decreased anti-correlation between the DMN and DAN in age or Mild Cognitive Impairment [45] due to decreased functional integrity of the DAN [14], learning a new and complex motor skill, like golf, may induce different network changes compared to repetitive training, as the observed negative correlations to frontal midline theta in the golf-novices group may suggest. Interestingly, Voss et al. [29] found increased functional connectivity in DMN regions of elderly people engaging in a combined low intensity balance, stretching and toning program after only 6 month of regular training, whereas elderly people in the moderate and repetitive aerobic exercise group showed increased DMN integrity after 1 year first.

Therefore, engagement in low-intensity but complex motor stimulating activities has an influence on functional brain network organization [46,47] beyond cardiovascular fitness and metabolic intense exercise [29]. The mechanisms causing these changes might be different. Aerobic exercises, like walking, are characterized by simple, repetitive, automatic movements and found to increase cerebral blood flow, induce several neurotrophic factors supporting synaptogenesis and angiogenesis, and result in an enhanced synthesis of cerebral tissue [23,48,49]. Therefore, aerobic exercise presumably has a rather general and unspecific effect on brain network organization, which positively affects cognitive functions. Golf on the other

hand might induce changes directly and more specifically depending on the training history. For instance, regular coordination exercises increased functional connectivity specifically in the visual-spatial network in elderly people [46].
Of note, the requirements of a golf match with some of the cognitive-behavioral symptoms of early AD, including attention, visual-spatial relations and working memory functions. Adapted to the patient's abilities, these findings encourage the idea of golf as a potential beneficial treatment for people at risk of AD.

However, golf is one of several lifestyle-related factors influencing cognitive performance and functional network characteristics, including cardiovascular fitness [29,50] leisure time activities like chess or playing an instrument [32], genetic predisposition [51–53] as well as diet [54,55]. The cross-sectional design impeded the examination of longitudinal changes in the DMN. Due to the explorative character of this study, conduction of multiple statistical tests raised the risk for type 1 errors, and both corrected and uncorrected p-values were reported. It should be noted, however, that the chosen Bonferroni correction is very conservative. As uncorrected consistent trends across different parameters were observed in both groups, which only partially remained after Bonferroni correction, our results may suggest that network changes within the DMN provide a method to investigate the impact of learning to play golf on age-related cognitive decline and could therefore provide the endpoints and basis for further investigations. Findings should therefore be replicated by focusing on the anterior DMN, a lower number of cognitive tests and controlling or investigating for other factors potentially influencing the correlation between external attention and (anterior) DMN network characteristics. Another limitation of our study is the small, but well characterized sample, which prohibited the application of more powerful parametric statistical tests. Combining MRI and EEG to improve spatial resolution of functional changes as performed in our study may further increase the sensitivity of the observed differences in the DMN despite the small sample. The dipole localization might be biased by its tendency to estimate the source too deep, when there is a more superficial source. However, frontal midline theta was located in or near the anterior cingulate cortex (BA 24), which is in line with previous findings [21,56,57]. Overall, the source connectivity approach reduces field spread and volume conduction problems of cortical EEG, but cannot completely diminish the effects [58].

Findings of this study indicated different source connectivity patterns in the DMN of elderly golf-novices compared to non-golfers. Therefore, our findings may provide a tool to investigate the impact of learning golf on age-related cognitive decline. Higher and presumably compensatory functional activity in the anterior DMN was observed in the non-golfer group, and uncorrected findings suggest a relation to worse performance on the Trail Making Test.

Other group differences were not found. Longitudinal studies with a larger sample size would provide a more detailed understanding of mechanisms induced by learning to play golf on functional characteristics of the DMN in the elderly brain and how it may prevent cognitive decline due to AD.

Methods

The data was collected during a 22-week randomized controlled trial from May to December 2018. Participants were recruited via local newspapers, social media advertisement, and by personal contact with organizations providing leisure activities for elderly people. During the intervention, elderly people with subjective memory complaints and no prior golf-experience learned to play golf under supervision of a professional golf trainer. The non-golfers served as a control group and continued with daily life. Both groups were asked to document daily activity habits with a questionnaire during the intervention (Physical Activity Scale for Elderly, PASE, [59]. The analyzed data set was collected immediately after the intervention. The trial was registered at the German Clinical Trials Register (DRKS00014921). The ethics committee of the "Westfälische Wilhelms-Universität Münster", Germany, approved the study protocol according to the declaration of Helsinki. Participants were informed about the main research aims and personal data management and gave their written consent before the start of the intervention.

