Aus der Professur für Degenerative und chronische Erkrankungen, Bewegung und der Fakultät für Gesundheitswissenschaften Brandenburg der Universität Potsdam

DISSERTATION

Kraft und Kognition

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Analyse des Zusammenhangs von muskulärer Kraftleistungsfähigkeit, funktionellen und strukturellen Gehirnparametern und kognitiver Leistungsfähigkeit

zur Erlangung des akademischen Grades

Dr. rer. medic. (Doctor rerum medicarum)

vorgelegt der Fakultät für Gesundheitswissenschaften Brandenburg

von

Fabian Herold

Datum der Promotion: 06. September 2022

Datum der Disputation: 18. Oktober 2023

Online veröffentlicht auf dem
Publikationsserver der Universität Potsdam:
https://doi.org/10.25932/publishup-61118
https://nbn-resolving.org/urn:nbn:de:kobv:517-opus4-611181

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Widmung

Diese Arbeit ist in liebevoller Erinnerung *Wilhelm Herold* und *Sherlock Archibald Bartholomiau Blättermann* gewidmet.

1. Zusammenfassung

Die in den letzten Jahren aus Querschnittstudien gewonnenen empirischen Erkenntnisse deuten auf einen Zusammenhang zwischen muskulärer Kraftleistungsfähigkeit und kognitiver Leistungsfähigkeit [a] hin [10]. Diese Beobachtung wird von Längsschnittstudien gestützt, bei denen in Folge gezielter Krafttrainingsinterventionen, welche typischerweise zur Steigerung der muskulären Kraftleistungsfähigkeit führen, Verbesserungen der kognitiven Leistungsfähigkeit dokumentiert werden konnten [11]. Die zugrundeliegenden Mechanismen, die den Zusammenhang zwischen muskulärer Kraftleistungsfähigkeit und kognitiver Leistungsfähigkeit begründen, sind jedoch noch nicht vollständig bekannt und bedürfen weiterer Forschung [10,12]. Vor diesem Hintergrund hatten die im Rahmen dieser Dissertation durchgeführten Forschungsarbeiten das übergeordnete Ziel, die Mechanismen zu untersuchen, welche den Zusammenhang zwischen der muskulären Kraftleistungsfähigkeit und der kognitiven Leistungsfähigkeit erklären können. In dieser Arbeit wurden dazu unterschiedliche Populationen (junge Menschen und ältere Menschen ohne und mit leichten kognitiven Störungen) unter Anwendung verschiedener untersuchungsmethodischer Ansätze (systematische Literaturrecherche, Doppelaufgabenparadigma und funktionelle Nahinfrarotspektroskopie) untersucht. Aufgrund der im Rahmen dieser Dissertation durchgeführten Forschungsarbeiten, die konsekutiv aufeinander aufbauen, konnten folgende Haupterkenntnisse gewonnen werden:

- Um einen umfassenden Überblick über die aktuelle Evidenzlage zum Thema Kraftleistungsfähigkeit und kognitiver Leistungsfähigkeit sowie den zugrundeliegenden neuronalen Korrelaten zu erlangen, wurde eine systematische Literaturrecherche zu diesem Forschungs-

[a] Der Begriff *Kognition* ist in der Literatur nicht einheitlich definiert [1,2] aber umfasst im Allgemeinen ein weites Spektrum von Aktivitäten und Prozessen des Gehirns bezüglich der Informationsaufnahme, -verarbeitung, -speicherung- und des Informationsabrufs [3,4]. In dieser Forschungsarbeit bezieht sich der Begriff *kognitive Leistungsfähigkeit* primär auf kognitive Funktionen und Domänen, deren Leistungsfähigkeit mit standardisierten und etablierten neuropsychologischen Tests erfasst werden kann (z.B. Mini Mental Status Test zur Erfassung der globalen kognitiven Leistungsfähigkeit [5] oder Trail Making Test A&B zur Erfassung der visuomotorischen Verarbeitungsgeschwindigkeit und der kognitiven Flexibilität [6]). In dieser Arbeit sind insbesondere die *exekutiven Funktionen* von übergeordneter Bedeutung. Der Begriff e*xekutive Funktionen* bezieht sich auf eine Reihe von höheren kognitiven Prozessen, die bei der Kontrolle und Steuerung des eigenen Verhaltens mit Ausrichtung auf ein übergeordnetes Ziel genutzt werden, wenngleich anzumerken ist, dass für exekutive Funktionen noch keine einheitliche Definition in der Literatur existiert [7-9]. Typischerweise werden den exekutiven Funktionen die drei folgenden Kernkomponenten zugeordnet: (i) Inhibition – Unterdrückung einer bestimmten Handlung, (ii) Arbeitsgedächtnis – im Form der zentralen Exekutive, die Aufmerksamkeitsressourcen adäquat auf Subprozesse aufteilt, die bei der kurzfristigen Informationsverarbeitung und -speicherung beteiligt sind - und (iii) kognitive Flexibilität – Anpassung des Denkens und Handelns an veränderte Bedingungen [9]. Als zentrales neuronales Korrelat der exekutiven Funktionen gilt der präfrontale Kortex [8].

thema durchgeführt. Die Ergebnisse dieser systematischen Literaturrecherche dokumentieren, dass ein gezieltes Krafttraining neben der Steigerung der kognitiven Leistungsfähigkeit zu funktionellen und strukturellen Veränderungen des Gehirns, insbesondere in frontalen Gehirnregionen, führen kann [13]. Ferner zeigen die Ergebnisse dieser systematischen Literaturrecherche, bei der eine begrenzte Anzahl verfügbarer Studien (n = 18) identifiziert wurde, den Bedarf weiterer Forschungsarbeiten zu diesem Themenfeld an [13].

- Zur Überprüfung der Hypothese, dass zur Ausführung von Krafttrainingsübungen höhere kognitive Prozesse benötigt werden, wurde in einer experimentellen Studie bei jüngeren gesunden Erwachsenen das Doppelaufgabenparadigma bei der Krafttrainingsübung Kniebeuge angewendet. Die in dieser Studie beobachteten Doppelaufgabenkosten bei der Ausführung der Krafttrainingsübung Kniebeuge (im Vergleich zur Kontrollbedingung Stehen) deuten auf die Beteiligung höherer kognitiver Prozesse zur Lösung dieser Bewegungsaufgabe hin und bestätigen die aufgestellte Hypothese [14].
- Um die Hypothese zu untersuchen, dass spezifische neuronale Korrelate (funktionelle Gehirnaktivität) den Zusammenhang zwischen muskulärer Kraftleistungsfähigkeit und kognitiver Leistungsfähigkeit vermitteln, wurde bei jungen gesunden Erwachsenen der Zusammenhang zwischen der Ausprägung der maximalen Handgriffkraft (normalisiert auf den Body-Mass-Index) und der kortikalen hämodynamischen Antwortreaktion untersucht, die bei der Durchführung eines standardisierten kognitiven Tests mittels funktioneller Nahinfrarotspektroskopie in präfrontalen Gehirnarealen gemessen wurde [b]. Im Rahmen dieser Querschnittsstudie konnte die initiale Hypothese nicht vollständig bestätigt werden, da zwar Zusammenhänge zwischen maximaler Handgriffkraft und kognitiver Leistungsfähigkeit mit Parametern der hämodynamischen Antwortreaktion beobachtet wurden, aber die Ausprägung der maximalen Handgriffkraft nicht im Zusammenhang mit der Kurzeitgedächtnisleistung stand [16].

[b] Zur Durchführung dieser Studie wurden in einem eigenen systematischen Übersichtsartikel, „Best-Practice“-Empfehlungen für die Datenverarbeitung der Signale der funktionellen Nahinfrarotspektroskopie erarbeitet und publiziert – siehe Referenz [15].

- Zur Untersuchung der Annahme, dass eine vorliegende neurologische Erkrankung (im Speziellen eine leichte kognitive Störung), die typischerweise mit Veränderungen von spezifischen neuronalen Korrelaten (z.B. des Hippokampus' [17-19] und des präfrontalen Kortex' [20,21]) einhergeht, einen Einfluss auf die Assoziation zwischen muskulärer Kraftleistungsfähigkeit und kognitiver Leistungsfähigkeit hat, wurde in einer Querschnittsstudie der Zusammenhang zwischen der Ausprägung der maximalen Handgriffkraft (normalisiert auf den Body-Mass-Index) und der Ausprägung der exekutiven Funktionen bei älteren Erwachsenen mit amnestischem und nicht-amnestischem Subtyp der leichten kognitiven Störung [c] sowie gesunden älteren Erwachsenen untersucht. In dieser Querschnittsstudie wurde nur bei älteren Erwachsenen mit dem amnestischen Subtyp der leichten kognitiven Störung ein Zusammenhang zwischen maximaler Handgriffkraft und exekutiven Funktionen beobachtet. Solch eine Korrelation existiert jedoch nicht bei älteren Erwachsenen mit dem non-amnestischen Subtyp der leichten kognitiven Störung oder bei gesunden älteren Erwachsenen [24].
- In einem Perspektivenartikel wurde aufgezeigt, wie durch die theoriegeleitete Nutzung physiologischer Effekte, die bei einer speziellen Krafttrainingsmethode durch die Moderation des peripheren Blutflusses mittels Manschetten oder Bändern auftreten, insbesondere Populationen mit niedriger mechanischer Belastbarkeit von den positiven Effekten des Krafttrainings auf die Gehirngesundheit profitieren könnten [25].

Insgesamt deuten die Ergebnisse der in dieser Dissertation zusammengeführten und aufeinander aufbauenden Forschungsarbeiten auf das Vorhandensein von gemeinsamen neuronalen Korrelaten (z.B. frontaler Kortex) hin, die sowohl für die muskuläre Kraftleistungsfähigkeit als auch für höhere kognitive Prozesse eine wichtige Rolle spielen [26]. Betrachtet man die in der vorliegenden Dissertation gewonnenen Erkenntnisse im Verbund mit den bereits in der Literatur existierenden empirischen Belegen, unterstützen sie die Sichtweise, dass eine relativ hohe muskuläre Kraftleistungsfähigkeit und deren Erhalt durch gezielte Krafttrainingsinterventionen über die Lebenspanne positive Effekte auf die (Gehirn-)Gesundheit haben können [27].

[c] Die Diagnose der leichten kognitiven Störung wurde im Einklang mit internationalen Leitlinien [22,23] von einem erfahrenen Neurologen gestellt. Eine Unterscheidung zwischen amnestischem („das Gedächtnis betreffend") und nicht-amnestischem Subtyp der leichten kognitiven Störung erfolgte anhand der Leistungsfähigkeit in Tests des episodischen Gedächtnisses [24].

2. Summary

In recent years, the findings from cross-sectional studies have suggested a relationship between muscular strength and cognitive performance [10]. This observation is supported by longitudinal studies in which improvements in cognitive performance have been documented in response to resistance training interventions which typically lead to an increase in muscular strength [11]. However, the underlying mechanisms that drive the association between muscular strength and cognitive performance are yet not fully understood and require further research [10,12]. With this in mind, the research conducted in this dissertation aimed to investigate the mechanisms that can explain the associations between muscular strength and cognitive performance. In this work, different populations (i.e., younger adults, and older adults without and with mild cognitive impairment) were studied using several methodological approaches (i.e., systematic literature review, dual-task paradigm, and functional near-infrared spectroscopy). The following key findings have emerged from the research that has been conducted in the context of this dissertation:

- In order to obtain a comprehensive overview of the current state of evidence regarding the associations of muscular strength and cognitive performance, as well as the underlying neuronal correlates, a systematic literature review has been conducted. The results of this systematic literature review revealed that resistance training not only improves cognitive performance but also leads to functional and structural changes in the brain, particularly in frontal brain regions [13]. Furthermore, the limited number of available studies (n = 18) that have been identified in the course of this systematic review, suggests that further research on this topic is necessary to draw more robust conclusions [13].
- To test the hypothesis that higher-level cognitive processes are required to perform resistance exercises, we conducted in younger adults an experimental study in which we utilized the dual-task paradigm while participants performed squats. In this study, we observed cognitive dual-task costs during the squatting condition (as compared to the control condition standing). The latter finding points towards an involvement of higher cognitive processes in the motor control of squats and confirms our above-stated hypothesis [14].

- To investigate the hypothesis that specific neural correlates (functional brain activity) mediate the relationship between muscular strength and cognitive performance, we studied in healthy younger adults the relationship between maximal handgrip strength (normalized to body mass index) and the cortical hemodynamic response measured in prefrontal brain areas during the performance of a standardized cognitive test by applying functional near-infrared spectroscopy. In this cross-sectional study, the initial hypothesis was only partly confirmed as we observed correlations between maximal handgrip strength and cognitive performance with parameters of the cortical hemodynamic response. However, we did not find compelling evidence for a relationship between maximal handgrip strength and short-term memory performance nor for a mediation [16].
- To investigate the hypothesis that the presence of a neurological disorder (in particular mild cognitive impairment), which is typically linked to changes in specific neural correlates (e.g. of the hippocampus [17-19] and prefrontal cortex [20,21]), has an effect on the association between muscular strength and cognitive performance, we studied in older adults with amnestic and non-amnestic subtypes of mild cognitive impairment and healthy older adults possible group differences concerning the associations between maximal handgrip strength (normalized to body mass index) and executive functions. In this cross-sectional study, a correlation between maximal handgrip strength and executive functions was only observed in older adults with the amnestic subtype of mild cognitive impairment. However, such a correlation was not noticed in older adults with the non-amnestic subtype of mild cognitive impairment or healthy older adults [24].
- In a perspective article, we provide a theory-driven rationale on how the physiological processes induced by a novel resistance training method that is based on the modulation of the peripheral blood flow by applying cuffs or bands (also known as blood flow restriction training; BFR) can be a promising intervention strategy to foster brain health, especially in populations with low mechanical stress tolerance [25].

Taken together, the results of the research being described and summarized in this dissertation suggest that the association between muscular strength and higher cognitive processes relies

upon shared neural correlates (e.g., frontal cortex) [26]. In conjunction with the empirical evidence that already exists in the scientific literature, the findings of the studies presented in this dissertation support the view that a relatively high level of muscular strength and its preservation over the lifespan by means of resistance training can have positive effects on (brain) health [27].

3. Manteltext

3.1. Einleitung und Präsentation der Publikationen

Im Zuge des demografischen Wandels wird weltweit [28] und auch insbesondere in Deutschland [29] die absolute und relative Anzahl älterer Menschen (älter als 60 Jahre [30]) in der Bevölkerung stark ansteigen. Da ein höheres Lebensalter als einer der bedeutendsten Risikofaktoren für verschiedene Erkrankungen gilt (z.B. für demenzielle Erkrankungen wie Alzheimer [31]), wird einhergehend mit der Verschiebung der gesellschaftlichen Altersstruktur auch die Zunahme der Anzahl von Menschen, die an altersbedingten Erkrankungen leiden, prognostiziert. Beispielsweise deuten Hochrechnungen auf einen Anstieg der absoluten Anzahl demenzieller Erkrankungen von weltweit circa 57,4 Millionen Fällen im Jahr 2019 auf circa 152,8 Millionen Fälle im Jahr 2050 hin [32]. In Deutschland wird erwartet, dass die Zahl der von Demenz Betroffenen von circa 1,5 Millionen im Jahr 2018 auf etwa 2,4 bis 2,8 Millionen Fälle im Jahr 2050 anwächst [32,33]. Durch den krankheitsbedingten und progredienten Rückgang der kognitiven Leistungsfähigkeit und den damit verbunden Autonomieverlust [31] stellen demenzielle Erkrankungen nicht nur für den Betroffenen und dessen Angehörige eine große Belastung dar, sondern sind durch die pflegeaufwendige und kostenintensive Versorgung (insbesondere in fortgeschrittenen Krankheitsstadien) auch eine große Herausforderung für die Ressourcen der Gesundheits- und Sozialsysteme [34-36].

Um den wachsenden Herausforderungen entgegenwirken zu können, die mit dem prognostizierten Anstieg demenzieller Erkrankungen entstehen, kommt insbesondere präventiven Interventionsansätzen eine bedeutende Rolle zu [36-39], die ein gesundes Altern durch die positive Beeinflussung von Lebensstilfaktoren (z.B. Ernährung, Schlaf und regelmäßige körperliche Aktivität) ermöglichen wollen [37-39], weil derzeitig verfügbare pharmakologische Ansätze zur Behandlung demenzieller Erkrankungen nur eine begrenzte Wirksamkeit zeigen [40]. In diesem Kontext weisen Studienergebnisse darauf hin, dass circa ein Drittel der Demenzfälle auf modifizierbare Risikofaktoren (z.B. körperliche Inaktivität, Rauchen) zurückgeführt werden kann [39,41]. Innerhalb der modifizierbaren Risikofaktoren nimmt vor allem der Risikofaktor körperliche Inaktivität eine zentrale Rolle ein [39,41], da nach neueren Berechnungen circa 217.000 der 305.000 in Deutschland auftretenden Fälle diesen modifizierbaren Risikofaktoren zugeordnet werden können [39]. Bei einer

Halbierung der Prävalenzrate des Risikofaktors körperliche Inaktivität könnten rechnerisch circa 95.000 Fälle der Demenz des Alzheimer-Typs in Deutschland vermieden werden (bezogen auf eine Prävalenz von 1 Millionen Fälle) [39]. Diese Beobachtung passt zu den Ergebnissen internationaler Studien, die von einem positiven Zusammenhang zwischen regelmäßiger körperlicher Aktivität (beispielsweise in Form eines körperlichen Trainings) und niedrigerem Risiko an Demenz zu erkranken [42,43] sowie einem positiven Einfluss auf die Leistungsfähigkeit von kognitiven Domänen (z.B. Merkfähigkeit) [44,45] berichten, deren Ausprägung typischerweise durch demenzielle Erkrankungen deutlich vermindert ist [31].

Zusammenfassend lässt sich festhalten, dass sich ein aktiver Lebensstil, der durch regelmäßige körperliche Aktivität (z.B. in Form eines körperlichen Trainings) gekennzeichnet ist, positiv auf ein gesundes (kognitives) Altern auswirken kann. Hinsichtlich der optimalen Belastungsnormative (z.B. Art der Körperübung, Trainingshäufigkeit), die zur Verbesserung oder dem Erhalt der kognitiven Leistungsfähigkeit durch körperliche Trainingsinterventionen berücksichtigt werden sollten, sind gegenwärtig kaum Erkenntnisse vorhanden [37,38]. Die bisherige Forschung in diesem Bereich hat sich anfangs stark auf den Zusammenhang zwischen kardiorespiratorischer Fitness und den Effekten von Ausdauertrainingsinterventionen fokussiert [27,44]. Jüngere Erkenntnisse weisen jedoch auch darauf hin, dass auch muskuläre Kraftleistungsfähigkeit [10] sowie ein gezieltes Krafttraining [11], das typischerweise zur Steigerung der muskulären Kraftleistungsfähigkeit führt, mit einer besseren kognitiven Leistungsfähigkeit assoziiert sind beziehungsweise zur Verbesserung dieser beitragen können. In diesem Kontext sind die Mechanismen, die den Zusammenhang zwischen körperlicher Fitness (z.B. kardiorespiratorischer, muskulärer oder motorischer Fitness) oder den Effekten von körperlichem Training (z.B. Ausdauertraining oder Krafttraining) auf die kognitive Leistungsfähigkeit erklären können, sowohl generell als auch in Bezug auf die muskuläre Kraftleistungsfähigkeit oder das Krafttraining noch nicht vollständig verstanden [45,46]. Zur umfassenderen Aufklärung und Kennzeichnung dieser Mechanismen wurde von Stillman und Kollegen [46] ein Modell postuliert, das aus drei Analyseebenen besteht (siehe Abbildung 1).

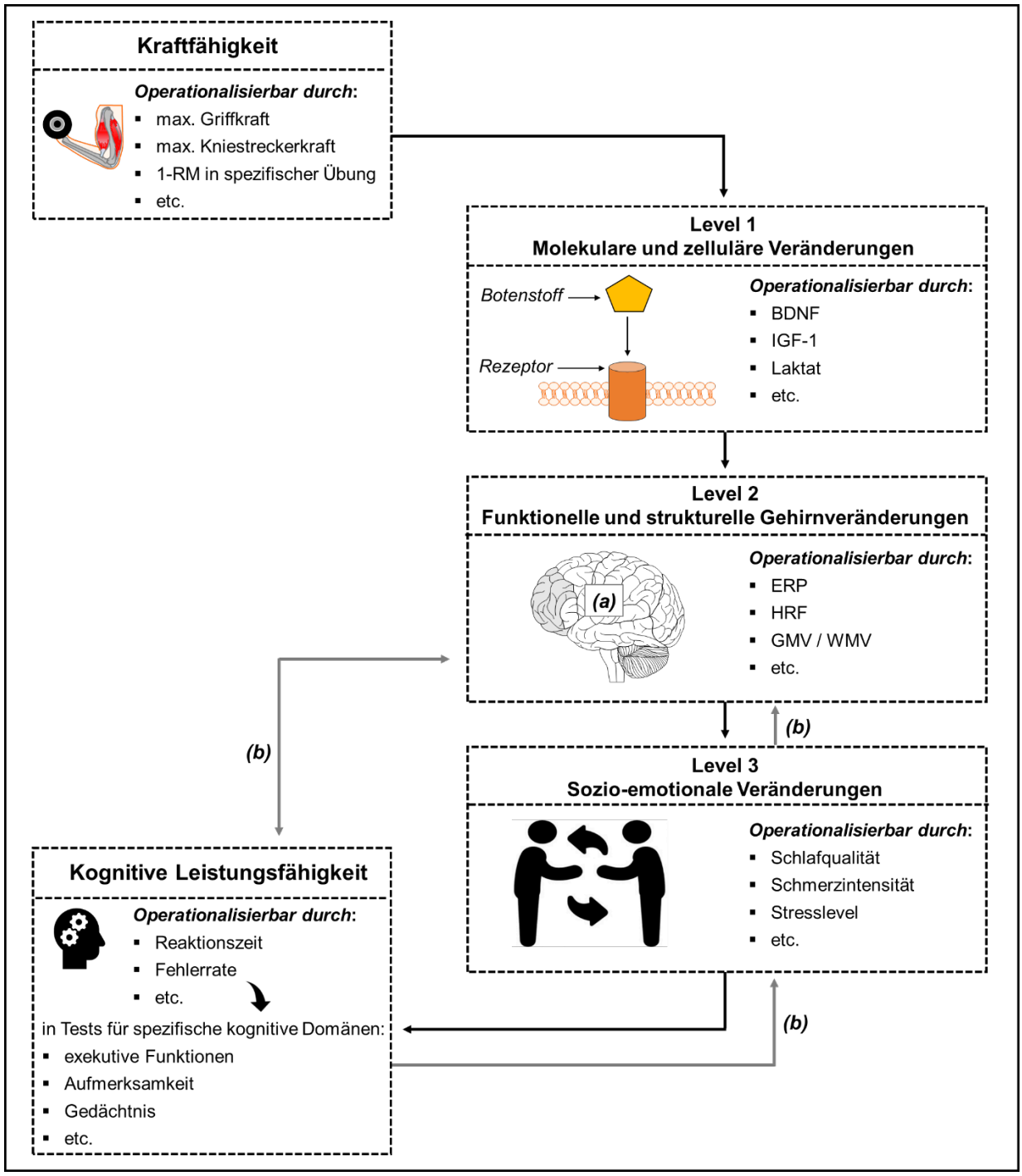

Abbildung 1: *Schematische Darstellung der Analyseebenen nach Stillman et al., [46] in Anlehnung an Herold et al., [13]. 'a' zeigt an, dass gehirnspezifische Parameter Ergebnis, Mediator und Prädiktor sein können [47]. 'b' zeigt an, dass strukturelle und funktionelle Gehirnveränderungen, sozi-emotionale Veränderungen und Veränderungen der kognitiven Leistungsfähigkeit eng miteinander verflochten sein können [47]. 1-RM: englisch: one-repetition-maximum, deutsch: Einer-Wiederholungs-Maximum; BDNF: englisch brain-derived neurotrophic factor, deutsch: vom Gehirn stammender Wachstumsfaktor; ERP: englisch: event-related potentials, deutsch: ereigniskorrelierte Potentiale; HRF: englisch: hemodynamic response function, deutsch: hämodynamische Antwortreaktion; max. englisch/deutsch: maximal GMV: englisch: grey matter volume, deutsch: Volumen der grauen Substanz; IGF-1: englisch: insulin-like growth factor 1, deutsch: insulinähnlicher Wachstumsfaktor 1; WMV: englisch: white matter volume, deutsch: Volumen der weißen Substanz.*

Im Hinblick auf das Krafttraining gibt es einige Forschungsarbeiten, die den Einfluss auf *molekulare und zelluläre Veränderungen* (z.B. Veränderungen von Myokinen [d], wie des brain-derived neurotropic factors [BDNF]) [49] und auf *sozio-emotionale Veränderungen* (z.B. Schlaf) [50] untersuchten, wenngleich nicht immer ein direkter Zusammenhang zur kognitiven Leistungsfähigkeit hergestellt wurde. Inwieweit Zusammenhänge zwischen muskulärer Kraftleistungsfähigkeit, *funktionellen und strukturellen Gehirnveränderungen* und kognitiver Leistungsfähigkeit bestehen, wurde noch nicht umfassend erforscht [13] und ist deshalb Gegenstand dieser Forschungsarbeit.

Um einen umfassenden Überblick über die verfügbare Evidenz bezüglich der neuronalen Korrelate zu erlangen, die den Zusammenhang zwischen muskulärer Kraftleistungsfähigkeit und kognitiver Leistungsfähigkeit vermitteln, wurde im Rahmen dieser Dissertation eine systematische Literaturrecherche zu diesem Forschungsthema durchgeführt [13]. Der Fokus dieser systematischen Literaturrecherche lag auf den Effekten von akutem und chronischem (regelmäßigem) Krafttraining auf funktionelle und strukturelle Gehirnveränderungen, unter Berücksichtigung der Auswirkungen auf die kognitive Leistungsfähigkeit [13]. Einerseits zeigen die Ergebnisse dieser systematischen Literaturrecherche, dass ein gezieltes Krafttraining neben der Steigerung der kognitiven Leistungsfähigkeit auch zu ausgeprägten funktionellen und strukturellen Gehirnveränderungen, primär in frontalen Kortexregionen, führen kann [13]. Anderseits verdeutlichen die Ergebnisse dieser Literaturrecherche auch, dass es derzeitig nur eine geringe Anzahl von Studien gibt, die die neuronalen Korrelate (funktionelle und strukturelle Gehirnveränderungen), welche die positive Assoziation zwischen muskulärer Kraftleistungsfähigkeit oder die positiven Effekte eines Krafttrainings auf die kognitive Leistungsfähigkeit erklären können, untersucht haben [13]. Insbesondere für die Population von jungen bis mittelalten Erwachsenen liegen kaum Forschungsarbeiten vor [13], was sich mit den Erkenntnissen anderer Übersichtsarbeiten deckt [45]. Deshalb wurde im Rahmen dieser Forschungsarbeit in einer Querschnittsstudie bei gesunden jüngeren Erwachsenen untersucht, inwieweit ein Zusammenhang zwischen muskulärer Kraftleistungs-

[d] Myokine sind Proteine (z.B. Botenstoffe), die von der Skelettmuskulatur bei Aktivität (Bewegung) freigesetzt werden und autokrin (in der selben Zelle), parakrin (auf benachbarte Zellen) oder endokrin (durch die Freisetzung in die Blutbahn auf weiter entfernte Zellen) wirken können [48].

fähigkeit (operationalisiert durch maximale Handgriffkraft, die auf den Body-Mass-Index normalisiert wurde), funktionellen Gehirnaktivitätsmustern und Kurzeitgedächtnisleistungsfähigkeit besteht [16]. In dieser Studie wurden funktionelle Gehirnveränderungen mittels funktioneller Nahinfrarotspektroskopie untersucht, für die in einer eigenständigen Publikation Empfehlungen hinsichtlich der Datenverarbeitung erarbeitet wurden [15]. In dieser Querschnittsstudie wurde bei jungen gesunden Erwachsenen schwache bis moderate Korrelationen zwischen der Ausprägung der Handgriffkraft und funktionellen Gehirnaktivitätsveränderungen in präfrontalen Kortexregionen beobachtet [16]. Ein Zusammenhang zwischen Handgriffkraft und Kurzeitgedächtnisleistung sowie ein statistischer Beleg, dass die funktionelle Gehirnaktivität als Mediator zwischen Handgriffkraft und Kurzzeitgedächtnisleistung fungiert, konnten nicht registriert werden [16]. Diese Ergebnisse hängen möglicherweise mit der hohen kognitiven Ausgangsleistungsfähigkeit der Teilnehmenden zusammen [16]. Außerdem passen diese Studienergebnisse zu den Beobachtungen einer anderen Querschnittsstudie, bei der ein Zusammenhang von Handgriffkraft und kognitiver Leistungsfähigkeit erst bei Erwachsenen mittleren Alters (45 bis 65 Jahre alt), jedoch nicht bei jüngeren Erwachsenen (20 bis 30 Jahre alt) festgestellt wurde [51].

Die Ergebnisse der durchgeführten Querschnittsstudie sind insgesamt somit teilweise im Einklang mit den Erkenntnissen der eigenen systematischen Literaturrecherche [13] und den Annahmen anderer Autoren, die postulieren, dass muskuläre Kraftleistungsfähigkeit und höhere kognitive Prozesse zumindest teilweise auf die Funktion derselben neuronalen Korrelate angewiesen sind (z.B. Integrität [e] der frontalen Kortexregionen) [11,26]. Diesbezüglich wird vermutet, dass insbesondere die kognitiven Domänen von einem Krafttraining profitieren, deren zugrundeliegende neuronale Korrelate während des Krafttrainings beansprucht werden (z.B. exekutive Funktionen, die von der Leistungsfähigkeit des präfrontalen Kortex abhängig sind) [11]. Letztere Vermutung wird durch die Ergebnisse einer im Rahmen dieser Forschungsarbeit durchgeführten Studie unterstützt, in der bei jüngeren gesunden Erwachsenen während der Ausführung der Krafttrainingsübung Kniebeuge kognitive Doppelaufgabenkosten (geringere Anzahl von richtigen Antworten)

[e] Der Begriff *Integrität* bezieht sich in dieser Dissertation auf die Intaktheit bzw. physiologisch normale Funktionsweise eines spezifischen Teils des zentralen Nervensystems. Zur besseren Lesbarkeit dient *Integrität* als Oberbegriff, der strukturelle Integrität (z.B. operationalisiert durch Volumen der grauen Substanz) und die funktionelle Integrität (z.B. operationalisiert durch Ausprägung der Amplitude der hämodynamischen Antwortreaktion bei einer standardisierten kognitiven Aufgabe) einschließt.

während der Ausführung der Kniebeugeübung im Vergleich zur Kontrollbedingung Stehen beobachtet wurden [14]. Diese Doppelaufgabenkosten deuten auf die Involvierung exekutiver Prozesse bei der Ausführung der Kniebeuge hin [14], die typischerweise als Leistung des präfrontalen Kortex angesehen werden [8,52]. Die Schlussfolgerung, dass insbesondere der präfrontale Kortex ein gemeinsames neuronales Korrelat für muskuläre Kraftleistungsfähigkeit und höhere kognitive Prozesse ist [26], wird auch durch die Ergebnisse einer im Rahmen dieser Forschungsarbeit durchgeführten Querschnittsstudie unterstützt [24]. In dieser Querschnittstudie traten signifikante Korrelationen zwischen Handgriffkraft und exekutiver Leistungsfähigkeit nur in der Kohorte der älteren Probanden mit amnestischer leichter kognitiver Störung, jedoch nicht bei gesunden älteren Erwachsenen oder älteren Erwachsenen mit nicht-amnestischer leichter kognitiver Störung auf [24]. In Übereinstimmung mit der Idee gemeinsamer neuronaler Korrelate zwischen muskulärer Kraftleistungsfähigkeit und höherer kognitiver Funktionen [26], könnte diese Beobachtung auf die bei älteren Erwachsenen mit amnestischer leichter kognitiver Störung im Vergleich zu gesunden älteren Erwachsenen auftretende Atrophie präfrontaler Kortexareale zurückgeführt werden, die mit der exekutiven Leistungsfähigkeit korreliert [20].

In der Literatur und in eigenen Arbeiten ist dokumentiert, dass ein Krafttraining nicht nur bei gesunden, sondern auch bei erkrankten Populationen (z.B. ältere Menschen mit leichten kognitiven Störungen) zur Steigerung der exekutiven und globalen kognitiven Leistungsfähigkeit [11,13,53] sowie zu funktionellen und strukturellen Veränderungen insbesondere frontaler Kortexregionen führen kann [13]. In diesem Kontext wurde im Rahmen dieser Forschungsarbeit innerhalb eines Perspektivenartikels diskutiert, wie ein Krafttraining durch den Einsatz von Blutflussmoderationstechniken angepasst werden kann, welche den peripheren Blutfluss durch die Applikation von Manschetten oder Bändern beeinflussen, um es auch Personen mit eingeschränkter mechanischer Belastbarkeit (z.B. ältere Menschen mit chronischen Gelenkschmerzen) zu ermöglichen, von den positiven Effekten eines Krafttrainings auf die Gehirngesundheit zu profitieren [25].

Zudem wurde im Einklang mit der Literatur, die sich bis jetzt primär auf die Analyse von Verhaltensdaten fokussiert hat [11,53], auch in eigenen Arbeiten festgestellt [13], dass hinsichtlich der Dosis-Wirkungs-Beziehung (z.B. Auswirkungen der gezielten Manipulation von Übungs- und Trainings-

variablen eines Krafttrainings) und der Aufklärung zugrundeliegender Mechanismen (z.B. funktionelle und strukturelle Gehirnveränderungen) noch weiterer Forschungsbedarf besteht. Weitere Forschung zu diesem Themenfeld ist insbesondere vor dem Hintergrund der Herausforderungen, die im Zuge des demografischen Wandels hinsichtlich der Beanspruchung der Ressourcen der Gesundheits- und Sozialsysteme auftreten werden, von übergeordneter gesamtgesellschaftlicher Bedeutung.

3.2. Diskussion

Die übergeordnete Zielstellung der im Rahmen dieser Forschungsarbeit durchgeführten Untersuchungen war die Kennzeichnung der Mechanismen, die den Zusammenhang zwischen der muskulären Kraftleistungsfähigkeit und der kognitiven Leistungsfähigkeit erklären können. Die Ergebnisse der durchgeführten Untersuchungen deuten auf das Vorhandensein von gemeinsamen neuronalen Korrelaten (z.B. präfrontaler Kortex) hin, die sowohl für die muskuläre Kraftleistungsfähigkeit als auch für höhere kognitive Prozesse eine wichtige Rolle spielen [26]. Diesbezüglich implizieren die Ergebnisse eigener Studien, bei denen sowohl bildgebende Verfahren (z.B. funktionelle Nahinfrarotspektroskopie) [16] als auch Verhaltenstests [14,24], die typischerweise kognitiven Domänen des präfrontalen Kortex (z.B. exekutiven Funktionen) zugeordnet werden, genutzt wurden, dass insbesondere letztgenannte Kortexregion ein gemeinsames neuronales Korrelat muskulärer Kraftleistungsfähigkeit und höherer kognitiver Funktionen sein könnte.

Der präfrontale Kortex ist Teil des Frontallappens und befindet sich an der Stirnseite des menschlichen Gehirns. Er weist verzweigte Verbindungen zu subkortikalen Arealen auf (z.B. hippokampales-präfrontales Netzwerk) und ist im Vergleich zu anderen Gehirnregionen (z.B. primär visueller Kortex) stark von altersbedingten strukturellen [54] und funktionellen [55] Veränderungen betroffen. Der präfrontale Kortex wird typischerweise mit der Leistungsfähigkeit der exekutiven Funktionen assoziiert [56], wenngleich neuere Forschungsarbeiten auch eine Beteiligung an anderen kognitiven Prozessen wie Arbeitsgedächtnisleistung nahelegen [56,57]. Bisherige Untersuchungen dokumentieren eine altersbedingte Abnahme der Leistungsfähigkeit der exekutiven Funktionen und des Gedächtnisses [58,59]. Dies ist insbesondere vor dem Hintergrund, dass bei älteren Menschen beispielsweise Korrelationen zwischen einer niedrigeren Ausprägung der exekutiven Funktionen

mit einem erhöhten Sturzrisiko [60], mit einem erhöhtem Unfallrisiko [61] und einer niedrigen (Lifespace-)Mobilität [62] bestehen, als praktisch relevant im Kontext des gesunden und autonomen Alterns zu bewerten. Folglich scheint es für ein gesundes und autonomes Altern wichtig, die neuronalen Korrelate, die diesem kognitiven Prozess zugrunde liegen, zu erhalten beziehungsweise frühzeitig Personen zu identifizieren, die aufgrund funktioneller und struktureller Gehirnveränderungen ein erhöhtes Risiko aufweisen, Leistungseinbußen in diesen kognitiven Funktionen zu erleiden.

Aufgrund der positiven Korrelation zwischen höherer Handgriffkraft und besserer kognitiver Leistungsfähigkeit sowie der Einfachheit der Erhebung von Handgriffkraft, gilt die Handgriffkraft als vielversprechender, wenngleich derzeitig noch nicht vollständig in der klinischen Routine etablierter Prädiktor zur frühzeitigen Identifikation und Risikostratifizierung von älteren Erwachsenen bezüglich des individuellen Risikos für altersbedingte kognitive Leistungseinbußen und für das Auftreten neurologischer Erkrankungen (z.B. demenzieller Erkrankungen wie Alzheimer) [10,63,64]. Beispielsweise deuten jüngere Studiendaten darauf hin, dass Erwachsene mit einer relativ niedrigen Handgriffkraft (niedrigstes Quintil) im Vergleich zu Erwachsenen mit relativ hoher Hangriffkraft (höchstes Quintil) ein um 72% erhöhtes Risiko für das Auftreten einer demenziellen Erkrankung aufweisen [65] und eine Abnahme der Handgriffkraft um je 5 kg mit einer je 14-prozentigen Zunahme des Risikos für dementielle Erkrankungen assoziiert ist [65]. Letztere Studienergebnisse unterstützen eindeutig die wichtige Rolle, die eine regelmäßige Erhebung der muskulären Leistungsfähigkeit (z.B. Hanggriffkraft) bei der Identifikation von Erwachsenen mit einem höheren Risiko für kognitive Leistungseinbußen und neurologische Erkrankungen spielen könnte, wenngleich die zugrundeliegenden Mechanismen, die die beobachtete Korrelation kausal vermitteln, noch relativ unbekannt sind [10,63,64].

Entsprechend dem Interpretationsansatz, der den Zusammenhang von muskulärer Kraftleistungsfähigkeit (z.B. operationalisiert durch die Handgriffkraft) und kognitiver Leistungsfähigkeit (z.B. exekutive Funktionen) durch das Vorhandensein gemeinsamer neuronaler Korrelate (z.B. präfrontaler Kortex) erklärt werden kann [26], deutet im Umkehrschluss die Veränderung der Hangriffkraft auch auf die Veränderung der Integrität spezifischer neuronaler Strukturen hin, obwohl zur Prüfung letzterer Annahme noch weitere Forschung notwendig ist [10,26]. Basierend auf der

Korrelation zwischen der Ausprägung der Handgriffkraft und des rechten Hippokampusvolumens [66], könnte vermutet werden, dass die Handgriffkraft möglicherweise nicht nur ein Indikator für funktionelle Veränderungen des präfrontalen Kortex, sondern ebenso für die Veränderungen des hippokampalen-präfrontalen Netzwerks ist. Dieser Interpretationsansatz wird im Allgemeinen durch die Beobachtung unterstützt, dass auch andere Indikatoren der muskulären Kraftleistungsfähigkeit (im Speziellen Kraft des Kniestreckers) mit dem Hippokampusvolumen korrelieren [67]. Zudem deuten auch die Ergebnisse einer eigenen Studie, bei der nur bei älteren Erwachsenen mit amnestischer kognitiver Störung signifikante Korrelationen zwischen Handgriffkraft und exekutiver Leistungsfähigkeit, aber nicht bei älteren gesunden Erwachsenen und älteren Erwachsenen mit non-amnestischer leichter kognitiver Störung, beobachtet wurden, entsprechend der im Nachfolgenden präsentierten Evidenz auf eine Verbindung von Hippokampus und muskulärer Kraftleistungsfähigkeit (z.B. operationalisiert durch Handgriffkraft) hin [24]. Neben der Volumenabnahme der grauen Substanz des präfrontalen Kortex, die mit der Abnahme der exekutiven Leistungsfähigkeit korreliert [20], ist bei älteren Erwachsenen mit amnestischer leichter kognitiver Störung im Vergleich zu älteren gesunden Menschen und älteren Menschen mit non-amnestischer leichter kognitiver Störung auch eine ausgeprägte Hippokampusvolumenabnahme detektierbar [17]. Entsprechend der Zusammenhänge zwischen exekutiven Funktionen und Hippokampus [68-70] sowie zwischen Hippokampusvolumen und maximaler Handgriffkraft [66] könnten die Ergebnisse unserer Querschnittsstudie dahingehend interpretiert werden, dass bei älteren Erwachsenen mit amnestischer leichter kognitiver Störung neben dem präfrontalen Kortex auch der Hippokampus als neuronales Korrelat, welches den Zusammenhang zwischen muskulärer Kraftleistungsfähigkeit und kognitiver Leistungsfähigkeit vermittelt, in Betracht gezogen werden muss. Diese Annahme passt zur Evidenz, dass neben exekutiven Dysfunktionen [71,72] sowohl eine niedrige Handgriffkraft [10,63,64] als auch Veränderungen des Hippokampus‘ [73-77] sowie das Auftreten von Sarkopenie [f] [79,80] als Prädikatoren für ein erhöhtes Risiko der Herausbildung manifester kognitiver Störungen und neurologischer Erkrankungen (z.B. demenzielle Erkrankungen wie Alzheimer) gelten.

[f] Sarkopenie bezeichnet eine progrediente und generalisierte Skelettmuskelerkrankung, die durch eine verminderte muskuläre Kraftleistungsfähigkeit (z.B. operationalisiert durch maximale Handgriffkraft) gekennzeichnet ist und deren Diagnose durch das Vorliegen einer verminderten Muskelmasse (z.B. operationalisiert durch dual energy X-ray absorptiometry, DEXA) konfirmiert wird [78]. Der Schweregrad der Sarkopenie wird durch die Einschränkungen der körperlichen Leistungsfähigkeit (z.B. operationalisiert durch Ganggeschwindigkeit) determiniert [78].

Inwieweit tatsächlich ein direkter Zusammenhang zwischen maximaler Handgriffkraft und kognitiver Leistungsfähigkeit vorliegt (z.B. durch gemeinsame neuronale Korrelate) muss noch durch weiterführende Untersuchungen unter Einsatz bildgebender Verfahren [13,16] und unter Berücksichtigung des verzerrenden Effektes weiterer Einflussvariablen vertiefend erforscht werden, die mit der Ausprägung der Handgriffkraft assoziiert sind (z.B. metabolische oder psychologische Risikofaktoren, wie Bluthochdruck und Depressionsschwere) [81,82]. Diesbezüglich sollten in zukünftigen Untersuchungen neben der maximalen Handgriffkraft auch andere Kenngrößen der muskulären Kraftleistungsfähigkeit erfasst (z.B. Kraftsymmetrie – Unterschied zwischen dominanter und nicht-dominanter Extremität) und der Einfluss unterschiedlicher Normalisierungsmethoden (z.B. Normalisierung der Hangriffkraft auf die Muskelmasse) geprüft werden, um ein umfassenderes Verständnis der Zusammenhänge zwischen muskulärer Kraftleistungsfähigkeit (z.B. Handgriffkraft), gesundheitsbezogenen Parametern (z.B. kognitive Leistungsfähigkeit) und der zugrundeliegenden Mechanismen (z.B. gemeinsame neuronale Korrelate) zu erlangen [83-85]. Zur umfassenderen Aufklärung möglicher kausaler Zusammenhänge zwischen muskulärer Kraftleistungsfähigkeit, funktionellen und strukturellen Gehirnparametern und kognitiver Leistungsfähigkeit sind auch Interventionsstudien von entscheidender Bedeutung.

Bisherig publizierte Interventionsstudien, die die Auswirkungen eines Krafttrainings auf die kognitive Leistungsfähigkeit und auf Veränderungen der funktionellen und strukturellen Gehirnparameter untersuchen und deren Ergebnisse in einer eigenen systematischen Literaturübersichtsarbeit zusammengefasst wurden [13], unterstützen die Annahme, dass ein Zusammenhang zwischen muskulärer Kraftleistungsfähigkeit und der Integrität des hippokampalen-präfrontalen Netzwerks besteht [86,87]. Zum Beispiel konnte bei älteren Erwachsenen mit leichter kognitiver Störung, die an einer 26-wöchigen Krafttrainingsintervention teilnahmen, bei der zwei bis drei Mal pro Woche für jeweils 90 Minuten trainiert wurde, im Vergleich zu einer Kontrollintervention neben den Verbesserungen der globalen und exekutiven Leistungsfähigkeit auch der Erhalt des Volumens spezifischer Hippokampusfelder dokumentiert werden [86]. Bei älteren gesunden Erwachsen wurde in Folge eines 52-wöchigen Krafttrainings, welches zwei Mal pro Woche für jeweils 60 Minuten durchgeführt wurde, im Vergleich zu einer Kontrollintervention eine Verbesserung der exekutiven Leistungsfähigkeit [87,88] und eine Veränderung der funktionellen Aktivitätsmuster des frontalen

Kortex (z.B. orbiofrontaler Kortex) beobachtet [87], die während des Flanker-Tests aufgezeichnet wurden. In letztgenannter Krafttrainingsinterventionsstudie wurde jedoch kein Hinweis für einen direkten Zusammenhang von veränderten Gehirnaktivitätsmustern und der Verbesserung der kognitiven Leistungsfähigkeit gefunden [87], was sich mit den Ergebnissen der vorliegenden Querschnittsstudie dieser Arbeit deckt [16]. Diese Ergebnisse legen die Schlussfolgerung nahe, dass eine Veränderung der funktionellen Gehirnaktivität nicht zwangsläufig mit einer Veränderung der kognitiven Leistungsfähigkeit assoziiert ist beziehungsweise zu dieser führt. Diese Beobachtung könnte auf vielfältige Ursachen zurückgeführt werden (z.B. Deckeneffekte bei bestimmten Populationen, fehlende Sensitivität des Operationalisierungsparameters). Beispielsweise könnte das Fehlen eines linearen Zusammenhangs zwischen funktionellen Gehirnveränderungen und Verhaltensleistung darin begründet liegen, dass die Interpretation funktioneller Gehirnaktivitätsveränderungen vielschichtig und individuell ist und nicht generell eine höhere Gehirnaktivität als „vorteilhaft“ sowie vice versa eine niedrigere Gehirnaktivität als „unvorteilhaft“ gewertet werden kann. Letztere Auslegung (niedrigere Gehirnaktivität ist „unvorteilhaft“) kann zu inadäquaten Schlussfolgerungen führen, da eine niedrigere Gehirnaktivität bei hohen Verhaltensleistungen auch auf eine bessere neurale Effizienz hindeuten kann und dementsprechend als „vorteilhaft“ bewertet werden müsste [89]. Aufgrund der geringen Anzahl verfügbarer Studien, die Zusammenhänge zwischen der Ausprägung der muskulären Kraftleistungsfähigkeit, funktionellen und strukturellen Gehirnveränderungen sowie kognitiver Leistungsfähigkeit untersuchen, ist eine abschließende Schlussfolgerung nicht möglich. Deshalb ist weitere Forschung notwendig, um die bestehende Evidenz zu erweitern und um die Verbindung zwischen den Analyseebenen zu erforschen [13]. Diesbezüglich sollten vor allem die neurobiologischen Mechanismen (Level 1 – Molekulare und zelluläre Veränderungen, siehe Abbildung 1) weiter erforscht werden [13], die die funktionellen und strukturellen Gehirnveränderungen hervorrufen. Tierstudien liefern erste Hinweise darauf, dass sich die neurobiologischen Signalwege zwischen Ausdauertraining und Krafttraining unterscheiden könnten, wobei ausdauertrainings-induzierte Gehirnveränderungen primär über die Konzentrationsveränderungen des BDNF und krafttrainings-induzierte Gehirnveränderungen primär über Konzentrationsveränderungen des insulinähnlichen Wachstumsfaktors (IGF-1) induziert werden [90]. Inwieweit diese Erkenntnisse auf den Menschen übertragbar sind, ist derzeitig relativ unklar,

da beim Menschen die Evidenz mit Hinsicht auf die krafttrainings-bedingten Veränderungen beim Wachstumsfaktor BDNF gemischt ist, wenngleich erste Hinweise auf eine Dosis-Wirkungs-Beziehung vorliegen, da Krafttraining mit hohen Lasten tendenziell zu einer vermehrten Produktion von BDNF führt [49]. Hinsichtlich IGF-1 konnte beobachtet werden, dass nach einem 12-monatigen Krafttraining, welches drei Mal in der Woche für jeweils 60 Minuten mit relativ hohen Lasten (75 bis 80% 1-RM) durchgeführt wurde, die Veränderungen des IGF-1 Levels mit den Veränderungen der kognitiven Leistungsfähigkeit (Reaktionszeiten) und funktionellen Gehirnaktivitätsveränderungen (P3b Amplitude beim Oddball Paradigma) korreliert [91]. Auch wenn in letztgenannter Studie keine komplexen statistischen Analysemethoden genutzt wurden, um zu untersuchen ob beispielsweise der Zusammenhang zwischen den krafttrainings-bedingten Veränderungen des IGF-1 Levels und der kognitiven Leistungsfähigkeit (operationalisiert durch die Reaktionszeit) durch die Veränderung der funktionellen Gehirnaktivität (P3 Amplitude) mediiert wurde, weisen diese Erkenntnisse darauf hin, dass weiterführende Forschung notwendig ist, die mehrere Analyseebenen und deren Verbindung berücksichtigt (siehe Abbildung 1), um die Mechanismen besser zu verstehen, die der Assoziation von muskulärer Kraftleistungsfähigkeit und kognitiver Leistungsfähigkeit zugrunde liegen. In diesem Kontext kommt der Untersuchung der Dosis-Wirkungs-Beziehung eine besondere Rolle zu, da diese nicht nur im Hinblick auf die zugrundeliegenden Mechanismen von Relevanz ist, sondern auch Erkenntnisse zur besseren Personalisierung von Krafttrainingsinterventionen liefern kann [13,92].

In diesem Zusammenhang sollte auch der Einfluss innovativer Trainingskonzepte evaluiert werden [25], wie z.B. das Krafttraining mit Blutflussmoderation. Im Rahmen der Blutflussmoderation wird durch an den proximalen Enden der Extremitäten angebrachte Manschetten oder Bänder der periphere Blutfluss zu den Muskeln beeinflusst. Der Vorteil des Krafttrainings mit Blutflussmoderation liegt darin begründet, dass im Vergleich zu einem Krafttraining mit relativ hohen Lasten (z.B. 70 bis 80% des 1-RM [g]) deutlich niedrigere Lasten (20 bis 50% des 1-RM) notwendig sind, um muskuläre Anpassungen auszulösen [95,96]. Im Vergleich zu einem Krafttraining mit hohen

[g] 1-RM: englisch: one-repetition-maximum, deutsch: Einer-Wiederholungs-Maximum. Als Einer-Wiederholungsmaximum wird die Last bezeichnet, die eine Person bei einer bestimmten Bewegung bzw. bei einem definierten Bewegungsumfang genau ein einziges Mal mit korrekter Technik bewegen kann (in Anlehnung an [93,94]).

Lasten (ohne Blutflussmoderation) führt ein Krafttraining mit niedrigen Lasten und mit Blutflussmoderation zu ähnlichen Verbesserungen hinsichtlich der Muskelmasse und Muskelkraft [96], wenngleich mit Bezug auf die Veränderungen der Muskelkraft aufgrund heterogener Ergebnisse noch keine eindeutige Evidenz besteht [95,97,98]. Im Hinblick auf die kognitive Leistungsfähigkeit wurde in einem eigenen Perspektivenartikel theoriegeleitet aufgezeigt, dass ein Krafttraining mit Blutflussmoderation durch die Verwendung niedriger Lasten und der positiven Auswirkungen auf physiologische Prozesse, die mit Neuroplastizität assoziiert sind, insbesondere für Menschen mit einer niedrigen mechanischen Belastbarkeit (z.B. ältere Menschen mit chronischen Gelenkschmerzen) eine vielversprechende Trainingsalternative sein könnte, um diesen mittels der positiven Effekte eines Krafttrainings ein gesundes (kognitives) Altern zu ermöglichen [25]. In diesem Zusammenhang gilt es jedoch, die vermutete Effektivität des Krafttrainings mit Blutflussmoderation hinsichtlich der kognitiven Leistungsfähigkeit durch weitere empirische Forschung unter Berücksichtigung mehrerer Analyseebenen (siehe Abbildung 1) zu bestätigen [25].

Zusammenfassend deuten die in den eigenen Forschungsarbeiten gewonnenen Erkenntnisse im Verbund mit der in der Literatur existierenden Evidenz darauf hin, dass der Zusammenhang zwischen muskulärer Kraftleistungsfähigkeit (z.B. operationalisiert durch Handgriffkraft) und kognitiver Leistungsfähigkeit (z.B. exekutive Funktionen) durch die Integrität gemeinsamer neuronaler Korrelate (z.B. hippokampales-präfrontales Netzwerk) vermittelt wird, wenngleich aufgrund der begrenzten Anzahl verfügbarer Daten zusätzliche Forschung notwendig ist, um diese Annahme durch weitere empirische Belege abzusichern.

3.3. Fazit bzw. Aussicht

In den Forschungsarbeiten der vorliegenden Dissertation konnte ein positiver Zusammenhang zwischen muskulärer Kraftleistungsfähigkeit und funktionellen und strukturellen Gehirnveränderungen sowie kognitiver Leistungsfähigkeit dokumentiert werden [13]. Die in den eigenen Studien gewonnenen Erkenntnisse [14,16,24] unterstützen die Sichtweise, dass gemeinsame neuronale Korrelate (z.B. Integrität des hippokampalen-präfrontalen Netzwerkes) den Zusammenhang zwischen muskulärer Kraftleistungsfähigkeit und kognitiver Leistungsfähigkeit erklären können [26].

Zudem liefert ein im Rahmen dieser Dissertation angefertigter Perspektivenartikel eine theoretische Fundierung wie ein Krafttraining unter Ausnutzung physiologischer Mechanismen (z.B. durch Blutflussmoderation) angepasst werden kann, um auch vulnerablen Gruppen (z.B. ältere Menschen mit chronischen Gelenkschmerzen) die Möglichkeit zu bieten, von den positiven Effekten eines Krafttrainings für die (Gehirn-) Gesundheit zu profitieren [25].

Aus wissenschaftlicher Perspektive erweitern die Erkenntnisse der in dieser Forschungsarbeit zusammengeführten eigenen Untersuchungen den bestehenden Wissensstand, indem primär die Auswirkungen des kardiorespiratorischen Fitnesslevels und des Ausdauertrainings auf funktionelle und strukturelle Gehirnveränderungen sowie kognitive Leistungsfähigkeit dokumentiert wurden [44,45]. Weitere Forschungsarbeiten sind jedoch notwendig, um die generellen und die spezifischen Mechanismen näher zu untersuchen [45,46], die den Zusammenhang zwischen verschiedenen Fitnessdimensionen (z.B. kardiorespiratorische, muskulärer und motorischer Fitness) und kognitiver Leistungsfähigkeit vermitteln (siehe Abbildung 1).

Aus der gesundheitspolitischen und gesundheitspraktischen Perspektive unterstützen die Erkenntnisse der im Rahmen dieser Dissertation durchgeführten eigenen Untersuchungen die Implementation folgender praktischer Maßnahmen. Die Kennzeichnung der muskulären Leistungsfähigkeit (z.B. operationalisiert durch Handgriffkraft) sollte in gesundheitsbezogenen Settings (z.B. Klinik, Altenpflegeheime) Bestandteil von einer regelmäßig durchzuführenden Erhebung der körperlichen und geistigen Fitness sein, um frühzeitig ältere Menschen mit einem höheren Risiko für negative gesundheitliche Folgen zu identifizieren und diesen entsprechende Interventionsmaßnahmen anbieten zu können [10,64]. Zudem sollte der Erhalt der muskulären Kraftleistungsfähigkeit (z.B. durch gezieltes Krafttraining) ein integraler Bestandteil bewegungsbezogener Empfehlungen sein, da diese nicht nur zum Erhalt der kognitiven Leistungsfähigkeit [11,27] und der zugrundeliegenden neuronalen Korrelate [13], sondern auch zur Prävention und unterstützenden Therapie von Erkrankungen, die gehäuft im höheren Lebensalter auftreten (z.B. Mobilitätseinschränkung, kardiovaskuläre Erkrankungen, Krebs), beitragen kann [99].

3.4. Literaturverzeichnis

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92. Herold, Fabian; Müller, Patrick; Gronwald, Thomas & Müller, Notger G. (2019). Dose-Response Matters! - A Perspective on the Exercise Prescription in Exercise-Cognition Research. *Frontiers in Psychology*, 10, 2338. doi:10.3389/fpsyg.2019.02338.
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4. Eidesstattliche Erklärung

Ich versichere an Eides statt durch meine Unterschrift, dass ich die vorstehende Arbeit selbständig und ohne fremde Hilfe angefertigt und alle Stellen, die ich wörtlich oder annähernd wörtlich aus Veröffentlichungen entnommen habe, als solche kenntlich gemacht habe, mich auch keiner anderen als der angegebenen Literatur oder sonstiger Hilfsmittel bedient habe. Die Arbeit hat in dieser oder ähnlicher Form noch keiner anderen Prüfungsbehörde vorgelegen. Zudem erkläre ich mich damit einverstanden, dass meine Arbeit mit einer Plagiatssoftware geprüft wird.

Sylda, den 6. September 2022 _____ _____

Ort, Datum Unterschrift Doktorand*in

5. Eigenanteilserklärung

Bezüglich meines Eigenanteiles an den im Rahmen dieser Dissertation durchgeführten Forschungsarbeiten und erstellten Publikationen, erkläre ich Folgendes.

Die Mitautor:innenschaft an den Publikationen wurde in Anlehnung an die Empfehlungen der *Deutschen Forschungsgemeinschaft* (*DFG*) [h] und des *International Committe of Medical Journal Editors* (*ICMJE*) [i] bestimmt. In allen aufgelisteten Publikationen, die im Rahmen dieser Dissertation angefertigt wurden, habe ich als Erstautor (oder bei einer geteilten Erstautorschaft) den/einen genuinen und maßgeblichen Anteil an der Entwicklung und Durchführung der Forschungsarbeit sowie dem Erstellen des Manuskriptes der Publikation. Im Speziellen hatte ich, bei den in dieser kumulativen Dissertation einbezogenen Forschungsarbeiten, den genuinen und maßgeblichen Anteil an:

- der Entwicklung und der Konzeption,
- der Methodenentwicklung und -anwendung,
- der Datenerhebung, -verwaltung, -verarbeitung und -darstellung,
- der Analyse und Auswertung der Ergebnisse sowie deren Interpretation,
- der Erstellung des Manuskriptes der Publikation und der dazugehöriger Literaturarbeit (z.B. Quellenrecherche) sowie der Kommunikationsarbeit (z.B. Antwortschreiben an die Gutachter verfassen).

Die Mitautor:innen haben mich bei der Datenerhebung unterstützt und haben mit mir zusammen zur kritischen inhaltlichen Überarbeitung des jeweiligen Manuskripts beigetragen. Entsprechend der *Contributor Roles Taxonomy* (auch als *CRediT author statement* bezeichnet [j]) sind in allen in dieser kumulativen Dissertation einbezogenen Publikationen die Anteile der jeweiligen (Mit-) Autor:innen im CRediT author statement der jeweiligen Publikation dezidiert ausgewiesen.

Sylda, den 6.September 2022 _____

Ort, Datum Unterschrift Doktorand*in

[h] Siehe folgende Literaturquelle: Deutsche Forschungsgemeinschaft (2022): Guidelines for Safeguarding Good Research Practice. Code of Conduct. DOI: 10.5281/zenodo.6472827.

i Siehe folgende Literaturquelle: International Committee of Medical Journal Editors (2022): Recommendations for the conduct, reporting, editing, and Publication of Scholarly Work in Medical Journals. Online verfügbar unter https://www.icmje.org/icmje-recommendations.pdf. (zuletzt geprüft am: 06.09.2022)

j Siehe folgende Literaturquelle: Brand, Amy; Allen, Liz; Altman, Micah; Hlava, Marjorie; Scott, Jo (2015): Beyond authorship: attribution, contribution, collaboration, and credit. In: Learn. Pub. 28 (2), S. 151–155. DOI: 10.1087/20150211.

6. Lebenslauf

Darstellung des Bildungsweges

ab November 2021	**Doktorand und wissenschaftlicher Mitarbeiter** an der Universität Potsdam an der Fakultät für Gesundheitswissenschaften Brandenburg in der Professur „Degenerative und chronische Erkrankungen, Bewegung“
April 2018 bis Oktober 2021	**Doktorand und wissenschaftlicher Mitarbeiter** im Deutschen Zentrum für Neurodegenerative Erkrankungen (DZNE) im Standort Magdeburg in der Forschungsgruppe „Neuroprotektion“ sowie der Klinik für Neurologie der Medizinischen Fakultät der Otto-von-Guericke Universität Magdeburg
Februar 2018 bis März 2018	**wissenschaftliche Hilfskraft** im Deutschen Zentrum für Neurodegenerative Erkrankungen (DZNE) im Standort Magdeburg in der Forschungsgruppe „Neuroprotektion“
Oktober 2014 bis Februar 2018	**Masterstudium (M.A.)** Sportwissenschaft mit Studienschwerpunkt „Intervention und Diagnostik“ an der Otto-von-Guericke Universität Magdeburg Masterarbeitsthema: *„Zur neuromotorischen kortikalen Gangkontrolle: Ein Vergleich zwischen dem Gehen auf dem ebenen Untergrund und dem Gehen auf dem Laufband“* Abschluss des Masterstudiums mit **„sehr gut“ (1,5)**
Januar 2015 bis September 2017	**wissenschaftliche Hilfskraft** am Lehrstuhl „Gesundheit und Körperliche Aktivität“ im Fachbereich Sportwissenschaft an der Otto-von-Guericke Universität Magdeburg
Oktober 2011 bis Oktober 2014	**Bachelorstudium (B.A.)** Sportwissenschaft mit Schwerpunkt „Gesundheitssport“ Bachelorarbeitsthema: *„Eine systematische Literaturrecherche zum Zusammenhang von kortikaler Gehirnaktivität und klinisch relevanten Gangparametern“* Abschluss des Bachelorstudiums mit **„sehr gut“ (1,5)**
Juli 2010 bis Mai 2011	Grundwehrdienstleistender im 3. Raketenartillerie-Bataillon 132 in Sondershausen
August 2004 bis Juli 2010	Gymnasium „Am Markt“ in Hettstedt
August 2002 bis Juli 2004	Sekundarschule Abberode
August 1998 bis Juli 2002	Grundschule Wippra

Darstellung erhaltener wissenschaftlicher Preise

2020	Best Paper Award im Journal of Clinical Medicine für den Artikel: "*Applications of Functional Near-Infrared Spectroscopy (fNIRS) Neuroimaging in Exercise-Cognition Science: A Systematic, Methodology-Focused Review*." (DOI: 10.3390/jcm7120466)

Editorentätigkeit für Zeitschriften mit Peer-Review-Verfahren

2019	Gasteditor folgender Sonderausgabe für Brain Sciences in Zusammenarbeit mit Prof. Dr. Notger G. Müller und Dr. Patrick Müller: *"Exercising against Age-Effects on the Brain"*	
ab 2021	Associate Editor für:	(i) Frontiers in Psychology (ii) Frontiers in Psychiatry
	Review Editor für:	(i) Frontiers in Public Health (ii) Frontiers in Human Neuroscience (iii) Frontiers in Neuroergonomics
ab 2022	Review Editor für:	(i) Frontiers in Physiology (ii) Frontiers in Sports & Active Living

Gutachtertätigkeit für Zeitschriften mit Peer-Review-Verfahren

- Acta Psychologica (Elsevier)
- Behavioural Brain Research (Elsevier)
- BMC Musculoskeletal Disorders (BioMed Central)
- Brain and Behaviour (Wiley)
- Brain Research (Elsevier)
- Brain Sciences (MDPI) [k]
- Cerebral Cortex (Oxford University Press)
- Clinical Interventions in Aging (Dove Medical Press)
- Cognitive Neurodynamics (Springer Nature)
- Evidence-based Complementary and Alternative Medicine (Hindawi Publishing)
- Experimental Brain Research (Springer Nature)
- Frontiers in Aging Neuroscience (Frontiers)
- Frontiers in Behavioral Neuroscience (Frontiers)
- Frontiers in Human Neuroscience (Frontiers)
- Frontiers in Neurology (Frontiers)
- Frontiers in Physiology (Frontiers)
- Frontiers in Public Health (Frontiers)

[k] MDPI: **M**ultidisciplinary **D**igital **P**ublishing **I**nstitute

- General Physiology and Biophysics (AEPress)
- Human Movement Science (Elsevier)
- IEEE Journal of Biomedical and Health Informatics (IEEE) [l]
- IEEE Transactions on Neural Systems and Rehabilitation Engineering (IEEE) [l]
- International Journal of Environmental Research and Public Health (MDPI)
- International Journal of Sports Medicine (Thieme)
- Journal of Clinical Medicine (MDPI) [k]
- Journal of Cognitive Neuroscience (MIT Press) [m]
- Journal of Functional Morphology and Kinesiology (MDPI) [k]
- Journal of Integrative Neuroscience (World Scientific Publishing)
- Journal of Sports and Health Science (Elsevier)
- Journal of Visualized Experiments (MYJoVE Corporation)
- Neuroscience and Biobehavioral Reviews (Elsevier)
- Neural Plasticity (Hindawi Publishing)
- Parkinsonism and Related Disorders (Elsevier)
- Photonics (MDPI) [k]
- Plos One (Public Library of Science)
- Psychophysiology (Wiley)
- Scientific Reports (Springer Nature)
- Sports (MDPI) [k]
- Sports Medicine – Open (Springer Nature)
- Systematic Reviews (Springer Nature)

Gutachtertätigkeiten für Fördermittelgeber

2021	• Fonds zur Förderung der wissenschaftlichen Forschung (FWF) – Wissenschaftsfonds (Österreich)

Sylda, den 6.September 2022

Ort, Datum

Unterschrift Doktorand*in

[l] IEEE: **I**nstitute of **E**lectrical and **E**lectronics **E**ngineers
[m] MIT Press: **M**assachusetts **I**nstitute of **T**echnology Press

7. Publikationsliste

7.1 Veröffentlichungen in Fachzeitschriften mit Peer-Review-Verfahren

Erstautorschaften

- *Herold, Fabian*; Aye, Norman; Hamacher, Dennis & Schega, Lutz (2019). *Towards the Neuromotor Control Processes of Steady-State and Speed-Matched Treadmill and Overground Walking*. Brain Topography, 32(3), 472–476. https://doi.org/10.1007/s10548-019-00699-8
- *Herold, Fabian*; Aye, Norman; Lehmann, Nico; Taubert, Marco & Müller, Notger G. (2020). *The Contribution of Functional Magnetic Resonance Imaging to the Understanding of the Effects of Acute Physical Exercise on Cognition*. Brain Sciences, 10(3), 175. https://doi.org/10.3390/brainsci10030175
- *Herold, Fabian*; Behrendt, Tom; Meißner, Caroline; Müller, Notger G. & Schega, Lutz. (2022). *The Influence of Acute Sprint Interval Training on Cognitive Performance of Healthy Younger Adults*. International Journal of Environmental Research and Public Health, 19(1), 613. https://doi.org/10.3390/ijerph19010613
- *Herold, Fabian*; Behrendt, Tom; Törpel, Alexander; Hamacher, Dennis; Müller, Notger G. & Schega, Lutz (2021). ***Cortical hemodynamics as a function of handgrip strength and cognitive performance: a cross-sectional fNIRS study in younger adults***. BMC Neuroscience, 22(1), 10. https://doi.org/10.1186/s12868-021-00615-6
- *Herold, Fabian*; Gronwald, Thomas; Scholkmann, Felix; Zohdi, Hamoon; Wyser, Dominik; Müller, Notger G. & Hamacher, Dennis (2020). *New Directions in Exercise Prescription: Is There a Role for Brain-Derived Parameters Obtained by Functional Near-Infrared Spectroscopy?.* Brain Sciences, 10(6). https://doi.org/10.3390/brainsci10060342
- *Herold, Fabian* & Hamacher, Dennis (2020). *Gibt es einen Zusammenhang zwischen biomechanischen Stabilitätsdefiziten bei nicht-antizipierten Einbeinlandungen und spezifischen Domänen der kognitiven Funktionen?*. Bewegungstherapie und Gesundheitssport, 36(03), 135–136. https://doi.org/10.1055/a-1153-5998
- *Herold, Fabian*; Hamacher, Dennis; Schega, Lutz & Müller, Notger G. (2018). *Thinking While Moving or Moving While Thinking - Concepts of Motor-Cognitive Training for Cognitive Performance Enhancement.* Frontiers in aging neuroscience*, 10,* 228. https://doi.org/10.3389/fnagi.2018.00228
- *Herold, Fabian*; Hamacher, Dennis; Törpel, Alexander; Goldschmidt, Leonard; Müller, Notger G. & Schega, Lutz (2020). ***Does squatting need attention? - A dual-task study on cognitive resources in resistance exercise***. PLOS ONE, 15(1), e0226431. https://doi.org/10.1371/journal.pone.0226431
- *Herold, Fabian*; Labott, Berit K.; Grässler, Bernhard; Halfpaap, Nicole; Langhans, Corinna; Müller, Patrick; Ammar, Ammar; Dordevic, Milos; Hökelmann, Anita & Müller, Notger G. (2022). ***A Link between Handgrip Strength and Executive Functioning: A Cross-Sectional Study in Older Adults with Mild Cognitive Impairment and Healthy Controls***. Healthcare (Basel, Switzerland), 10(2), 230. https://doi.org/10.3390/healthcare10020230
- *Herold, Fabian*; Müller, Patrick; Gronwald, Thomas & Müller, Notger G. (2019). *Dose-Response Matters! - A Perspective on the Exercise Prescription in Exercise-Cognition Research*. Frontiers in Psychology, 10, 2338. https://doi.org/10.3389/fpsyg.2019.02338

- *Herold, Fabian*; Orlowski, Katja; Börmel, Sabrina & Müller, Notger G. (2017). *Cortical activation during balancing on a balance board*. Human Movement Science, 51, 51–58. https://doi.org/10.1016/j.humov.2016.11.002
- *Herold, Fabian*; Theobald, Paula; Gronwald, Thomas; Rapp, Michael A. & Müller, Notger G. (2022). *Going digital – a commentary on the terminology used at the intersection of physical activity and digital health*. European Review of Aging and Physical Activity, 19(1). https://doi.org/10.1186/s11556-022-00296-y
- *Herold, Fabian*; Törpel, Alexander; Hamacher, Dennis; Budde, Henning & Gronwald, Thomas (2020). *A Discussion on Different Approaches for Prescribing Physical Interventions - Four Roads Lead to Rome, but Which One Should We Choose?.* Journal of Personalized Medicine, 10(3), 55. https://doi.org/10.3390/jpm10030055
- *Herold, Fabian*; Törpel, Alexander; Hamacher, Dennis; Budde, Henning; Zou, Liye; Strobach, Tilo; Müller, Notger G. & Gronwald, Thomas. (2021). *Causes and Consequences of Interindividual Response Variability: A Call to Apply a More Rigorous Research Design in Acute Exercise-Cognition Studies*. Frontiers in Physiology, 12, 682891. https://doi.org/10.3389/fphys.2021.682891
- *Herold, Fabian*; Törpel, Alexander; Schega, Lutz & Müller, Notger G. (2019). ***Functional and/or structural brain changes in response to resistance exercises and resistance training lead to cognitive improvements - a systematic review***. European Review of Aging and Physical Activity: official journal of the European Group for Research into Elderly and Physical Activity, 16(1), 10. https://doi.org/10.1186/s11556-019-0217-2
- *Herold, Fabian*; Wiegel, Patrick; Scholkmann, Felix & Müller, Notger G. (2018). ***Applications of Functional Near-Infrared Spectroscopy (fNIRS) Neuroimaging in Exercise-Cognition Science: A Systematic, Methodology-Focused Review***. Journal of Clinical Medicine, 7(12), 1–43. https://doi.org/10.3390/jcm7120466
- *Herold, Fabian*; Wiegel, Patrick; Scholkmann, Felix; Thiers, Angelina; Hamacher, Dennis & Schega, Lutz (2017). *Functional near-infrared spectroscopy in movement science: a systematic review on cortical activity in postural and walking tasks: A systematic review on cortical activity in postural and walking tasks*. Neurophotonics, 4(4), 41403. https://doi.org/10.1117/1.NPh.4.4.041403
- Törpel, Alexander; *Herold, Fabian*; Hamacher, Dennis; Müller, Notger G. & Schega, Lutz (2018). ***Strengthening the Brain - Is Resistance Training with Blood Flow Restriction an Effective Strategy for Cognitive Improvement?***. Journal of Clinical Medicine, 7(10), 377. https://doi.org/10.3390/jcm7100337

Die Publikationen mit “fett” hervorgehobenen Titel sind Bestandteil dieser wissenschaftlichen Qualifikationsarbeit. Die aufgelisteten Publikationen sind alphabetisch sortiert.

Mitautorschaften

- Ammar, Achraf; Boukhris, Omar; Halfpaap, Nicole; Labott, Berit K.; Langhans, Corinna; *Herold, Fabian*; Grässler, Bernhard; Müller, Patrick; Trabelsi, Khaled; Chtourou, Hamdi; Zmijewski, Piotr; Driss, Tarak; Glenn, Jordan M.; Müller, Notger G. & Hökelmann, Anita (2021). *Four Weeks of Detraining Induced by COVID-19 Reverse Cardiac Improvements from*

Eight Weeks of Fitness-Dance Training in Older Adults with Mild Cognitive Impairment. International Journal of Environmental Research and Public Health, *18*(11), 5930. https://doi.org/10.3390/ijerph18115930

- Behrendt, Tom; Bielitzki, Robert; Behrens, Martin; ***Herold, Fabian*** & Schega, Lutz (2022). *Effects of Intermittent Hypoxia-Hyperoxia on Performance- and Health-Related Outcomes in Humans: A Systematic Review.* Sports Medicine - Open, 8(1), 70. https://doi.org/10.1186/s40798-022-00450-x
- Cai, Kelong; Yu, Qian; ***Herold, Fabian***; Liu, Zhimei; Wang, Jingui; Zhu, Lina; Xiong, Xuan; Chen, Aiguo; Müller, Patrick; Kramer, Arthur F.; Müller, Notger G. & Zou, Liye (2020). *Mini-Basketball Training Program Improves Social Communication and White Matter Integrity in Children with Autism*. Brain Sciences, 10(11), 803. https://doi.org/10.3390/brainsci10110803
- Cao, Long; Zhang, Yuanchao; Huang, Ruiwang; Li, Lunxiong; Xia, Fengguang; Zou, Liye; Yu, Qian; Lin, Jingyuan; ***Herold, Fabian***; Perrey, Stephane; Müller, Patrick; Dordevic, Milos; Loprinzi, Paul Dinneen; Wang, Yue; Ma, Yudan; Zeng, Hongfa; Qu, Sicen; Wu, Jinlonmg & Ren, Zhanbing (2021). *Structural and functional brain signatures of endurance runners*. Brain Structure and Function, 226(1), 93–103. https://doi.org/10.1007/s00429-020-02170-y
- Cui, Jie; Zou, Liye; ***Herold, Fabian***; Yu, Qian; Jiao, Can; Zhang, Yanjie; Chi, Xinli; Müller, Notger G.; Perrey, Stephane; Li, Lin & Wang, Chenbo (2020). *Does Cardiorespiratory Fitness Influence the Effect of Acute Aerobic Exercise on Executive Function?*. Frontiers in Human Neuroscience, 14, 569010. https://doi.org/10.3389/fnhum.2020.569010
- Cunha, Paolo M.; Nunes, João P.; Werneck, André O.; Ribeiro, Alex S.; Da Silva Machado, Daniel G.; Kassiano, Witalo; Costa, Bruna D. V.; Cyrino, Letícia T.; Antunes, Melissa; Kunevaliki, Gabriel; Tomeleri, Crisieli M.; Fernandes, Rodrigo R.; Junior, Paulo. S.; Teixeira, Denilson C.; Venturini, Danielle; Barbosa, Décio S.; Qian, Yu; ***Herold, Fabian***; Zou, Liye; Mayhew, Matthew L.; Stubbs, Brendon & Cyrino, Edilson S. (2022). *Effect of Resistance Exercise Orders on Health Parameters in Trained Older Women: A Randomized Crossover Trial*. Medicine and science in sports and exercise. Vorab-Onlinepublikation. https://doi.org/10.1249/MSS.0000000000003030
- Grässler, Berhard; Dordevic, Milos; Darius, Sabine; Vogelmann, Lukas; ***Herold, Fabian***; Langhans, Corinna; Halfpaap, Nicole; Böckelmann, Irina; Müller, Notger G. & Hökelmann, Anita (2021). *Age-Related Differences in Cardiac Autonomic Control at Resting State and in Response to Mental Stress*. Diagnostics (Basel, Switzerland), 11(12), 2218. https://doi.org/10.3390/diagnostics11122218
- Grässler, Bernhard; Dordevic, Milos; ***Herold, Fabian***; Darius, Sabine; Langhans, Corinna; Halfpaap, Nicole; Labott, Berit K.; Müller, Patrick; Ammar, Aachraf; Thielmann, Beatrice; Böckelmann, Irina; Müller, Notger G. & Hökelmann, Anita (2021). *Relationship between Resting State Heart Rate Variability and Sleep Quality in Older Adults with Mild Cognitive Impairment.* International Journal of Environmental Research and Public Health, 18(24). https://doi.org/10.3390/ijerph182413321
- Grässler, Bernhard; ***Herold, Fabian***; Dordevic, Milos; Gujar, Tariq Ali; Darius, Sabine; Böckelmann, Irina; Müller, Notger G. & Hökelmann, Anita (2021). *Multimodal measurement approach to identify individuals with mild cognitive impairment: study protocol for a cross-sectional trial*. BMJ open, 11(5), e046879. https://doi.org/10.1136/bmjopen-2020-046879

- Gronwald, Thomas; Törpel, Alexander; Herold, Fabian & Budde, Henning (2020). *Perspective of Dose and Response for Individualized Physical Exercise and Training Prescription*. Journal of Functional Morphology and Kinesiology, 5(3), 48. https://doi.org/10.3390/jfmk5030048
- Hamacher, Dennis; Hamacher, Daniel; *Herold, Fabian* & Schega, Lutz (2016). *Are there differences in the dual-task walking variability of minimum toe clearance in chronic low back pain patients and healthy controls?* Gait & Posture, 49, 97–101. https://doi.org/10.1016/j.gaitpost.2016.06.026
- Hamacher, Dennis; Hamacher, Daniel; *Herold, Fabian* & Schega, Lutz (2016). *Effect of dual tasks on gait variability in walking to auditory cues in older and young individuals*. Experimental Brain Research, 234(12), 3555–3563. https://doi.org/10.1007/s00221-016-4754-x
- Hamacher, Dennis; Hamacher, Daniel; Törpel, Alexander; Krowicki, Martin; *Herold, Fabian* & Schega, Lutz (2016). *The reliability of local dynamic stability in walking while texting and performing an arithmetical problem*. Gait & Posture, 44, 200–203. https://doi.org/10.1016/j.gaitpost.2015.12.021
- Hamacher, Dennis; *Herold, Fabian*; Wiegel, Patrick; Hamacher, Daniel & Schega, Lutz (2015). *Brain activity during walking: A systematic review*. Neuroscience and Biobehavioral reviews, 57, 310–327. https://doi.org/10.1016/j.neubiorev.2015.08.002
- Kong, Chuidan; Chen, Aiguo; Ludyga, Sebastian; *Herold, Fabian*; Healy, Sean; Zhao, Mengxian; Taylor, Alyx; Müller, Notger G.; Kramer, Arthur F.; Chen, Sitong; Tremblay, Mark S. & Zou, Liye (2022). *Associations between meeting 24-hour movement guidelines and quality of life among children and adolescents with autism spectrum disorder*. Journal of Sport and Health Science. Vorab-Onlinepublikation. https://doi.org/10.1016/j.jshs.2022.08.003
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Die aufgelisteten Publikationen sind alphabetisch sortiert.

7.2 Veröffentlichungen in anderen Medien

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- ***Herold, Fabian*** (2016). *Klinisch relevante Gangparameter und Gehirnaktivität: Eine systematische Literaturrecherche*. 1.Auflage. Saarbrücken: AV Akademikerverlag. ISBN: 978-3-639-87666-6.

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8. Danksagung

Mein allergrößter Dank gilt meinen Eltern Heike und Frieder, meinen Großeltern Renate und Wilhelm sowie Brunhilde und Jürgen und meiner Freundin Susann für deren Liebe und Unterstützung in allen erdenklichen Lebenslagen. Außerdem möchte ich an dieser Stelle meinen wärmsten Dank an meine Schwiegereltern Christiane und Jens, meine Schwager Marcus und Marian, Schwiegeropa Ulli und Schwiegeronkel Volker für deren tatkräftige Unterstützung beim „Nebenprojekt“ Hausbau ausdrücken.

Ich möchte mich auch herzlichst bei meinem Doktorvater, Herrn Prof. Dr. med. Notger Germar Müller bedanken, dessen Betreuung und Unterstützung die Erstellung dieser Dissertation erst möglich gemacht haben.

Ferner gilt mein Dank Herrn Prof. Dr. phil. habil. Lutz Schega, in dessen Lehrstuhl ich meine ersten wissenschaftlichen „Gehversuche“ unternehmen durfte und der mir zur Studiendurchführung seine Labore dankenswerterweise zur Verfügung gestellt hat.

Zudem möchte ich mich insbesondere bei Prof. Dr. rer. medic. Dennis Hamacher bedanken, der mein Interesse für eine wissenschaftliche Laufbahn geweckt sowie diese geebnet und gefördert hat. Dabei stand er mir nicht nur mit wissenschaftlichen Ratschlägen, sondern auch durch vielfältige Lebensweisheiten stets zur Seite.

Mein herzlichster Dank gilt auch Prof. Dr. phil. habil. Thomas Gronwald und Dr. phil. Alexander Törpel, durch die ich bei konstruktiv-kritischen Diskussionen einen tiefen Einblick in wissenschaftliches Arbeiten, insbesondere im Bereich der Trainingswissenschaften, erhalten habe. Außerdem möchte ich mich auch bei meinen zahlreichen Koautoren, in die Projekte involvierten Teilnehmern und Kollegen bedanken, da ohne sie die Umsetzung dieser wissenschaftlichen Arbeit nicht möglich gewesen wäre. Insbesondere möchte ich hier Dr. phil. Patrick Wiegel und Herr Tom Behrendt hervorheben, die mir nie einen Freundschaftsdienst abgeschlagen haben. Auch Dr. phil. Daniel Carius möchte ich an dieser Stelle besonders erwähnen, da unsere Diskussionen über die funktionelle Nahinfrarotspektroskopie und ihre Tücken meinen Wissenstand deutlich bereichert haben. Zudem bedanke ich mich bei Herr Björn Wölfer für das Korrekturlesen dieser wissenschaftlichen Arbeit.

9. Anhang mit Publikationen

Die aufgelisteten Publikationen sind nach ihrem Erscheinungsjahr sortiert.

Journal of
Clinical Medicine

MDPI

Review

Applications of Functional Near-Infrared Spectroscopy (fNIRS) Neuroimaging in Exercise–Cognition Science: A Systematic, Methodology-Focused Review

Fabian Herold [1,*], Patrick Wiegel [2,3], Felix Scholkmann [4] and Notger G. Müller [1,5,6]

1 Research Group Neuroprotection, German Center for Neurodegenerative Diseases (DZNE), Magdeburg 39120, Germany; notger.mueller@dzne.de
2 Department of Sport Science, University of Freiburg, Freiburg 79117, Germany; patrick.wiegel@sport.uni-freiburg.de
3 Bernstein Center Freiburg, University of Freiburg, Freiburg 79104, Germany
4 Biomedical Optics Research Laboratory, Department of Neonatology, University Hospital Zurich, University of Zürich, Zürich 8091, Switzerland; felix.scholkmann@usz.ch
5 Center for Behavioral Brain Sciences (CBBS), Magdeburg 39118, Germany
6 Department of Neurology, Medical Faculty, Otto von Guericke University, Magdeburg 39120, Germany
* Correspondence: fabian.herold@dzne.de; Tel.: +49-39-1672-4506

Received: 24 October 2018; Accepted: 15 November 2018; Published: 22 November 2018

Abstract: For cognitive processes to function well, it is essential that the brain is optimally supplied with oxygen and blood. In recent years, evidence has emerged suggesting that cerebral oxygenation and hemodynamics can be modified with physical activity. To better understand the relationship between cerebral oxygenation/hemodynamics, physical activity, and cognition, the application of state-of-the art neuroimaging tools is essential. Functional near-infrared spectroscopy (fNIRS) is such a neuroimaging tool especially suitable to investigate the effects of physical activity/exercises on cerebral oxygenation and hemodynamics due to its capability to quantify changes in the concentration of oxygenated hemoglobin (oxyHb) and deoxygenated hemoglobin (deoxyHb) non-invasively in the human brain. However, currently there is no clear standardized procedure regarding the application, data processing, and data analysis of fNIRS, and there is a large heterogeneity regarding how fNIRS is applied in the field of exercise–cognition science. Therefore, this review aims to summarize the current methodological knowledge about fNIRS application in studies measuring the cortical hemodynamic responses during cognitive testing (i) prior and after different physical activities interventions, and (ii) in cross-sectional studies accounting for the physical fitness level of their participants. Based on the review of the methodology of 35 as relevant considered publications, we outline recommendations for future fNIRS studies in the field of exercise–cognition science.