Golf training

The golf training consisted of three sessions per week, each lasting 60 min over a period of 22 weeks. Two of three sessions were supervised and instructed by trainers. The third session was not supervised, but participants were asked to practice the previously acquired skills independently at the driving range.

The supervised golf program included 18 practice sessions and 25 sessions at the driving range. All sessions started with a short warm-up (10 min), which consisted of coordination and stretching exercises. In the practice sessions (week 1 to 8), participants learned basic golf techniques, starting with putting and chipping. After 5 weeks, pitching was introduced and practiced and after 7 weeks, participants learned the full golf swing. Golf trainers gave individual feedback to improve the techniques, e.g. via videos or verbal instructions during the sessions. At week 9, participants started to practice at the driving range.

EEG measurements

Resting-state measurements were conducted with a high-density 128-channel Electroencephalography (EEG) actiCap system from Brain Products (Brain Products GmbH, Gilching, Germany). The cap was positioned according to the international 10-10 system and impedances were constantly checked and kept below 15 kΩ. The sampling rate was set to 500 Hz. The ground electrode replaced FPz, and the reference electrode replaced FCz. Participants were measured in supine position with eyes closed in an acoustically attenuated darkened room and were instructed to relax but stay awake during the 4 min recording. Individual electrode locations were registered with the BrainVision CapTrack software (Brain Products GmbH, Gilching, Germany).

Source connectivity preprocessing and analysis

An overview of data analysis is presented in figure 2.

>> *insert figure 2 around here* <<

The preprocessing was done with BrainVision Analyzer Version 2.1.2 (Gilching, Germany: Brain Products GmbH, www.brainproducts.com). The raw data was first visually screened for bad channels, and the sampling rate was downsampled from 500 Hz down to 256 Hz. Then, a Matlab-based (Matlab R2017a, Mathworks Inc., MA, USA; www.mathworks.com) screening algorithm eBridge [60] and magnitude squared coherence values between 0.9 and 1 for visual inspection were both used to detect electrical bridges in the data. If the results from the visual inspection and the algorithm were identical, the bridged channels were interpolated with the spherical spline method as implemented in the BrainVision Analyzer software. If the identified electrode bridges of both methods were not identical, the electrodes were additionally visually inspected (difference between both channels) and interpolated, if necessary. Participants were excluded from analysis if more than 15% of all channels or the reference electrode was bridged [50].

Then, the individual electrode coordinates were loaded into the software and the data were re-referenced to the average. Zero Phase Shift Butterworth Filters were applied, with a low cutoff at 1 Hz (time constant 0.159 s, order: 4) and a high cutoff at 30 Hz. Sinusoidal line noise was reduced by application of a 50 Hz notch filter. Before applying independent component analysis (ICA) to the data, stationary artifacts were removed via visual inspection. Then, extended infomax ICA implemented in the BrainVision Analyzer software was used to exclude eye movements and electrocardiographic artifacts. The cleaned data was subsequently cut into epochs of 2048 data points, resulting in 8 s per epoch. For phase based connectivity measures in source space, epoch lengths of at least 6 s were recommended in order to

produce stable results [61]. Each epoch was visually inspected for remaining artifacts. An experienced neurologist (CR) further screened epochs for signs of drowsiness and excluded them, if necessary. The first 4 “artefact-free” epochs of the 4 min recording were used for the source connectivity analysis as recommended in [62]), resulting in an overall analysis window of 32 s per subject. The epochs were converted into ASCII files and exported to Brainstorm [63].

Prior to the EEG recordings, participants were scanned with a 1.5-T MRI Scanner (Hitachi Medical Systems, Hitachi, Japan). A 3D RSSG (RF-spoiled SARGE) protocol with 170 axial slices, echo time (TE) = 2.3 ms, repetition time (TR) = 10.6, slice thickness = 1.0 mm was used. Cortical reconstruction and volumetric segmentation of the individual MRIs was performed using the automated Freesurfer stream (http://surfer.nmr.mgh.harvard.edu/). Data quality was checked for each MRI, and manual editing was applied to correct artifacts (movement artifacts and surfaces).