Keywords: fNIRS; optical imaging; physical activity; cognition; executive functions; working memory

1. Introduction

Availability of oxygen is crucial for cognitive processes to be intact [1–4] and a lack of oxygen in the brain leads to lower cognitive performance [1,5]. Emerging evidence suggests that oxygen availability can be enhanced by physical activity. For example, an acute bout of physical activity increases cognitive performance and is accompanied by higher levels of oxygenated hemoglobin in the prefrontal areas of the human brain [6–9]. A similar relationship was noticed in cross-sectional studies, which found that more hours of weekly physical activity [10] and higher cardiorespiratory fitness levels [11–13] are

associated with higher cerebral oxygenation levels and superior cognitive performance. However, since physical-activity-induced neurobiological mechanisms (e.g., cerebral oxygen availability), which may contribute to improved cognitive performance are not fully understood yet [14–16], it seems helpful to apply state-of-the-art neuroimaging methods in order to foster our understanding of the effects of physical activity on cognition [17,18]. Based on the crucial role of oxygen availability for cognition together with findings suggesting that physical activity positively influences oxygen availability and cognitive performance, neuroimaging tools that can quantify tissue oxygenation (metabolism) and hemodynamics (blood flow) seem especially suitable to answer emerging research questions in the field of exercise–cognition science (for review of emerging research questions please see References [17–20]). While cerebral oxygenation and hemodynamics can be quantified with functional magnetic resonance imaging (fMRI), positron-emission-tomography (PET) and functional near-infrared spectroscopy (fNIRS) [21–24], electroencephalography (EEG) is a frequently used electrophysiological technique to record the electric signals of the brain [25–28]. However, all mentioned neuroimaging techniques have unique methodological advantages and disadvantages that have to be traded off with regard to the intended research purpose.

fMRI is often considered as the gold standard for the assessment of brain activity as it offers the advantage to measure functional changes across the whole brain with a high spatial resolution (e.g., <4.0 mm) [29–33]. However, fMRI acquisition costs are relatively high, fMRI is susceptible to movement artefacts (e.g., requires rigorous head stabilization), fMRI is relatively noisy during the measurements, fMRI provides a relative low temporal resolution (e.g., ≈0.5 Hz), and fMRI cannot be used in special cohorts (e.g., individuals with metallic implants or claustrophobia) [29,30,32,34–36]. PET allows the assessment of changes in various substances (e.g., glucose), but PET scans are relatively expensive and repeated measurements within short time intervals are ethically not feasible due to the use of radioactive tracer substances [22,31]. EEG, which measures the brain activation directly and non-invasively based on neuroelectric signals of neurons [37], offers a high temporal resolution (e.g., >1000 Hz) but suffers from a relatively weak spatial resolution (e.g., ≈5.0–9.0 cm) [27,29,30,38–41]. Furthermore, EEG is relative susceptible to artefacts (e.g., due to sweat or muscle activity), is time consuming in preparation (e.g., when gel is used), and the obtained signals are hard to interpret for non-experts [27,29,38,42,43]. Hence, fMRI, PET, and EEG have specific restrictions that hamper their efficient utilization in exercise–cognition settings (e.g., after an acute bout of physical activity).

fNIRS is an optical neuroimaging technique that is based on the theory of neurovascular coupling and optical spectroscopy (see Figure 1a,b and Figure 2) [44,45]. As shown in Figure 1b, an increase in neural activity causes an increase in the oxygen metabolism, which is necessary to satisfy energetic demands of the neuronal tissue (neurometabolic coupling) [40,46,47]. Within the neuronal oxygen metabolism, oxygen is consumed to produce energy, leading to a decrease in the concentration of oxyHb and to an increase in the concentration of deoxyHb [46–48]. Neural activity triggers local changes in cerebral hemodynamics that induce an intensified blood flow to the activated brain regions (neurovascular coupling) [40,46,49,50]. Since the local supply of oxygen is greater than its consumption, in activated brain regions, a higher concentration of oxyHb and a decreased concentration of deoxyHb is to be observed (see Figure 1b) [40,47].

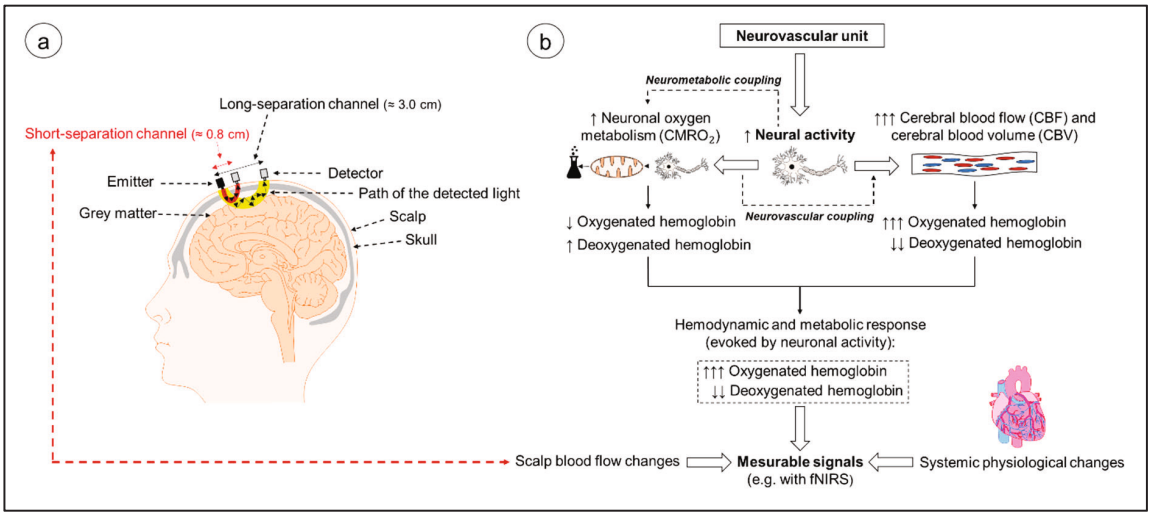

Figure 1. (**a**) Schematic illustration of the neurovascular unit and the changes in cerebral hemodynamics and oxygenation induced by neural activity. (**b**) Exemplary illustration of a possible NIRS montage on the human head and the assumed banana-shaped course of detected light of "short-separation channels" and of "long-separation channels". fNIRS, functional near-infrared spectroscopy; $CMRO_2$, cerebral metabolic rate of oxygen; ↑, increase; ↓, decrease.

When applying fNIRS, light with different wavelengths in the near-infrared spectrum is emitted by a source on the scalp and after the travelling through different layers (skull, cerebrospinal fluid), this light reaches neuronal tissue [39,40,51]. Inside the tissue, the light undergoes absorption and scattering that contributes to light attenuation [51–53]. During absorption, the energy of the photons is transformed into internal energy of the respective medium (see Figure 2, Photon 1 and 2) [40]. Scattering forced the photons to deviate from their initially straight trajectories and increase the length of their travelled paths (see Figure 2, Photons 3 and 4) [40,52]. The non-absorbed components of the scattered light can be measured by a detector placed on the head's surface (e.g., see Figure 1a) [39,51]. Based on the activity-dependent regional increase of oxyHb and decrease of deoxyHb, the light absorption rate of the neuronal tissue in the activated brain region changes and influences, in turn, light attenuation [40,51,54]. The regional changes in light absorption as a function of neuronal activity and the different light absorption spectra of the chromophores (e.g., $\lambda > 800$ nm mainly oxyHb, $\lambda < 800$ nm mainly deoxyHb) allow for the non-invasive quantification of local changes in cortical oxyHb and deoxyHb concentration via the modified Beer–Lambert law [39,40,51]. The cortical concentration changes in oxyHb and deoxyHb are used as an indirect indicator of regional brain activation (such as in functional magnetic resonance imaging) [36,39,54]. The basic principles of fNIRS are summarized in Figures 1 and 2. We will focus on the description of continuous-wave fNIRS because commercially available fNIRS devices are mainly based on the continuous-wave technology [40,47]. In continuous-wave fNIRS the absolute changes in the attenuation coefficient are determined (e.g., difference between the intensity of the emitted light and detector-determined light intensity; see Figure 2). Thus, the fNIRS signals obtained reflect relative concentration changes (e.g., relative to the first measured values) [47,49,55–57]. A detailed description about other types of NIRS devices is given in the Supplementary Material.

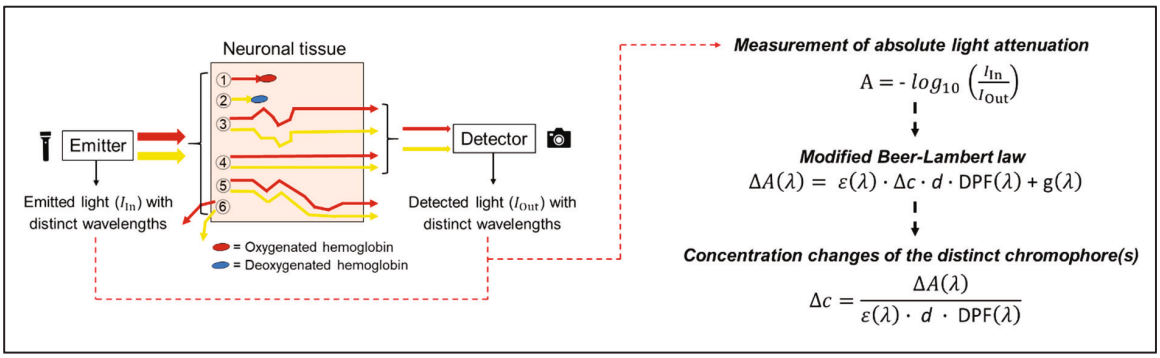

Figure 2. Schematic illustration of light propagation through the neuronal tissue. On the left side of the illustration, possible photon paths for different wavelengths are depicted (red colors represent wavelengths of λ > 800 nm (mainly absorbed by oxyHb—see Photon 1), whereas yellow colors represent wavelengths of λ < 800 nm (mainly absorbed by deoxyHb—see Photon 2). Path 3 represents a photon that undergoes some scattering events before being recorded by a detector. Path 4 represents a ballistic photon. Path 5 represents a photon that, after some scattering events, is not recorded by a detector (lost due to forward scattering). Path 6 represents a photon that is lost due to backward scattering. In the right part of the illustration, the formulas to calculate concentration changes in chromophores are shown (based on continuous-wave NIRS). The symbols have the following meanings: A: light attenuation, or ΔA(λ): changes in light attenuation at a certain wavelength (λ); I_{In}: intensity of emitted light; I_{Out}: intensity of recorded light; ε(λ): the extinction coefficient of the chromophore at a certain wavelength (λ); Δc: changes in chromophore concentration; d: separation (distance) between source and detector; DPF(λ): differential path length factor (DPF) for a certain wavelength (λ); g(λ): scattering at a certain wavelength (λ), where g is cancelled out since it is assumed to be negligible when only light attenuation (as in continuous-wave NIRS) is considered [45,54,58].

fNIRS provides some advantages that make it well-situated to investigate the effects of physical activity on cognitive performance and cerebral oxygenation/hemodynamics. Advantages of fNIRS compared to other neuroimaging techniques (e.g., fMRI and PET) are: non-invasiveness, a relatively good spatial (≈1.0–3.0 cm) and temporal resolution (normally up to 10 Hz), portability, a low noise level during operation, relative low acquisition costs, robustness against motion artefacts that make a strict immobilization or sedation of participants unnecessary, the possibility to investigate cortical activity in individuals with metallic implants or claustrophobia, and the opportunity to conduct repeated measures in short time intervals (since no radioactive tracer substance as in PET is used) [21,22,29,30,32,34,38,40,41,52,54,59]. The mentioned advantages make fNIRS eminently suitable for application in special cohorts such as children [29,34] or neurological patients [23,60,61]. Furthermore, while fMRI mainly relies on the paramagnetic properties of deoxyHb, fNIRS can be used to quantify both changes of deoxyHb and of oxyHb [53,54,58,59,62]. The simultaneous assessment of deoxyHb and oxyHb allows the quantification of further markers of cortical activation such as tissue oxygenation (TOI: oxyHb concentration/total hemoglobin concentration) and cortical hemodynamics (blood volume, total hemoglobin concentration (totHb)) [22,30,54,58]. Moreover, fNIRS is even capable of evaluating changes in cytochrome oxidase levels, which constitute a marker of the cellular oxygen metabolism [63–67]. On the downside, fNIRS is limited to cortical layers [32,40,52] because the penetration depth is, in general, less than half of the source-detector separation [54,62,68]. Furthermore, fNIRS suffers from its vulnerability to changes in scalp blood flow and to changes in systemic physiology (e.g., increase in heart rate) [30,32,40,69–72]. Of note, while fNIRS has proven to be a useful and reliable tool in some research fields (e.g., motor control) [25,36,73], currently no standardized procedures regarding the processing of fNIRS data are available [21,30,38,41,74]. Moreover, the methods used to measure cortical hemodynamics during cognitive tasks are diverse [74]. There is no consensus yet regarding a standardized methodology (e.g., application, processing and analysis) that limits the comparability across studies because

numerous parameters vary in the (pre-)processing and analysis algorithms (e.g., value of differential path length factor, filter cut-off frequencies). While first attempts were undertaken to standardize the application, processing, and analysis of fNIRS in other research areas (e.g., motor control) [36,41], in the field of exercise–cognition science, so far only systematic reviews summarizing the findings but not the methodology of fNIRS are available [52,75]. Moreover, a systematic review pooling fNIRS studies investigating the influence of physical activities (e.g., 10 min of cycling) or assessing the influence of habitual physical activity on the performance of standardized cognitive tests and the corresponding cortical hemodynamic responses is completely lacking. Since (i) the recommendations of previously methodologically focused reviews [36,41] are not fully transferable to the field of exercise–cognition (e.g., due to differences in biasing factors such as the influence of physiological artefacts on temporal delay between being physically active and cognitive testing), and (ii) the great interest from various scientific disciplines in the relationship between physical activity, central nervous system, and cognition (e.g., sport science, neuroscience, psychology), this systematic review aims to summarize the methodological details and findings of studies investigating the influence of physical activity on cognition while measuring cortical hemodynamics with fNIRS. Based on the results of this systematic literature survey, we derive recommendations for future studies.

2. Methods

2.1. Search Strategy and Process

On the 13 October 2018, two independent researchers performed a systematic literature search in seven electronic databases to identify all relevant studies employing fNIRS to measure cortical hemodynamics during a standardized cognitive task (i) prior and after a single bout of physical activities and/or long-term physical exercise programs (>two exercise sessions), and (ii) linking cortical hemodynamics to measures of physical activity or physical fitness (e.g., cardiorespiratory fitness) [76]. In all databases, the following search strings were used:

- exercis* OR fitness OR physical activity OR training OR strength OR endurance OR aerobic OR agility OR cycling OR running OR dance OR dancing OR walking OR “going outdoor”
- cogniti* OR mental OR executive OR memory OR attention OR “reaction time” OR “response time” OR processing OR Stroop OR Flanker OR Sternberg OR “Verbal Fluency Task” OR “Tower of Hanoi” OR “Tower of London” OR “Wisconsin card sorting task” OR “Trail Making Test” OR “visual search” OR visuospatial OR “decision making” OR oddball OR accuracy OR error
- NIR OR fNIR* OR "functional near-infrared spectroscopy" OR "near-infrared spectroscopy" OR "functional near-infrared spectroscopic" OR "optical imaging system" OR "optical topography" OR oxygenation

In PubMed, PsycInfo, CINAHL, and Sportdiscus, no restriction was applied. In Cochrane Library, we limited the search to “trials,” in Web of Science to “topic,” and in Scopus to “title, abstract, keywords.” We identified and added four relevant studies [10,77–79] after screening of the references of the included studies and after searching for further studies of the included workgroups.

Afterwards, the results of the systematic search were loaded in a citation manager, which was used for further analyses and for removing of the duplicates (see Figure 3).

2.2. Inclusion and Exclusion Criteria

Screening for relevant studies was conducted according to the PICOS-principle [76,80]. PICOS stands for participants (P), intervention (I), comparisons (C), outcomes (O), and study design (S) [76,80]. All age groups, regardless of pathology, were included given that brain activity had been measured with fNIRS during a cognitive test prior and after a physical intervention. Furthermore, cross-sectional studies were included when they had assessed the physical activity level (e.g., via questionnaire) or the physical fitness level (e.g., cardiorespiratory fitness level) and conducted cognitive testing while

measuring the cortical hemodynamics with fNIRS. Studies written in a non-English language [81–83], conducted by performing the cognitive tests without measuring brain activation with fNIRS [84–89], measuring brain activation during the physical exercises [88–91], and those with a focus on the effect of nutritional supplement on cognitive performance [92] were excluded from the present literature survey.

2.3. Data Extraction

From the 35 studies considered to be relevant, we extracted information about first author, year of publication, population characteristics including age, gender, health status, cardiorespiratory fitness level, exercise characteristics (e.g., intensity, duration, type of exercise), and cognitive testing (e.g., tested cognitive domain, administration after exercise cessation). Furthermore, information about fNIRS methodology regarding optode placement, source-detector separation, differential path length factor (DPF), the applied filter methods, the data processing procedures, data analysis (e.g., markers of cortical activation), and the main findings were extracted. When articles provided an incomplete description of their methodology, we contacted the authors via e-mail.

Please note that in this review a single session of physical exercise is referred as "physical activity" rather than "physical exercise" because "exercise" is per definition a structured and planned form of physical activity that is intended to improve or maintain a distinct fitness level [17,93–95].

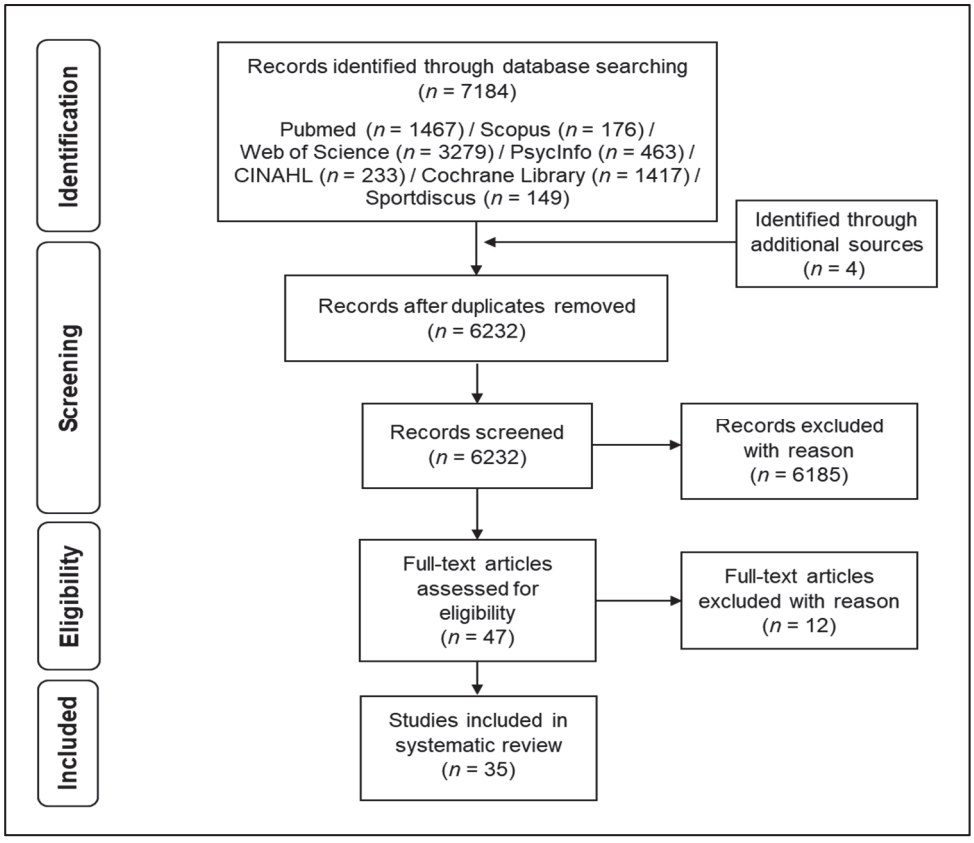

Figure 3. Flow chart with information about the search, screening, and selection processes, which led to the identification of relevant articles included in this review.

3. Results

In the following section, information about methodological approaches (e.g., recording, processing, and analysis of fNIRS data) and findings of the 35 reviewed studies are provided.

3.1. fNIRS Optode Placement

The majority of the reviewed studies used the international EEG system for the placement of the optodes [6–8,11–13,77,79,96–109] and set the source-detector separations at 3.0 cm [6–8,12,77–79,96,99,100,102,104,106,107,109–111]. A detailed overview about the used source-detector separations utilized in the remaining studies is given in Figure 4a. In two studies, individual fMRI-scans [111,112], and in seven studies, virtual registration (e.g., using 3-D digitizer), was performed [6–8,12,109,113,114]. In almost all reviewed studies, the optodes were placed over distinct parts of the prefrontal cortex. A detailed overview is provided in Table 1.

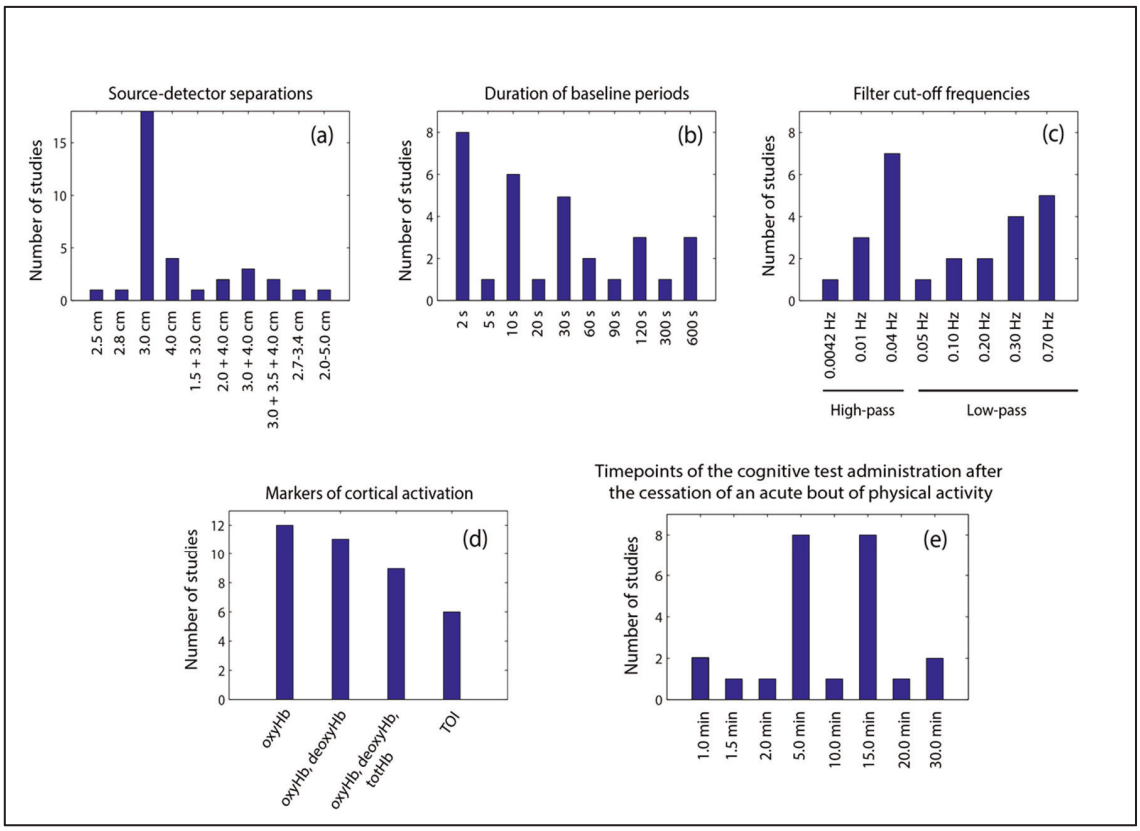

Figure 4. Overview on (**a**) source-detector separations, (**b**) durations of baseline periods, (**c**) filter cut-off frequencies, (**d**) markers of cortical activation, and (**e**) timepoints of the cognitive test administration after the cessation of an acute bout of physical activity. cm: centimeters; deoxyHb: deoxygenated hemoglobin; Hz: Hertz; min: minutes; oxyHb: oxygenated hemoglobin; s: seconds; TOI: tissue oxygenation index; totHb: total hemoglobin.

3.2. fNIRS Experimental Paradigms of Data Recording

In almost all studies baseline brain activation was assessed in a sitting position [6–8,11–13,77–79,96–111,115–120]. The quantification of baseline brain activation lasted from 2 s [6–8,12,77,106,109] to 10 min [97,116,119]. Other commonly used durations for the evaluation of baseline brain activation were 10 s [13,79,99,100,107], 30 s [102,104,105,108,120], or 120 s [103,111,118]. An overview about baseline durations is provided in Figure 4b.

A block design was used in eleven studies [11,13,78,99,100,102–104,107,112,113], whereas an event-related design was applied in ten studies [6–8,12,77,106,109–111,114]. In the remaining studies, cognitive testing was performed after the assessment of baseline brain activity [79,96–98,101,105,108,115–120].

3.3. DPF Values

The differential path length factor (DPF) is a dimensionless correction factor that accounts for the increase in the optical pathlength caused by the scattering of light in biological tissue and is multiplied with the source-detector separation to estimate the "true" path length that light has travelled [12,121,122]. A constant wavelength-independent DPF was used in six studies [11,97,101,105,118,119]. In those six studies, DPF values of 4.0 [97,105,119], 5.9 [101], and 5.93 [11,118] were applied. A constant, wavelength-dependent DPF with the values of 7.25/6.38 (760 nm/850 nm) was used in two studies [103,110]. Two studies [108,120] used age-dependent DPF values calculated as described in Duncan et al. [123]. In the remaining studies, arbitrary units [6–8,12,13,77–79,96,100,102,104,106,107,109,111] or saturation index/tissue oxygenation index (StO_2 or TOI = oxyHb/totHb) [10,105,108,115,116,120], which do not rely on specific DPF values [124,125], were used.

3.4. fNIRS Signal Filtering

In three studies the filtering of fNIRS signals was conducted using a low-pass filer [13,100,107] or a high-pass filter [11,97,116]. In eight studies a bandpass filter, which consists of low-pass filter and high-pass filter, was used [6–8,12,96,103,109,110]. The cut-off frequencies of low-pass filters and high-pass filters are shown in Figure 4c. In addition to low-pass filters, high-pass filters, bandpass filters, or—in one study each—filter methods based on principal component analysis (PCA) [11], Gaussian smoothing [119], or moving averages [79] were applied. In two studies, spike artefact removal [103,110] was conducted, and in four studies, signals from short-separation channels were used to correct for superficial artefacts [105,113,116,120].

3.5. Final fNIRS Data Processing

In almost all of the studies reviewed, a baseline correction [6–8,11–13,77–79,97–103,105–109,111,117–120] and averaging (e.g., across channels, trials and/or distinct time periods) were conducted [6–8,10–13,77,96–99,101–104,106,107,109–111,115,116,119,120].

In 33 studies, the mean (average) values of the measures of cortical activity (e.g., oxyHb, deoxyHb, or TOI) were calculated over a distinct time period and were used for further statistical analysis [6–8,10–13,77–79,96–103,105–117,119,120]. In other studies, the median value of the proxies of cortical activity over a distinct time period [118] or the peak value obtained during the task period [104] were used to perform the statistical analysis. The fNIRS data of the entire task period were used for averaging and statistical analysis in 18 studies [11,79,97–103,105,107,108,113,116–120]. As outlined in the following, 17 studies used different time periods for the subsequent statistical analysis: 4–11 s after trial onset [6,8,106,109], 6–9 s after trial onset [12,77], 6–10 s after trial onset [114], 6–8 s after trial onset for oxyHb, and 7–9 s after trial onset for deoxyHb [7], first 10 s after trial onset [115], 2 s before trial onset to 13.5 s after trial onset [111], 5 to 19.2 s after the onset of stimulation [112], first 4 s of a trial for the preparatory period and 4–12 s after trial onset for regulatory period [110], time to peak [104], a 12 s time period [96], 90 s prior onset of cognitive testing [10], last 10 s of task period for regular statistical analysis and 100-s stimulation windows for slope method analysis [13] and a 6-s delayed boxcar function convolved with a Gaussian kernel of dispersion of 6-s full-width at half-maximum for oxyHb [78].

The cortical activity was assessed in twelve studies using soley oxyHb [77–79,96,99,100,103,104,106,107,111,113]; in eleven studies using oxyHb and deoxyHb [6–8,12,13,98,102,108,109,112,114]; in nine studies using oxyHb, deoxyHb, and totHb [11,97,101,105,110,117–120], and in six studies using a tissue oxygenation/saturation index [10,105,108,115,116,120] (for overview see Figure 4d).

In the majority of reviewed studies, statistical inference analysis was conducted using parametric methods such as analysis of variance (e.g., ANOVA) [6–8,11,13,77,96,97,101–103,105,107–109,113–117,119,120] or t-test(s) [78,79,98,99,104,111]. To account for the multiple comparison problem, a Bonferroni correction was used most frequently in the studies reviewed [6,8,77,97,102,105,107,109,110,113,114,116,119].

3.6. Cortical Hemodynamics during Cognitive Testing in Response to Physical Activity

In the majority of the reviewed studies cortical hemodynamics were assessed during cognitive tests targeting executive functions. Thereby, in fifteen studies, a Stroop test [6–8,77,79,96–98,101,106,109,110,115,116,119], in one study a flanker test [102], a Go/No-Go test [78], and in another one, a random number generation test [13] were used. In two studies, a modified Sternberg task [99,100], or in one study, a spatial working memory task [111], were applied to assess the cortical hemodynamic responses during a short-term working memory task. One study utilized a two-back task to quantify the cortical hemodynamic responses during working memory assessment [117]. Furthermore, in the remaining studies, a verbal fluency task [104,107], a cognitive reappraisal task [110], a visual search task [108], a reaction time task [120], and a combination of Go/No-Go task with a spatial delayed response task [105] were employed to test cognitive functions while assessing cortical hemodynamics. In most studies, cognitive tests were administered after a temporal delay of 5 min [8,77,98,108,111,113,116,117] or 15 min [7,97,99,109,114,115,119] after the cessation of acute physical activities (for an overview see Figure 4e).

While the aforementioned studies assessed prefrontal activity (e.g., via oxyHb or TOI) before physical activity, eight studies observed a higher activity of the prefrontal cortex after a single bout of aerobic activities when there was at least a one-minute delay between cessation of aerobic activities and beginning of cognitive testing [97–99,109,116,117,119,120]. In six studies, a higher cortical activity (e.g., higher oxyHb concentration) in prefrontal areas was noticed when the cortical activity after the cessation of aerobic activities was compared to the control condition (sitting) [6–8,98,100,113]. Furthermore, the activation of the prefrontal cortex during completion of cognitive testing was influenced by the type of physical activity. For instance, a lower TOI was observed during cognitive testing after high-intensity resistance activities compared to the TOI obtained after moderate aerobic activities or no physical activities [115]. Cortical activity did not change significantly after (i) slow aerobic dance [77], (ii) stretching [108], or (iii) 2 min after maximal exercise test [105]. A significantly lower oxyHb concentration during cognitive testing was noticed (i) after cycling under normobaric hypoxic conditions [114], and (ii) if the cognitive test was conducted after the cessation of moderate-intensity cycling [78]. A positive neurobehavioral relationship between measures of cortical activity in prefrontal cortex (e.g., higher oxyHb concentration) and cognitive performance (e.g., faster response times) was observed in children [119], in healthy young adults [6,8,105,109], and in healthy older adults [7]. Whereas in younger adults, concentrations of oxyHb in the left dorsolateral prefrontal cortex [6,8,109] and the left frontopolar area [8] was associated with reaction times, in healthy, older adults improved reaction times after ten minutes of moderate-intensity cycling were related to the concentration of oxyHb in the right frontopolar area [7]. In addition, one study observed that right ventrolateral oxyHb concentration was enhanced in responders (participants that showed improved task performance in post-exercise cognitive testing) during low-intensity cycling in comparison to non-responders [111].

In the long-term physical exercise studies, after a four-week intervention, an increased concentration of oxyHb in the prefrontal cortex during the cognitive testing was associated with higher weight loss [96]. Furthermore, distinct cortical hemodynamic responses during executive tests were observed after training programs with different exercise characteristics [101], but a 24 weeks Tai-Chi intervention did not significantly change the oxyHb concentration during the cognitive testing [79].

In cross-sectional studies, a higher level of cardiovascular fitness [11–13] or higher level of habitual physical activity [104,106,107,110,118] were associated with measures of cortical activity in the prefrontal cortex during the cognitive testing (e.g., higher oxyHb concentration and faster response times). Furthermore, in young adults, the area under the fNIRS curve (during cognitive testing) in the prefrontal cortex was associated with total sleep time [104]. In children, high levels of moderate-to-vigorous physical activity were not linked to higher oxyHb levels during cognitive testing [103]. A more detailed overview about the findings of the reviewed studies is provided in Table 1.

Table 1. Overview about the population characteristics, fNIRS methodology and data processing, exercise characteristics and cognitive testing, and main outcomes of reviewed studies.

First Author	Sample Characteristics—Number of Participants (*n*)/ Mean Age in Years ± SD	Main Findings	Region of Interest (ROI)
Studies conducting an acute bout of physical activity			
Ando et al. [120]	Healthy young adults *n* = 10 m/25.1 ± 3.4	After cycling vs. prior cycling (normoxia): - ↑ oxyHb and TOI in rt. PFC during CT	rt. PFC
Bediz et al. [117]	Healthy young adults HP *n* = 18 m/21.0 ± 2.6 LP *n* = 17 m/20.6 ± 2.1	After cycling vs. prior cycling: - ↑ oxyHb and total Hb in md. PFC during CT in both groups - ↑ deoxyHb in md. PFC during CT in HP - ↑ oxyHb and totHb in lt. and md. PFC during CT in HP - PP is correlated with oxyHb	lt., rt. and md. PFC
Byun et al. [8]	Healthy young adults *n* = 25 (12 f, 13 m)/20.6 ± 1.0	After cycling vs. control condition (sitting): - ↑ oxyHb in lt. DLPFC and lt. FPA during CT - oxyHb in lt. DLPFC and lt. FPA are associated with RT in CT	lt. and rt. DLPFC, VLPFC; FPA
Chang et al. [115]	Healthy young adults HC *n* = 9 f/21.8 ± 1.4 HIR *n* = 9 f/21.1 ± 1.6 MIC *n* = 9 f/20.4 ± 1.5 HIA *n* = 9 f/22.1 ± 1.4	Post-test (neutral condition): - ↓ TOI in lt. PFC (HIR vs. CON/MIC) Post-test (incongruent condition): - ↓ TOI in lt. PFC (HIR vs. CON/MIC) - ↓ TOI in rt. PFC (HIR vs. CON/MIC/HIA)	lt. and rt. PFC
Endo et al. [98]	Healthy young adults *n* = 13 (8 f, 5 m)/23.0 ± 1.0	After cycling vs. prior cycling: - ↑ oxyHb in DLPFC during CT (40% and 60% intensity) After cycling vs. control condition (sitting): - ↑ oxyHb in DLPFC during CT (60% intensity) (results for 15 min exercise condition/test administration 5 min after exercise cessation)	lt. and/or rt. DLPFC
Faulkner et al. [116]	Healthy young adults *n* = 17 m/24.6 ± 4.3	After cycling vs. prior cylcing: - ↑ rSO_2 in PFC during CT	lt. and rt. PFC

Table 1. *Cont.*

First Author	Sample Characteristics—Number of Participants (*n*)/ Mean Age in Years ± SD	Main Findings	Region of Interest (ROI)
Faulkner et al. [97]	Patients with TIA and HC TIA *n* = 11 (2 f, 9 m)/65.0 ± 10.0 HC *n* = 15 (2 f, 13 m)/62.0 ± 7.0	After cycling vs. prior cycling: - ↑ oxyHb, deoxyHb and totHb in PFC during CT (for test administration 1.5 min after exercise cessation)	dominant side of PFC [1]
Hyodo et al. [7]	Healthy older adults *n* = 16 (5 f, 28 m)/69.3 ± 3.5	After cycling vs. control condition (sitting): - ↑ oxyHb in rt. FPA during CT - oxyHb in rt. FPA is associated with RT in CT	lt. and rt. DLPFC, VLPFC; FPA
Hyodo et al. [77]	Healthy older adults *n* = 13 (6 f, 7 m)/69.7 ± 2.7 (f); 69.3 ± 2.8 (m)	Cycling vs. dancing: - no significant differences between timepoints or groups	lt. and rt. DLPFC, VLPFC; FPA
Kujach et al. [109]	Healthy, sedentary young adults *n* = 25 (9 f, 16 m)/20.7 ± 1.9 (f); 21.1 ± 1.9 (m)	After cycling vs. prior cycling: - ↑ oxyHb in lt. DLPFC post-exercise during CT - oxyHb in lt. DLPFC is associated with RT in CT	lt. and rt. DLPFC, VLPFC; FPA
Lambrick et al. [119]	Healthy children *n* = 20 (11 f, 9 m)/8.8 ± 0.8	After running vs. prior running: - ↑ oxyHb and totHb in PFC post-exercise during CT (at all three time points) - ↑ oxyHb and totHb in PFC post-exercise during CT (1 min vs. 15 min and 30 min post exercise) - total Hb is associated with Stroop completion time (for intermittent group)	dominant side of PFC [1]
Moriya et al. [99]	Patients suffering from stroke *n* = 11 (4 f, 7 m)/69.6 ± 12.0	After cycling vs. prior cycling: - ↑ oxyHb in rt. PFC post-exercise during CT	rt. and lt. PFC
Murata et al. [78]	Healthy young adults *n* = 15 (6 f, 9 m)/21.7 ± 2.4; 21.6 ± 3.0 (f); 21.8 ± 2.2 (m)	After cycling vs. prior cycling: - ↓ lt. DLPFC and SMA post-exercise during CT (Go-trials)	rt. and lt. DLPFC, SMA
Ochi et al. [114]	Healthy young adults *n* = 15 (8 f, 7 m)/20.7 ± 2.1 (18-25)	After cycling (normobaric hypoxia) vs. control condition (sitting/normobaric hypoxia): - ↓ oxyHb in lt. DLPFC post-exercise during CT - oxyHb in lt. DLPFC is associated with RT in CT	lt. and rt. DLPFC, VLPFC; FPA

Table 1. *Cont.*

First Author	Sample Characteristics—Number of Participants (*n*)/ Mean Age in Years ± SD	Main Findings	Region of Interest (ROI)
Sudo et al. [108]	Healthy young adults Stretching group *n* = 8 m/23.9 ± 2.3 Control group *n* = 8 m/23.8 ± 2.1	After stretching vs. prior stretching: - oxyHb, deoxyHb and TOI in lt. PFC no significant differences between timepoints or groups	lt. PFC
Sudo et al. [105]	Healthy young adults Cycling group *n* = 18 m/23.2 ± 2.1 Control group *n* = 14 m/22.3 ± 2.3	After cycling vs. prior cycling: - oxyHb, deoxyHb, totHb and cerebral oxygenation in rt. PFC no differences during CT - Δcerebral oxygenation (TOI) is associated with Δ reaction time	rt. PFC
Tsuchiya et al. [113]	Healthy young adults *n* = 25 (19 f, 6 m)/19.88 ± 0.60 (18-21)	Housework activities vs. control condition: - ↑ oxyHb (trend) in rt. VLPFC during CT (Stroop interference score between post- and pre-sessions)	lt. and rt. DLPFC, VLPFC; FPA
Tsujii et al. [100]	Healthy older adults *n* = 14 (9 f, 7 m)/65.9 ± 1.0	After cycling vs. control condition (sitting): - ↑ oxyHb in lt. PFC during CT	rt. and lt. PFC
Yamazaki et al. [111]	Healthy young adults *n* = 14 (6 f, 8 m)/22 ± 0.6	After recumbent cycling vs. prior cycling: - oxyHb no difference in the ROI's during CT Responders vs. Non-Responders [2]: - ↑ (maximum peak) oxyHb in rt. VLPFC during exercise	lt. and rt. DLPFC, VLPFC; FPA
Yanagisawa et al. [6]	Healthy young adults *n* = 20 (3 f, 17 m)/21.5 ± 4.8	After cycling vs. control condition (sitting): - ↑ oxyHb in lt. DLPFC post-exercise during CT - oxyHb in lt. DLPFC is associated with RT in CT	lt. and rt. DLPFC, VLPFC; FPA
Studies conducting long-term physical exercises			
Chen et al. [102]	Healthy young adults *n* = 42 (26 f, 16 m)/22.5 ± 2.0	Post-test vs. pre-test: - ↑ oxyHb in lt. PFC in BMB (incongruent condition)	lt. and rt. PFC

Table 1. *Cont.*

First Author	Sample Characteristics—Number of Participants (*n*)/ Mean Age in Years ± SD	Main Findings	Region of Interest (ROI)
Coetsee et al. [101]	Healthy older adults HIIT *n* = 13 (10 f, 3 m)/64.5 ± 6.3 MCT *n* = 13 (10 f, 3m)/61.6 ± 5.8 ReT *n* = 22 (15 f, 7 m)/62.4 ± 5.1 CON *n* = 19 (11 f, 8 m)/62.5 ± 5.6	Post-test vs. pre-test: - ↑ oxyHb in lt. PFC in CON (naming condition) - ↑ deoxyHb in lt. PFC in MCT and HIIT (naming and executive condition) - ↓ THI in lt. PFC in MCT (naming and executive condition) - ↓ oxyHb in lt. PFC in ReT (Stroop interference effect) - ↓ THI in lt. PFC in ReT and MCT (Stroop interference effect)	lt.and rt. PFC
Wang et al. [79]	Healthy older adults *n* = 12 (8 f, 4 m)/64.25 ± 3.14 (60 - 68)	Post-test vs. pre-test (after Tai-Chi intervention): - no significant differences between timepoints	frontal cortex
Xu et al. [96]	Obese young adults *n* = 31 (12 f, 19 m)/18.2 ± 3.2	Participants with higher weight reduction vs. participants with lower weight reduction: - ↑ oxyHb in lt. and rt. DLPFC, VLPFC; FPA during CT	lt. and rt. DLPFC, VLPFC; FPA
Cross-sectional studies			
Albinet et al. [13]	Healthy older adults *n* = 40 f/60-77 (low-fit group *n* = 17/high-fit group *n* = 17)	High-fit group vs. low-fit group: - ↑ oxyHb in rt. DLPFC Low-fit group: - ↑ oxyHb in rt. DLPFC compared to lt. DLPFC Correlation between hemodynamic responses during CT and physical fitness: - relationship between aerobic fitness (assessed via VO_2 *max*) and cognitive performance is partly mediated by slope coefficient of oxyHb in the rt. DLPFC (at 1.5 s pace condition)	lt. and rt. DLPFC

Table 1. *Cont.*

First Author	Sample Characteristics—Number of Participants (*n*)/ Mean Age in Years ± SD	Main Findings	Region of Interest (ROI)
Cameron et al. [118]	Healthy young adults *n* = 52 f/20.7 ± 2.3	Correlation between hemodynamic response during CT and measures of physical activity or cognition - higher chronic physical activity level is linked to higher oxyHb and superior cognitive performance - correlation between oxyHb and deoxyHb with RT (difficult condition)	rt. PFC
Dupuy et al. [11]	Healthy younger adults *n* = 22 f/24.6 ± 3.6 (19-34) Healthy older adults *n* = 36 f/62.9 ± 5.4 (55-72)	High-fit individuals vs. low-fit individuals: - ↑ oxyHb in rt. inferior frontal gyrus during CT (naming and executive condition) - ↑ totHb in rt. inferior frontal gyrus during CT (naming and executive condition)	lt. and rt., ant. and post. DLPFC and VLPFC
Fabiani et al. [112]	Healthy, high-fit older adults *n* = 20 (11 f, 9 m)/70.3 ± 4.2 Healthy, low-fit older adults *n* = 24 (13 f, 11 m)/72.2 ± 5.2	High-fit older adults vs. low-fit older adults: - VO_2 peak is correlated with oxyHb but not deoxyHb changes	lt. and rt. occipital cortex
Giles et al. [110]	Healthy young adults *n* = 74 (50 f, 24 m)/19.55 ± 0.27	Correlation between hemodynamic responses during CT and habitual exercise level: - greater habitual exercise level is associated with↓ oxyHb and totHb during CT (negative and neutral pictures/during preparatory period)	ant. PFC and DLPFC
Hyodo et al. [12]	Healthy older adults *n* = 60 m/70.3 ± 3.2	Correlation between hemodynamic responses during CT and physical fitness or cognition: - activation in lt. DLPFC is positively associated with VT - activation in lt. DLPFC is negatively associated with Stroop interference time	lt. and rt. DLPFC

Table 1. *Cont.*

First Author	Sample Characteristics—Number of Participants (*n*)/ Mean Age in Years ± SD	Main Findings	Region of Interest (ROI)
Kato et al. [104]	Healthy young adults *n* = 23 (10 f, 13 m)/22.0 ± 2.2	Correlation between hemodynamic responses during CT and measures of physical activity or sleep duration: - exercise amount is associated with the AUC during CT - exercise amount is correlated with reaction time on fNIRS - percentage of correct responses in CPT-IP are correlated with peak oxyHb - total sleep time is associated with the AUC during CT	lt. and rt. frontal areas
Makizako et al. [107]	Healthy older adults *n* = 20 (10 f, 10 m)/76.1 ± 6.7 (66-89)	Group with high physical activity level vs. group with low physical activity level: - ↑ oxyHb in lt. and rt. IFG during CT	lt. and rt. IFG
Matsuda et al. [106]	Healthy young adults *n* = 40 (15 f, 25 m)/20.4 ± 1.1	Group with high physical activity level vs. group with low physical activity level: - ↑ oxyHb in lt. DLPFC during CT (Interference condition)	lt. DLPFC
Mücke et al. [103]	Healthy children *n* = 50 (24 f, 26 m)/10.6 ± 0.3 (low MVPA *n* = 20/high MVPA *n* = 30)	Group with low MVPA vs. group with high MVPA: - no significant differences in cortical activity between group with low MVPA and group with high MVPA	lt. and rt. ant. PFC; lt. and rt. intermediate and md. frontal region
Suhr and Chellenberg [10]	Healthy, older adults *n* = 22 (17 f, 5 m)/68.26 ± 8.39 (54-89)	Correlation between hemodynamic response during CT and measures of physical activity or cognition: - hours of physical activity are associated with rSO_2 - memory performance is correlated with rSO_2	lt. and rt. DLPFC

Ant: anterior; AUC: area und the curve; BMB: Baduanjin Mind-Body Intervention; CON: control group; CPT-IP: continuous performance test-identical pairs; CT: cognitive testing; deoxyHb: deoxygenated hemoglobin; DLPFC: dorsolateral prefrontal cortex; f: female; FPA: frontopolar area; HC: healthy controls; HIA: high-intensity aerobic exercise; HIIT: high-intensity aerobic interval training; HIR; high-intensity resistance training; HP: high performer; IFG: inferior frontal gyrus; LP: low performer; lt.: left; m: male; MCT: moderate continuous aerobic training; md.: middle; MIC: moderate-intensity exercise combining resistance training and walking; min: minute; MVPA: moderate-to-vigorous physical activity; *n* = number of participants; oxyHb: oxygenated hemoglobin; PFC: prefrontal cortex; post.: posterior; PP: peak performance in exercise test; ROI: region of interest; ReT: resistance training; rt.: right; RT: reaction time; s: second; SD: standard deviation; SMA: supplementary motor area; THI: total hemoglobin index; TIA: patients with transient ischemic attack; TOI (or rSO_2): tissue oxygenation index; totHb: total hemoglobin; VLPFC: ventrolateral prefrontal cortex; VO_2 *max*/VO_2 *peak*: maximal oxygen uptake; vs.: versus; VT: ventilatory threshold; ↑: significant increase; ↓: significant decrease / [1] In right-side dominant participants the probe is placed over right prefrontal cortex while in left-side dominant participants the probe is placed over left prefrontal cortex. / [2] Responders are participants who showed improved task performance in cognitive testing conducted at 5 min after cycling. Non-responder showed no significant improvement in cognitive functions after performing the acute bout of cycling.

4. Discussion

In the following section, we summarize and discuss the methodology and findings of the 35 studies reviewed. With regard to (i) our discussion of the obtained findings, and (ii) general considerations concerning the application and data processing in fNIRS, we derive methodological recommendations for future studies using fNIRS to investigate the influence of physical activity on cognitive performance and cortical hemodynamics (see Table 2).

4.1. How Should the fNIRS Optodes be Placed?

A crucial point in neuroscience is the exact localization of functionally active parts of the human brain [126]. While fNIRS does not provide anatomical information per se, a standardized placement strategy is important to ensure (i) the comparability between studies (and neuroimaging methods, e.g., fMRI), and (ii) a reproducible data assessment of the same cortical structures when conducting repeated measurements [127–130]. The gold standard for anatomical localization of fNIRS optodes is the co-registration with fMRI [29,131]. The co-registration procedure using fMRI scans may ensure high accuracy but is often not feasible because it (i) requires an fMRI scanner, (ii) is costly, (iii) is time consuming, and (iv) may not be used in special cohorts (e.g., children, individuals with metallic implants or claustrophobia) [131]. Alternatively, a digitizer can be used to register 3-D coordinates of the fNIRS channels and project their positions onto an anatomical atlas [131,132].

The most common and practical strategy is to use the EEG 10–20 (or 10–10; 10–5) system to place the optodes [36,61,131,133]. Nearly all fNIRS studies reviewed here used this approach (see Table 1). The standardized EEG positions can be used for a virtual spatial registration of fNIRS optodes [132,134–138]. This procedure allows the probabilistic estimation of the most likely MNI (Montreal Neurological Institute) coordinates of the corresponding fNIRS channels [132,133,136]. Furthermore, EEG positions can be used in conjunction with IBCM (International Consortium for Brain Mapping) head model to accurately place optodes [139,140]. Freely available toolboxes, such as the "Optodes Location Decider (fOLD)" [141] or "Array Designer" [142], can support the placement of the optodes according to the desired cortical region-of-interest (ROI; e.g., derived on the basis of previous fMRI studies). These approaches enhance the anatomical specificity and sensitivity of the probe arrangement [141,142]. Another software package, the "ATLAS-viewer" (downloadable for free), can be applied (i) to ensure that the optodes are placed over a predefined ROI, and (ii) to calculate a spatial sensitivity profile of the distinct probe arrangement assuring that the used probe setup is capable of measuring the cortical compartment of the ROI [143]. In order to achieve highly reproducible hemodynamic responses and to substantially reduce the commonly observed spatial reposition error [144], it can be advantageous to use a neuronavigation system. Indeed, the spatial error significantly decreased when neuronavigation was employed, for instance, in transcranial magnetic stimulation studies [145], but also in fNIRS placing optodes with a neuronavigational device showed promising results regarding applicability and accuracy [146].

Another crucial point in fNIRS is the separation distance between the source and detector because the source–detector separation influences the measurement depth [31,54,62,68,147–149]. Most of the studies reviewed here employed a source–detector separation of 3.0 cm (see Figure 4a). In the literature, 4.0 cm [147] or 3.0 cm [131,150] are recommended as an optimal source–detector distance for adults. For children or infants, source–detector separations below 2.0 cm are recommended [29,131]. In general, longer source–detector separations enhance the contribution of cerebral layers to the obtained hemodynamic signal with the result that with a source–detector separation of 4.0 cm (3.0 cm), the cerebral tissue contributes to 69% (55%) to the optical signal [151]. Given (i) that at longer source-detector distances the contribution of cerebral layers to the signal is larger [148,152–154], (ii) that "too long" source-detector separations (exceeding 4.0–5.0 cm) may degrade the signal quality because of noisier and weaker light input to the detectors [131,149], and (iii) that application of "too long channels" reduces spatial resolution (as less channels can be used) [149], we recommend a source-detector separation of 3.0 to 5.0 cm in adults to ensure (i) that the signal quality is high,

and (ii) that the fNIRS signal mainly depicts cortical activity. In addition, the freely available toolbox "Phoebe" can be used, which allows to calculate an objective measure of the signal-to-noise ratio of the optical signal (based on optode–scalp coupling of the distinct optode) before data recording [155]. These measures can improve the optode–scalp coupling and can, therefore, ensure that the fNIRS data are recorded with an appropriate signal-to-noise ratio. Furthermore, we recommend the usage of long-separation and short-separation channels (also known as "short-distance channels"; see "4.4.2. How should physiological artefacts be removed?").

4.2. How fNIRS Data be Recorded?

Pivotal for neuroscience experiments assessing task-evoked brain activations is the selection of an appropriate baseline condition [21,23,156]. Based on the results of the reviewed studies, baseline brain activation should be assessed in a sitting position to ensure comparability across studies because spontaneous physiological oscillations (e.g., Mayer waves with a period length of about 10 s), which could influence the fNIRS signal quality [69,157], are posture dependent [158,159]. Indeed, substantial changes in oxyHb and deoxyHb concentration [160], as well as in TOI [161], were observed with changes in body position, which, in turn, possibly limits the comparability across studies using different body positions for data acquisition (e.g., supine vs sitting). Consequently, it seems also clear that caution should be paid when findings from fNIRS (e.g., mainly obtained in sitting position) are compared to findings of fMRI (e.g., mainly obtained in supine position).

However, regarding the duration of baseline data assessment, there are two different approaches to be found in the reviewed studies (for an overview, see Figure 4b). In one approach, a relatively short baseline with a maximum of 30 s is used [6–8,12,13,79,99,100,102,104,106,108,109,113,117,120]. Other studies employ relatively long baseline measurements with more than 1 min duration [11,101,103,118]. For the choice of baseline duration, it is crucial to keep in mind that fNIRS is sensitive to mind wandering [162]. Mind wandering occurs in approximately half of the wakening hours [163], especially during situations with low perceptual requirements [164]. Hence, during the baseline period, which constitutes a situation with low perceptual requirements (e.g., still sitting), it is likely that mind wandering will occur. The wandering of the mind leads to the processing of task-unrelated thoughts [165,166] and induces stronger activations in the so-called default network [167]. Activation of the default network changes the recruitment of the prefrontal cortex [162,168] and may influence further analytic steps [36]. To prevent mind wandering, Holtzer and colleagues [169,170] incorporated a simple counting task during the baseline period. This approach could eventually minimize the potentially disadvantageous effects of mind wandering on the analysis of brain activation. However, before such a simple counting task can be recommended, its influence on brain activity and the reproducibility, have to be examined [36].

In addition to mind wandering, it should also be considered that relatively short baseline durations (e.g., 2 s) are assumed to be more affect by random physiological fluctuations and, as consequence, previous reviews recommended a baseline duration of ≈10–30 seconds to ensure appropriate signal-to-noise ratio [68]. Furthermore, especially in studies utilizing block-designs, it seems preferable to use baselines (and inter-stimulus durations) with approximately the same duration as the stimulus because (i) the refraction time (time period with reduced responsiveness) is almost as long as the stimulation phase [171], and (ii) a certain time is required to let the stimulus-evoked cortical hemodynamic responses return to the baseline level [149]. In contrast, in event-related designs, shorter time periods are used for the analysis of the baseline (e.g., 2 s before trial onset) than for the analysis of the cortical hemodynamic responses (e.g., 4–8 s after trial onset) [149,172–174]. Furthermore, since age affects neurovascular coupling and, in turn, the time-shape of the cortical hemodynamic response and its return to baseline levels [149,175], age should be considered as a moderating factor regarding optimal baseline duration. Moreover, it should be considered that the baseline periods between the tasks should not be a multiplier of the Mayer-wave (e.g., $n \times 0.1$ Hz). Consequently, it is more appropriate to use, for instance, 15 s than 10 s for a baseline period. In addition, the duration

of the baseline between trials should vary in their length (e.g., 12–18 s instead of a consistent 12 s) to diminish possible resonance effects.

However, so far, only the required minimum duration for the assessment of connectivity measures in fNIRS studies was investigated [176,177], while, to our knowledge, no study has investigated the optimal duration for baseline brain activity in fNIRS assessment yet. Hence, further investigations are needed to define optimal characteristics (e.g., duration) for baseline brain activity assessment in fNIRS [21,36]. Based on the currently available knowledge, the appropriate baseline duration should be chosen carefully and influencing factors, such as (i) mind wandering, (ii) random physiological fluctuations, (iii) study design (block design versus event-related design), and (iv) age of participants, should be taken into account [149].

In the reviewed studies, both block and event-related designs were commonly applied. The block design provides, for instance, the advantage of an adequate signal-to-noise ratio [178–180]; the obtained results are robust [181] and statistical power is high [179,182]. Disadvantages of the block design are (i) the impossibility of performing a trial-to-trial analysis as in event-related designs [181,183], and (ii) the occurrence of cancelling effects [184]. However, a detailed discussion of the advantages and disadvantages of different study designs in neuroimaging is beyond the scope of this article and the interested reader may find valuable information in the referenced literature [181,183,185].

4.3. How Should the "Optimal" Value for the DPF be Found?

DPF is a dimensionless correction factor that accounts for the increase in the optical pathlength caused by the scattering of light in biological tissue and is multiplied by the source–detector separation to estimate the "true" path length which light has travelled [23,52,121,122]. In the modified Beer–Lambert law, the DPF is used to calculate chromophore concentrations (e.g., oxyHb and deoxyHb; see Figure 2) [186,187]. If the DPF is calculated inaccurately, serious cross-talk error could occur in the determined fNIRS parameters [188], which, in turn, alter the findings and negatively affects the conclusion drawn. Given that the DPF is an such important factor, it is obviously that he should be precisely determined [47,122,123,188–192].

The usage of constant DPF values seems less-than-ideal because DPF values vary largely across individuals [122,123,193,194] and depend on (i) the wavelength used [122,123,192,194], (ii) the cortical area measured [122,123,190,192,195,196], (iii) the participants' age [122,123,192,197], (iv) the size of the detector area [189], and (v) the source–detector separation [189]. Furthermore, as recently observed, the DPF can also change during the experiment [198]. Hence, we recommend the use of formulas allowing the calculation of individual, age-specific (and wavelength-specific) DPF values [122,123] or the direct quantification of the DPF value using frequency- or time-domain fNIRS (optimal solution) [36]. Arbitrary units and saturation or tissue oxygenation indexes, which has also been used in the reviewed studies, provide the advantage that they do not rely on specific DPF values [124,125].

4.4. How Should the Artefacts from the fNIRS Data be Removed?

In the fNIRS signal, three main sources of noise are present: (i) instrumental noise (e.g., low frequency drifts and short noise produced by light instabilities of light sources), (ii) motion-related artefacts (e.g., baseline shifts evoked by movements), and (iii) physiological oscillations (e.g., due heart beats—0.5 to 2.0 Hz, Mayer waves—0.07 to 0.13 Hz; and respiration—0.2 to 0.4 Hz) [47,69,199–203]. To remove those artefacts and physiological components, low-pass filters (e.g., to remove heart rate artefacts) and high-pass filters (e.g., to remove instrumental noise) are employed [29,36,47,69,204]. In most of the reviewed studies, band-pass filters (consisting of low- and high-pass filters) with a cut-off frequency of 0.7 Hz or 0.3 Hz for the low-pass filter and 0.04 Hz for the high-pass filter were applied (Figure 4c and Table S1 in Supplementary Material). Recent reviews recommend cut-off frequencies in the range of 0.5 Hz for low-pass filters and 0.01 Hz for high-pass filters [36,56,205,206]. However, the selection of appropriate filter frequencies in functional neuroimaging also depends on the stimulus protocol [207,208]. Hence, we recommend choosing the cut-off frequencies for (band-pass)

filtering with care in order to avoid the unintended removal of task-evoked cortical hemodynamic responses [204].

As an alternative to the FIR/IIR bandpass filter, we recommend the use of the Savitzky-Golay filter [209], which is widely applied in fNIRS studies [210–212] and ensures that mostly non-related components of the evoked hemodynamic response could be removed, whereas task-related components are preserved [213]. Furthermore, the data obtained from resting-state functional connectivity could also be used to substantially reduce trial-to-trial variability (e.g., arising from low-frequency spontaneous fluctuations) in fNIRS studies [214]. In addition, it is advisable to use more sophisticated filter methods to remove physiological and motion-related noise [36,204–206], which cannot be removed by simple band-pass-filtering (e.g., respiration [204,215]). Examples of such advanced filter methods for the removal of motion-related and physiological noise are given in the next sections.

Additionally, open-source toolboxes such as "HOMER" [204], "NIRS Brain AnalyzIR" [216], "POTATo" [217], "FC-FNIRS" [218], "NIRS-SPM" [219] or "NIRS Analysis Package" [220], "NeuroDOT" [221], or "NIRSTORM" [222] could be used to process and analyze fNIRS data.

4.4.1. How Should Motion-Related Artefacts be Removed?

To remove motion-related artefacts in fNIRS data, a collection of methods is available [199] including task-related component analysis [223–225], correlation-based signal improvement [226], autoregressive algorithm based filters [227], Kalman filter [228], Wiener filter [229], wavelet based filters [201,230–233], accelerometer-based filter methods [234], principal component analysis [201,235,236], Temporal Derivative Distribution Repair method [237], and/or methods based on signal reconstruction using an artificial neural network [238].

Interestingly, sophisticated filter methods like principal component analysis (PCA) were only used in one study so far [11], leaving the potential to optimize data quality with these filter methods in future studies. Wavelet filters or spline interpolation seem especially favorable to remove motion artefacts (e.g., produced by speaking during the cognitive tests) [36,205,206], whereas sudden shifts in fNIRS data (baseline shifts) could be removed using the approach developed by Scholkmann et al. [202]. Remarkably, hybrid filter techniques (e.g., combining spline interpolation method and Savitzky–Golay filtering) provide reasonable improvements in motion artefact removal (e.g., compared to existing approaches such as wavelet filters) [239]. Hence, the application of high-performing filter methods (e.g., hybrid filter methods) should be considered in future studies [239]. Furthermore, movement artefacts can also be reduced by applying multi-distance configurations of the NIRS channels, resulting in a more stable acquisition of the signals [240].

4.4.2. How Should Physiological Artefacts be Removed?

Since a vast amount of literature shows that fNIRS is vulnerable to physiological noise, such as blood flow changes in the extracerebral compartment [30,70,210,211,241–252], which may cause false positive results [69], these artefacts should be reduced. A powerful tool to reduce extracerebral physiological noise is to use a combination of NIRS light channels with a short source–detector separation and with a long source–detector separation [61,152,210,211,253–260]. The integration of short-separation channels is suggested based on the following facts. The penetration depth of light is almost half the source–detector distance [148] so that channels with short separations (around 1.0 cm) mostly detect signals from non-cerebral layers [61,68,243,256,261] (see Figure 1a). The signals from these extracerebral layers can then be used to filter the signals of the "long-separation channels" (e.g., 3.0 cm source–detector separation; see Figure 1b). The optimal separation for the short-separation channels may vary across different cortical regions [253,256], but it is generally accepted that short-separation channels (i) should have a source–detector separation of < 1.0 cm [256], and (ii) should not be located further away than 1.5 cm from the standard fNIRS channel [253]. While both short-separation channels and long-separation channels were measured only in four

reviewed studies [105,113,116,120], the application of additional short-separation channels should be the standard procedure in future studies [61]. However, it should also be noted that short-separation channels could be more prone to motion artefacts and that the use of "too noisy" short-separation channels as regressors could introduce additional error in the data analysis [262].

In addition, we recommend the usage of a heart rate monitor. Assessment of the heart rate can be helpful for the interpretation of the cortical hemodynamic changes measured with fNIRS since (i) the heart rate is associated with systematic changes in blood flow (blood pressure) [69], (ii) the heart rate variability provides additional information about the state of the autonomic nervous system [263,264], (iii) the heart rate variability is associated with cognitive performance and mental workload [265–267], and (iv) the heart rate is suggested to be a potential marker for the optimal timing of post-exercise cognitive test administration [268]. Furthermore, devices measuring electrodermal activity, respiration, or mean arterial pressure may be useful tool for the assessment of systemic changes in bodily functions that could alter the fNIRS signal [30,69,71,72,249,269,270]. Mean arterial pressure is important in order to identify the real source of the observed oxygenation changes over the head and to avoid false positive results (for a review, please see Reference [69]), and future studies should measure fNIRS signals in parallel with multiple physiological parameters [72,270–272]. The combination of fNIRS neuroimaging with the parallel measurement and analysis of systemic physiological signals has been termed "systemic physiological augmented fNIRS" (SPA-FNIRS) recently [72,271].

4.5. How Should the fNIRS Data be Processed after Filtering?

As almost all studies reviewed in this work did so, and based on another methodological fNIRS review [36], we recommend performing a baseline correction/normalization and averaging across channels and/or trials after filtering the data. Baseline correction/normalization accounts for the individual variability of fNIRS data [118,273], while averaging across channels and/or trials enhances the reproducibility of fNIRS measurements [130,274–276]. However, we strongly recommend reporting on which criteria the averaging procedures are based (e.g., selected channels belong to the same ROI).

Furthermore, the majority of reviewed studies used mean values calculated over a distinct time period to analyze cortical activity. The usage of mean values is preferable compared to the use of peak values because peak values are more dependant on the accurate removal of motion and other artefacts [277]. In one study the median values over the whole task period were used for statistical analysis [118]. The median values calculated across a distinct task period are less influenced by outliers as compared to mean or peak values [278]. As frequently shown [72,210–212,271], median values are best suited in fNIRS studies with small sample sizes that are otherwise prone to statistical effects driven by outliers [278]. However, Khan and colleagues [279] propose that several measurement parameters should be provided (e.g., mean signal value, signal peak, and the sum of peaks) in order to best describe the brain state [279]. In addition, future studies may use the variability of brain signals (e.g., oxyHb or deoxyHb) to study the effect of exercise on cognitive performance because the investigation of variability may allow a deeper understanding of the functioning of the central nervous system [280–285].

Regarding the temporal window for the analysis, it should be considered that there is in general a certain delay (e.g., ≈6 s) after stimulus representation and the peak of the cortical hemodynamic [34,41,59,131,286–288], whereby this latency is influenced by the performed task [289,290], and that the temporal courses of deoxyHb and oxyHb concentration changes are different [290–295]. The cortical hemodynamic response does not normally go back to the baseline level before ≈10 s (≈16 s) after stimulus presentation [296,297]. However, a consensus about an optimal temporal window for analysis has not been achieved yet [131] because what temporal duration is suited best depends on the used paradigm and the participants' characteristics (e.g., age).

Regarding the analysis of fNIRS data, there is an ongoing debate regarding which measure (e.g., oxyHb, deoxyHb, totHB) is the optimal proxy of neuronal activation in the cortex [29,58,147,298,299]. We recommend assessing and reporting the changes of at least oxyHb

and deoxyHb because (i) typically neuronal activity is assumed to be mirrored by an increase of oxyHb and a decrease in deoxyHb [34,48,49,58]; (ii) in deoxyHb signals, less physiological noise is present [58,70,144,298,300–302], but oxyHb signals have a higher signal-to-noise ratio as compared to deoxyHb signals [298,303]; (iii) the decrease in deoxyHb [304–307] and the increase in oxyHb [303,308] are both related to an increase in the BOLD contrast obtained in fMRI; (iv) oxyHb exhibits an acceptable high reproducibility [127,128,275,309], but deoxyHb is spatially more focused [144,310,311]; (v) deoxyHb sometimes shows an arbitrary and paradoxical signal changes [196,312–315], whereas oxyHb is assumed to be the more sensitive marker of regional blood flow changes [195,316]; (vi) pathologies may influence neurovascular coupling so that an decrease in deoxyHb does not necessarily reflect an increase in neural activity [48]; and (vii) single measures (oxyHb or deoxyHb) may not be sufficient to characterize the neurovascular response of neuronal tissue [293]. Noteworthy, sometimes researchers are confronted with atypical changes in oxyHb and deoxyHb concentration (e.g., decrease in oxyHb and increase in deoxyHb). There are several explanations for this phenomenon. Atypical changes in fNIRS signals can be caused in part by systemic physiological noise [69,71,249], by partial volume effects (e.g., caused by the mixing of signals from different tissue types) [303,306,317,318], or by the presence of certain pathophysiological changes (e.g., where the inverse response is perhaps a sign of brain activation) [48]. Furthermore, such inverse hemodynamic responses (e.g., decrease oxyHb and increase deoxyHb) could also be related to subject-specific factors (e.g., individual cognitive processes) [318]. However, as of today, this phenomenon is only partially understood, and an in-depth discussion of current explanative approaches can be found in Holper et al. [318].

While the optimal way to statistically analyze fNIRS data is still discussed and no standardized procedure has been established yet [36,69,319,320], the majority of studies reviewed used ANOVAs to statistically analyze their fNIRS data. If an ANOVA is used for statistical analysis of fNIRS data, setting ROIs as a factor should be avoided because the optical properties vary systematically across different ROIs, which could cause systematic biases in the statistical analysis of the data [6–8,109,114]. Furthermore, most studies reviewed used a Bonferroni correction to account for the multiple comparison problem. Notably, Singh and Dan [321] recommend the use of the false discovery rate (FDR) instead of the Bonferroni correction since FDR is less conservative than a Bonferroni correction [322,323]. Hence, future studies using fNIRS to investigate the exercise–cognition interaction should consider the application of FDR instead of a Bonferroni correction. Moreover, some authors favor the use of general linear models (GLM) to analyze fNIRS data statistically [219,319,320]. A GLM offers the possibility (i) to take the temporal shape of the hemodynamic response into account [319], and (ii) to incorporate multiple regressors (e.g., confounding signals such as scalp blood flow or heart rate) into a single statistical framework [69,320]. The latter point is especially interesting in (statistical) analysis of fNIRS data since fNIRS signals can be affected by a variety of artefacts (e.g., motion artefacts or systemic physiological artefacts) influencing the analysis and results negatively. For instance, if fNIRS data are preprocessed inappropriately (e.g., inappropriate filtering), so that the statistical assumption is violated, this will increase the type-I error substantially [262,320]. Consequently, an approach to achieve more trustworthy results is the use of sophisticated filter methods (e.g., describe in Sections 4.4, 4.4.1, and 4.4.2), which appropriately remove artefacts so that they will no longer violate the assumptions of the statistical model [320]. A second approach is the application of statistical model correction methods (e.g., adopting the GLM by using "noise prewhitening") to ensure that artefacts do not violate any statistical assumption of the used model, which, in turn, helps to obtain more reliable results [320]. From another point of view, multiple and different experimental conditions (crossed) and/or multiple measurements per experimental condition (nested) are regularly used to study the human brain [324,325]. Moreover, researchers are faced with (i) unbalanced and/or incomplete data sets, and (ii) categorical or continuous confounding variables (e.g., gender, educational level, responsiveness, genetic background), which have to be considered in the statistical analysis [324,326,327]. Hence, further fNIRS studies should also consider the application

of sophisticated statistical methods such as linear mixed-effect models to account for the mentioned issues [324,325].

To sum up, in general, the statistical methods used should depend on the research question(s) and the experimental design [36,328]. For instance, whereas in event-related designs, the GLM is an appropriate method [328], simple statistics (e.g. t-tests) are commonly used in block-design studies [36,319]. Finally, the statistical methods and procedures applied to analyze fNIRS data should be chosen carefully and should consider, for instance, the experimental design, data recording and processing characteristics as well as the distribution of the recorded data (e.g., normal versus non-normal distributed data) [36]. Since a complete discussion of statistical analyses is beyond the scope of this review, the interested reader will find valuable and more detailed information in the referenced literature [219,319,320,329].

4.6. Cortical Hemodynamics during Cognitive Testing in Response to Physical Activity

In general, a higher activity of cortical structures (during cognitive testing) was observed after the cessation of an acute bout of physical activity (e.g., aerobic activities such as cycling) when compared to the cortical activity (i) measured before being physically active, or (ii) in a control condition (e.g., sitting). Since fNIRS signals are substantially affected by systemic physiological artefacts [70–72,241,242,247–249,251,252,271], it could be assumed that effects of physical activity on measured cortical oxygenation levels (after being physically active) are mainly caused by the systemic physiological artefacts (e.g., higher heart rate or superficial blood flow). Indeed, the findings of a methodological study suggest that fNIRS signals after the cessation of ten minutes of cycling are influenced up to approximately eight minutes by systemic physiological artefacts (depending on the intensity of the physical activity) [87]. Hence, the results of studies performing cognitive testing in close succession to physical activity (<~ 8 min) [8,77,78,97,98,105,108,111,113,116,117,119,120] should be treated with caution because the observed fNIRS signal changes could be, at least partly, influenced by systemic physiological artefacts. However, based on the following findings, it also becomes evident that changes in neuronal activity contributed to the measured fNIRS signal, too. For example, one study tested cognitive functions after the cessation of cycling and noticed a significantly lower cortical activity in the prefrontal cortex as compared to cortical activity before cycling [78]. Such decreased cortical activity after the cessation of moderate-intensity cycling stands in contrast to the to-be-expected effects of systemic physiological artefacts occurring after being physically active (e.g., higher heart rate). The latter would presumably induce a higher (but "false positive") cortical activity. Hence, it seems reasonable to assume that at least a certain degree of the observed fNIRS signal is of neuronal origin if during a cognitive test, which was performed after the cessation of moderate-intensity cycling, a lower cortical activity is noticed [78]. Furthermore, if the observed higher cortical activity after an acute bout of physical activity was mainly caused by systemic physiological artefacts, the whole prefrontal cortex should be affected by the systemic physiological changes. Notably, higher cortical activity was observed only in distinct parts rather than in the whole prefrontal cortex [6–8,109,114] supporting the notion that the fNIRS signal is at least partly of neuronal origin. This assumption is further supported by the observation of a positive neurobehavioral relationship between cortical activity in distinct parts of prefrontal cortex and cognitive performance [6–8,105,109,119]. In addition to systemic physiological changes, it could be speculated that the commonly observed increase in cortical activity after being physically active is attributable to learning effects, which may occur in a repeated-measures design. However, a significantly higher cortical activity during cognitive testing was even observed in studies employing a counterbalanced order of conditions (e.g., cycling versus sitting) [6–8]. Hence, it is unlikely that the pronounced cortical activation seen after physical activity is predominantly caused by learning effects. This assumption is underpinned by findings of decreased cortical activity in response to learning (e.g., motor learning) [330–332].

The observations that (i) oxyHb concentration did not increase significantly after slow dancing [77], stretching [108], or after maximal exercise testing [105] is likely to be related to the moderating effects

of (i) the characteristics of the physical activities (e.g., to low intensity (dancing, stretching)), and (ii) the study methodology (e.g., time point of cognitive test administration; i.e., 2 min after maximal exercise test), which are known to influence cognitive performance [17,333–335]. The lower concentration of oxyHb in DLPFC after cycling under normobaric hypoxic conditions [114] may explain why cognitive performance is commonly found to be lower after exposure to hypoxia [336].

Regarding long-term exercise studies and cross-sectional studies, the link between a higher level of cardiorespiratory fitness and/or physical activity and higher levels of cortical activity [10–13,96,101,104,106,107,112,118] is in accordance with the cardiorespiratory fitness hypothesis, which claims that cardiorespiratory fitness has a positive influence on cerebrovascular structure and function [90,337–339]. However, in none of these longitudinal and cross-sectional studies (e.g., using continuous-wave NIRS), physiological artefacts were corrected by measures of systemic physiological changes (e.g., extracerebral noise via short-separation channel regression). While the relationships between measures of cortical activity and cognitive performance [10,12,104,118] suggest that the fNIRS signals stem to a certain degree from neuronal activity, the application of, for instance, short-separation channel regression, allowing for a more accurate localization of the signal origin (extracerebral changes versus neuronal activity changes). As a consequence of the improved signal quality (e.g. through short-separation channel regression), the conclusions derived from fNIRS-measured proxies of cortical activity (e.g., oxyHb and deoxyHb) become more valid and reliable, which, in turn, fosters our understanding of the relationship of physical activity, cortical hemodynamics and cognition.

To sum up, based on the evidence that (i) systematic artefacts may contaminate fNIRS signals up to 8 min after being physically active [87], and (ii) higher effect sizes were evident after a temporal delay compared to cognitive testing immediately after being physically active [333], we recommend that future studies aimed at investigating the effects of an acute bout of physical activities incorporate a temporal delay (e.g., ≈8 min) between the cessation of the physical activity and the beginning of cognitive testing. Furthermore, we recommend the assessment of multiple physiological measures (see Section 4.4.2 "How Should Physiological Artefacts be Removed?") to improve the signal quality and, in turn, validity of the observations.

Additionally, in future studies, follow-up measurements should be undertaken because only four of the reviewed studies performed follow-up testing [97,98,111,119], which limits our knowledge about the temporal course of the relationship between physical activity, cortical hemodynamics, and cognition. Finally, the following general recommendations should also be considered when designing studies investigating the influence of physical activity on cognition while measuring cortical hemodynamics with fNIRS:

(i) Chronobiological effects (circadian variability) affects cognitive performance [340–342], although it is reported that the hemodynamic response is relatively unaffected by circadian variability [343].

(ii) Cognitive tasks that necessitate (inner) speech could induce hypocapnia (i.e. a decrease in the arterial carbon dioxide (CO_2) concentration in the blood), which provokes a cerebral vasoconstriction and lower cerebral blood flow that results in a reduced concentration of total hemoglobin and thus also oxygenated and deoxygenated hemoglobin [270,344–346]. Exemplarily, if the task is changing the respiration (rate or depth) of the subject, the fNIRS data will likely be influenced by this CO_2 effect and will not represent changes in neurovascular coupling primarily.

(iii) Participants should be familiarized with the cognitive test to avoid (or at least minimize) learning effects [347,348] and to increase the reproducibility of the observed cognitive effects [349].

(iv) The biological sex of the participants influences the relationship between physical activity and cognition [350–353]. Sex-specific changes are also noticed in fNIRS signals obtained during cognitive testing [354,355]. Hence, the biological sex of the participants should be considered as a moderating factor in future studies.

Table 2. Recommendations for fNIRS application, fNIRS data processing and fNIRS data analysis

fNIRS recording	
Optode placement	Optimal solution: ▪ Use a neuronavigational approach Alternative solution: ▪ Use 10-20 (10-10 or 10-5) international EEG-system ➢ If MRI scan is possible → Co-registration ➢ If MRI scan is not possible → Registration via 3-D-Digitizer *or* → Virtual spatial (probabilistic) registration
Source–detector separation	▪ At least 3.0 cm for "long-separation channels" ▪ Around 0.8 cm for "short-separation channels"
Baseline recording	▪ Record baseline in sitting position ▪ Choose an appropriate baseline duration (e.g., with regard to study design) ▪ Ensure that the fNIRS channels have a good SNR (e.g., look for blood volume pulsation)
fNIRS data processing: conversion and artefact removal	
Conversion of optical density changes into concentration changes of chromophores (e.g. oxyHb, deoxyHb, totHb)	▪ Apply modified Beer–Lambert law with appropriate μa and DPF values
- DPF value determination	Optimal solution: ▪ Direct quantification of DPF values using frequency- or time-domain fNIRS Alternative solution: ▪ Use formulas allowing the calculation of individual, age-specific, and wavelength-specific DPF values
Artefact removal	
Removal of motion artefacts *	▪ Use of high-performing methods (e.g., Wavelet filtering or hybrid filter methods)
Removal of physiological artefacts	▪ Use of high-performing methods (e.g., SDS regression to filter out extracerebral signal components)
General artefact removal	▪ Use a band-pass filtering with appropriate cut-off frequencies (e.g. considering stimulus or task paradigm)
fNIRS data processing: further analysis	
Detrending	▪ Perform baseline correction or normalization
Analysis	▪ Perform averaging across channels and trials *or* perform GLM analysis [#] ▪ Choose an appropriate temporal window (e.g., consider delay in hemodynamic responses) ▪ Use at least oxyHb and deoxyHb for statistical analysis

deoxyHb: deoxygenated hemoglobin; DPF: differential path length factor; EEG: electroencephalography; fNIRS: functional near-infrared spectroscopy; GLM: general linear model; μa: absorption coefficient; MRI: magnetic resonance imaging; oxyHb: oxygenated hemoglobin; SDS: short-separation channel (also known as short-distance channel); SNR: signal-to-noise ratio/* Filtering of motion artefacts can also be conducted on optical density data (before conversion into concentration changes) depending on the used filter methods and/or software solution. / [#] Please note, if distinct types of GLM are used (e.g., GLM with model correction methods) the processing steps are divergent from those shown in the table and some of the given recommendations do not apply in this particular case.

5. Conclusions

All in all, the application of neuroimaging tools (e.g., fNIRS) is pivotal to better understand the influence of physical-activity-induced mechanisms on cognitive performance. Based on the advantages of fNIRS, this neuroimaging method is a promising tool to shed light on physical-activity-induced functional brain changes (e.g., changes in cortical hemodynamics during cognitive testing). However, currently no standardized procedures with respect to the application of fNIRS and processing of fNIRS data in exercise–cognition science have been established which clearly limits the comparability across studies. To come closer to more standardized protocols, this systematic review aims to summarize the methodological details of studies applying fNIRS to investigate the influence of physical activity on cognitive performance and underlying neurobiological processes (e.g., cortical hemodynamics). Therefore, 35 fNIRS studies were carefully reviewed and based on our finding's, methodological recommendations for further fNIRS studies in the field of exercise–cognition were derived (see Table 2). Hopefully, this methodology-focused, systematic review encourages further research in this field which is strongly needed to better understand underlying neurobiological mechanisms of exercise–cognition interaction. A growing knowledge in exercise–cognition interaction may contribute to the development of more efficient physical intervention approaches [356] aiming to prevent (or deaccelerate the onset of) age-related cognitive decline which is associated with neurological diseases such as dementia [357–359].

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/7/12/466/s1, Figure S1: Overview on (**a**) number of subjects investigated, (**b**) sampling frequencies (**c**) wavelengths, (**d**) number of channels, (**e**) differential pathlength factors (DPF), (**f**) types of physical activities/exercises and (**g**) durations of physical activities/exercises. Table S1: Overview about data recording (e.g., used sampling frequency, wavelengths, number of measurement channels, fNIRS devices, optode placement and source-detector separation), data processing (e.g., filter frequencies, DPF values, markers of cortical activity) and characteristics of physical activities (e.g., type, duration and intensity of the physical activity) in the studies reviewed.

Author Contributions: F.H. wrote the manuscript and conducted the systematic literature search. P.W. conducted the systematic literature search and reviewed the drafted versions. F.S. reviewed the drafted versions and assisted with data visualization. N.G.M. reviewed the drafted versions. All authors have read and approved the final version.

Funding: No funding information is applicable.

Acknowledgments: The authors have nothing to acknowledge.

Conflicts of Interest: The authors declare no conflict of interest.

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Hypothesis

Strengthening the Brain—Is Resistance Training with Blood Flow Restriction an Effective Strategy for Cognitive Improvement?

Alexander Törpel [1,*], Fabian Herold [2], Dennis Hamacher [1], Notger G. Müller [2,3,4] and Lutz Schega [1]

1 Institute III, Department of Sport Science, Otto von Guericke University Magdeburg, Zschokkestr. 32, 39104 Magdeburg, Germany; dennis.hamacher@ovgu.de (D.H.); lutz.schega@ovgu.de (L.S.)
2 Research Group Neuroprotection, German Center for Neurodegenerative Diseases (DZNE), Leipziger Str. 44, 39120 Magdeburg, Germany; Fabian.Herold@dzne.de (F.H.); notger.mueller@dzne.de (N.G.M.)
3 Center for Behavioral Brain Sciences (CBBS), Universitätsplatz 2, 39106 Magdeburg, Germany
4 Department of Neurology, Medical Faculty, Otto von Guericke University, Leipziger Str. 44, 39120 Magdeburg, Germany
* Correspondence: alexander.toerpel@ovgu.de; Tel.: +49-391-67-56600

Received: 11 September 2018; Accepted: 5 October 2018; Published: 9 October 2018

Abstract: Aging is accompanied by a decrease in physical capabilities (e.g., strength loss) and cognitive decline. The observed bidirectional relationship between physical activity and brain health suggests that physical activities could be beneficial to maintain and improve brain functioning (e.g., cognitive performance). However, the exercise type (e.g., resistance training, endurance training) and their exercise variables (e.g., load, duration, frequency) for an effective physical activity that optimally enhance cognitive performance are still unknown. There is growing evidence that resistance training induces substantial brain changes which contribute to improved cognitive functions. A relative new method in the field of resistance training is blood flow restriction training (BFR). While resistance training with BFR is widely studied in the context of muscular performance, this training strategy also induces an activation of signaling pathways associated with neuroplasticity and cognitive functions. Based on this, it seems reasonable to hypothesize that resistance training with BFR is a promising new strategy to boost the effectiveness of resistance training interventions regarding cognitive performance. To support our hypothesis, we provide rationales of possible adaptation processes induced by resistance training with BFR. Furthermore, we outline recommendations for future studies planning to investigate the effects of resistance training with BFR on cognition.