The source connectivity analysis was conducted as described in Kabbara et al. [40]. Briefly, the MRI was co-registered with the individual electrode location file in order to compute a precise forward model. A cortical mesh with 642 vertices per layer (scalp, skull, brain) was computed with the Boundary Element Method (BEM) using OpenMEEG [64]. To solve the inverse problem, the weighted Minimum Norm Estimate (wMNE) approach with constrained dipole orientations and current density maps as a measure was used. 60 seconds of the individual resting-state recording served as a noise covariance matrix. Only the diagonal elements were saved to account for variance measured at each sensor. The reconstructed time series from 15 regions of interest (ROI), which were previously identified as DMN hubs, were selected based on the Desikan-Killiany atlas and used for further analysis [40]. The phase locking value (PLV) was applied to calculate source functional connectivity in the DMN. The combination of wMNE and PLV was shown to precisely identify functional brain networks in the beta frequency band derived from scalp EEG [40,65].

The 15 ROI for the DMN were: left and right isthmus cingulate, left and right medial orbito frontal, left and right posterior cingulate, left and right precuneus, left and right rostral anterior cingulate, left and right lateral orbitofrontal, left and right parahippocampal, right caudal anterior cingulate [40]. Moreover, fMRI studies observed age and AD-related changes of the DMN in subsystems, and we therefore subdivided it into anterior and posterior [66] as well as core portions [67] (see figure 3). The anterior DMN was defined as: left and right rostral anterior cingulate cortex, left and right lateral orbito-frontal, left and right medial orbito-frontal, right caudal anterior cingulate cortex. The posterior DMN was defined as: left and right isthmus cingulate, left and right posterior cingulate cortex. The core of the DMN included the right caudal anterior cingulate cortex and the left and right posterior cingulate cortex.

>> insert figure 3 around here <<

The PLV was calculated for each of the 4 epochs, and the mean PLV of each epoch was averaged per subject. The resulting connectivity matrices were then exported for beta frequency band (14-25 Hz) [40] to MATLAB or SPSS.

Frontal midline theta examination and power analysis

After excluding electrical bridges, raw data was band-pass filtered between 2-9 Hz and exported to EEGLAB 14.1.2 [68]. Data was decomposed by using the AMICA algorithm [69], which resulted in 128 independent components. Frontal midline theta components were defined and extracted as described in [21,57]. This resulted in one frontal midline theta component per participant, from which maximum power spectral density was extracted with the Welch Method (time window = 240 s, window length = 2 s). For dipole localization, the individual components were averaged over the whole sample. The average component was localized with a single dipole in a 3-shell-sphere head model.

Graph theoretical analysis

Functional network characteristics of the DMN, based on the weighted and undirected PLV matrices, were calculated with algorithms of the Brain Connectivity Toolbox [70]. Strength was characterized as the sum of weights of edges connected to a node. An average was computed for the whole DMN and each subsystem. To evaluate strength, an absolute threshold was applied to the connectivity matrix at t = 0.95. The results were exported to SPSS for statistical analyses.

Neuropsychological tests

Executive functions were assessed with the response inhibition task (INHIB, reaction time and percentage correct responses), and the Trail Making Test part A and B (time to complete the test). Working memory was measured with the Corsi-Block Tapping Task forward (visual-spatial short term memory) and backward (visual-spatial working memory). All tests were implemented in the automated computer-based Vienna Test Battery 6.82.000 (Schuhfried GmbH, Mödling, Austria).

Statistics

SPSS 26 for Windows (IBM, Armonk, NY, United States) was used for all statistical analyses. Spearman-rank correlations were used for all correlation analyses to account for non-normal distributed variables and outliers. The Kruskal-Wallis-Test was used for detecting group differences. A significance level of $p = 0.05$ was set for all analyses. Type 1 errors were corrected with Bonferroni.