Keywords: cognition; strength training; blood flow restriction; neuroplasticity

1. Introduction

From the third decade of life, degenerative changes of the human organism increase which leads on the one hand to a reduced physical performance and on the other hand to a decline of cognitive functions. In terms of physical performance, especially the loss of muscle mass [1–4] contributes to a decrease in muscular strength which, in turn, impairs activities of daily living (e.g., walking) [5,6]. However, musculature is the main effector organ for developing muscular strength which is important to ensure motion respectively locomotion (e.g., walking safely) [7–9]. Therefore, the integrity of the musculature and the muscle strength is of great importance throughout the entire life span. Moreover, the mentioned age-related decreases in muscle mass and strength (because of aging) are also associated with morphological losses in the brain and decreased cognitive functions [10–13]. Because

of those changes, especially cognitive functions such as memory and processing speed are negatively affected [14–18]. Furthermore, aging-related changes of the brain are considered risk factors for the development of neurological diseases (e.g., dementia) [19,20]. Dementia is associated with cognitive impairments negatively affecting quality of life and independent living [19,21]. Based on the limited ability of individuals with neurological diseases (e.g., dementia) to live independently, an intensive medical care is needed which, in turn, consumes a large amount of resources of the welfare systems of industrialized nations [22–25].

So far, no pharmacological interventions are sufficient to treat the mentioned age-associated declines [26–30]. But, there is growing evidence with respect to positive effects of physical activity preventing and treating morphological and functional losses in muscles [31] and the brain [32,33]. In recent years, evidence has emerged emphasizing the existence of a bidirectional relationship between physical performance and brain health [34,35]. For instance, as mentioned above, a decrease in muscular performance is associated with a decrease in cognitive functioning [36–38]. Consequently, the bidirectional relationship suggests that physical training (means a structured, planned, dosed, and systematic form of physical activity with the focused aim to increase physical performance and/or health; e.g., through resistance training) may be a valuable intervention strategy to deaccelerate not only physical but also cognitive decline in old age. However, the exercise type (e.g., resistance training, endurance training) and exercise variables (e.g., load, duration, frequency), which would be optimal to efficiently enhance cognitive performance are largely unknown [39–49].

A promising and cost-effective physical intervention strategy [50–52] which preserves and enhances both, physical performance (especially with regard to the musculature) [53–60] and cognitive functions [61–65], is resistance training (also known as strength training). The underlying neurobiological mechanisms and effects of resistance training on cognition are described in the following section.

2. Effects and Mechanisms of Resistance Training on Cognition

The underlying neurobiological processes which are triggered by resistance exercises and have been related to cognitive performance improvements, are not fully understood, yet [61,65,66]. Based on the promising framework of Stillman et al. [67] about mediators of physical activity (in this case resistance exercises) influencing cognitive performance on different levels (cellular and molecular level, structural and functional level and behavioral/socioemotional level) [67], the current knowledge of possible neurobiological mechanisms contributing to the improvement of cognitive functions in response to resistance training are summarized in the following.

On the cellular and molecular level, a possible key mechanism of resistance training that contributes to cognitive improvements is the pronounced release of the multifaceted acting insulin-like growth factor 1 (IGF-1) [61,62,66,68–70]. In response to resistance training, IGF-1 is mainly expressed by the liver (global output, ~70% of total circulating IGF-1), musculature (local output) and the brain (local output) itself [71,72]. Circulating IGF-1 can cross the blood-brain barrier (BBB) which is therefore also available to the brain [71,72]. While an increased IGF-1 level is associated with proliferation, differentiation, survival, and migration of neuronal progenitors [73,74], synaptic processes (e.g., Long-Term Potentiation) [74,75], angiogenesis in the brain, neuroprotection, axon outgrowth, dendritic maturation, and synaptogenesis [72,76], a deficiency of IGF-1 is associated with the risk of harmful cerebrovascular events (e.g., ischemic stroke or impaired neurovascular coupling) [77,78]. Consequently, it is not surprising that a relationship between cognitive functions and IGF-1 level in older individuals [79] and in individuals with mild cognitive impairments was observed [80]. Furthermore, it is assumed that there is a potential relationship between diminished IGF-1 levels and neurodegenerative diseases [73,80,81], which suggests that influencing IGF-1 levels is a promising target for efficient treatments.

In fact, serum IGF-1 concentration levels are increased after a single bout of resistance activities (short-term) [82] and long-term (also known as “chronic”; >2 exercise sessions) resistance training in

humans [83,84]. However, currently there is only low evidence postulating a solid relationship between physical exercise-induced modulation of IGF-1 release and cognitive functions [85]. Nevertheless, one study reveals that basal changes of IGF-1 concentrations after a long-term resistance exercise intervention are associated with cognitive performance improvements [83]. Hence, further studies are needed to get a deeper understanding of the relationship of exercise-induced modulation of IGF-1 release and cognition [85].

On the structural level, Fontes et al. [86] observed that in older individuals, the grey matter density increases in the posterior and anterior lobe of the cerebellum, superior frontal gyrus in the frontal lobe and anterior cingulate cortex in the limbic lobe in response to a 12 weeks resistance training [86]. After a 6 months resistance exercise training program, an increase in cortical thickness in posterior cingulate cortex was observed which correlated with improvements in an overall cognition score [87]. Furthermore, in the study of Liu-Ambrose et al. [88], a reduced whole-brain volume after the end of 12 months resistance intervention as compared to control groups (balance and tone group) was noticed [88]. The reduced brain volume might be the consequence of dissolve degenerative changes of the brain such as amyloid plaques [46,88,89]. However, the distinct neuronal adaptions in response to resistance exercise interventions with different exercise variables suggest that a certain dose-response relationship between physical exercise variables and neural adaptations exists, although this dose-response relationship is currently poorly understood and has to be investigated in further studies [42,64,90–93].

In addition, long-term resistance training is associated with decreased white matter atrophy at follow-up measurements [94] and lower white matter lesions volume was observed after 52 weeks of a resistance training exercise regime [95]. White matter changes are known to influence cognitive performance especially in processing-speed-dependent cognitive tasks [96–99].

On the functional level, changes can be quantified either by measuring the activity of brain regions (for instance with electroencephalography [EEG], functional near-infrared spectroscopy [fNIRS], or functional magnetic resonance imaging [fMRI]) and/or by testing cognitive functions. Both, brain activity and cognitive functions were investigated after short-term and long-term resistance training to identify beneficial effects of this type of exercise on brain as well as cognitive performance [64]. In response to an acute bout of moderate-load [100] and high-load resistance training, an improvement in cognitive functions (higher number of solved items and lower reaction times in neutral Stroop task condition compared to non-exercising control group) and a decrease in the tissue oxygenation index in left and right prefrontal cortex was observed [101]. In the same manner, it has been shown that resistance training lasting several months can lead to a substantial increase in cognitive functions [62–64,83,88,94,102,103]. Furthermore, after a long-term resistance training intervention, a decreased cortical activation in prefrontal areas (lower concentration of oxygenated hemoglobin and total hemoglobin index values measured by fNIRS) during a standardized cognitive test (e.g., Stroop-test) was noticed [104]. A decreased activation in prefrontal areas and a simultaneous increase in cognitive functions may point towards a higher automatization in behavioral tasks or the redistribution of resources in other task-relevant cortical areas. The notion that higher levels of strengths are beneficial for cognitive performance is further supported by numerous cross-sectional studies observing that an improvement of hand grip strength [38,105,106], quadriceps strength [37], leg power [107], or whole body muscle strength [36] are linked to higher cognitive performance. Regarding the longitudinal and cross-sectional studies, the question arises whether (baseline) strength level per se [108] or adaptation processes evoked by regularly conducted resistance training (see above mentioned adaptations on cellular, molecular and structural level) are more beneficial for cognitive performance. Based on the current available scientific literature, we cannot unequivocally answer this question. As shown, there is evidence for both approaches (baseline strength vs. adaptation processes evoked by regularly conducted resistance training). But maybe just the combination of both has positive effects on cognitive functions.

On the behavioral/socioemotional level, the improvements in cognitive functions (e.g., executive functions) and the reduced activity of the prefrontal cortex are, for instance, linked to the functioning of the motor control of activities of daily living such as walking safely [109–113]. This phenomenon underpins the need to persevere the capacity of executive functions especially in older individuals in order to ensure mobility and independent living. Furthermore, because of the relationship between cognitive functions and quality of life [114], improvements in cognitive functions might be associated with an enhanced socioemotional status (e.g., decreased symptoms of depression and anxiety, increased joyful activities of daily living). Here, positive effects of resistance training on quality of life have been noticed [115].

However, concerning the effectiveness of the type of exercise, it was reported that resistance training is less effective than aerobic exercises regarding the improvement of cognitive performance on behavioral/socioemotional level [116] or on functional level regarding the task-related oxygenation of brain regions [101,104]. Nevertheless, there are several strategies to increase the effectiveness of resistance exercise regimes. A potential strategy which is likely to be beneficial to increase the efficiency of resistance training is the application of devices (e.g., cuffs) modulating the blood flow to and away from the muscles. This type of training is known as blood flow restriction training (BFR). So far, the higher effectiveness of resistance training with BFR compared to resistance training without BFR has only been investigated in the context of muscle physiological adaptions and strength improvements [117–119]. Whether resistance training with BFR provides also positive neurocognitive effects that are potentially greater than those effects observed after "traditional" resistance training interventions (resistance training without BFR) will be discussed in detail in the following section.

3. Resistance Training with Blood Flow Restriction—An Added Value for Cognition?

A way to increase the efficiency of resistance training is the specific manipulation of different exercise variables such as load, volume (repetitions, sets), rest periods, repetition velocity, choice of exercise, order of exercise, frequency or muscle action. [120]. Here, a certain dose-response relationship regarding certain exercise variables (e.g., load) can be observed [61,121,122]. Another, newer "manipulation strategy" to increase the efficiency of resistance training includes the application of hypoxic stimuli [123–126]. Hypoxic stimulation during resistance exercises could be achieved by applying (i) localized hypoxia or (ii) systemic hypoxia [125]. Localized hypoxia can be achieved with applying BFR which is in the literature also referred to as *occlusion training*. The training method BFR is characterized by the restriction / manipulation of the blood flow to and away from the limbs due to the application of elastic straps or inflatable pressure cuffs (e.g., blood pressure cuffs) to the proximal portion of the limbs (see Figure 1A,B) [117,125,127–130]. The manipulation of the blood flow especially decreases the venous return, which increases the accumulation of metabolites in the muscle triggering pronounced adaptational processes [117,125,127–130]. A particular type of BFR is KAATSU where special inflatable cuffs with pressure sensors are used [131]. Even though KAATSU is considered a type of BFR, this term is in a strict sense only applicable if KAATSU-equipment in BFR training is used. As consequence of the special construction of KAATSU-cuffs and their distinct application protocol, it is likely that differences between KAATSU and other BFR methods regarding the physiological stimuli occur. So far, these possible physiological differences between KAATSU and other BFR methods have not been directly and systematically compared. In this manuscript, the term BFR will therefore also include KAATSU training studies.

In general, systemic hypoxia is provided by breathing oxygen-reduced air [125]. Here, the oxygen-reduced air can be applied, for instance, with mask-system hypoxicators or via a stay in special rooms where the fraction of inspired oxygen is decreased (also known as normobaric altitude chambers) [132].

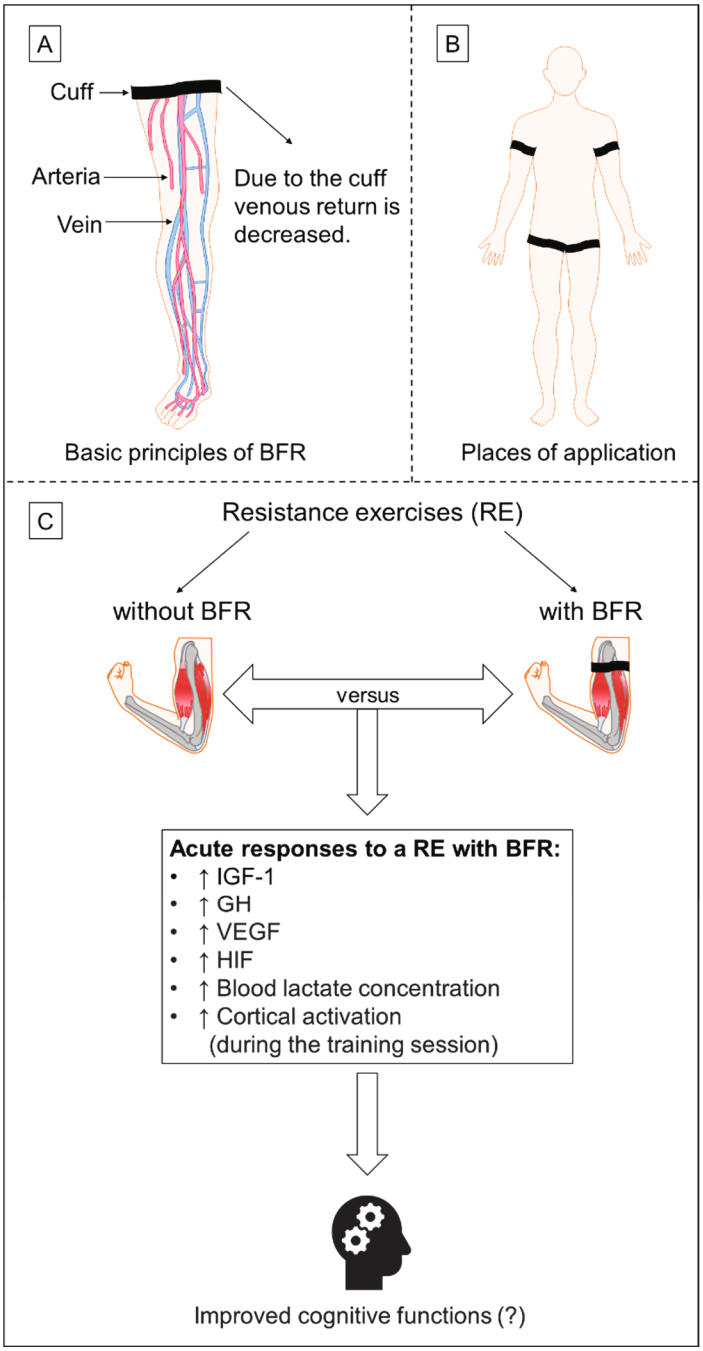

Figure 1. Schematic illustration of (**A**) the basic principles of blood flow restriction, (**B**) the application places of the cuffs for blood flow restriction and (**C**) the possible neurobiological mechanisms of resistance training with blood flow restriction that are likely to contribute to improved cognitive functions; blood flow restriction (BFR), growth hormone (GH), hypoxia-inducible factor (HIF), insulin-like growth factor 1 (IGF-1), resistance training (RE), vascular endothelial growth factor (VEGF).

Both, localized hypoxia (induced by BFR) and systemic hypoxia are harmless (when conducted appropriately) and well feasible [133–135]. However, due to the cuffs on the limbs during the BFR, petechial haemorrhage beneath the skin and/or numbness of extremities can appear in few cases [125,134,136]. Compared to localized hypoxia (e.g., BFR), systemic hypoxia has the advantage that it is not limited to the limbs [125]. Remarkably, cross-transfer effects in muscles that were not directly affected by the application of blood flow manipulation cuffs were observed in response to resistance exercises with BFR. Both, muscles proximal to the restricted extremities and muscles distal to the

restricted extremities experience beneficial effects [137,138]. Systemic-endocrinological (e.g., expression of growth factors) as well as neuronal adaptations (e.g., higher recruitment of supportive muscles because of the increased fatigued muscles under BFR) are discussed for this phenomenon. However, regarding brain adaptions, systemic hypoxia leads to an oxygen deficit directly in the brain which is to a certain extent the decisive stimulus triggering positive neurophysiological adaptations [135,139,140]. In this regard, first studies have shown improved cognitive functions following interventions with systemic, normobaric hypoxia [141,142].

Also, for resistance training with BFR, a first investigation by Sardeli et al. [143] had observed positive effects on cognitive functions (Stroop-test) immediately after a low-load resistance training with BFR (30% of 1RM) [143]. Except for this first investigation of Sardeli et al. [143], there are to our knowledge currently no further studies available (neither short-term nor long-term study) which directly examine the effects of localized hypoxic exposure on cognitive performance. Based on the first hint that localized hypoxia is beneficial for cognition, we want to outline several reasons why localized hypoxia during a resistance training (e.g., trough BFR) might be a promising intervention strategy which is likely to increase the efficiency of resistance training regarding the enhancement of cognitive functions in the following:

(i) On the cellular and molecular level: Some investigations showed a significant higher release of hormones which is associated with positive neurophysiological adaptations, such as serum IGF-1 [144,145], growth hormone (GH) [146–149] and vascular endothelial growth factor (VEGF) [145,147,150,151], in response to acute resistance activities with BFR when compared to resistance training without BFR. Regarding the IGF-1, also a long-term intervention (two weeks) of low-intensity BFR training which was provided twice a day led to a higher basal level of IGF-1 in comparison to the same resistance training without BFR [152]. As mentioned in the previous section, IGF-1 plays an important role in synaptic functioning and cognitive processes [75]. Because of the link between a deficiency in serum GH level and a cognitive impairment, increases in GH are associated with benefits for cognitive performance [153,154]. Furthermore, in older adults who regularly perform physical exercises, a higher level of GH and better cognitive performance was noticed compared to sedentary older adults [155]. VEGF is involved in angiogenesis [39,156–161] and it is speculated that a decrease in angiogenic factors (e.g., serum VEGF) might be associated with cognitive impairments (e.g., in Alzheimer disease) [162,163]. Notably, the increases in neurochemical substances (e.g., IGF-1) was predominantly observed after an acute bout of resistances activities with BFR, thus long-term studies are needed to investigate whether a pronounced release of those neurochemicals would be persistent after longer time intervals (e.g., 6 months).

Furthermore, there is a robust body of evidence suggesting that the blood lactate concentrations are higher after an acute bout of resistance activities with BFR as compared to a resistance exercise without BFR [145,148,149,164–170]. The levels of post-exercise blood lactate concentration are associated with acute improvements in cognitive functions such as short-term memory [171] and executive functions [172,173]. This phenomenon occurs because peripherally expressed lactate can cross the BBB by monocarboxylate transporters (MCTs) and will be utilized as fuel for cognitive processes due to oxygenation [174–178]. Moreover, lactate is associated with changes in peripheral brain-derived neutrophic factor (BDNF). Here, Ferris et al. [179] showed a correlation between blood lactate concentrations and BDNF [179]. Besides, Schiffer et al. [180] observed an increase in BDNF after a lactate infusion in rest [180]. These insights suggest a potential neurobiological relationship between both neurochemical substances. BDNF is a member of neurotrophins and contributes to neuroplasticity which, in turn, facilitates cognitive performance [181,182].

In addition, systemic hypoxia [183,184] as well as local hypoxia [185] increase the hypoxia-inducible factor 1α (HIF-1α) which is the master regulator for adaptions of oxygen homeostasis. An increase of HIF-1α in response to systemic and/or localized hypoxia (e.g., induced by BFR) might be meaningful for cognition or the integrity of the brain considering the following two aspects: Firstly, the HIF-1α has a neuroprotective effect [186] and secondly, this transcription factor

triggers the increase of neurotrophic factors such as the VEGF and IGF-1 [187,188]. Therefore, the HIF-1α may be also a crucial factor for neurocognitive adaptations following a resistance training with BFR.

(ii) On the functional level: After a resistance training with BFR, increases in the cortical excitability [189] and higher levels of oxygenated hemoglobin were observed in cortical motor areas (compared to same resistance exercises without BFR) [190]. Furthermore, in prefrontal areas, a higher concentration of deoxygenated hemoglobin was observed during knee extension with BFR whereas the increase in oxygenated hemoglobin was diminished when compared to knee extensions without BFR [191]. In general, decreased levels of deoxygenated hemoglobin and increased levels of oxygenated hemoglobin are associated with increased cortical activity [192–195]. Since deoxygenated hemoglobin is assumed to be less affected by physiological artefacts than oxygenated hemoglobin [192,196–201], it is perhaps a better proxy of cortical activity (in this particular case) and it could therefore be speculated that a pronounced decrease of deoxygenated hemoglobin may point towards a higher cortical activation during knee extensions with BFR. Nevertheless, further research is necessary to verify or falsify these assumptions.

In general, higher levels of cortical activity (e.g., shown by higher concentration of oxygenated hemoglobin in the brain) after physical exercises are associated with improved cognitive performance [202,203]. It was observed that participants with an improved cognitive performance after exercise showed a higher cortical activity in prefrontal areas during the exercise sessions (termed as responders) in comparison to participants with no cognitive improvements (termed as non-responders) [204]. In consideration of these insights, the enhanced performance in the Stroop test after a low-load resistance training with BFR observed in the investigation of Sardeli et al. [143] may have been caused by higher levels of oxygenated hemoglobin in the prefrontal cortex [143].

3.1. Hypothesis

According to the potential neurobiological advantages of a resistance training with BFR compared to a resistance training without BFR on cellular and molecular level as well as on functional level of the brain (see Figure 1C), we hypothesize that a short-term and long-term resistance training with BFR is more efficient regarding the enhancement of cognitive functions than a "traditional" resistance exercise regime without BFR.

3.2. Considerations to Evaluate the Hypothesis

To test the hypothesis stated in the previous section, there are a number of general aspects that should be considered regarding (i) the participants' characteristics, (ii) designing the resistance training program and (iii) the outcome measures.

(i) Regarding the selection of participants, it should be considered that individual characteristics moderate the outcomes and underlying neurobiological processes. Exemplarily, sex is a key moderator for the effect of physical exercise interventions on cognitive performance which is perhaps related to underlying neurobiological processes [116,205,206]. Here, it is assumed that women may benefit more from exercise than men with respect to cognitive functions like executive functions [116]. While the reason for this sex-phenomenon is not fully understood, it is assumed that those findings are related to sex-dependent neurobiological mechanisms (e.g., exercise-induced release of BDNF) and the higher level of habitual physical inactivity in older women (compared to older men) [68,116,205,206]. Another moderator which potentially influences the exercise-cognition interaction is the genotype of the participant [68,116] and through matching the individuals' genotypes to an appropriate resistance training program, a greater outcome regarding muscular strength can be evoked [207]. However, currently there is not enough evidence available which would allow validly designing resistance training regimes/programs with or without BFR as a function of individual genotypes. Hence, further investigations in this field are needed. Here, moderator and mediator variables should be carefully assessed and their influence on outcomes measures as well as neurobiological processes evaluated.

A deeper understanding of moderator and mediator variables would assist the development of more personalized training regimes which may provide greater intervention efficiency [68].

Additionally, further studies should consider and test the "human baseline hypothesis" which proposes that the baseline values of strength (e.g., grip strength and/or knee extensor strength) assessed prior to resistance training or after a detraining period are more appropriate markers of long-term health outcomes compared to training-related strength gains [108]. Therefore, in relation to brain-health gains (brain volume, cognitive functions), the baselines of strength as well as muscle mass should be taken into account.

(ii) For designing resistance training programs, in general, the following exercise variables should be considered [120,208,209]:

Variables of a resistance training session:

(1) *load* (amount of weight that is used for an exercise; usually given as a percentage of the one repetition maximum [1RM]);
(2) number of repetitions;
(3) number of sets;
(4) inter-set rest periods;
(5) inter-exercise rest periods;
(6) *number of exercises* (for the whole training session or for a muscle or a muscle group with the same function);
(7) *repetition velocity* (temporal details should be given for: concentric phase–inter-repetition rest periods–eccentric phase rest period up to the start of the next repetition, e.g., 2–0–2–1 s);
(8) *muscle action* (concentric, eccentric, isometric);
(9) *exercise selection* (e.g., multi-joint or single joint exercises);
(10) *exercise order* (e.g., squat, leg extension, biceps curl and concentration curl or squat, biceps curl, leg extension and concentration curl);
(11) *volitional muscle failure*
(12) *range of motion.*

Variables for structuring resistance training:

(13) *frequency* (number of training sessions per week);
(14) *density* (distribution of training sessions across a week with regard to recovery time in-between training sessions) and
(15) *duration* (duration over which a training program is carried out before exercise variables are changed).

It should be noted that some exercise variables are usually summarized into variables with a different designation: e.g., volume (exercise variables 2, 3 and 6) or time under tension (TUT, sum of the exercise variables 2 and 7) [120,209]. Additionally, the cuff pressure is of particular importance in resistance exercises with BFR, as it is intended to induce an appropriate level of localized hypoxia as physiological stimuli [210–217]. Here, the cuff pressure should be applied in such a way that venous pooling without an arterial occlusion would occur. To achieve this, the cuff pressure must be below the arterial occlusion pressure [124]. However, various moderator variables can influence the cuff pressure:

(1) *Cuff width*: wide BFR-cuffs restrict arterial blood flow more than narrow BFR-cuffs using the same cuff pressure. Therefore, the cuff pressure should be applied relative to the cuff width [214,215,218–222].
(2) *Cuff material*: it might be that the cuff material has an impact on the arterial blood flow restriction [211]. However, current investigations comparing different cuff materials (5 cm nylon vs. 3 cm elastic cuffs) do not consider the cuff width [223]. In contrast, Loenneke et al. [224]

compared nylon and elastic cuffs with the same width (5 cm) and observed no differences in the arterial occlusion pressure [224].

(3) *Restricted extremity* (upper or lower limbs): cuff pressures should be determined individually for the upper and lower limbs [225].

(4) *Systolic / arterial blood pressure*: the cuff pressure depends on the systolic / arterial blood pressure [213,218,226–232].

(5) *Body composition / anthropometry*: the circumference of the limbs is the biggest predictor for the cuff pressure to reach arterial blood flow restriction and should be considered [218,225,233–235].

(6) *Body position*: the cuff pressure to reach arterial blood flow restriction must be lower in the supine position compared to the seated position and standing position [210,212].

(7) *Exercise protocol*: applying intermittent or continuous pressure; it might be that a BFR applied with a continuous pressure on the cuffs during the exercise leads to another physiological stimulus as compared to a BFR applied in an intermittent fashion [124,226,236–238].

(8) *Blood flow restriction system*: different blood flow restriction systems (automatic pressure control vs. manual handheld pressure control) lead to diverging pressure on the limbs at rest and during exercise. However, one first investigation by Hughes et al. [239] compared several blood flow restriction systems with different cuff widths. Therefore, the influence of blood flow restriction systems for inducing effective BFR-stimuli needs further investigations [239].

Since those mentioned moderator variables are crucial for an effective BFR-stimulus and the physiological response, as well as the psychological response, it is likely that those also alter neurocognitive adaptations, which, in turn, influence the changes in cognitive functions. To evoke the above mentioned cognition-related neurobiological adaptations through a resistance training with BFR, it is strongly recommended to determine a personalized cuff pressure be chosen [217,240] which takes the above mentioned relationships of the moderator variables and the cuff pressure into account. From a practitioner's view, the optimal solution(s) to determine the cuff pressure ensuring an appropriate stimulus would be using a pressure that is relative to the used cuffs and individual's characteristics [117,241] or to use a BFR system that automatically adjust the cuff pressure [239,240]. Furthermore, even moderate cuff pressures induce adaptions comparable to high cuff pressures [227,242]. Hence, moderate cuff pressures are recommended because higher cuff pressures increase the risk of full arterial occlusion and in turn of adverse effects [131,243,244].

In resistance training without BFR, only the following exercise variables are considered and recommended to enhance cognitive functions, by now (to 1.) load: 60 to 80% of 1RM; (to 2.) number of repetitions: 7; (to 3.) number of sets: 2; (to 4.) inter-set rest periods: 2 min; (to 13.) frequency: at least twice per week; (to 15.) duration of a training period 2 to 12 months [61]. However, in short-term and long-term resistance training interventions with (and even without) BFR, the optimal selection of exercise variables to efficiently enhance cognitive functions are largely unknown, and should be investigated in future studies. Nevertheless, we would like to recommend the following exercise variables for a resistance training with BFR aiming to induce neurocognitive adaptations (Table 1). We chose these exercise variables because of their effectiveness to increase muscular strength as well as muscular hypotrophy [124,130,137,144,216,245–248]. As described above, functional and structural adaptations of the musculature are moderating factors for the neurocognitive status. Furthermore, based on our above mentioned deliberations, it can be assumed that these exercise variables are efficient to trigger adaptations on the above mentioned neurocognitive levels (cellular, molecular, structural and functional level).

Table 1. Recommendations for exercises variables for a resistance training with blood flow restriction (BFR); n.a.: not available; reps: repetitions; 1RM: one repetition maximum; s: seconds; min: minute.

Exercise Variables	Recommendations for Resistance Training with BFR
(1.) load	20 to 50% of 1RM
(2.) number of repetitions	15 to 30 per set, 50 to 80 repetitions per exercise (e.g., 30–15–15–15 reps)
(3.) number of sets	3 to 5 sets per exercise
(4.) inter-set rest periods	30 to 60 s
(5.) inter-exercise rest periods	5 min (without BFR)
(6.) number of exercises	n.a.
(7.) repetition velocity	1 (to 2)–0–1 (to 2)–1 s
(8.) muscle action	dynamic muscle action, eccentric is more effective than concentric
(9.) exercise selection	single- and multi-joint exercise
(10.) exercise order	n.a., depending on the training goal
(11.) volitional muscle failure	until volitional fatigue/repetition failure/technical failure
(12.) range of motion	full range of motion
(13.) frequency	2 to 3 sessions per week
(14.) density	n.a., depending on the performance level
(15.) duration	n.a., but according to the general physiological view, exercise variables or exercises should be changed after a mesocycle of 8 to 12 weeks

Furthermore, so far, there have been no consistent recommendations for the cuff pressure. However, the following criteria are often used to apply an optimal cuff pressure: 130% of the systolic blood pressure [226,237]; 10 mm Hg below the arterial occlusion pressure [225]; ~50% arterial occlusion pressure [243]. The most effective cuff pressure has still to be identified [124].

In general, resistance training with BFR is a harmless treatment strategy when applied appropriately [117,133,136,222,241,249–251], but in order to minimize the occurrence and/or to avoid adverse health effects, safety recommendations should be considered [134] and available risk assessment tools should be used [252]. Furthermore, we want to point out that during the practical implementation of a resistance training with BFR, the following general safety recommendations should be strictly adhered to minimize the occurrence of adverse events: We strongly recommend that an individual and adequate cuff pressure should be applied. Furthermore, based on the currently available recommendations the maximal duration for continuous BFR should in general not exceed a time period of circa 10 to 15 min for the upper limbs and circa 15 to 20 min for the lower limbs because longer time periods may increase the risk of adverse events [134].

(iii) Physical exercises influence cognitive performance on multiple levels: (1) cellular and molecular level; (2) structural and functional level and (3) behavioral/socioemotional level [67]. Based on these mentioned levels, multiple outcome measures should be considered in the study design and analysis in order to understand the complex interaction of physical exercises (e.g., resistance training with BFR) and cognition:

(1) On the cellular and molecular level, neurochemical markers such as IGF-1, GH, VEGF, blood lactate concentrations and BDNF might be used since the exhibited associations with cognitive performance (see the previous sections).

(2) On the structural and functional level, different neuroimaging modalities such as fNIRS, EEG, fMRI or a combination of those should be applied in order to understand physical exercise induced structural and functional brain changes [49,253]. Since fNIRS and EEG can in particular be used during physical exercises [254–256], both measuring systems are suitable for the evaluation of cognitive activity while performing resistance training with BFR. Here, short-term and long-term effects of this intervention strategy could be objectified. Regarding functional brain changes, it seems recommendable (a) to use standardized and established cognitive test (e.g., Stroop test [101,104], Sternberg test [257–259], Eriksen Flanker test [102]) to ensure comparability with existing studies and (b) to consider attention and perceptual tasks which were currently not in the focus of exercise-cognition research [260] but could be important for special cohorts (e.g., individuals with dementia) [48].

(3) On the behavioral/socioemotional level, established questionnaires such as "Felt Arousal Scale" [261], "Ratings of perceived exertion" [262], "Visual Analogue Scales" (e.g., to assess motivation or mental fatigue) [172,263–265], "SF-36" (to assess physical and mental components of the quality of life) [266] and "Pittsburgh Sleep Quality Index" (to assess various components of the sleep quality) [267] which are widely used in exercise–research with a neuropsychological and behavioral/socioemotional focus [141,172,263–265,268,269], should be used to elucidate the (moderating) effects of socioemotional states.

4. Conclusions

The type of physical exercise (e.g., resistance training) in combination with related exercise variables (e.g., load, number of repetitions and sets) which efficiently enhance cognitive performance are largely unknown [39–49]. A promising physical exercise intervention which fends off physical and cognitive decline (e.g., due to the aging process) is resistance training. Hypothetically, the efficiency of resistance training interventions on cognition could be increased due to the application of BFR.

Resistance training with BFR is more efficient to increase muscle hypertrophy and strength as compared to the same resistance training without BFR [247,270] and for a resistance training with BFR, lower exercise loads are needed to achieve comparable muscular adaptions (e.g., increase in muscle mass) as compared to high-load resistance training [271,272]. The lower exercise load during a resistance training with BFR could be beneficial for special cohorts since those lower exercise loads pose lower mechanical stress to the joints and the risk of adverse cardiovascular effects is decreased [124,217,244,273]. The currently available evidence suggests (i) that strength gains in response to a resistance training mediate, at least partly, the cognitive improvements [274] or (ii) that strength performance per se is a more appropriate indicator regarding health outcomes (e.g., cognition) [108]. Hence, at the moment no reliable assumptions can be made whether (i) a regular participation in resistance training, (ii) a relative high individual (baseline) strength level or (iii) the combination of both (high muscular strength level and regular resistance training) are most beneficial for cognitive functions. Notably, since an optimal level of neurochemical substances (e.g., IGF-1) is beneficial for cognitive performance [275], it could be speculated that, in turn, also an optimal level of muscular strength and/or continuously performed effective resistance activities, which may contribute substantially to the maintenance of an optimal level of neurochemical substances, exists. In this manner, a low-load resistance training with BFR could be a promising strategy especially for special cohorts (e.g., older adults unable to tolerate high loads) to ensure an adequate level of strength and profit from biological mechanisms which would without BFR only be possible when (not well tolerated) high loads are applied. Furthermore, relative low muscle damage is induced by low-load resistance training with BFR [148,168,276,277], which may allow a higher training frequency than in high load-resistance training [124,125,246].

However, testing the hypothesis suggesting that short-term and long-term resistance training with BFR improve cognitive performance as well as brain health to a greater extent than resistance training without BFR may provide deeper insights into the interplay between neurobiological mechanisms and cognitive processes. A deeper understanding of underlying exercise-induced and cognition-related neurobiological mechanisms is urgently needed to develop efficient prevention strategies (e.g., decelerate cognitive decline due to aging process) and to optimize rehabilitation strategies for individuals with worsened cognitive functions (e.g., older individuals with dementia). Here, the resistance training with BFR might be a promising strategy of exercise intervention.

Author Contributions: A.T. and F.H. wrote the manuscript and share the first authorship. L.S., N.G.M. and D.H. reviewed the drafted versions. All authors have read and approved the final version.

Funding: No funding information is applicable.

Acknowledgments: The authors have nothing to acknowledge.

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

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Herold *et al. European Review of Aging and Physical Activity* (2019) 16:10
https://doi.org/10.1186/s11556-019-0217-2

European Review of Aging and Physical Activity

REVIEW ARTICLE Open Access

Functional and/or structural brain changes in response to resistance exercises and resistance training lead to cognitive improvements – a systematic review

Fabian Herold[1*], Alexander Törpel[4], Lutz Schega[4] and Notger G. Müller[1,2,3]

Abstract

Background: During the aging process, physical capabilities (e.g., muscular strength) and cognitive functions (e.g., memory) gradually decrease. Regarding cognitive functions, substantial functional (e.g., compensatory brain activity) and structural changes (e.g., shrinking of the hippocampus) in the brain cause this decline. Notably, growing evidence points towards a relationship between cognition and measures of muscular strength and muscle mass. Based on this emerging evidence, resistance exercises and/or resistance training, which contributes to the preservation and augmentation of muscular strength and muscle mass, may trigger beneficial neurobiological processes and could be crucial for healthy aging that includes preservation of the brain and cognition. Compared with the multitude of studies that have investigated the influence of endurance exercises and/or endurance training on cognitive performance and brain structure, considerably less work has focused on the effects of resistance exercises and/or resistance training. While the available evidence regarding resistance exercise-induced changes in cognitive functions is pooled, the underlying neurobiological processes, such as functional and structural brain changes, have yet to be summarized. Hence, the purpose of this systematic review is to provide an overview of resistance exercise-induced functional and/or structural brain changes that are related to cognitive functions.

Methods and results: A systematic literature search was conducted by two independent researchers across six electronic databases; 5957 records were returned, of which 18 were considered relevant and were analyzed.

Short conclusion: Based on our analyses, resistance exercises and resistance training evoked substantial functional brain changes, especially in the frontal lobe, which were accompanied by improvements in executive functions. Furthermore, resistance training led to lower white matter atrophy and smaller white matter lesion volumes. However, based on the relatively small number of studies available, the findings should be interpreted cautiously. Hence, future studies are required to investigate the underlying neurobiological mechanisms and to verify whether the positive findings can be confirmed and transferred to other needy cohorts, such as older adults with dementia, sarcopenia and/or dynapenia.

Keywords: Cognition, Neuroplasticity, Strength exercises, Strength training, Physical activity

* Correspondence: fabian.herold@dzne.de
[1]Research Group Neuroprotection, German Center for Neurodegenerative Diseases (DZNE), Leipziger Str. 44, 39120 Magdeburg, Germany
Full list of author information is available at the end of the article

Background

Aging, the brain, and cognition

Throughout the lifespan, the human organism undergoes considerable changes. As a consequence of aging, the structure and function of organic systems (i.e., brain) can be negatively affected, which in turn can converge in a decline of individual capabilities (e.g., cognition). In this regard, in recent years, evidence has shown that the hippocampus [1–4] and the grey matter in the frontal lobe [1–3, 5–12] are affected by age-related shrinking. In contrast, the grey matter volume of other brain structures such as the parietal and occipital cortices have been reported to change slightly with increasing age [1, 5, 8], whereas a severe decline in white matter volume of the prefrontal cortex (PFC) is most pronounced in the very oldest [1, 8, 9, 13, 14]. These age-related changes in brain structure [15, 16] are assumed to play major roles in the worsening of cognition functions, such as processing speed and memory [17–20]. In fact, in older adults, it was observed that a decrease in hippocampal volume is associated with worsening of memory performance [21–23]. Conversely, an increase in hippocampal volume after a yearlong aerobic training intervention was associated with memory improvements [24]. These findings suggest that the preservation of brain structures (e.g., hippocampus) is important to ensure the proper functioning of cognitive processes (e.g., memory). Similar to the relationship of brain structure and cognition, it is assumed that changes in brain function (e.g., brain activation during a cognitive task) contribute to changes in cognition [16, 25–27]. Such an intertwined relationship between brain activation and cognition is underpinned by the findings linking activation of the PFC to behavioral performance in executive function tasks [28–31], in visuomotor tasks [32], or in working memory tasks [33–35]. Currently, several hypotheses exist that aim to explain age-related alterations in brain activation and cognition [16, 25–27]. For instance, the HAROLD model predicts that there is hemispheric asymmetry reduction in older adults in the PFC during the execution of memory tasks [27, 36]. In the compensation-related utilization of the neural circuits hypothesis (CRUNCH), it is postulated that adults will recruit more brain regions (mainly the PFC) as the task load increases and that older adults need to recruit these brain regions at lower levels of cognitive load than younger adults (e.g., during working memory tasks) [26, 37–39]. In the Scaffolding Theory of Aging and Cognition (STAC), it is postulated that increased brain activity with age, especially in the PFC, is a compensatory mechanism caused by reorganization of the brain in response to the age-related decline in neural structures and neural functioning [16, 39, 40]. To date, none of these hypotheses satisfactorily explain the observed age-related changes in brain function [41], but all of these hypotheses emphasize the important role of the PFC in age-related functional brain changes. It is well recognized in the literature that physical exercises [28–30, 42, 43] and physical training [44–47] lead to positive changes in cognitive performance (e.g., executive functions) and brain activation patterns. Furthermore, the changes in brain activation patterns (i.e., shown by higher levels of oxygenated hemoglobin in brain regions) are associated with cognitive performance improvements [28–30, 47], which illustrate the important role of physical interventions in preserving cognition and brain health.

In summary, distinct cognitive functions (e.g., memory) are negatively affected, and substantial changes in brain structure (e.g., shrinkage of hippocampus) and brain function (e.g., compensatory brain activation; i.e., of PFC) occur as consequences of "normal" aging. Notably, regular engagement in physical exercise is a valuable strategy to counteract age-related decline in brain and cognition [48–52].

Aging, muscular system, and cognition

There is solid evidence in the literature that muscle mass (sarcopenia) [53–57] and muscular strength (dynapenia) [53, 57–59], which constitute the ability to produce muscular force and power [60], decline gradually as a function of age. Notably, the age-related decrease in muscular strength was noticed to be more pronounced than the decrease in muscle mass [61–63]. Moreover, the decline in maximum muscular strength is more serious in the lower limbs than in upper limbs [62, 64–67]. In general, it was observed that the age-related loss in, for instance, maximum isokinetic hip/leg extensor strength is rather minimal until the fifth decade of life but accelerates considerably thereafter [58, 68–70]. Potential reasons for the pronounced decline in muscular strength are the reduction in cross-sectional area of the muscle fibers [64, 71] as well as the loss of muscle fibers and motor units [55, 56, 58, 61, 72, 73]. However, appropriate levels of muscular strength are needed for independent and healthy living. For instance, an appropriate level of muscular strength in the muscles of the lower limbs (e.g., hip and leg extensors) is required to ensure proper function for engaging in activities of daily living (e.g., balance and gait) [74, 75]. Hence, it is not surprising that a decline in isokinetic muscular strength in leg extensors is associated with reduced mobility [76–78] and increased risk of mortality [77, 79, 80].

However, there is growing evidence that an appropriate level of muscular strength is also linked to brain health and functioning (e.g., cognitive functions). In this regard, it has been reported in the literature that higher levels of isokinetic strength of the *M. quadriceps femoris* are linked to better performance in general cognitive abilities (operationalized by Mini-Mental State Examination [MMSE]) [81] and to better performance in

executive functions [82, 83]. This link is further reinforced by the findings that higher leg power [84] and higher whole-body muscle strength [85] are associated with higher scores in standardized cognitive test batteries. Furthermore, higher handgrip strength is linked to higher scores in general cognitive abilities (e.g., operationalized by MMSE) [86, 87] and to higher scores in standardized cognitive test batteries [88–90]. Moreover, it was observed that gains in dynamic muscular strength (assessed by one repetition maximum in different resistance exercises) after 6 months of progressive resistance training mediate improvements in global cognitive performance (according to the Alzheimer's Disease Assessment Scale–cognitive subscale) [91]. Similar to the previously mentioned finding, it was reported that changes in isokinetic knee extension and knee flexion torques after 3 months of progressive resistance training mediate improvements in executive functions [92]. Notably, a meta-analysis did not observe a correlation between muscle size and cognition [93] but reported that both muscle function (e.g., muscular strength) and muscle structure (e.g., muscle size) were linked to brain structure [93].

Taken together, during aging processes, a substantial decline in muscular strength, especially in lower limb muscles, occurs, and accumulating evidence suggests that lower muscular strengths are linked to poorer cognitive performance. Hence, resistance (strength) exercises (a single bout of resistance exercise, also referred to as acute exercise) and resistance (strength) training (more than one resistance exercise session, also referred to as chronic exercise; see also section 'Data extraction') seem to be promising activities to ensure the preservation of physical functioning and cognitive functions with aging.

Resistance exercises, resistance training, brain, and cognition

One physical intervention strategy that is frequently recommended to counteract the age-related deterioration of both physical functioning and cognition is the continuous and regular execution of resistance exercises and/or resistance training [94–106]. There is solid evidence in the form of systematic reviews and meta-analyses indicating that resistance exercises and resistance training (for distinction, see section 'Data extraction') have substantial benefits for specific domains of cognitive functions (e.g., executive functions) [105, 107–111], but the underlying neurobiological mechanisms of resistance exercise-induced improvements in cognitive functions are not yet fully understood [107, 110].

As shown in Fig. 1, cognitive improvements in response to resistance exercises and/or resistance training are based on changes on multiple levels of analysis [112, 113]. At the first level, molecular and cellular changes occur, which are summarized in the "neurotrophic hypothesis" [114–117]. The "neurotrophic hypothesis" claims that in response to physical exercises (e.g., resistance exercises), a pronounced release of distinct neurochemicals occurs (e.g., brain-derived neurotrophic factor [BDNF]) [114–117]. The pronounced release of specific neurochemicals triggers complex neurobiological processes evoking functional and/or structural brain changes that facilitate, at best, improvements in cognitive functions [24, 50, 114, 118–120]. With regard to the molecular and cellular levels, a systematic review summarized the evidence of resistance exercise and resistance training-induced changes in the release of several myokines (e.g., BDNF) and highlighted their positive effects on cognitive functions [121]. However, with respect to functional and structural brain changes and socioemotional changes (see Level 2 and Level 3 in Fig. 1),

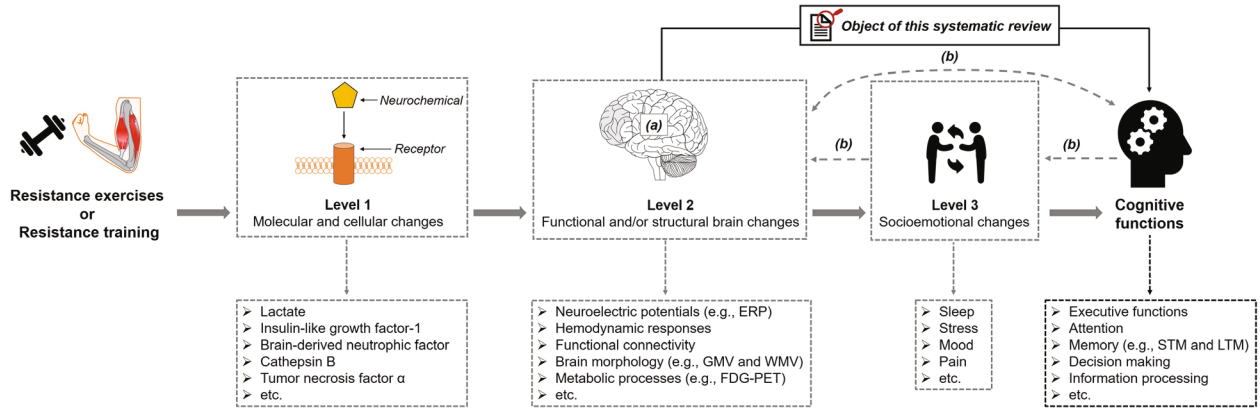

Fig. 1 Schematic illustration of the objective of the present systematic review and the levels of analysis. 'a' indicates that the brain could be regarded as an outcome, a mediator or a predictor [122]. 'b' indicates several possibilities for how structural and functional brain changes, socioemotional changes, and cognitive changes are intertwined [112]. ERP: event-related potentials; FDG-PET: F-2-deoxy-D-glucose (FDG) positron-emissions tomography (PET); GMV: grey matter volume; LTM: long-term memory; STM: short-term memory; WMV: white matter volume

knowledge about resistance exercise and/or resistance training-induced changes is still relatively scarce, and the available literature has not yet been systematically pooled. In particular, the pooling of available evidence regarding functional and structural brain changes is needed because the brain may act as a mediator for the effect of resistance exercises and/or resistance training on cognition [112, 122]. Such a systematic pooling of available evidence is needed to provide evidence-based recommendations for individualized exercise prescriptions [123–125]. Because resistance exercises and/or resistance training is a promising strategy that could "hit many birds with one stone" (i.e., simultaneously counteracting different types of physical and brain-related health problems), the objective of this systematic review is to provide an overview of resistance exercise and/or resistance training-induced functional and/or structural brain changes that are related to changes in cognitive functions.

Methods

Search strategy and process

In accordance with the guidelines for systematic reviews [126], two independent researchers conducted a systematic literature search on the 25th of April 2019 across the following six electronic databases (applied specifications): PubMed (all fields), Scopus (title, abstract, keywords), Web of Science (title), PsycInfo (all text), SportDiscus (abstract), and the Cochrane Library (title, abstract, keywords; trials). The following terms were used as search strings:

- "strength exercise" OR "strength training" OR "resistance exercise" OR "resistance training" OR "weight exercise" OR "weight training" OR "weight lifting" OR "weight bearing" OR "elastic band" OR toning OR calisthenics OR "functional training"

AND

- mental OR neuropsychological OR brain OR cogniti* OR neurocogni* OR executive OR attention OR memory OR "response time" OR "reaction time" OR accuracy OR error OR inhibition OR visual OR spatial OR visuospatial OR processing OR recall OR learning OR language OR oddball OR "task switching" OR "problem solving" OR Flanker OR Stroop OR Sternberg OR "Trail Making" OR "Tower of London" OR "Tower of Hanoi" OR "Wisconsin Card Sorting" OR "Simon task"

AND

- cortex OR hemodynamic OR oxygenation OR "grey matter" OR "gray matter" OR "white matter" OR "brain volume" OR plasticity OR neuroelectric OR electrophysiological OR "P 300" OR "P 3" OR "event-related potentials" OR ERP OR Alpha OR Beta OR Gamma OR Theta OR NIR OR fNIRS OR "functional near-infrared spectroscopy" OR "near-infrared spectroscopy" OR "functional near-infrared spectroscopic" OR "optical imaging system" OR "optical topography" OR fMRI OR MRI OR "MR imaging" OR "magnetic resonance imaging" OR EEG OR electroencephalography OR electrocorticography OR MEG OR magnetoencephalography OR PET OR "positron emission tomography"

Afterwards, the results of the systematic search were loaded into a citation manager (Citavi 6.3), which was used for further analyses and for removing duplicates (see Fig. 2).

Inclusion and exclusion criteria

Screening for relevant studies was conducted using the established PICOS-principle [126, 127]. The acronym "PICOS" stands for participants (P), intervention (I), comparisons (C), outcomes (O), and study design (S) [126, 127]. The following inclusion and exclusion criteria were used: (P) we applied no restrictions and included all age groups regardless of pathologies; (I) only studies involving resistance exercises and/or resistance training were included; (C) in this systematic literature search, no specific restrictions were used; (O) studies considered relevant assessed functional brain changes and/or structural brain changes related to cognitive changes; (S) interventional or cross-sectional studies.

As shown in Fig. 3, 46 studies were excluded after full text screening because they did not meet our inclusion criteria. Eight studies were excluded because they only assessed functional or structural brain changes but did not measure cognitive performance [128–135]. Vice versa, 38 studies were excluded because they solely measured changes in cognitive performance without quantifying functional or structural brain changes [81, 91, 136–171].

Data extraction

We extracted information about the first author, year of publication, population characteristics including age, gender, cognitive status, exercise characteristics (e.g., muscle action, loading and volume, rest period between sets/between exercises, repetition velocity, frequency, resistance exercise selection), cognitive testing (e.g., tested cognitive domain, administration after exercise cessation), and functional and structural brain data. The extraction of information followed the recommendations of Hecksteden et al. [173].

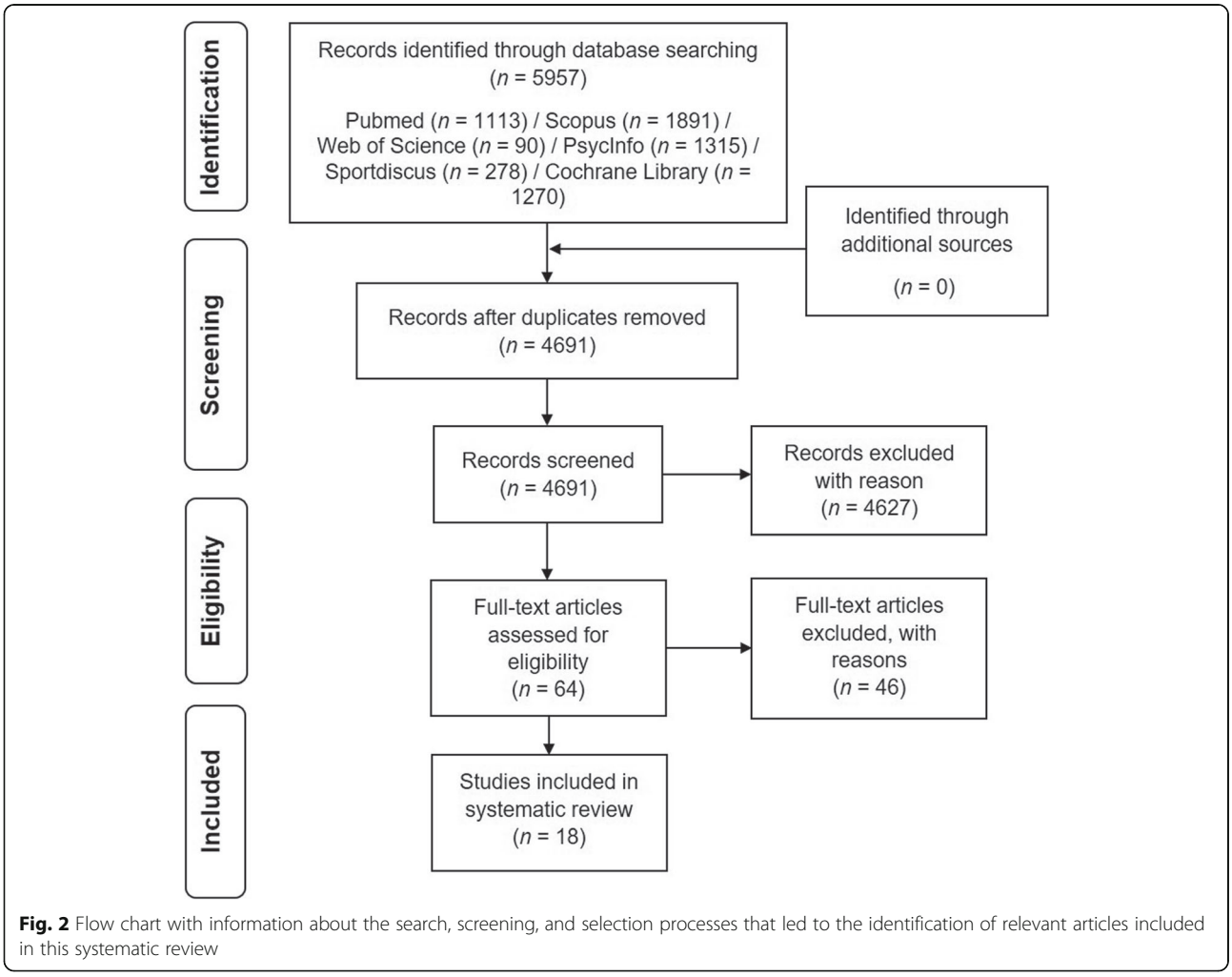

Fig. 2 Flow chart with information about the search, screening, and selection processes that led to the identification of relevant articles included in this systematic review

Prior to presentation of the findings, it is necessary to clarify the different terms used in the field of exercise cognition. 'Physical activity' is defined as any muscle-induced bodily movements that increase energy expenditure from 1.0 to 1.5 MET [174, 175]. Hence, physical activity covers a wide range of acute and chronic physical activities (e.g., from housework to resistance exercises/resistance training). Specific forms of structured, planned, and regularly (chronically) conducted physical activities aiming to increase individual capabilities in a certain fitness domain are referred to as 'training' or 'chronic (repetitive) exercises' [174, 176–178]. Single sessions of physical activities (exercises) are referred to as 'an acute (single) bout of physical activities' or 'physical exercises' [174, 179, 180]. In this article, we use the term 'resistance training' when more than two exercise sessions were conducted. Consequently, a single session of resistance exercises is referred to as 'a single (acute) bout of resistance exercises' and/or 'resistance exercises'. Furthermore, we use 'exercise prescription' as an umbrella term to denote exercise (e.g., load for an exercise) and training variables (e.g., frequency).

Risk of bias assessment

Two evaluators independently performed the risk of bias assessment using the Cochrane Collaboration's Risk of Bias tool [181]. The Cochrane Collaboration's Risk of Bias tool evaluates the methodological quality of a study by rating the risk of bias in distinct criteria (see Figure 3) as being 'low', 'high', or 'unclear' [181]. Any discrepancies in the ratings of the risk of bias were resolved by a discussion among the two evaluators or/and the consultation of the third author of the review. The risk of bias assessment is summarized in Fig. 3.

Results

Risk of bias

As shown in Fig. 3, the results regarding the judgment of risk of bias are heterogeneous. In the domains of sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment, the majority of studies were rated as low risk of bias or unclear risk of bias. The reviewed studies were judged as having an unclear risk of bias in those domains because procedures

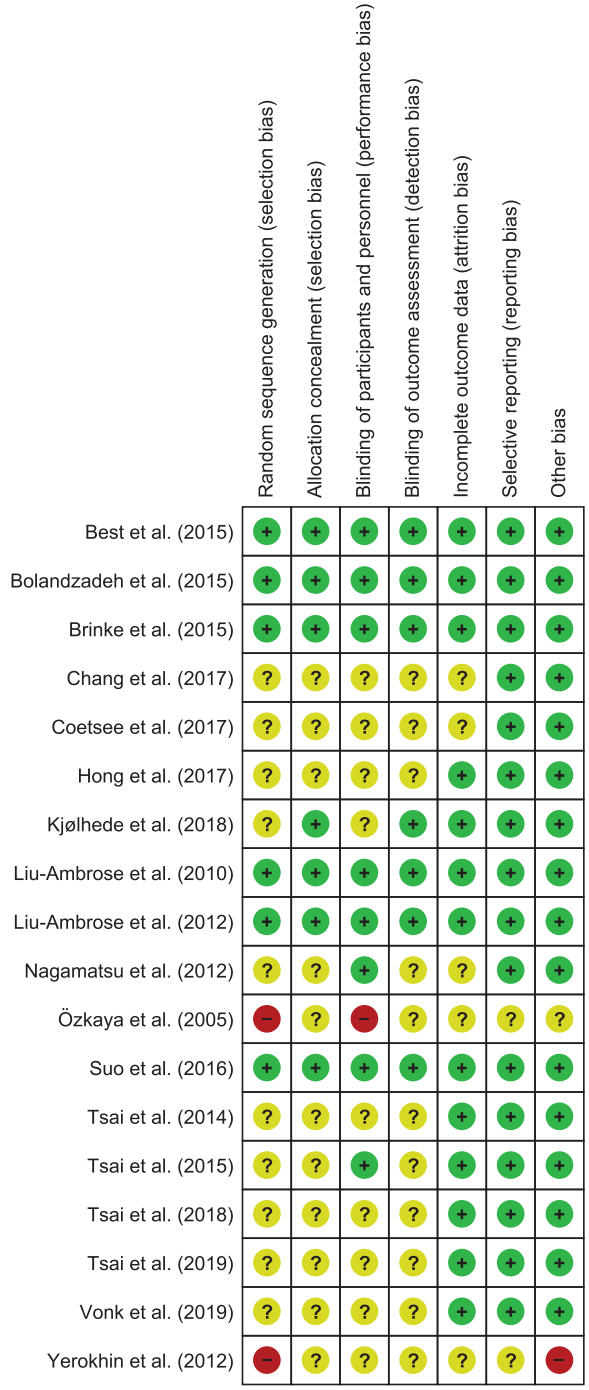

Fig. 3 Analysis of the risk of bias in the included studies in accordance with the Cochrane Collaboration guidelines. This figure was created using Review Manager [172]. A "green plus" indicates a low risk of bias, a "yellow question mark" indicates an unclear risk of bias, and a "red minus" denotes a high risk of bias

were not described in sufficient detail (e.g., method of random sequence generation). In the domains of incomplete outcome data, selective reporting, and other bias, most studies were judged as having a low risk of bias.

Participants' characteristics and study design

In the reviewed studies, the effect of resistance exercises and/or resistance training on cognition and the brain was investigated in different cohorts, including healthy young adults [43, 182, 183], healthy older adults [44, 45, 184–188], older adults with mild cognitive impairment [188–191], older adults in an early stage of dementia [192], and individuals with multiple sclerosis [193]. Detailed information about participant characteristics (e.g., age, height, body mass) is provided in Table 1.

Regarding the study design, almost all studies could be classified as interventional and as randomized controlled trials [43–45, 183–186, 188–190, 195, 197].

Additionally, three resistance exercise studies [43, 182, 183, 195] accounted for circadian variability as a possible moderating factor.

Resistance exercise characteristics

In four studies investigating the acute effects of single resistance exercise sessions on cognitive performance and on functional neuroelectric or hemodynamic brain processes, the exercise sessions lasted approximately 30 min [183] or 40 min [43, 182, 195].

Studies on the effects of resistance training on cognition and functional and/or structural brain changes involved groups who trained 1 day [45, 184–186], 2 days [45, 184–186, 188–190, 193, 197], or 3 days per week [44, 187, 191]. Exercise sessions in the resistance training studies lasted 30 min [44], 40 min [191], 60 min [45, 184–189, 197] or 90 min [190]. The regimes were conducted for 9 weeks [194], 10 weeks [192], 12 weeks [188], 16 weeks [44, 191], 24 weeks [193], 26 weeks [190, 197], 48 weeks [187], or 52 weeks [45, 184–186, 189]. In most of the resistance training studies reviewed, the exercise sessions were conducted in supervised classes [44, 45, 184–187, 189–191, 193, 197]. Furthermore, in most of the reviewed studies, participants were asked to perform two or three sets during the exercise sessions with a minimum of six and a maximum of ten repetitions of upper and lower body exercises at a load ranging from 50 to 92% of 1RM (one repetition maximum) using free weights and/or machines (for a detailed overview, see Table 1).

Main findings

Functional brain changes and cognition

Hemodynamic functional brain changes and cognition

With regard to an acute bout of resistance exercises, in healthy young adults, a decrease in tissue oxygenation index in the left prefrontal cortex during the Stoop test and improved behavioral performance (i.e., faster reaction time and higher number of solved items in neutral condition) was observed after a single bout of high-intensity resistance exercise [43].

Table 1 Overview of the population characteristics and resistance exercises and/or resistance training characteristics of the reviewed studies

First author [ref.]	Study design and sample characteristics	Resistance exercise characteristics
	(1) Design / Comparison groups (2) Participants characteristics (2.1) Number of participants (N) (N female / N male), [included in fMRI or EEG], gender / mean age in years ± SD (2.2) Mean height in cm ± SD / mean body mass in kg ± SD / BMI ± SD in kg/m^2 (3) Cognitive status / disability status	(1) Muscle action (2) Load, number of sets, and number of repetitions (3) Inter-set rest periods and inter-exercise rest periods (4) Repetition velocity (5) Resistance exercise selection (6) Duration of an exercise session (7) Training frequency (8) Training density (9) Training duration (10) Training setting
Functional near-infrared spectroscopy		
Chang et al. [43]	(1) IS (RCT, between-group design) / CON (n), HIRE, MIC, HIA (2) Healthy young adults (2.1) - CON: *N* = 9 (9 f / 0 m) / 21.8 ± 1.4 - HIRE: *N* = 9 (9 f / 0 m) / 21.1 ± 1.6 - MIC: *N* = 9 (9 f / 0 m) / 20.4 ± 1.5 - HIA: *N* = 9 (9 f / 0 m) / 22.1 ± 1.4 (2.2) - CON: 160.8 ± 4.1 / 52.2 ± 6.2 / 20.3 ± 3.1 - HIRE: 162.1 ± 5.0 / 56.3 ± 5.0 / 21.4 ± 1.8 - MIC: 162.9 ± 5.5 / 56.4 ± 5.8 / 21.2 ± 1.3 - HIA: 166.0 ± 5.3 / 59.6 ± 5.7 / 21.6 ± 2.1 (3) N.A.	(1) Dynamic (2) 3 sets with 8 to 10 repetitions per exercise at 80% of 1RM (3) Work to rest ratio of 1:2 (4) N.A. (5) Machines and free weights (e.g., leg extension, leg curl, lat pull-down, seated row, squat, bench press, and arm curl) (6) Ca. 40 min (10 min warm-up, 30 min exercising) (7) One single session (8) N.A. (9) N.A. (10) Individual and supervised
Coetsee et al. [44]	(1) IS (RCT, between-group design) / CON (n), HIIT, MCT, RT (2) Healthy older adults (2.1) - CON: *N* = 19 (11 f / 8 m) / 62.5 ± 5.6 - HIIT: *N* = 13 (10 f / 3 m) / 64.5 ± 6.3 - MCT: *N* = 13 (10 f / 3 m) / 61.6 ± 5.8 - RT: *N* = 22 (15 f / 7 m) / 62.4 ± 5.1 (2.2) - CON: 168.7 ± 7.9 / 76.8 ± 13.7 / 26.9 ± 3.7 - HIIT: 166.0 ± 8.9 / 73.8 ± 13.7 / 26.6 ± 4.0 - MCT: 163.5 ± 8.6 / 71.0 ± 14.4 / 26.5 ± 4.2 - RT: 167.8 ± 7.8 / 73.3 ± 15.5 / 25.8 ± 4.0 (3) MOCA score - CON: 28.2 ± 1.6 - HIIT: 27.9 ± 1.5 - MCT: 27.6 ± 1.3 - RT: 27.5 ± 1.3	(1) Dynamic (2) 3 sets with 10 repetitions per exercise at 50, 75, and 100% of 10RM (first 8 weeks) / at 75, 85, and 100% of 10RM (second 8 weeks) (3) N.A. (4) N.A. (5) Machines and free weights (e.g., upper and lower body resistance exercises) (6) Ca. 30 min (+ warm-up and cool-down) (7) 3 days/week (8) N.A. (9) 16 weeks (10) Group-based and supervised
Electroencephalography		
Hong et al. [188]	(1) IS (RCT, between-group design) / CON (n), RT (2) Healthy older adults / older adults with MCI (2.1) - HOA CON: *N* = 13 (6 f / 7 m) / 73.5 ± 5.6 (f); 73.0 ± 4.8 (m) - HOA RT: *N* = 12 (10 f / 2 m) / 75.8 ± 4.5 (f); 76.5 ± 6.4 (m) - MCI CON: *N* = 12 (9 f / 3 m) / 75.1 ± 4.5 (f); 78.3 ± 5.5 (m) - MCI RT: *N* = 10 (7 f / 3 m) / 75.1 ± 4.5 (f); 78.3 ± 5.5 (m) (2.2) - HOA CON: N.A. / 49.7 ± 4.5 (f); 63.4 ± 10.7 (m) / N.A. - HOA RT: N.A. / 57.3 ± 8.4 (f); 68.9 ± 4.7 / N.A. - MCI CON: N.A. / 56.3 ± 5.4 (f); 57.2 ± 7.6 (m) / N.A. - MCI RT: N.A. / 54.1 ± 7.6 (f); 65.0 ± 3.3 / N.A. (3) MOCA score - HOA CON: 26.0 ± 1.7 (f) / 26.3 ± 1.6 (m) - HOA RT: 26.4 ± 1.7 (f) / 25.0 ± 1.4 (m) - MCI CON: 18.8 ± 5.6 (f) / 21.3 ± 2.4 (m) - MCI RT: 20.0 ± 4.0 (f) / 22.3 ± 1.2 (m)	(1) Dynamic (2) 15 repetitions per exercise correspond to ca. 65% of 1RM (3) N.A. (4) N.A. (5) Elastic bands (6) Ca. 60 min (10 min warm-up, 40 min exercising, 10 min cool-down) (7) 2 days/week (8) N.A. (9) 12 weeks (10) N.A.
Özkaya et al. [194]	(1) IS (RCT, between-group design) / CON (n), AT, RT (2) Healthy older adults (2.1) - CON: *N* = 12 (N.A.) / 72.3 ± 2.1 - AT *N* = 12 (N.A.) / 70.9 ± 3.1 - RT: *N* = 12 (N.A.) / 75.8 ± 2.8 (2.2) - CON: N.A. / N.A. / 29.5 ± 1.3	(1) Dynamic (2) 1 set of 12 repetitions per exercise at 60% of 1RM (in the first week); 3 sets of 12 repetitions per exercise at 60% of 1RM (in the second week); increase in load of 5% every 2 weeks until participants lifted 80% of 1RM (3) N.A.

Table 1 Overview of the population characteristics and resistance exercises and/or resistance training characteristics of the reviewed studies *(Continued)*

First author [ref.]	Study design and sample characteristics	Resistance exercise characteristics
	- AT: N.A. / N.A. / 29.1 ± 1.4 - RT: N.A. / N.A. / 31.2 ± 2.9 (3) MMSE score - CON: 27.1 ± 0.6 - AT: 26.5 ± 0.6 - RT: 25.6 ± 0.7	(4) N.A. (5) Free weights (e.g., hip extension, knee flexion, seated lower-leg lift, chair squat, arm raise, biceps curl, and abdominal crunch) (6) N.A. (10 min warm-up, N.A., 10 min cool-down) (7) 3 days/week (8) N.A. (9) 9 weeks (10) Group-based and supervised
Tsai et al. [182]	(1) IS (RCT, between-group design) / CON (r), HIRE, MIRE (2) Healthy young adults (2.1) - CON: *N* = 20 (0 f / 20 m) / 23.2 ± 2.1 - MIRE: *N* = 20 (0 f / 20 m) / 23.2 ± 2.5 - HIRE: *N* = 20 (0 f / 20 m) / 22.4 ± 2.4 (2.2) - CON: N.A. / N.A. / 22.0 ± 2.6 - MIRE: N.A. / N.A. / 20.8 ± 1.5 - HIRE: N.A. / N.A. / 21.5 ± 1.8 (3) MMSE score - CON: 28.9 ± 0.9 - MIRE: 29.1 ± 1.0 - HIRE: 29.3 ± 1.0	(1) Dynamic (2) 2 sets of 10 repetitions per exercise at 50% of 1 RM in MIRT and at 80% of 1RM in HIRT (3) 90 s between sets / 2 min between exercises (4) "average speed" (5) Machines and free weights (e.g., bench presses, biceps curls, triceps extensions, leg presses, vertical butterflies, and leg extensions) (6) Ca. 40 min (10 min warm-up, 30 min exercising) (7) One single session (8) N.A. (9) N.A. (10) Individual and supervised
Tsai et al. [187]	(1) IS (RCT, between-group design) / CON (n), RT (2) Older adults (2.1) - CON: *N* = 24 (0 f / 24 m) / 72.0 ± 4.1 - RT: *N* = 24 (0 f / 24 m) / 70.8 ± 3.4 (2.2) - CON: N.A. / N.A. / 24.6 ± 3.6 - RT: N.A. / N.A. / 26.0 ± 2.5 (3) MMSE score - CON: 28.2 ± 1.0 - RT: 28.0 ± 1.2	(1) Dynamic (2) 3 sets of 10 repetitions per exercise at 75 to 80% of 1RM (3) 90 s between sets / 3 min between exercises (4) "average speed" (5) Machines and free weights (e.g., biceps curls, leg presses, triceps extensions, hamstring curls, latissimus dorsi pull-downs, calf raises, seated rowing) (6) Ca. 60 min (10 min warm-up, 40 min exercising, 10 min cool-down) (7) 3 days/week (8) N.A. (9) 48 weeks (10) Group-based and supervised
Tsai et al. [195]	(1) IS (RCT, between-group design) / CON (r), AE, RE (2) Older adults with amnestic MCI (2.1) - CON: *N* = 20 (12 f / 8 m) / 64.5 ± 7.0 - AE: *N* = 25 (14 f / 11 m) / 65.5 ± 7.5 - RE: *N* = 21 (12 f / 9 m) / 66.1 ± 6.6 (2.2) - CON: 159.7 ± 8.81 / 61.4 ± 13.0 / 23.8 ± 3.1 - AE: 160.6 ± 7.85 / 62.1 ± 13.7 / 23.8 ± 3.2 - RE: 159.9 ± 8.51 / 62.1 ± 12.1 / 24.5 ± 3.2 (3) MMSE score - CON: 27.00 ± 1.59 - AE: 26.96 ± 1.21 - RE: 26.76 ± 1.38	(1) Dynamic (2) 2 sets of 10 repetitions per exercise at 75% of 1RM (3) 90 s between sets / 2 min between exercises (4) "average speed" (5) Machines and free weights (e.g., biceps curls, triceps extensions, bench presses, leg presses, leg extensions, and vertical butterflies) (6) Ca. 40 min (5 min warm-up, 30 min exercising, 5 min cool-down) (7) One single session (8) N.A. (9) N.A. (10) Individual and supervised
Tsai et al. [191]	(1) IS (RCT, between-group design) / BAST, AT, RT (2) Older adults with amnestic MCI (2.1) - CON: *N* = 18 (13 f / 5 m) / 65.2 ± 7.0 - AT: *N* = 19 (14 f / 5 m) / 66.0 ± 7.7 - RT: *N* = 18 (11 f / 7 m) / 65.4 ± 6.8 (2.2) - CON: N.A. / N.A. / 23.4 ± 2.8 - AT: N.A. / N.A. / 23.5 ± 3.3 - RT: N.A. / N.A. / 24.4 ± 3.1 (3) MMSE score - CON: 27.00 ± 1.65 - AT: 27.16 ± 1.26 - RT: 26.56 ± 1.34	(1) Dynamic (2) 3 sets of 10 repetitions at 60 to 70% of 1RM in the first 2 weeks and at 75% of 1RM in the remaining weeks (3) 90 s between sets / 2 min between exercises (4) N.A. (5) Machines and free weights (e.g., biceps curls, vertical butterflies, leg press, seated rowing, hamstring curls, and calf raises) (6) Ca. 40 min (5 min warm-up, 30 min exercising, 5 min cool-down) (7) 3 days/week (8) N.A. (9) 16 weeks (10) Group-based and supervised
Vonk et al. [183]	(1) IS (RCT, within-subject design) / RE, LM (2) Healthy younger adults	(1) Dynamic (2) 2 sets of 10 repetitions at 70% of 10RM

Table 1 Overview of the population characteristics and resistance exercises and/or resistance training characteristics of the reviewed studies *(Continued)*

First author [ref.]	Study design and sample characteristics	Resistance exercise characteristics
	(2.1) $N = 20$ (11 f / 9 m) / 23.0 ± 2.0 (2.2) N.A. (3) N.A.	(3) 60 s between sets / 90 min between exercises (4) N.A. (5) Machines and free weights (e.g., leg press, pull-down, hamstring curls, vertical chest press, bilateral bicep curl, bilateral triceps extension) (6) Ca. 30 min (5 min warm-up, ca. 25 min exercising) (7) Two separate sessions (RE and LM) (8) N.A. (9) N.A. (10) Individual and supervised
Yerokhin et al. [192]	(1) IS (no RCT, between-group design) / RT (2) Healthy older adults (2.1) - RT: $N = 9$ [5] (1 f / 8 m) / 62.8 ± 7.2 (2.2) - RT: N.A. / N.A. / N.A. Individuals with early dementia (2.1) - RT: $N = 13$ [9] (0 f /13 m) / 79.3 ± 11.0 (2.2) - RT: N.A. / N.A. / N.A. (3) MMSE score - N.A. in both groups	(1) Dynamic (2) N.A. (detailed information can be found in Seguin et al., [196]) (3) N.A. (detailed information can be found in Seguin et al., [196]) (4) N.A. (detailed information can be found in Seguin et al., [196]) (5) Small free weights and body weight (e.g., different exercise such as squat, toe stands, [detailed information could be found in Seguin et al., [196]) (6) Ca. 45 min (7) 3 to 5 days/week (8) N.A. (9) 10 weeks (10) Supervised (older adults with early dementia) / individual and home-based (HC)
Functional and structural magnetic resonance imaging		
Best et al. [184]	(1) IS (RCT, between-group design) / BAT, 1x RT, 2x RT (2) Older adults (2.1) - BAT: $N = 49$ [25/18/8] (49 f / 0 m) / 70.0 ± 3.3 - 1x RT: $N = 54$ [32/29/10] (54 f / 0 m) / 69.5 ± 2.7 - 2x RT: $N = 52$ [26/21/9] (52 f / 0 m) / 69.4 ± 3.0 (2.2) - BAT: 161.0 ± 6.9 / 67.0 ± 11.5 / N.A. - 1x RT: 160.9 ± 7.0 / 69.2 ± 16.2 / N.A. - 2x RT: 162.8 ± 6.5 / 72.1 ± 16.8 / N.A. (3) MMSE score - BAT: 28.8 ± 1.2 - 1x RT: 28.5 ± 1.3 - 2x RT: 28.6 ± 1.5	(1) Dynamic (2) 2 sets of 6 to 8 repetitions of 7RM per exercise (progressively increased) (3) N.A. (4) N.A. (5) Exercises with pneumatic resistance machines (e.g., biceps curls, triceps extensions, seated rows, latissimus dorsi pull-downs, leg presses, hamstring curls, and calf raises) and free weights (e.g., mini-squats, mini-lunges, and lunge walks) (6) Ca. 60 min (10 min warm-up, 40 min exercising, 10 min cool-down) (7) 1 day/week (in 1x RT) or 2 days/week (in 2x RT) (8) One week-in-between (in 1x RT) / N.A. (in 2x RT) (9) 52 weeks (10) Group-based and supervised
Brinke et al. [197]	(1) IS (RCT, between-group-design) / BAT, AT, RT (2) Older adults with probable MCI (2.1) - BAT: $N = 28$ [13/11] (28 f / 0 m) / 75.5 ± 3.9 - AT: $N = 30$ [14/10] (30 f / 0 m) / 76.1 ± 3.4 - RT: $N = 28$ [12/8] (30 f / 0 m) / 73.8 ± 3.8 (2.2) - BAT: 157.5 ± 8.1 / 64.8 ± 13.8 / N.A. - AT: 158.8 ± 5.8 / 61.7 ± 6.8 / N.A. - RT: 161.6 ± 8.1 / 63.3 ± 7.5 / N.A. (3) MMSE score - BAT: 27.17 ± 1.85 - AT: 27.54 ± 1.51 - RT: 26.67 ± 2.64	(1) Dynamic (2) 2 sets of 6 to 8 repetitions of 7RM per exercise (progressively increased) (3) N.A. (4) N.A. (5) Exercises with pneumatic resistance machines (e.g., biceps curls, triceps extensions, seated rows, latissimus dorsi pull-downs, leg presses, hamstring curls, and calf raises) and free weights (e.g., mini-squats, mini-lunges, and lunge walks) (6) Ca. 60 min (10 min warm-up, 40 min exercising, 10 min cool-down) (7) 2 days/week (8) N.A. (9) 26 weeks (10) Group-based and supervised
Bolandzadeh et al. [185]	(1) IS (RCT, between-group design) / BAT, 1x RT, 2x RT (2) Older adults (2.1) - BAT: $N = 15$ [11] (15 f / 0 m) / 69.3 ± 2.8 - 1x RT: $N = 22$ [18] (22 f / 0 m) / 69.6 ± 2.6 - 2x RT: $N = 17$ [13] (17 f / 0 m) / 69.2 ± 3.1 (2.2) - BAT: 162.9 ± 5.8 / 69.5 ± 9.4 / N.A.	(1) Dynamic (2) 2 sets of 6 to 8 repetitions of 7RM per exercise (progressively increased) (3) N.A. (4) N.A. (5) Exercises with pneumatic resistance machines (e.g., biceps curls, triceps extensions, seated rows, latissimus dorsi

Table 1 Overview of the population characteristics and resistance exercises and/or resistance training characteristics of the reviewed studies *(Continued)*

First author [ref.]	Study design and sample characteristics	Resistance exercise characteristics
	- 1x RT: 160.7 ± 6.4 / 68.2 ± 14.6 / N.A. - 2x RT: 161.3 ± 7.4 / 68.1 ± 12.5 / N.A. (3) MMSE (MOCA) score - BAT: 28.7 (24.4) ± 1.3 (3.5) - 1x RT: 28.9 (25.8) ± 1.0 (2.9) - 2x RT: 28.8 (25.6) ± 1.8 (2.9)	pull-downs, leg presses, hamstring curls, and calf raises) and free weights (e.g., mini-squats, mini-lunges, and lunge walks) (6) Ca. 60 min (10 min warm-up, 40 min exercising, 10 min cool-down) (7) 1 day/week (in 1x RT) or 2 days/week (in 2x RT) (8) One week-in-between (in 1x RT) / N.A. (in 2x RT) (9) 52 weeks (10) Group-based and supervised
Kjølhede et al. [193]	(1) IS (RCT, cross-over design) / WL, RT (2) Adults with multiple sclerosis (2.1) - WL: *N* = 17 [12] (N.A.) - RT: *N* = 18 [17] (N.A.) - mean of both groups: 43.2 ± 8.1 (2.2) - mean of both groups: 171.0 ± 8.0 / 75.0 ± 13.0 / N.A. (3) EDSS score - WL: 2.9 ± 0.2 - RT: 2.9 ± 0.2	(1) Dynamic (2) Progressively increased with adjustment in sets, repetitions, load [detailed information can be found in Kjølhede et al. [198] (3) 2 to 3 min [detailed information can be found in Kjølhede et al. [198] (4) N.A. (5) Exercises with resistance machines (e.g., horizontal leg press, hip flexion, leg extension, prone hamstring curl, cable pull-down and cable triceps extension) (6) N.A. (7) 2 days/ week (8) N.A. (9) 24 weeks (10) Group-based and supervised
Liu-Ambrose et al. [186]	(1) IS (RCT, between-group design) / BAT, 1x RT, 2x RT (2) Older adults (2.1) - BAT: *N* = 49 [20/18] (49 f / 0 m) / 70.0 ± 3.3 - 1x RT: *N* = 54 [28] (54 f / 0 m) / 69.5 ± 2.7 - 2x RT: *N* = 52 [18] (52 f / 0 m) / 69.4 ± 3.0 (2.2) - BAT: 161.0 ± 6.9 / 67.0 ± 11.5 / N.A. - 1x RT: 160.9 ± 7.0 / 69.2 ± 16.2 / N.A. - 2x RT: 162.8 ± 6.5 / 72.1 ± 16.8 / N.A. (3) MMSE score - BAT: 28.8 ± 1.2 - 1x RT: 28.5 ± 1.3 - 2x RT: 28.6 ± 1.5	(1) Dynamic (2) 2 sets of 6 to 8 repetitions of 7RM per exercise (progressively increased) (3) N.A. (4) N.A. (5) Exercises with pneumatic resistance machines (e.g., biceps curls, triceps extensions, seated rows, latissimus dorsi pull-downs, leg presses, hamstring curls, and calf raises) and free weights (e.g., mini-squats, mini-lunges, and lunge walks) (6) Ca. 60 min (10 min warm-up, 40 min exercising, 10 min cool-down) (7) 1 day/week (in 1x RT) or 2 days/week (8) One week-in-between (in 1x RT) / N.A. (in 2x RT) (9) 52 weeks (10) Group-based and supervised
Liu-Ambrose et al. [45]	(1) IS (RCT, between-group design) / BAT, 1x RT, 2x RT (2) Older adults (2.1) - BAT: *N* = 17 [17] (17 f / 0 m) / 69.2 ± 3.2 - 1x RT: *N* = 20 [20] (20 f / 0 m) / 69.7 ± 2.8 - 2x RT: *N* = 15 [15] (15 f / 0 m) / 68.9 ± 3.2 (2.2) - BAT: 162.4 ± 5.9 / 67.3 ± 9.5 / N.A. - 1x RT: 161.7 ± 7.5 / 70.7 ± 13.8 / N.A. - 2x RT: 162.7 ± 6.6 / 68.7 ± 10.9 / N.A. (3) MMSE score - BAT: 29.1 ± 1.1 - 1x RT: 28.6 ± 1.2 - 2x RT: 29.1 ± 0.85	(1) Dynamic (2) 2 sets of 6 to 8 repetitions of 7RM per exercise (progressively increased) (3) N.A. (4) N.A. (5) Exercises with pneumatic resistance machines (e.g., biceps curls, triceps extensions, seated rows, latissimus dorsi pull-downs, leg presses, hamstring curls, and calf raises) and free weights (e.g., mini-squats, mini-lunges, and lunge walks) (6) Ca. 60 min (10 min warm-up, 40 min exercising, 10 min cool-down) (7) 1 day/week (in 1x RT) or 2 days/week (in 2x RT) (8) One week-in-between (in 1x RT) / N.A. (in 2x RT) (9) 52 weeks (10) Group-based and supervised
Nagamatsu et al. [189]	(1) IS (RCT, between-group design) / BAT, 2x AT, 2x RT (2) Older adults with probable mild cognitive impairment and subjective memory complaints (2.1) - BAT: *N* = 28 [8] (28 f / 0 m) / 75.1 ± 3.6 - AT: *N* = 30 [7] (30 f / 0 m) / 75.6 ± 3.6 - RT: *N* = 28 [7] (28 f / 0 m) / 73.9 ± 3.5 (2.2) - BAT: 158.2 ± 7.3 / 66.4 ± 14.0 / N.A. - AT: 159.2 ± 5.9 / 64.8 ± 12.8 / N.A. - RT: 158.7 ± 7.0 / 65.2 ± 10.7 / N.A.	(1) Dynamic (2) 2 sets of 6 to 8 repetitions of 7RM per exercise (progressively increased) (3) N.A. (4) N.A. (5) Exercises with pneumatic resistance machines (e.g., biceps curls, triceps extensions, seated rows, latissimus dorsi pull-downs, leg presses, hamstring curls, and calf raises) and free weights (e.g., mini-squats, mini-lunges, and

Table 1 Overview of the population characteristics and resistance exercises and/or resistance training characteristics of the reviewed studies *(Continued)*

First author [ref.]	Study design and sample characteristics	Resistance exercise characteristics
	(3) MMSE (MOCA) score - BAT: 27.1 (22.5) ± 1.7 (2.8) - AT: 27.4 (22.2) ± 1.5 (2.8) - RT: 27.0 (21.4) ± 1.8 (1.3)	lunge walks) (6) Ca. 60 min (10 min warm-up, 40 min exercising, 10 min cool-down) (7) 2 days/week (8) N.A. (9) 52 weeks (10) Group-based and supervised
Suo et al. [190]	(1) IS (RCT, between-group design) / SHAM, RE + SHAM, RE + CCT, CCT + SHAM (2) Older adults with dementia prodrome mild cognitive impairment (2.1) - ALL: *N* = 100 (68 f / 32 m) / 70.1 ± 6.7 (55–87) - SHAM: *N* = 27 [22] (N.A.) - RE + SHAM: *N* = 22 [19] (N.A.) - RE + CCT: *N* = 27 [22] (N.A.) - CCT + SHAM: *N* = 24 [20] (N.A.) (2.2) - N.A. (3) MMSE score - ALL: 24–28 (29 was acceptable only if error noted in memory registration)	(1) Dynamic (2) 5 to 6 exercises with 3 sets of 8 repetitions per exercise at 80 to 92% of 1RM (3) N.A. (4) N.A. (5) Exercises with pneumatic resistance machines (e.g., chest press, leg press, seated row, standing hip abduction, knee extension, hip flexion, hip extension, calf raise) and free weights (e.g., lateral raise, biceps curls) (6) Ca. 90 min (7) 2 days/week (8) N.A. (9) 26 weeks (10) Group-based and supervised

Please note that the sham treatments in Suo et al. [190] were conducted as follows: (i) the cognitive training group (CCT + SHAM) included physical exercises that did not significantly increase heart rate or improve aerobic capacity balance or strength performance (e.g., stretching, toning, and seated calisthenics), and (ii) the resistances exercise group (RE + SHAM) included a computerized, active cognitive control training

AE Aerobic exercises, *AT* Aerobic training, *BAT* Balance and toning exercise, *BAST* Balance and stretching training, *BMI* Body mass index, *cm* Centimeters, *CON (n)* Non-exercising control group, *CON (r)* Control group read magazines, *EDSS* Expanded disability status scale, *f* Female, *HIA* High-intensity aerobic exercise, *HIIT* High-intensity aerobic interval training, *HIRE* High-intensity resistance exercises, *HIRT* High-intensity resistance training, *HOA* Healthy older adults, *kg* Kilogram, *LM* Loadless movement group, *MCI* Mild cognitive impairments, *MIC* Moderate-intensity exercise combining resistance training and walking, *MCT* Moderate continuous aerobic training, *MIRE* Moderate-intensity resistance exercises, *m* Male, *min* Minute, *MMSE* Mini-mental state examination, *MOCA* Montreal cognitive assessment, *N* Number of participants, *N.A.* Not applicable, *RCT* Randomized controlled trials, *RM* Repetition maximum, *RE* Resistance exercises, *RT* Resistance training, *SD* Standard deviation, *WL* Wait list

With regard to resistance training, after a 16-week intervention with healthy older adults, oxygenated hemoglobin and total hemoglobin were lowered in the left prefrontal cortex during the Stroop task (Stroop interference effect, posttest compared with pretest), while cognitive task performance (i.e., reaction time) was improved [44]. At the end of 52 weeks of resistance training, older adults who had conducted resistance exercises twice a week exhibited better performance in tasks of executive functions (i.e., Stroop test) than those who had performed balance and toning exercises [45]. Furthermore, in the same study, the hemodynamic response during the incongruent flanker condition was increased in the left anterior insula and the left lateral orbitofrontal cortex, whereas the hemodynamic response during the congruent flanker condition decreased in the same areas [45].