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Figure Legends

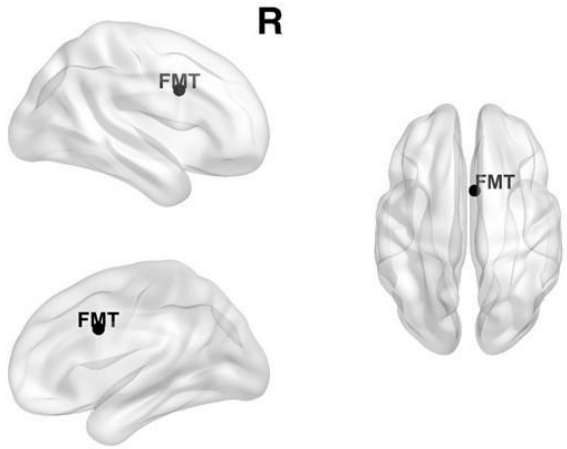

Figure 1. Localization of frontal midline theta (FMT, 4-7 Hz) based on the 22 individual components. MNI coordinates: X=4.2 Y=7.9 Z=30.8. The brain networks were visualized with the BrainNet Viewer [41]

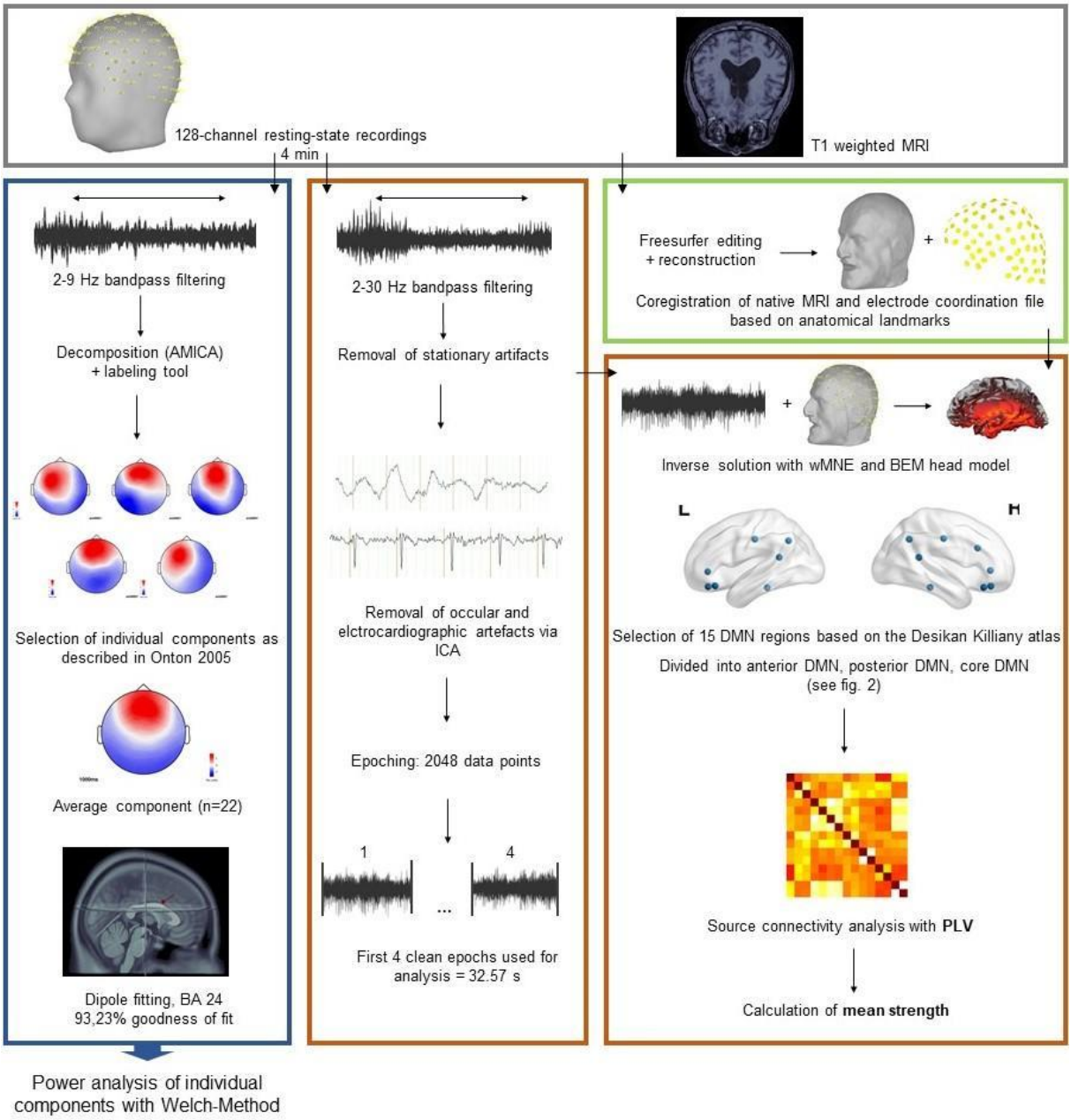

Figure 2. Data processing stream overview adapted from Kabbara et al. [40] Blue box: Determination of frontal midline theta with independent component analysis. The average component was localized within Brodman Area (BA) 24. Power spectrum density (Welch method) was used to extract relative power over the whole epoch. Orange box: Preprocessing steps and selection of epochs for source connectivity and power analysis in the Default Mode Network (DMN). Green box: Preprocessing of native MRI and co-registration with the electrode coordinates. AMICA = Adaptive Mixture Independent Component Analysis, ICA = independent component analysis, wMNE = weighted minimum norm estimation, BEM = boundary element model, PLV = Phase Locking Value