In older individuals with mild cognitive impairment (MCI), the right lingual and occipital-fusiform gyri and the right frontal pole exhibited increased activation during the associative memory test after a twice-weekly performed resistance training lasting for 52 weeks when compared with older individuals conducting balance and toning exercises in this time period [189]. Furthermore, in this study, a positive correlation between increased hemodynamic activity in the right lingual gyrus and improved associative memory performance was observed [189]. After 26 weeks of resistance training, decreased resting-state functional connectivity of the PC_{FC} with the left inferior temporal lobe and the anterior cingulate cortex and between the HIP_{FC} and the right inferior temporal lobe was observed in older adults with MCI [190]. In the same study, an increase in resting-state functional connectivity between the HIP_{FC} and the right middle frontal lobe was evident in older adults with MCI in the resistance training group [190].

Neuroelectric functional brain changes and cognition

With regard to an acute bout of resistance exercises, cognitive performance was improved in younger adults [182, 183] and older adults with MCI [195]. After exercising in younger adults, an increase in the P3 amplitude during a Go/No-Go task combined with the Eriksen Flanker paradigm was observed [182], and in older adults with MCI, the P3 amplitude across all electrode positions (except Pz) during the Eriksen Flanker task was larger posttest compared with pretest [195]. Furthermore, in younger adults, a time-dependent and condition-dependent increase in P3 amplitude (obtained during the Stroop task) was observed [183]. In incongruent trials, larger P3 amplitudes were observed 30 min and 40 min after exercise cessation, whereas in congruent trials, larger P3 amplitudes were observed 10 min

and 40 min after exercise cessation [183]. However, in the same study, no statistically significant differences between the resistance exercise group and the loadless movement group were observed [183]. Additionally, larger P3 amplitudes were associated with lower serum cortisol levels after an acute bout of resistance exercise in younger adults [182].

With regard to resistance training, after 9 weeks of training (three times per week), the elderly participants showed a significant decrease in N1 latencies at the Fz and Cz positions during an auditory task, whereas the N1-P2, P2-N2 and N2-P3 amplitudes (at Fz) and the N1-P2 amplitude (at Cz) increased [194]. In comparison to both an aerobic training group and an inactive control group, the resistance training group showed a greater absolute reduction in P2 and N2 latencies and larger absolute increase in N1-P2, P2-N2, and N2-P3 amplitudes [194]. Furthermore, after 10 weeks of resistance training in healthy older adults and in older adults at an early stage of dementia, a decrease in beta asymmetry, a decrease in N200 A asymmetry, and an increase in theta asymmetry was observed [192]. The decrease in N200 A asymmetry was significantly negatively correlated with improvements in the Fuld immediate recall score and the Fuld delayed recall score, while the increase in delta asymmetry was significantly positively correlated with a better Fuld delayed recall score [192]. After resistance training with elastic bands for 12 weeks, healthy older adults showed a decrease in relative theta power at P3 and P4, but their cognitive measures remained unchanged [188]. However, in the same study, exercising older adults with MCI exhibited significantly higher scores in the digit span backward test than their non-exercising counterparts [188]. Furthermore, from pre- to posttest, theta power at F3 increased and alpha power at T3 decreased in exercising older adults with MCI [188]. After 16 weeks of resistance training in older adults with amnestic MCI, larger P3 amplitudes during a task-switching paradigm were observed [191]. Furthermore, in the same study, decreased reaction times (i.e., in the non-switching condition and in the switching condition) and higher accuracy rates (i.e., in the pure condition, in the non-switching condition, and in the switching condition) were noticed in the resistance training group and the aerobic training group when the posttest was compared with the pretest [191]. Additionally, in the resistance training group, a positive correlation between changes in serum levels of insulin-like growth factor 1 (IGF-1) and P3 amplitudes (measured during switching condition) and a negative correlation between serum levels of tumor necrosis factor-alpha and accuracy rates in the switching condition were observed, which both barely failed to attain statistical significance [191]. In another study, 48 weeks of resistance training led to superior cognitive performance (i.e., reaction time) as well as to larger P3a and P3b amplitudes in an oddball task [187]. Moreover, serum IGF-1 concentrations increased and were correlated with faster reaction times and larger P3b amplitudes only in the resistance group [187].

Structural brain changes and cognition

After resistance training performed once or twice weekly for 52 weeks, compared with older adults conducting balance and toning exercises, older adults in the resistance training groups exhibited (i) an increased performance in Stroop test [186], (ii) a reduction in whole brain volume [186], (iii) a lower volume of cortical white matter atrophy [184], and (iv) a lower degree of cortical white matter lesions [185]. In older female adults with probable MCI, resistance training over 26 weeks did not led to significant changes in hippocampal volume [197]. In another study, older adults with MCI resistance training performed twice a week for 26 weeks exhibited improved ADAS-Cog scores (global cognition assessed with Alzheimer's Disease Assessment Scale) and increased the cortical thickness of grey matter in the posterior cingulate gyrus [190]. Moreover, the increase in grey matter thickness was negatively correlated with ADAS-Cog scores, indicating better cognitive performance [190]. In individuals with multiple sclerosis (MS), resistance training lasting 24 weeks led to an increase in cortical thickness in the anterior cingulate sulcus and gyrus, the temporal pole, the inferior temporal sulcus, and the orbital H-shaped sulcus [193]. The increased thickness in the temporal pole was significantly negatively correlated with lower scores on the Expanded Disability Status Scale (i.e., lower disability) [193]. More detailed information on the main findings is provided in Table 2.

Discussion

Risk of bias

In general, our results regarding the source of the risk of bias are somewhat heterogeneous (see Fig. 3); nevertheless, the overall quality of the majority of the reviewed studies can be regarded as sufficiently high. However, the risk of bias could be further minimized by proper planning of the study, which would strengthen the plausibility of observed effects. To ensure and enhance the study quality, it appears imperative that future studies report their procedures in sufficient detail (e.g., exercise and training variables) and pay attention to established guidelines such as the CONSORT statement [202] or the STROBE statement [203].

Selection of participants and study design

The reviewed studies were conducted with healthy young adults, healthy older adults, or older adults with

Table 2 Overview of the characteristics of cognitive testing and the main outcomes of the reviewed studies

First author [ref.]	(1) Cognitive testing (2) Main findings (related to functional and/or structural brain changes in response to resistance exercises or resistance training)
Functional near-infrared spectroscopy	
Chang et al. [43]	(1) Executive functions (Stroop test) during fNIRS (conducted 15 min after exercise cessation) (2) Between group comparisons (postexercise, neutral condition): - ↓ TOI in lt. PFC during CT (HIR vs. CON (n) / MIC) - ↑ Solved items and ↓ response time during CT (HIR vs. CON (n)) Between group comparisons (postexercise, incongruent condition): - ↓ TOI in lt. PFC (HIR vs. CON (n) / MIC) - ↓ TOI in rt. PFC (HIR vs. CON (n) / MIC / HIA) (ROI: lt. and. rt. PFC)
Coetsee et al. [44]	(1) Executive functions (Stroop test) during fNIRS (2) Posttest vs. pretest: - ↓ OxyHb in lt. PFC in RT during CT (Stroop interference effect) - ↓ THI in lt. PFC in RT and MCT during CT (Stroop interference effect) - ↓ Reaction time in RT during CT (naming and executive condition) (ROI: lt. and rt. PFC)
Electroencephalography	
Hong et al. [188]	(1) Cognitive test battery (Stroop test, COWAT, DFDB; Rey 15-Item Memory Test) and resting EEG (2) Posttest versus pretest: - ↓ Relative theta power (at F3) in MCI RT - ↑ Relative alpha power (at T3) in MCI RT - ↓ Relative theta power (at P3 and at P4) in HOA RT - DB scores were significantly higher in MCI RT than in MCI CON (at posttest)
Özkaya et al. [194]	(1) Auditory task during EEG (2) Posttest vs. pretest: - ↓ Latencies of N1 (at Fz) and N1 (at Cz) in RT and AT - ↑ Amplitudes of N1-P2, P2-N2 and N2-P3 (at Fz) and N1-P2 (at Cz) in RT Between group comparisons: - ↓ Absolute changes in latencies of P2 and N2 (at Fz and at Cz) in RT compared with AT and CON - ↑ Absolute changes in amplitudes of N1-P2, P2-N2, and N2-P3 (at Fz) and N1-P2 and N2-P3 (at Cz) in RT compared with AT and CON
Tsai et al. [182]	(1) Executive functions (Go/No-Go task combined with the Eriksen Flanker paradigm) during EEG measurements (CT was conducted after exercise cessation when the participant's body temperature and HR had returned to within 10% of pre-exercise levels, which was on average approximately 5 min after acute resistance exercise cessation.) (2) Posttest vs. pretest: - ↑ P3 amplitude (i.e., at Fz, Cz, and Pz) in MIRT and HIRT during CT - ↓ Reaction time in MIRT and HIRT during CT (Go condition) - ↑ Accuracy in MIRT and HIRT during CT (incongruent No-Go condition) - ↑ Serum GH and serum IGF-1 in MIRE and HIRE (prior to cognitive testing at pretest vs. prior to cognitive testing at posttest) - ↓ Serum cortisol in MIRE and HIRE (prior to cognitive testing at pretest vs. prior cognitive testing at posttest) - ↓ Serum GH and serum IGF-1 in HIRE (prior to cognitive testing at posttest vs. after cognitive testing at posttest) - ↑ Serum GH in MIRE and HIRE, serum IGF in MIRE (prior to cognitive testing at pretest vs. after cognitive testing at posttest)

Table 2 Overview of the characteristics of cognitive testing and the main outcomes of the reviewed studies *(Continued)*

	- ↓ Serum cortisol in MIRE (prior to cognitive testing at pretest vs. after cognitive testing at posttest)
	- Lower serum cortisol levels were associated with higher P3 amplitude
Tsai et al. [187]	(1) Executive functions (oddball task) during EEG measurements
	(2) Between group comparisons:
	- ↑ P3a amplitude (i.e., at F3 and F4) and P3b amplitude (i.e., at Cz, Pz, and Oz) in RT during CT compared with CON (n)
	- ↑ Accuracy in RT during CT compared with CON (n)
	- ↓ Reaction time in RT during CT compared with CON (n)
	Posttest vs. pretest:
	- ↓ Reaction time in RT during CT
	- ↑ Serum IGF-1 levels in RT
	- ↓ Serum homocysteine levels in RT
	- Higher serum IGF-1 levels in RT were associated with the faster reaction times and larger P3b amplitudes
Tsai et al. [195]	(1) Working memory (Memory span from WAIS-IV); executive functions (Flanker task) during EEG measurements (CT was conducted after exercise cessation when the participant's body temperature and HR had returned to within 10% of pre-exercise levels, which was on average approximately 5 min after acute resistance exercise cessation.)
	(2) Posttest vs. pretest:
	- ↑ P3 amplitudes (i.e., at Fz, Cz, and Pz, except the Pz electrode in RE) in AE and RE during CT (in all conditions)
	- ↓ Reaction time in AE and RT during CT (congruent and incongruent condition)
	- ↑ Serum IGF-1 in AE and RE; serum BDNF and serum VEGF in AE (prior to cognitive testing at pretest vs. prior to cognitive testing at posttest)
	- ↓ IGF-1 in AE and RE and serum BDNF in AE (prior to cognitive testing at posttest vs. after cognitive testing at posttest)
	- Lower P3 latency across all participants was associated with higher IGF-1 levels (prior to cognitive testing at posttest)
Tsai et al. [191]	(1) Working memory (Memory span from WAIS-IV); executive functions (Task switching) during EEG measurements
	(2) Posttest vs. pretest:
	- ↑ P3 amplitudes in AE and RT
	- ↓ Reaction time in AE and RT during CT (non-switching condition and switching condition)
	- ↑ Accuracy rate in AE and RT during CT (pure condition, non-switching condition, and switching condition)
	- ↑ Serum IGF-1 in RT and serum BDNF in AT
	- ↓ Serum TNF-α and serum IL-15 in RT and AT / ↑ serum TNF-α in CON
	- Higher levels of VO_{2max} are associated with higher levels of serum BDNF in RT and AT
Vonk et al. [183]	(1) Executive functions (Stroop test) during EEG measurements (conducted 10 min, 20 min, 30 min, and 40 min after exercise cessation)
	(2) Posttest vs. pretest:
	- ↓ Response time in RE and LM during CT (congruent and incongruent condition, 10 min after exercise cessation vs. pretest)
	- ↓ Response time in RE and LM during CT (congruent condition, 10 min vs. 30 min after exercise cessation)
	- ↓ Accuracy in RE and LM during CT (incongruent condition, 30 min after exercise cessation vs. pretest)
	- ↑ P3 amplitude in RE and LM during CT (incongruent condition, 30 min and 40 min after exercise cessation vs. pretest)
	- ↑ P3 amplitude in RE and LM during CT (congruent condition, 10 min and 30 min after exercise cessation vs. pretest)
Yerokhin et al. [192]	(1) Cognitive test battery (Stroop test, FOME; CFT); executive functions (oddball paradigm) during EEG

Table 2 Overview of the characteristics of cognitive testing and the main outcomes of the reviewed studies *(Continued)*

	(2) Posttest vs. pretest: - ↓ Beta asymmetry and ↓ N200 A asymmetry - ↑ Delta asymmetry - ↑ Figure delayed recall and Fuld immediate recall - Decreased N200 A asymmetry was significantly correlated with improvements in Fuld immediate and Fuld delayed recall - Increase in delta asymmetry was significantly correlated with an improvement in Fuld delayed recall (ROI: frontal lobe [FP1, FP2, F7, F8])
Functional and structural magnetic resonance imaging	
Best et al. [184]	(1) Cognitive test battery (Stroop test, TMT A&B, DB, RAVLT, DSST) (2) Between group comparisons: - ↓ Cortical WM atrophy 2x RT compared with BAT at 2-year follow-up - ↑ Executive functions in 1x RT compared with BAT considering changes from baseline to postintervention - ↑ Executive functions in 1x RT and 2x RT compared with BAT considering changes from baseline to a 2-year follow-up - ↑ Memory performance in 2x RT compared with BAT considering changes from baseline to 2-year follow-up - ↑ Peak muscle power in 2x RT compared with BAT considering changes from baseline to postintervention and to a 2-year follow-up
Brinke et al. [197]	(1) Memory (RAVLT) (2) Between group comparisons: - No significant differences between AT and RT in hippocampal volume after 26 weeks - ↑ Hippocampal volume in rt. and lt. hemisphere / total hippocampal volume in AT compared with AT after 26 weeks - Positive partial correlation between increase in left hippocampal volume and change in RAVLT (loss after interference condition)
Bolandzadeh et al. [185]	(1) Executive functions (Stroop test) (2) Between group comparisons: - ↓ Cortical WML volume 2x RT compared with BAT at 2-year follow-up - ↓ WML progression in 2x RT at postintervention was associated with maintenance of gait speed
Kjølhede et al. [193]	(1) Working memory & auditory information processing speed (PASAT) (2) Changes in cortical thickness in response to RT: - ↑ E.g., in subcentral sulcus and gyrus; anterior cingulate sulcus and gyrus, middle anterior cingulate sulcus and gyrus, inferior parietal angular gyrus, inferior temporal gyrus, middle temporal gyrus, temporal pole, superior circular sulcus of insula, superior and transverse occipital sulcus, inferior temporal sulcus, orbital H-shaped sulcus, inferior and superior parts of the precentral sulcus, inferior and superior temporal sulcus Between group comparisons regarding cortical thickness: - ↑ Anterior cingulate sulcus and gyrus, temporal pole, inferior temporal sulcus, orbital H-shaped sulcus in RT compared with WL after 24 weeks - Greater thickness in the temporal pole was correlated with lower EDSS scores
Liu-Ambrose et al. [186]	(1) Cognitive test battery (Stroop test, TMT A&B, DFDB) (2) Between group comparisons: - ↑ Stroop test performance in 1x RT and 2x RT compared with BAT at 2-year follow-up - ↑ Peak muscle power in 2x RT compared with BAT at postintervention and to a 2-year follow-up - ↓ Whole brain volume (from baseline) in 1x RT and 2x RT compared with BAT at a 2-year follow-up - Improvement in Stroop test performance during intervention was significantly associated with increased gait speed
Liu-Ambrose et al. [45]	(1) Executive functions test (modified Eriksen Flanker task) during fMRI (2) Between group comparisons: - ↑ Activation of the left anterior insula extending into the lateral orbital frontal cortex in 2x RT compared with BAT at posttest in the incongruent condition

Table 2 Overview of the characteristics of cognitive testing and the main outcomes of the reviewed studies *(Continued)*

	- ↓ Activation of the left anterior insula extending into the lateral orbital frontal cortex and anterior portion of the left middle temporal gyrus in 2x RT compared with BAT at posttest in the congruent condition
	- ↓ Reduction in interference score (better performance) in 2x RT compared with BAT
Nagamatsu et al. [189]	(1) Cognitive test battery (Stroop test, TMT A&B, DFDB; EPT) and associative memory (memorizing face-scene pairs) during fMRI
	(2) Between group comparisons:
	- ↑ Stroop test performance and associate memory task performance in RT compared with BAT at postintervention
	- ↑ Activation of the right lingual and occipital-fusiform gyri and the right frontal pole in 2x RT during CT compared with BAT at postintervention (encoding and recall of associations)
	- Higher hemodynamic activity in the right lingual gyrus was correlated with better performance in the associative memory test
Suo et al. [190]	(1) Cognitive test battery (e.g. ADAS, TMT A&B, BVRT, COWAT, Category Fluency, SDMT, Logical Memory WMS-III, Matrices WMS-III, Similarities WMS-III)
	(2) Between group comparisons:
	- ↓ ADAS-Cog score (i.e., improved cognition) at posttest in the RT groups compared with all other groups
	- ↑ Posterior cingulate cortex grey matter thickness at postintervention in RT groups compared with all other groups
	- ↓ White matter hyperintensities volumes in the rt. periventricular zone and the rt. parietal zone in RT groups compared with all other groups (significant when analyzed at the regional level / not-significant when whole brain-corrected)
	- Greater posterior cingulate cortex grey matter thickness was significantly correlated with lower ADAS-Cog score (i.e. improved cognition)
	Functional connectivity changes:
	- ↓ PC_{FC} connectivity with the left inferior temporal lobe and the anterior cingulate cortex in RT + SHAM / ↓ PC_{FC} connectivity between the PC and the anterior cingulate cortex in CCT + SHAM
	- ↓ PC_{FC} between the PC and the anterior cingulate cortex in RT + CCT
	- ↑ HIP_{FC} connectivity with the right middle frontal lobe and ↓ connectivity with the right inferior temporal lobe in RT + SHAM
	- ↑ HIP_{FC} connectivity between the hippocampus and the left superior frontal lobe in CCT + SHAM
	- ↑ Hippocampal–anterior cingulate cortex connectivity and the hippocampal–right superior frontal lobe connectivity in RT + CCT
	- ↑ Superior functional connectivity between the hippocampus and the superior frontal lobe is associated with improved memory domain performance

Please note that the sham treatments in Suo et al. [190] were conducted as follows: (i) the cognitive training group (CCT + SHAM) included physical exercises that did not significantly increase heart rate or improve aerobic capacity balance or strength performance (e.g., stretching, toning, and seated calisthenics), and (ii) the resistances exercise group (RE + SHAM) included a computerized, active cognitive control training.
ADAS-Cog Alzheimer's disease assessment scale, *AE* Aerobic exercises, *AT* Aerobic training, *BAT* Balance and toning exercise, *BDNF* Brain-derived neurotrophic factor, *BVRT* Benton visual retention test, *CFT* Complex figure test, *CON (n)* Non-exercising control group, *CON (r)* Control group read magazines, *COWAT* Controlled oral word association test, *CT* Cognitive test, *DB* Verbal digits backward test, *DFDB* Verbal digits forward and verbal digits backward tests, *DSST* Digit symbol substitution test, *EEG* Electroencephalography, *EDSS* Expanded disability status scale, *EPT* Everyday problem solving test, *fMRI* Functional magnetic resonance imaging, *fNIRS* Functional near-infrared spectroscopy, *FOME* Fuld object memory evaluation, *GH* Growth hormone, *HIA* High-intensity aerobic exercise, *HIIT* High-intensity aerobic interval training, *HIRE* High-intensity resistance exercises, *HIRT* High-intensity resistance training, *HOA* Healthy older adults, *IGF-1* Insulin-like growth factor 1, *MCI* Mild cognitive impairments, *MIC* Moderate-intensity exercise combining resistance training and walking, *MCT* Moderate continuous aerobic training, *MIRE* Moderate-intensity resistance exercises, *LM* Loadless movement group, *lt.* Left, *min* Minute, *oxyHb* Oxygenated hemoglobin, *PASAT* Paced auditory serial addition test, *PFC* Prefrontal cortex, *RAVLT* Rey auditory verbal learning test, *RCT* Randomized controlled trials, *RM* Repetition maximum, *RE* Resistance exercises, *RT* Resistance training, *rt.* Right, *SDMT* Symbol digit modalities test, *THI* Total hemoglobin index, *TMT A&B* Trail making test A&B, *TOI* Tissue oxygenation index, *TNF-α* Tumor necrosis factor-alpha, *VEGF* Vascular endothelial growth factor, VO_{2max} Maximal oxygen uptake during a graded exercise test, *vs.* Versus, *WL* Wait list, *WM* White matter, *WML* White matter lesion volume, *WAIS-IV* Wechsler-IV adult intelligence test, *WMS* Wechsler memory scale, ↑: significant increase; ↓: significant decrease / F3, F4, F7, F8, FP1, FP2, P3, T3, Cz, Fz, Oz and Pz are specific positions in the international system for EEG electrode placement [199], whereas N1, N2, P1, P2, P3 (P300) constitute specific EEG parameters [200, 201]

MCI or beginning dementia. Therefore, our knowledge about the effect of resistance exercises and/or resistance training on cognitive functions is limited to these cohorts, and further investigations with other cohorts are required. In particular, older adults with sarcopenia are a key group because there is a high prevalence (ranging from 1 to 33%) of this condition in various older populations [204], which poses major economic costs to the

welfare system [205]. Sarcopenia comprises the age-related loss of muscle mass [206–210] but in the literature the term has often been (incorrectly) extended to the age-related loss of muscle function (e.g., muscle strength) [210–219]. The latter one should be referred to as dynapenia which encompasses the age-related loss of muscle function (e.g., loss of muscular strength and power) [209–211, 220]. However, age-related muscular changes (e.g., sarcopenia) could also lead to a decline in cognitive performance [221, 222]. Hence, older adults with sarcopenia and/or dynapenia may profit in two ways (physically and cognitively) from resistance exercises/resistance training.

In the terms of study design, in future resistance exercise and/or resistance training studies, moderator variables such as gender [223–226] or genotype [227, 228], which may influence the effectiveness of the resistance exercise and/or resistance training, should be considered and analyzed. The assessment and analysis of moderators may help provide a better understanding of the observed inter-individual variability regarding the effect of physical exercise (e.g., resistance training) on the brain and on cognitive functions and help to foster the optimization of physical exercise interventions [125]. Furthermore, chronobiological factors (such as circadian variability) should be considered since they affect muscular adaptions in response to resistance exercises [229–232] and affect cognitive performance [233–235]. However, hemodynamic responses are reported to be relatively unaffected by, for instance, circadian variability [236].

Moreover, larger cohorts and longer intervention intervals could be beneficial (especially in [f] MRI studies) for increasing the external validity and for adaptation processes to manifest [237]. In addition, concerning cognitive testing, it seems advisable to use standardized sets of cognitive tests or to employ the latent variable approach (create an unobserved [latent] variable for a distinct set of cognitive tests) [238]. In this context, the 'human baseline hypothesis' should be considered, which claims that the baseline values of strength (e.g., grip strength, knee extensor strength) assessed prior to resistance training and/or after a detraining period are a more appropriate indicator of health outcomes than the training-related increase in strength values [239].

With regard to upcoming cross-sectional studies, neuroimaging methods (e.g., fNIRS, see [179]) should be employed as they help to better understand the association between superior cognitive performance (e.g., in global cognitive abilities) and superior muscular performance previously operationalized by (i) hand grip strength [86, 88, 89], (ii) isokinetic quadriceps strength [82, 83], (iii) leg power [84], or (iv) whole-body muscular strength [85].

Functional brain changes and cognition in response to resistance exercises or resistance training

Hemodynamic functional brain changes and cognition

Currently, only a few studies have investigated the influence of resistance exercises and/or resistance training on functional brain parameters in healthy adults during standardized cognitive tasks. However, regardless of whether resistance exercises were conducted as an acute bout [43] or over a period of 16 weeks [44], proxies of cortical activation in the prefrontal cortex during the Stroop test were found to be decreased. In another resistance training study (52 weeks), a decrease in brain activation was observed exclusively during the relatively easy task condition, whereas increased activation was found in the more difficult task condition [45]. These observations stand in contrast to the findings of acute aerobic exercise studies [28, 29, 43] and aerobic training studies [44], in which, in general, increased activation of prefrontal areas during cognitive testing was observed after exercising [180]. Notably, similar to the findings of most aerobic exercise or aerobic training studies, the reviewed resistance exercise and/or resistance training studies also reported improved cognitive functions [43–45]. Hence, decreases in the applied proxies of neuronal activity might indicate more efficient processing or automatization of cognitive processes. Moreover, it is likely that the decrease in brain activation in response to resistance exercises and/or resistance training is related to neurobiological mechanisms different from those induced by aerobic exercises or aerobic training [107, 223, 240]. Future studies are urgently needed to investigate the underlying neurobiological mechanisms of different types of acute physical exercises (e.g., resistance exercises vs. aerobic exercises) and chronic physical training (e.g., resistance training vs. aerobic training). Analysis of the neurobiological changes in response to different physical exercise/training interventions will also contribute to a better understanding of the functional changes in the brain. In this regard, Liu-Ambrose et al. [45] noticed that after the completion of a 52-week long resistance training program, functional brain activations in the left anterior insula extending from the lateral orbital frontal cortex and in the anterior portion of the left middle temporal gyrus during execution of a cognitive task were altered [45]. The left anterior insula, for instance, plays an important role in successful performance in response inhibition tasks [241], which may be based on their involvement in (i) the stopping ability [242], (ii) the assurance of general task accuracy [242], and (iii) maintaining a stable task set control [243, 244]. The left middle temporal gyrus is especially activated in complex Go–/No-Go situations [245]. However, in contrast, in comparable aerobic training, higher task-related

activation in prefrontal areas and parietal cortices and decreased activation of the anterior cingulate cortex was observed [246]. Parietal areas [247] and prefrontal areas [248, 249] are involved in a variety of cognitive processes, among them attention [250, 251]. In particular, the parietal areas [252, 253] and the prefrontal areas [254, 255] are strongly involved in selective attention and the frontoparietal network in maintaining and manipulating task-relevant information in working memory [243]. In the context of attentional processes, the anterior cingulate cortex is also an important structure because it allocates attentional resources based on the recruitment of task-appropriate processing centers [256]. Moreover, the anterior cingulate cortex is activated in conflict processing where erroneous responses are highly probable [257–260]. Taken together, resistance training might be beneficial for cognitive processes that aim to avoid unwanted responses (e.g., maintaining stable task set control and increased stop efficacy), whereas aerobic exercises may enhance cognitive processes such as selective attention (e.g., maintaining task-relevant information) [45]. Further research is needed to verify this assumption.

The positive effect of resistance training on brain health is also underpinned by findings of Nagamatsu et al. [189], who observed higher cortical activation during an associative memory task in older individuals with MCI after they had undergone long-term resistance training (52 weeks). Moreover, this higher cortical activity was positively correlated with improvements in cognitive performance [189]. Another mechanism through which resistance training may ensure or/and improve brain health in MCI may be related to the modulation of functional connectivity. It was observed that (i) the resting-state functional connectivity between posterior cingulate cortex and other brain regions is generally decreased in individuals with MCI [261–264], (ii) functional connectivity between the posterior parietal cortex and the temporal cortex is associated with performance on neuropsychological tests [261], and (iii) the resting-state functional connectivity between the hippocampus and other brain regions is disturbed in individuals with MCI [265] or Alzheimer's disease [266, 267]. Notably, resistance training lasting 26 weeks increases the functional connectivity among the posterior cingulate cortex, the left inferior temporal lobe, and the anterior cingulate cortex and between the hippocampus and the right middle frontal lobe [190]. Based on the mentioned changes in resting-state functional connectivity in neurological diseases (e.g., MCI) and the positive influence of resistance training on resting-state functional connectivity, it can be speculated that resistance training may be a beneficial intervention strategy for ensuring or/and improving brain health and cognition in those cohorts.

Neuroelectric functional brain changes and cognition

A higher P3 amplitude (also known as P 300) was observed in younger adults after an acute bout of resistance exercises [182, 183] and in healthy older adults after 48 weeks of resistance training [187]. Furthermore, a higher P3 amplitude was observed in individuals with MCI after an acute bout of resistance exercises [195] or after 16 weeks of resistance training [191]. Elevated P3 amplitudes are generally associated with neural activity and cognitive processes [268, 269]. Upregulation of the P3 amplitude after resistance exercises and/or resistance training may be beneficial for brain health because diminished P3 amplitudes were observed in older individuals [270, 271] and individuals with neurological diseases (e.g., Alzheimer's disease) [272]. The associations between event-related potentials (e.g., P3 amplitude) and neurotrophic factors obtained after acute resistance exercises [182, 195] and/or resistance training [191] support the "neurotropic hypotheses" [114–117]. Profound changes in neuroelectric outcomes were also observed after 12 weeks of resistance training with decreased resting-state theta power in older adults with and without MCI and increased resting-state alpha power in older adults with MCI [188]. The relevance of these findings is currently unclear because contradictory observations regarding meaningful changes in alpha and theta power are found in the literature. For instance, on the one hand, more resting-state alpha power and less resting-state theta power were associated with better cognitive performance [273, 274], whereas, on the other hand, it has also been reported that higher resting-state theta power is linked to superior cognitive performance (e.g., in category fluency task) [275, 276]. Nevertheless, the notion that resistance training positively affects brain health was clearly confirmed by the observation of statistically significant correlations between neuroelectric changes (e.g., in asymmetry index) and changes in memory performance in older adults in response to a resistance intervention lasting 10 weeks [192]. In addition, Özkaya et al. [194] observed differences in neuroelectric parameters as a function of the type of physical training. This observation supports the idea that resistance and aerobic training have different impacts on the underlying neurobiological processes [223, 225, 240].

In sum, based on the small number of studies, it is too early to draw generalizable conclusions with respect to functional brain changes, but the available results suggest that resistance exercises and/or resistance training can be a promising strategy to ensure brain health. However, further studies are urgently needed to investigate the effect of an acute bout of resistance exercises and/or resistance training on functional brain changes. Here, upcoming studies should also pay attention to the investigation of neurobiological processes that may cause functional brain changes.

Structural brain changes and cognition in response to resistance training

In response to resistance training over an intervention period of 52 weeks (performed two times per week), (i) a reduction in whole brain volume [186], (ii) a reduction in cortical white matter atrophy [184], and (iii) a reduction in white matter lesions [185] were observed in comparison to training with balance or toning exercises. The reduction in whole brain volume is surprising because, in general, 'more' is often associated with 'better'. However, it is assumed that the reduction in whole brain volume is perhaps caused by the improvement of certain brain pathologies, in particular the removal of amyloid plaques and shifts in cerebral fluids [186, 277, 278], which, in turn, might positively influence brain health. This view is supported by the recent findings of Yoon et al. [279], who observed a relationship between brain amyloid-β levels and hand grip strength (e.g., high levels of brain amyloid-β and low grip strength). The removal of amyloid plaques could be one possible neurobiological mechanism explaining the observed improvements in executive functions [186] because accumulation of amyloid-β plaque is commonly linked to worsened domain-specific cognitive functions (e.g., executive functions and memory) [280–282], and neurological diseases such as Alzheimer's disease [283–286].

Furthermore, given that white matter abnormalities (e.g., high load of white matter lesions) are linked to a decline in cognitive functions (i.e., global cognition and processing speed) [13, 287–290] and are associated with neurological diseases such as dementia [291, 292], the resistance training-induced changes in white matter (e.g., reduced volume of lesions and reduced atrophy) are likely to be beneficial for brain health. Notably, the reduced volumes of white matter lesions after 52 weeks of resistance training are linked to increased gait speed [185]. Based on the findings that both slower gait speed [293] and white matter lesion load [294] are linked to an increased fall risk, the positive changes within the white matter in response to resistance training suggest that engaging in resistance training could play a substantial role in preservation of the neural correlates of all-day tasks (e.g., safe walking).

In response to resistance training, which was performed twice a week for 26 weeks, grey matter thickness in the posterior cingulate cortex was found to increase significantly [190]. This increase in cortical thickness of the posterior cingulate cortex was linked to improved global cognitive performance [190]. This neurobiobehavioral relationship underpins the assumption that the posterior cingulate cortex is important for cognition, although there is still no agreement about its exact role [295]. However, reductions in metabolism [296] and volume [297] were observed in the posterior cingulate cortex in Alzheimer's disease. Hence, the possible ability to shape this cortical structure by engaging in resistance training is a promising approach to ensure brain health and to prevent neurological diseases. In the context of neurological diseases, it was also observed that resistance training for 24 weeks increased the cortical thickness in distinct areas, such as the temporal pole, in individuals with MS. The increased cortical thickness in the temporal pole was associated with better scores on the Expanded Disability Status Scale (EDSS), suggesting that resistance training has a positive impact on brain health and functional abilities in this cohort. There are even reports in the literature that a single resistance exercise (leg press) has profound effects on brain volumes (but without a relation to cognitive functions) in healthy older adults. Here, statistically significant increases in grey matter density in the posterior and anterior lobe of the cerebellum, the superior frontal gyrus in the frontal lobe, and the anterior cingulate cortex in the limbic lobe were observed [131]. In summary, these results support the view that robust neuroplastic changes can be evoked through resistance training, which contribute to the maintenance of brain health.

Interestingly, one of the reviewed studies directly compared resistance and aerobic trainings and found no statistically significant difference in hippocampal volume changes between trainings [197]. Although an increase in hippocampal volume was reported after both aerobic [24] and resistance training in older adults [130], few brain imaging studies are currently available that directly compare different types of physical training. For instance, it was observed that dancing conducted for several months led to a greater increase in cortical grey matter in frontal and temporal regions [298–300] and in hippocampal volumes [301] than a combination of resistance, endurance, and flexibility training. Hence, comparing different types of physical interventions (e.g., resistance training vs. aerobic training vs. dancing) with regard to their effectiveness in evoking structural and functional brain changes is an interesting topic for further studies. Such knowledge is necessary to foster the development of individualized physical interventions, which are deemed to be more effective than the 'one-size-fits-all approach' [125, 223, 302].

Taken together, resistance training reduces white matter atrophy and increases grey matter volumes in distinct brain areas. Based on the observed relationship between structural changes and behavior [185, 190], the positive role of resistance training in ensuring (and improving) brain health is reinforced. Further studies comparing different types of physical interventions with respect to structural brain changes are required.

Neurophysiological adaptation processes in connection with resistance exercises and resistance training

Structural brain changes in response to resistance training rely at least partly on the modulation of specific molecular and cellular pathways that are involved in neuroplasticity and – consequently – in positive effects of cognitive performance [112, 240]. In this context, the modulating role of resistance exercises and/or resistance training on the release of neurochemicals such as BDNF, IGF-1, and homocysteine is discussed in the literature [121, 223, 303, 304]. In the following, we briefly outline how these neurochemicals may contribute to the observed functional and structural brain changes.

BDNF

In particular, structural brain changes after physical interventions are assumed to be mediated by BDNF [114, 118, 119, 223, 240]. In addition, serum BDNF concentrations have been linked to spatial memory performance [21] and higher serum BDNF concentrations in response to acute physical exercises [305] or physical training [306] have been associated with improvements in executive functions. Furthermore, BDNF is involved in many neuroplastic processes, such as synaptogenesis, long-term potentiation of synaptic transmission, regulation of the differentiation of neuronal precursor cells, and neuronal survival [120]. The important role of BDNF in neuroplasticity is underpinned by the findings that reduced serum BDNF concentrations were linked to a decline in hippocampal volume and that changes in serum BDNF concentrations after aerobic training were associated with hippocampal volume changes [24]. Although hippocampal changes could not be observed in one of the reviewed studies after 26 weeks of resistance training [197], there is solid evidence that resistance exercises (especially at high-load conditions) [307–311] and resistance training (especially in males) [308, 312] upregulate serum BDNF concentrations. Such an increase in response to resistance exercise and resistance training was also reported for plasma BDNF [313]. Notably, it is assumed that concentrations of BDNF stored in immune cells and/or platelets are mirrored in the level of serum BNDF, while plasma BDNF is a marker of the concentration of freely circulating BDNF [314, 315]. Based on the previously mentioned connections between (serum) BDNF, brain physiology, and cognition (i.e., executive functions), it can be speculated that BDNF-driven mechanisms might contribute to neurocognitive changes after resistance exercises and/or resistance training. However, further studies are urgently needed to deepen our knowledge regarding the interrelationship between resistance exercises and/or resistance training-induced expression of (serum) BDNF in humans and its relation to functional and structural brain changes as well as to cognitive performance (as a function of age).

IGF-1

Engaging in resistance exercises [316] and resistance training [187, 317] fosters the expression of IGF-1, which is predominantly released by the liver (global output, ~ 70% of total circulating IGF-1), the musculature (local output), and the brain (local output) itself [318, 319]. Because circulating IGF-1 can cross the blood-brain barrier (BBB), locally expressed IGF-1 (e.g., from musculature) is likely to be available in the brain [318, 319]. IGF-1 triggers various mechanisms that contribute to neuroplasticity in the human brain, such as synaptic processes (e.g., long-term potentiation) [320, 321], angiogenesis in the brain, axon outgrowth, dendritic maturation, and synaptogenesis [319, 322]. Moreover, IGF-1 likely plays an important role in structural grey matter changes because it is involved in neuroplastic mechanisms that foster neuronal survival [323] such as (i) proliferation of neural cells [324, 325], (ii) inhibition of apoptosis of neural cells [324, 325], and (iii) protection of neurons against toxicity by, for instance, amyloid peptides [324]. While there is some evidence that higher serum IGF-1 levels are linked to greater total brain volumes [326] or hippocampal volume [327], the exact roles of IGF-1 in the central nervous system remain elusive [328]. However, the assumption that IGF-1-activated pathways play an important role in changing brain function is underpinned by the findings of a reviewed study that reported higher peripheral serum IGF-1 concentrations after 52 weeks of resistance training in healthy older individuals alongside behavioral (e.g., improved accuracy and reaction times in executive function tests) and functional improvements (e.g., P3 amplitude) [187, 191]. Such a relationship between cognitive performance and peripheral serum IGF-1 concentrations would be in accordance with previous findings linking peripheral serum IGF-1 levels to cognitive performance (e.g., global cognition assessed by MMSE) in older individuals [329] and individuals with MCI [330]. Notably, it has also been reported that solely an optimal concentration of peripheral serum IGF-1 is associated with superior global cognition (assessed by MMSE) and processing capacity [331], which could be related to the multiple and divergent roles that IGF-1 plays in the human brain [319, 332]. On the one hand, IGF-1 is linked to beneficial processes (e.g., stimulating synaptogenesis and contributing to neuronal cell survival), but on the other hand, IGF-1 is also associated with detrimental processes (e.g., generation of reactive oxygen species and inhibition of autophagy) [319]. There is currently insufficient evidence to draw firm conclusions regarding the relationship between physical exercise, modulation of IGF-1, structural and functional brain changes, and cognitive functions [333]. Hence, further

studies are urgently needed to gain deeper insights into the relationship between exercise-induced modulation of IGF-1 release, functional and structural brain changes, and cognitive performance [332, 333].