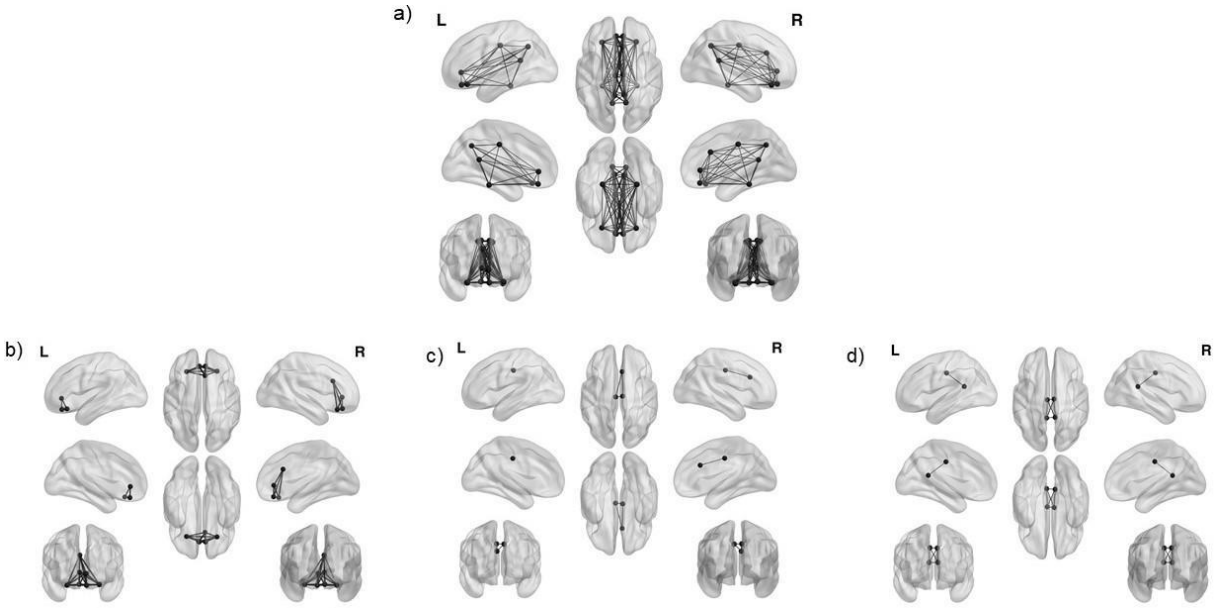

Figure 3. Analyzed subsystems of the Default Mode Network (DMN) a) All 15 regions of interest of the DMN, b) 7 regions of interest of the anterior DMN, c) 3 regions of interest for the core DMN d) 4 regions of interest for posterior DMN. The brain networks were visualized with the BrainNet Viewer [41].

Tables

	Golf-Novices	**Non-Golfer**	**p-value**
n	12	10	
gender male female	 6 6	 4 6	
age (years)	67 (4.79)	68 (3.77)	0.842
education (years)	15.17 (4.86)	12.40 (3.86)	0.165
ADAS-Cog (score)	6.75 (2.26)	6.60 (3.27)	0.789
6MWT (m)	625.94 (168.99)	699.60 (131.14)	0.102
PASE (score)	158.79 (49.96)	143.65 (47.95)	0.364
BMI	26.70 (3.76)	25.27 (2.62)	0.291
handedness (n)	left-handed: 1	left-handed: 0	

Table 1. Baseline characteristics of the participants, presented as means with standard deviation, except for gender and handedness. Group differences were tested with the Mann-Whitney U test.

ADAS-Cog = Alzheimer ’s disease Assessment Scale – Cognitive Subscale, 6MWT = 6-Minute-Walk Test, BMI = Body-Mass-Index

	Golf-Novices (n = 12)	Non-Golfer (n = 10)	Un-corrected p-value	Bonferroni-corrected p-value
Corsi forward (sequ)	7.91 (2.43)	7.60 (2.37)	0.815	
Corsi backward (sequ)	6.83 (2.17)	7.50 (3.06)	0.443	
INHIB reaction time (sec)	0.37 (0.05)	0.34 (0.05)	0.248	
INHIB correct responses (%)	94.58 (3.47)	91.90 (7.12)	0.425	
TMT A (sec)	26.58 (5.47)	27.50 (9.82)	0.817	
TMT B (sec)	48.15 (13.07)	52.72 (30.05)	0.843	
beta DMN PLV	0.27 (0.03)	0.29 (0.03)	0.107	
beta DMN strength	3.79 (0.41)	4.04 (0.39)	0.123	
beta aDMN PLV	0.41 (0.07)	0.52 (0.06)	**0.002***	**0.028***
beta aDMN strength	2.49 (0.41)	3.17 (0.39)	**0.002***	**0.028***
beta pDMN PLV	0.43 (0.07)	0.47 (0.07)	0.123	
beta pDMN strength	1.28 (0.21)	1.33 (0.31)	0.821	
beta core DMN PLV	0.32 (0.13)	0.41 (0.12)	0.107	
beta core DMN strength	0.82 (0.28)	0.83 (0.28)	0.628	

Table 2. Group differences were examined with the Mann-Whitney-U Test at a significance level of $p < 0.05$. Uncorrected and Bonferroni-corrected p-values are reported. Variables are presented as means with standard deviation. INHIB = Response Inhibition, TMT = Trail Making Test, DMN = Default Mode Network, PLV = Phase Locking Value, aDMN = anterior Default Mode Network, pDMN = posterior Default Mode Network, core DMN = caudal anterior cingulate cortex and posterior cingulate cortex

mean PLV		Golf-Novices				Non-Golfer		
		Frontal Midline Theta Power (r_s, p-value)						
DMN	**uncorrected**	-0.448 0.145	**Bonferroni-corrected**	0.176	**uncorrected**	0.310 0.383	**Bonferroni-corrected**	
aDMN		**-0.699** **0.011***				-0.182 0.614		
pDMN		-0.182 0.572				-0.030 0.934		
core DMN		**-0.650** **0.022***		0.352		-0.267 0.455		
mean strength								
DMN	**uncorrected**	-0.448 0.145	**Bonferroni-corrected**	0.240	**uncorrected**	0.310 0.383	**Bonferroni-corrected**	
aDMN		**-0.678** **0.015***				-0.091 0.802		
pDMN		-0.175 0.587				-0.109 0.763		
core DMN		-0.490 0.106				-0.006 0.987		

Table 3. Spearman correlations (r_s) between frontal midline theta power and connectivity of the DMN (Default Mode Network) for the golf-novices (n=12) and non-golfer group (n=10). *p < 0.05, aDMN = anterior Default Mode Network, pDMN = posterior Default Mode Network, core DMN = caudal anterior cingulate cortex and posterior cingulate cortex

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Additional Information

Competing interests

The golf training was financially supported by the Heinz Nixdorf Westfalian foundation. The authors declare no other conflicts of interest.

Author contributions

JKS, CG, SV, FvdB and CR contributed to the study conception and design. Data collection was performed by JKS, CG and FvdB. JKS analyzed the data and CG supported code

generation. JKS and CR wrote the first draft of the manuscript and all authors commented on previous versions. All authors read and approved the final manuscript

Ethical approval

All conducted procedures including human participants have been approved by the ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent to participate

All subjects gave their informed consent to participate prior to study inclusion.

Data availability

The data that support the findings of this study are available on reasonable request from the corresponding author (CR).