Homocysteine

A possible neurobiological mechanism that elucidates, at least partly, the effects of resistance training on white matter and cognition could be derived from the known effects of resistance training on the amino acid homocysteine. First, it is important to remember that a higher total homocysteine level is linked to (i) a higher extent of white matter lesions [334], (ii) a higher (faster) brain atrophy rate [335–337], (iii) an increased risk of neurological diseases [338–344], and (iv) poorer global cognitive performance and executive functioning [345–350]. Second, it is known that resistance training decreases the level of plasma [351] and serum homocysteine [187, 352]. Hence, it could be speculated that reducing the homocysteine level in response to resistance training may, at least partly, have positive effects on brain structure (e.g., white matter changes such as reduced atrophy) and/or cognitive functions. However, such relationships have not been directly observed in the studies reviewed [187] and have to be investigated in future studies.

Influence of exercise variables and training variables on neurocognition

With regard to all studies reviewed, the exercise and training variables of the resistance intervention protocols were chosen as to induce muscle hypertrophy and muscle strength improvements, which is not surprising, as resistance training programs generally focus on improving these two factors. Moreover, this observation is consistent with two other reviews summarizing the results of resistance exercise and resistance training studies on outcomes on a behavioral level [107, 353]. However, given that the dose provided by a physical intervention (e.g., resistance exercise or resistance training) is a function of exercise variables and training variables and that the reviewed studies are relatively homogenous regarding the selection of exercise variables and training variables, our knowledge about the dose-response relationship in resistance exercise and resistance training is relatively meager (especially in view of the fact that resistance exercises and resistance training can be designed in many different ways to focus on different aims for muscular performance). A deeper understanding of the dose-response relationship is needed [105, 108, 110] because the dose (the design of exercise variables and training variables, see Table 3) is a key factor influencing responsiveness [357, 358] and individualizing physical interventions [123, 124, 359].

Table 3 Overview of exercise variables and training variables [60, 113, 354–356]

Variables for structuring a single resistance exercise session (exercise variables)

- (i) *Load* (amount of weight that is used for an exercise; usually given as a percentage of the one repetition maximum [1RM])
- (ii) *Number of repetitions*
- (iii) *Number of sets*
- (iv) *Inter-set rest period*
- (v) *Inter-exercise rest period*
- (vi) *Number of exercises* (for the whole training session or for a muscle or a muscle group with the same function)
- (vii) *Repetition velocity* (with respect to the conducted resistance exercise and the starting position, temporal details should be given as follows: i.e., biceps curls starting with fully extended arms [e.g., bench press starting with fully extended arms]: concentric phase [eccentric phase] – inter-repetition rest periods – eccentric phase [concentric phase] – rest period up to the start of the next repetition, e.g., 2–0–2–1 s)
- (viii) *Muscle action* (concentric, eccentric, isometric)
- (ix) *Exercise selection* (e.g., multi-joint or single-joint exercises)
- (x) *Exercise order* (e.g., squat, leg extension, biceps curl, and concentration curl or squat, biceps curl, leg extension, and concentration curl)
- (xi) *Volitional muscle failure*
- (xii) *Range of motion*

Variables for structuring resistance training (training variables)

- (1.) *Frequency* (number of training sessions per week)
- (2.) *Density* (distribution of training sessions across a week with regard to recovery time in-between training sessions)
- (3.) *Duration* (duration over which a training program is carried out; e.g., before exercise variables will be changed)

Please note, that some exercise variables are usually summarized into variables with different designations: e.g., *volume* [exercise variables (ii), (iii), and (iv)], *time under tension* [TUT, sum of the exercise variables (ii) and (vii)] or *duration of an exercise session* [depends on exercise variables (ii), (iii), (iv), (v), (vi), (vii), and the duration of warm-up and cool-down] [354, 356]

In the following section, we outline promising starting points for investigating the dose-response relationship in resistance exercise and/or resistance training studies.

With regard to *load*, on the behavioral level, it was observed that an acute bout of moderate-load resistance exercises (70 to 100% of the 10RM, 10RM = the load needed for 10 repetitions until maximum exhaustion) improves the speed of processing, while resistance exercises with low load (40% of the 10RM) improve executive functions [138]. Furthermore, it was reported that improvements in executive functions were larger after moderate-load (70% of 10RM) than low-load (40% of 10RM) resistance exercises [156]. The finding that resistance exercises with moderate loads are especially beneficial for cognitive performance is supported by the observation that resistance exercises with moderate loads (60% 1RM) lead to larger positive effects on higher cognitive functions (i.e., Stroop interference score)

compared with resistance exercises with heavier loads (≥ 75% 1RM) [360]. In another study, it was noticed that a single bout of high-load (100% of 10RM) resistance exercises resulted in less interference and fastened reaction times for the Stroop task 15 min after exercise cessation, while 180 min after exercise cessation, low-load (40% of 10RM) and moderate-load (70% of 10RM) resistance exercises were associated with increased performance on the plus-minus and the Simon task [146]. However, at the moment, only two studies have employed neuroimaging methods to investigate the dose-response relationship with respect to the exercise load [182, 183]. In this study, no statistically significant differences in neuroelectric outcomes between conditions were observed [182, 183]. Based on the sparse evidence in this area, further research is required to investigate whether such load-dependent cognitive improvements are mirrored in acute processes of the central nervous system (e.g., measured prior and after resistance exercises by fNIRS [180] or EEG [201, 360–362].

With regard to *number of sets*, on the behavioral level, it was reported that younger adults performing three or five sets of a resistance exercise showed after a 8-week intervention period greater improvements in inhibitory control (i.e., assessed by accuracy and mean response time in the Stroop test) than younger adults performing one set of the same resistance exercise [363]. Because the above-mentioned study did not apply neuroimaging techniques or quantify neurotrophic markers (e.g., BDNF) [363], future investigations are needed to elucidate the underlying neurobiological mechanisms.

With regard to *frequency*, on the behavioral level, resistance training three times a week was more efficient than training twice a week [109]. Since most reviewed studies conducted resistance training twice a week [45, 184–186, 189, 190] and observed beneficial results or did not compare a training with two sessions per week to other training frequencies [44, 187], the findings of Li et al. [109] are not supported by functional or structural data. Hence, future studies are required to investigate the influence of training frequency on functional and structural brain changes (e.g., one time per week vs. three times per week).

Since changes at the molecular and cellular levels (e.g., metabolic response, such as peripheral blood lactate concentration) are linked to behavioral changes, a promising approach to positively influence neurocognition could be the alteration of molecular and cellular processes by adjusting the exercise prescription via exercise and training variables.

In particular, after an acute bout of physical exercise, postexercise concentrations of peripheral blood lactate were found to be linked to improvements in executive functions [364–366]. In this context, peripherally (e.g., in the musculature) released lactate is expected to be utilized as 'fuel' for cognitive processes because it can cross the BBB with the help of monocarboxylate transporters [367–371]. Furthermore, peripheral lactate may trigger the release of serum BDNF [309, 311, 372], but this relationship seems to be highly reliant on the correct selection of resistance exercise variables [309]. Notwithstanding, it has been well demonstrated that serum BDNF contributes significantly to changes in brain structure [21, 24] and performance (e.g., cognition) [21, 305, 306]. Consequently, given that the peripheral concentration of blood lactate is a function of resistance exercise variables such as repetition velocity [373, 374] or inter-set rest periods [375], it seems reasonable to speculate that a purposeful modification of these exercise variables may also influence neurocognition outcomes. Notably, in this context, it was also hypothesized that resistance exercises with blood flow restriction (BFR) could be beneficial for neurocognition because resistance exercises with BFR or resistance training with BFR induce beneficial processes on a molecular and cellular level (for review see [113]). However, further research in this area with a strong focus on underlying neurobiological processes, functional and structural brain changes, and cognition is required.

Finally, similar to the major ongoing discussions regarding which variables may be optimal to improve muscular adaptions, such as muscle hypertrophy or strength [376–390], the optimal exercise prescription (e.g., exercise variables and training variables) for resistance exercises and/or resistance training with respect to brain health (including appropriate functional and structural brain changes as well as enhancement of cognitive functions) are largely unknown and have to be elucidated in future studies [105, 108, 110]. In addition, the interested reader may find further and more detailed information regarding the design of resistance exercise sessions or resistance training in the referenced literature [355, 391–394].

Recommendations for future studies

- Based on the available evidence derived from the reviewed studies and other recommendations [107], resistance exercises and/or resistance training aiming to enhance cognitive functions and evoke positive functional and structural brain changes should be designed to induce muscle hypertrophy.
- Future studies are needed to investigate the influence of the adjustment of different resistance exercise variables (e.g., load, number of sets, training frequency, training duration) on functional and structural brain changes in conjunction with cognitive functions.
- To understand the time-course of functional and structural brain changes, neuroimaging should be performed at several time points after an acute bout

of resistance exercise or during the resistance training intervention.
- The inclusion of further cohorts (e.g., older individuals with sarcopenia and/or dynapenia) is needed to verify whether resistance exercise-induced improvements also occur in such needy cohorts and how this is related to functional and structural brain changes.
- Interventional studies (or cross-sectional studies) investigating the relationship of resistance exercises (or strength, muscle function/structure) and cognition should utilize different neuroimaging methods during standardized cognitive testing and assess neurochemical substances (e.g., neurotransmitters, neurotrophic factors) to elucidate underlying neurobiological mechanisms.
- Bed rest studies, which reported a worsening of executive functions [395–397], profound brain changes [397–399], and a decrease in muscle mass as well as muscle strength [400–408], could be an interesting model to study the relationship between the muscular system, functional and structural brain changes, and cognition.

Conclusions

In summary, resistance exercises and resistance training are powerful physical intervention strategies to induce meaningful functional brain changes, especially in the frontal lobe, which are accompanied by improvements in executive functions. Furthermore, based on the studies reviewed, resistance training leads to lower white matter atrophy and lower volumes of white matter lesions. However, given the small number of available studies that have mostly been part of greater study projects (Brain Power Study and SMART [Study of Mental and Resistance Training]), further research investigating the influence of an acute bout of resistance exercise and chronic resistance training on cognition and the underlying neurobiological mechanisms (e.g., functional and/or structural brain changes) is needed. This future research should also focus on the effects of systematically manipulating exercise and training variables (dose-response relationship) and further including specific cohorts with the greatest need (e.g., older individuals with sarcopenia and/or dynapenia). Most importantly, engaging regularly in resistance exercises and/or resistance training across the whole lifespan appears to be imperative for ensuring physical and brain health because muscular weakness in the early years of life (e.g., adolescence) has been shown to be associated with disability in later life (e.g., after 30 years) [409] and even 4 weeks of detraining (being physical inactive) completely reversed the physical and cognitive improvements of 22-week resistance training in older adults [410]. Hence, to summarize in a metaphorical sense: "May the force be with you across your lifespan."

Acknowledgments
The authors have nothing to acknowledge.

Authors' contributions
FH and AT wrote the manuscript. LS and NGM reviewed the drafted versions. All authors have read and approved the final version.

Funding
No funding information applicable.

Availability of data and materials
Not applicable.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Research Group Neuroprotection, German Center for Neurodegenerative Diseases (DZNE), Leipziger Str. 44, 39120 Magdeburg, Germany. [2]Center for Behavioral Brain Sciences (CBBS), Brenneckestraße 6, 39118 Magdeburg, Germany. [3]Department of Neurology, Medical Faculty, Otto von Guericke University, Leipziger Str. 44, 39120 Magdeburg, Germany. [4]Institute III, Department of Sport Science, Otto von Guericke University Magdeburg, Zschokkestr. 32, 39104 Magdeburg, Germany.

Received: 5 March 2019 Accepted: 26 June 2019
Published online: 10 July 2019

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Publisher's Note

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RESEARCH ARTICLE

Does squatting need attention?—A dual-task study on cognitive resources in resistance exercise

Fabian Herold[1], **Dennis Hamacher**[2]*, **Alexander Törpel**[2], **Leonard Goldschmidt**[2], **Notger G. Müller**[1,3,4‡], **Lutz Schega**[2‡]

1 Research Group Neuroprotection, German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany, **2** Institute III, Department of Sport Science, Otto von Guericke University Magdeburg, Magdeburg, Germany, **3** Center for Behavioral Brain Sciences (CBBS), Magdeburg, Germany, **4** Department of Neurology, Medical Faculty, Otto von Guericke University Magdeburg, Magdeburg, Germany

‡ These authors are joint senior authors on this work.
* dennis.hamacher@ovgu.de

Citation: Herold F, Hamacher D, Törpel A, Goldschmidt L, Müller NG, Schega L (2020) Does squatting need attention?—A dual-task study on cognitive resources in resistance exercise. PLoS ONE 15(1): e0226431. https://doi.org/10.1371/journal.pone.0226431

Editor: Samuel Stuart, Oregon Health and Science University, UNITED STATES

Received: June 26, 2019

Accepted: November 26, 2019

Published: January 21, 2020

Data Availability Statement: The public sharing of the data from this trial has been restricted by the local Research Ethics Committee in order to protect participants' privacy. Data are therefore available on request from the German Center for Neurodegenerative Diseases (DZNE) by contacting the Data Management of the Clinical Research team via data-management-kf@dzne.de, as well as from the corresponding author.

Funding: The authors received no specific funding for this work.

Abstract

Introduction

Accumulating evidence shows that acute resistance exercises and long-term resistance training positively influence cognitive functions, but the underlying mechanisms have been rarely investigated. One explanatory approach assumes that the execution of resistance exercises requires higher cognitive processes which, in turn, lead to an 'indirect' training of higher cognitive functions. However, current knowledge on the engagement of higher cognitive functions during the execution of resistance exercises is relatively sparse. Hence, the purpose of this study was to examine to what extent cognitive resources are needed to perform a resistance exercise in the form of barbell back squatting.

Methods

Twenty-four young adults performed a cognitive task (serial subtraction of 7's) during standing and during barbell back squatting on a Smith machine. The total number and the number of correct responses were analyzed and taken as indicators of the cognitive load imposed by the experimental condition (squatting) and the control condition (standing). Additionally, participants' perceived exertion, mean heart rate, and the number of squats they were able to perform were assessed.

Results

While accuracy scores were found not to be significantly different between conditions, the numbers of total and of correct responses were significantly lower during squatting than during standing. Additionally, during squatting a higher number of total answers was given in the fifth set compared to the first set. We attribute this phenomenon to a learning effect. Furthermore, there was no statistically significant correlation between cognitive measures and perceived exertion.

Competing interests: The authors have declared that no competing interests exist.

Conclusion

Results suggest that perceived exertion cannot explain the higher dual-task costs observed during squatting. They rather reflect that more cognitive resources are needed to perform low-load barbell back squats than during standing. However, further research is necessary to confirm and generalize these findings.

Introduction

There is growing evidence in the literature that acute resistance exercises and long-term resistance training improve cognitive functions [1–4]. However, the underlying mechanisms for these cognitive improvements are not fully understood yet, although they seem to rely on changes at multiple levels [5–7]. One assumption is that resistance exercises may act as an 'indirect' form of cognitive training since for their execution subjects need to constantly engage cognitive resources as they have to pay attention to perform the movement with an appropriate technique (e.g., squat), to produce an appropriate level of force, and to observe the surroundings in order not to harm themselves or others [3]. Engaging specific cognitive resources to execute a specific motor task (e.g., resistance exercise such as squatting) is deemed a necessary prerequisite to guide the facilitation effects of physical exercises. The latter provides the basis for cognitive improvements in response to physical training interventions [8]. However, to our current knowledge, there is currently no study that investigated the cognitive resources needed to execute dynamic resistance exercises (e.g., squats). Therefore, the assumption that resistance exercises 'indirectly' train cognitive functions due to the engagement of cognitive resources requires further exploration.

An established behavioral approach to quantify the cognitive resources which are needed to execute a motor task is the dual-task paradigm. For instance, the dual-task paradigm is frequently utilized to investigate the amount of cognitive resources required during walking or postural tasks [9–13]. Using the dual-task paradigm, an individual's performance during a single-task condition (e.g., performing a cognitive task) is compared with his/her performance during a dual-task condition (e.g., performing a motor task [e.g., squatting] and a cognitive task simultaneously). The changes in performance from single-task to dual-task (also known as dual-task costs) are used to probe the amount of cognitive resources needed to execute the motor task (e.g., squatting). In this study, we aimed to investigate whether higher cognitive resources are required to perform barbell back squatting. To do so, a dual-task paradigm was applied and the relative increase in cognitive resources needed to perform the resistance exercise 'barbell back squats' was examined.

Materials and methods

Twenty-four (10f /14m) healthy adults participated in this randomized study (mean age (± SD): 24.38 ± 3.15 years; mean height: 173.92 ± 8.29 cm; mean body mass: 70.25 ± 11.56 kg). All study procedures were in accordance with the Declaration of Helsinki (1964) and were approved by the local ethics committee of the Medical Faculty of the Otto von Guericke University Magdeburg (181/18). Each participant was asked to visit the laboratories for two sessions at least 48 hours apart. At the first session, the participants were informed about the experimental procedures and had to complete the German version of the Physical Activity Readiness Questionnaire (PARQ) which screens for individuals at increased health risk when

exercising physically [14–16]. All individuals interested in participating in this study verified by self-reports that they were not suffering from musculoskeletal, cardiovascular, and/or neurological disorders. Based on the results of the PARQ and self-reports, individuals at an increased health risk while exercising were excluded from this study. Furthermore, all participants gave their written informed consent to participate in this study and received a compensation of 24€.

In addition, all participants completed the Minimal Mental State Examination (MMSE) [17], Trail Making Test (TMT A&B) [18], the Beck Depression Inventory (BDI-II) [19], and a physical activity questionnaire (BSA; derived from the German Bewegungs- und Sportaktivitätsfragebogen) [20] at their first visit. The MMSE consists of 11 items and screens for cognitive impairments (indicated by lower scores) [17]. The TMT A is considered to measure abilities of visual search while TMT B quantifies the performance of higher cognitive abilities such as cognitive flexibility [21,22]. The difference between the performance of TMT B and TMT A is presumed to be a measure of shifting ability [23]. BDI-II reflects a measure of depressive symptoms whereas higher scores reflect a higher severity of depression [19]. The BSA measures the level of physical activity and physical exercise engaged within the last four weeks [20]. Additionally, the participants' experience in resistance training was quantified using a visual analogue scale ranging from 0 (i.e., no experience) to 100 (i.e., strong experience). After the completion of the questionnaires, a standardized warm-up was conducted to prepare the participants for a one-repetition maximum (1-RM) test. The warm-up consisted of five minutes of stationary cycling (1 W per kilogram body weight at 60 to 80 revolution per minute) and one set of barbell back squats with ten repetitions at light loads [24]. Then, based on established testing protocols [25], several sets of barbell back squats were performed until a load was found which the participants could lift exactly one time with a proper technique (stance width: shoulder width / squat depth: at least horizontal thighs). Between the testing sets, participants rested for at least three minutes and immediately after each set the perceived exertion was quantified using the Repetitions in Reserve scale (RIR) [26]. The RIR was used as countermeasure to verify that the 1-RM is the maximal load that the participants can lift. The 1-RM of the participants was determined within four (± 1) sets and the corresponding mean RIR was ten. The barbell back squats were performed using a Smith machine (integrated in the squat rack by MAXXUS®; version 9.1).

During the second visit, the participants performed a single-task condition (solving a cognitive task during standing, [ST]) and a dual-task condition (squatting while solving a cognitive task, [DT]). The conditions were separated by a rest period of ten minutes and conducted in a randomized order (balanced permuted block randomization) by using the Web site 'Randomization.com' (http://www.randomization.com). To make ST and DT comparable, the time of each set was limited to 30 seconds and between the sets, a rest in a standing position of 60 seconds was given (see Fig 1). In this study, a set is defined as the 30 seconds in which the participants solve the cognitive tasks while standing or performing barbell back squats. In DT ten seconds just before the end of the rest period, a cue was given that enable the participants to take the starting position of the barbell back squats to make sure that they had have the full 30 seconds to solve the cognitive task as in ST. After finishing the set in DT, the barbell was placed back into the squat rack. In DT the participants were allowed to squat with their preferred repetition velocity. In each condition, five sets were conducted and in DT the load of the barbell was set to of 40% of 1-RM. We choose 40% of 1-RM because it was shown that even this low load leads to cognitive improvements [27]. As cognitive task, we used the serial subtraction of 7's from a three-digit number [28]. A new, randomly assigned three-digit number was given to the participants at the beginning of each set in ST and DT. Furthermore, as shown in Fig 1, the

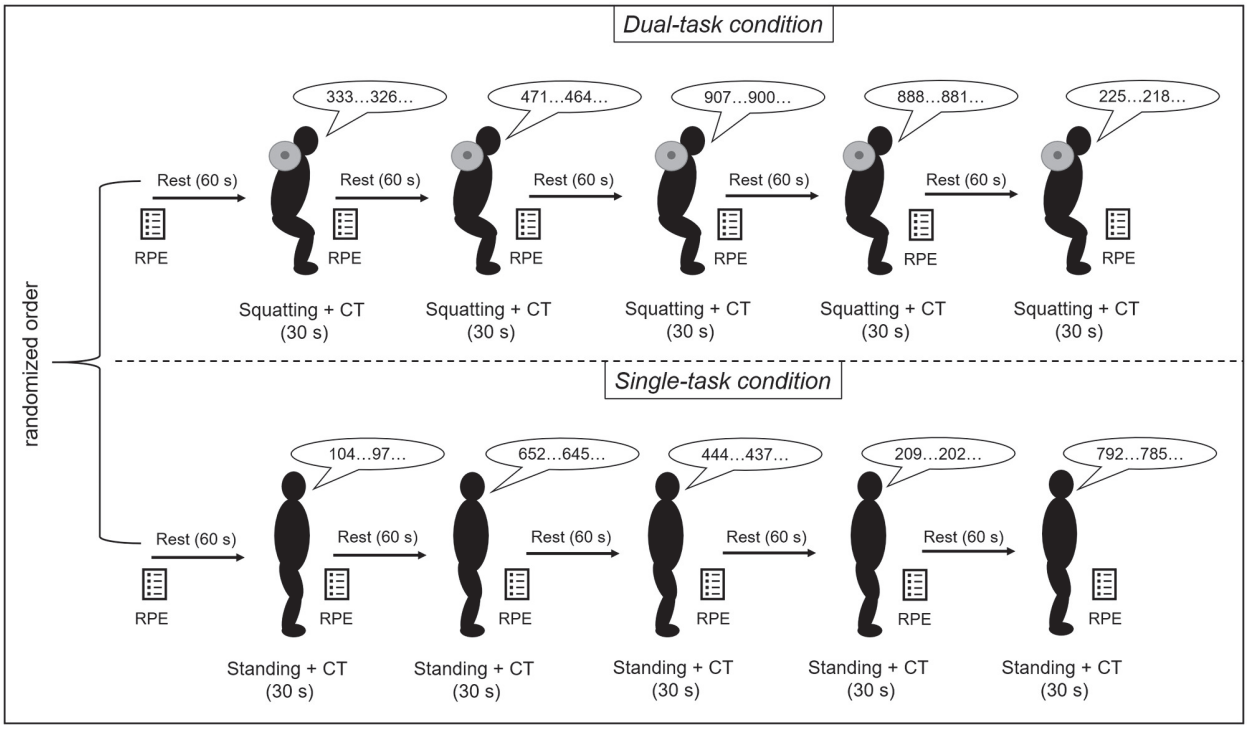

Fig 1. Overview of the experimental protocol in the second session and the time points of the assessment of RPE. The cognitive task was solved in a standing position (single-task) and during squatting (dual-task). Both tasks were performed for 30 seconds and afterwards the participants rested in a standing position for 60 seconds. RPE: Rating of perceived exertion.

https://doi.org/10.1371/journal.pone.0226431.g001

rating of perceived exertion (RPE) using a RPE scale which ranged from 6 (no exertion) to 20 (maximal exertion) was administered during the second visit [29].

Furthermore, we measured mean heart rate (HR) continuously with a portable heart rate (HR) monitor (V800, Polar Electro Oy®, Kempele, Finland) and analyzed HR data using 'Kubios HRV' (Biosignal Analysis and Medical Imaging Group, Universität Kuopio, Finland; Version 3.3.1) [30]. In Kubios artefacts were removed by applying the threshold-based artefact correction algorithm. Therefore, we set the threshold to a medium level (i.e., values that differ more than 0.25 s from average were replaced with interpolated values using a cubic spline interpolation) [30–32]. Furthermore, the HR time series was detrended by using the smoothness-priors-based detrending approach (smoothing parameter, $\lambda = 500$) [30]. Thereafter, the mean heart rate was calculated from corrected and detrended HR time series using whole 30 seconds of task periods (i.e., Squatting + DT and Standing + DT; see Fig 1) and the middle 30 seconds of the first rest period (for 'Pre'; see Fig 1 and Table 1).

Additionally, during the sets in DT the number of squat repetitions was counted.

Statistical analysis

The statistical analysis was performed using IBM SPSS (Statistical Package for social science, Version 22, Chicago, IL, USA) and non-parametric tests were conducted because not all data were normally distributed. To compare performance in single-task conditions versus performance in dual-task conditions, the Wilcoxon test was performed. To identify a possible main effect of time (respectively set), a Friedman test with post-hoc analyses (i.e., Wilcoxon tests)

Table 1. Personal data for the characterization of the participants and results of the screening test in the investigated sample; BDI: Becks Depression Inventory; BSA: Physical activity questionnaire, derived from German 'Bewegungs- und Sportaktivitätsfragebogen'; MMSE: Minimal Mental State Examination; PA: Physical activity; PE: Physical exercise; 1-RM: One-repetition maximum; TMT: Trail Making Test.

Parameters	Mean ± SD
Years of education [years]	15.8 ± 3.0
MMSE score	29.60 ± 0.63
BDI-II	3.29 ± 3.43
BSA [min per week]	PA: 313.60 ± 237.33 / PE: 338.95 ± 223.25
TMT A time [sec] / errors	20.87 ± 5.16 / 0.04 ± 0.20
TMT B time [sec] / errors	41.46 ± 9.25 / 0.08 ± 0.40
TMT B-A time [sec]	20.59 ± 7.77
1-RM [kg]	97.70 ± 27.26
1-RM normalized to body mass	1.39 ± 0.41
Self-rated experience in resistance training	49.79 ± 25.43
Resistance training sessions per week	2.06 ± 1.69

https://doi.org/10.1371/journal.pone.0226431.t001

were conducted. Outliers were not removed from statistical analyses because non-parametric test are relatively robust against the effects of those [33,34]. The effect sizes for the Wilcoxon tests were calculated using following formula $r = \frac{|z|}{\sqrt{N}}$ and were rated as follows: 0.5 large effect, 0.3 medium effect, and 0.1 small effect [35,36].

Furthermore, in order to examine possible relationships between cognitive measures and RPE, mean HR, number of squat repetitions, or self-rated experience in resistance training, correlation analyses were performed. Therefore, Spearman's Rho (r_s) was calculated and rated as follows: 0.00 to 0.19 no correlation; 0.20 to 0.39 low correlation; 0.40 to 0.59 moderate correlation; 0.60 to 0.79 moderately high correlation; ≥ 0.8 high correlation [37]. The level of significance was initially set to $\alpha = 0.05$ for all statistical analyses. In order to account for the multiple comparison problem in post-hoc tests and correlation analyses (correction within one tested condition between the five sets), the Holm correction method was applied [38]. Therefore, the n p_{raw}-values (where n is the number of p_{raw}-values corresponding to one hypothesis) were ordered in an ascending order starting with the smallest p_{raw}-value ($p_{raw(1)}, \ldots, p_{raw(n)}$). Afterwards, the ordered p_{raw}-values are compared to the threshold α_j calculated as follows: $p_{(i)} \leq \alpha_j = \alpha/(n - (i\text{-}1))$. The Holm correction will stop at the i^{th} test for which the first non-rejection occurs (i.e., the i for which $p_{raw(i)} > \alpha_i$) [38,39]. Furthermore, the corrected p-values ($p_{corrected}$) were calculated by using the following formula [40,41]: $p_{corrected} = p_{(i)raw} \times /(n - (i\text{-}1))$. Please note that for the calculation of $p_{corrected}$ the $p_{raw\ values}$ were ordered as described in Holm correction.

Results

The general characteristics of the participants are displayed in Table 1.

Cognitive measures

A descriptive overview about the number of total answers and number of correct answers in ST and DT for the task serial subtraction of 7's is provided in Table 2.

To evaluate the effect of DT on the number of total answers and number of correct answers, performance in DT was compared to the performance in ST.

With regard to the number of total answers in the first set (Z (N = 24) = -3.759, $p_{corrected}$ = 0.001; r = 0.77), the second set (Z (N = 24) = -3.462, $p_{corrected}$ = 0.002; r = 0.71), the third set

Table 2. Median (interquartile range) of cognitive measures and RPE in single-task condition and dual-task condition are shown. Additionally, the number of repetitions of barbell back squats in dual-task condition is presented.

Parameter	Pre	1st set	2nd set	3rd set	4th set	5th set
Single-task condition						
Total number of answers	n.a.	12.0 (5.0) *	12.0 (6.0) *	14.0 (5.0) *	12.0 (5.0) *	13.0 (5.0) *
Number of correct answers	n.a.	12.0 (7.0) *	12.0 (8.0) *	13.0 (6.0) *	12.0 (5.0) *	12.5 (5.0) *
Accuracy score (in %)	n.a.	100.0 (9.1)	100.0 (0.0)	100.0 (9.2)	100.0 (0.0)	100.0 (7.7)
RPE score	6.0 (1.0) b	7.0 (3.0) *, b	8.0 (4.0) *, b	7.5 (3.0) *, b	7.5 (4.0) *, b	8.0 (4.0) *, b
Mean HR	87.0 (19.5)	92.5 (24.3) *, b	86.0 (22.8) *	87.0 (23.3) *	86.5 (20.5) *	87.5 (25.0) *
Dual-task condition						
Total number of answers	n.a.	9.0 (4.0) *, a	10.0 (3.0) *	10.0 (5.0) *	11.0 (4.0) *	11.0 (4.0) *, a
Number of correct answers	n.a.	9.0 (3.0) *	9.5 (4.0) *	9.5 (4.0) *	10.5 (5.0) *	10.0 (4.0) *
Accuracy score (in %)	n.a.	100.0 (9.1)	100.0 (10.0)	96.2 (11.1)	100.0 (12.2)	100.0 (9.8)
RPE score	6.0 (1.0) b	13.0 (2.0) *, b	13.0 (1.0) *, b, c	14.0 (2.0) *, b, c, d	15.0 (3.0) *, b, c, d, e	15.5 (3.0) *, b, c, d, e, f
Mean HR	80.5 (17.5)	121.0 (17.3) *, b	127.5 (25.8) *, b, c	130.5 (34.0) *, b, c, d	131.0 (36.3) *, b, c, d, e	139.5 (41.0) *, b, c, d, e, f
Number of squat repetitions	n.a.	11.0 (3.0)	11.0 (2.0)	12.0 (3.0)	12.0 (2.0)	12.0 (2.0)

[a]: indicates a significant difference between 1st and 5th set;

[b]: indicates significant difference between 'Pre' and sets;

[c]: indicates significant difference between 1st set and the respective set;

[d]: indicates significant difference between 2nd set and the respective set;

[e]: indicates significant difference between 3rd set and the respective set;

[f]: indicates significant difference between 4th set and respective set;

n.a.: not applicable; HR: heart rate; RPE: Rating of relative perceived exertion.

*: indicates a significant difference between single-task condition and dual-task-condition.

https://doi.org/10.1371/journal.pone.0226431.t002

(Z (N = 24) = -3.505, $p_{corrected}$ = 0.002; r = 0.72), the fourth set (Z (N = 24) = -3.034, $p_{corrected}$ = 0.005; r = 0.62), and the fifth set (Z (N = 24) = -2.414, $p_{corrected}$ = 0.016; r = 0.50) a lower number of total answers was given in DT compared to ST.

The statistical comparison concerning the number of correct answers shows that in the first set (Z (N = 24) = -3.324, $p_{corrected}$ = 0.003; r = 0.68), the second set (Z (N = 24) = -3.576, $p_{corrected}$ = 0.001; r = 0.73), the third set (Z (N = 24) = -3.633, $p_{corrected}$ = 0.001; r = 0.74), the fourth set (Z (N = 24) = -3.304, $p_{corrected}$ = 0.002; r = 0.67), and the fifth set (Z (N = 24) = -2.476, $p_{corrected}$ = 0.013; r = 0.51) a lower number of correct answers was given in DT compared to ST.

Furthermore, a significant effect of time was observed for the number of total answers in DT (X^2 = 13.741 (df = 4, n = 24), p = 0.008) but not in ST. After post-hoc tests and the following Holm adjustment, it was observed that in DT in the fifth set a higher number of total answers was given compared to the first set (Z (N = 24) = -3.143, $p_{corrected}$ = 0.017; r = 0.64).

A significant effect of time was registered for correct answers in DT (X^2 = 10.047 (df = 4, n = 24), p = 0.040) but not in ST. However, the effects observed in post-hoc tests in DT did not remain their statistical significance after the application of Holm correction method.

With regard to the accuracy score, we did neither observe significant differences between ST and DT ($p_{corr} > 0.05$) nor was a statistically significant effect of time in ST (X^2 = 6.194 (df = 4, n = 24), p = 0.185) and in DT (X^2 = 0.712 (df = 4, n = 24), p = 0.950) noticed.

Psychophysiological measures

Ratings of perceived exertion. A descriptive overview about RPE ratings obtained in ST and DT is provided in Table 2. The difference between RPE values obtained prior to ST

or DT were not statistically significant (Z (N = 24) = 0.000, $p_{corrected}$ = 1.000; r = 0.00), whereas after first set (Z (N = 24) = -4.214, $p_{corrected} < 0.001$; r = 0.86), second set (Z (N = 24) = -4.296, $p_{corrected} < 0.001$; r = 0.88), third set (Z (N = 24) = -4.295, $p_{corrected} < 0.001$; r = 0.88), fourth set (Z (N = 24) = -4.295, $p_{corrected} < 0.001$; r = 0.88), and fifth set (Z (N = 24) = -4.291, $p_{corrected} < 0.001$; r = 0.88) the RPE score were significantly larger in DT (see Table 2).

In the ST condition, a main effect of time was observed (X^2 = 36.684 (df = 5, n = 24), $p > 0.001$) and post-hoc test indicate that the RPE scores obtained prior the sets was significantly lower than after first set (Z (N = 24) = -2.953, $p_{corrected}$ = 0.035; r = 0.60), second set (Z (N = 24) = -3.324, $p_{corrected}$ = 0.012; r = 0.68), third set (Z (N = 24) = -3.219, $p_{corrected}$ = 0.015; r = 0.66), fourth set (Z (N = 24) = -3.453, $p_{corrected}$ = 0.008; r = 0.70), and fifth set (Z (N = 24) = -3.321, $p_{corrected}$ = 0.012; r = 0.68). Between the sets no significant changes in RPE scores were observed ($p_{corrected} > 0.05$).

In the DT condition we observed a significant main effect of time (X^2 = 104.526 (df = 5, n = 24), $p < 0.001$). The post-hoc analyses show that the RPE score obtained prior the sets was lower than after first set (Z (N = 24) = -4.219, $p_{corrected} < 0.001$; r = 0.86), second set (Z (N = 24) = -4.313, $p_{corrected} < 0.001$; r = 0.88), third set (Z (N = 24) = -4.308, $p_{corrected} < 0.001$; r = 0.88), fourth set (Z (N = 24) = -4.299, $p_{corrected} < 0.001$; r = 0.88) and fifth set (Z (N = 24) = -4.295, $p_{corrected} < 0.001$; r = 0.88). Furthermore, following statistically significant changes between sets were observed: first set vs. second set (Z (N = 24) = -3.466, $p_{corrected}$ = 0.002; r = 0.71), first set vs. third set (Z (N = 24) = -3.685, $p_{corrected}$ = 0.001; r = 0.75), first set vs. fourth set (Z (N = 24) = -4.140, $p_{corrected} < 0.001$; r = 0.85), first set vs. fifth set (Z (N = 24) = -4.220, $p_{corrected} < 0.001$; r = 0.86), second set vs. third set (Z (N = 24) = -2.758, $p_{corrected}$ = 0.006; r = 0.56), second set vs. fourth set (Z (N = 24) = -4.008, $p_{corr} < 0.001$; r = 0.82), second set vs. fifth set (Z (N = 24) = -4.162, $p_{corrected} < 0.001$; r = 0.85), third set vs. fourth set (Z (N = 24) = -3.499, $p_{corrected}$ = 0.002; r = 0.71), third set vs. fifth set (Z (N = 24) = -3.858, $p_{corrected}$ = 0.001; r = 0.79), and forth set vs. fifth set (Z (N = 24) = -3.211, $p_{corrected}$ = 0.003; r = 0.66).

Mean heart rate. The difference between mean HR obtained prior to ST or DT were not statistically significant (Z (N = 24) = -1.121, $p_{corrected}$ = 0.262; r = 0.23), whereas during the first set (Z (N = 24) = -4.258, $p_{corrected} < 0.001$; r = 0.87), second set (Z (N = 24) = -4.286, $p_{corrected} < 0.001$; r = 0.87), third set (Z (N = 24) = -4.288, $p_{corrected} < 0.001$; r = 0.88), fourth set (Z (N = 24) = -4.287, $p_{corrected} < 0.001$; r = 0.88), and fifth set (Z (N = 24) = -4.287, $p_{corrected} < 0.001$; r = 0.88) the mean HR was significantly larger in DT (see Table 2).

Furthermore, we observed in ST a significant main effect of time (X^2 = 15.524 (df = 5, n = 24), p = 0.008). The post-hoc analyses show that the mean HR obtained prior to the sets was lower than during the first set (Z (N = 24) = -2.992, $p_{corrected}$ = 0.042; r = 0.61).

In DT we observed a significant main effect of time regarding the change in mean HR (X^2 = 96.037 (df = 5, n = 24), $p < 0.001$). The post-hoc analyses showed that the mean HR score obtained prior the sets was lower than during the first set (Z (N = 24) = -4.292, $p_{corrected} < 0.001$; r = 0.88), second set (Z (N = 24) = -4.286, $p_{corrected} < 0.001$; r = 0.87), third set (Z (N = 24) = -4.287, $p_{corrected} < 0.001$; r = 0.88), fourth set (Z (N = 24) = -4.286, $p_{corrected} < 0.001$; r = 0.87) and fifth set (Z (N = 24) = -4.287, $p_{corrected} < 0.001$; r = 0.88). The following statistically significant changes were observed: first set vs. second set (Z (N = 24) = -3.409, $p_{corrected}$ = 0.003; r = 0.70), first set vs. third set (Z (N = 24) = -3.653, $p_{corrected}$ = 0.001; r = 0.75), first set vs. fourth set (Z (N = 24) = -3.803, $p_{corrected}$ = 0.001; r = 0.78), first set vs. fifth set (Z (N = 24) = -4.201, $p_{corrected} < 0.001$; r = 0.86), second set vs. third set (Z (N = 24) = -3.036, $p_{corrected}$ = 0.005; r = 0.62), second set vs. fourth set (Z (N = 24) = -3.361, $p_{corrected}$ = 0.002; r = 0.69), second set vs. fifth set (Z (N = 24) = -4.124, $p_{corrected} < 0.001$; r = 0.84), third

set vs. fourth set (Z (N = 24) = -2.910, $p_{corrected}$ = 0.004; r = 0.60), third set vs. fifth set (Z (N = 24) = -4.033, $p_{corrected} < 0.001$; r = 0.82), fourth set vs. fifth set (Z (N = 24) = -3.983, $p_{corrected} < 0.001$; r = 0.81).

Number of repetitions

Regarding the number of repetitions, there was no significant differences between the sets (main time effect: X^2 = 8.846 (df = 4, n = 24), p = 0.065) and, hence, no post-hoc tests were performed.

Correlation between specific outcome variables

We neither found statistically significant correlations between measures of cognition (i.e., total number of answers, number of correct answers, and accuracy score) and RPE or mean HR in each of the five sets nor were there statistically significant correlations between measures of cognition and self-rated experience in resistance training or resistance training sessions per week (see Table 3). A significant moderate positive correlation between number of squats and total number of correct answers was observed in the first set of DT condition (see Table 3).

Discussion

The aim of this study was to quantify the amount of cognitive resources needed to perform resistance exercises in the form of low-load barbell back squats. To that end, the dual-task paradigm was applied. The observed behavioral performance costs during low-load barbell back squatting would allow to draw conclusions about the necessary higher cognitive resources [9–12]. Based on the observed decrease in total number of answer and number of correct answers in the DT condition (squatting while performing serial subtraction of 7's), our results suggest that higher cognitive resources are required to perform low-load barbell back squats on a Smith machine. Furthermore, our results imply that the observed dual-task effect is rather quantitative than qualitative in nature because the accuracy of the answers remains unaltered. Our findings are in line with previously published studies reporting a significant decrease in cognitive performance (e.g., number of solved items) in DT conditions involving dynamic motor actions (e.g., walking) [42–44]. Such a decrease in cognitive performance in DT conditions could be explained by the 'limited resource hypothesis' which postulates that the pool of available cognitive resources is restricted [45,46]. In DT situations, the motor task and the cognitive task compete for limited cognitive resources. When the resources do not suffice in a way that the demands of both tasks are fully satisfied, this could lead to a decrease in the performance of the motor and/or cognitive task [45]. In the light of the limited resources hypothesis, our results suggest that the execution of low-load barbell back squats (as motor task) withdraw a considerable amount of cognitive resources (significant lower cognitive performance in conjunction with high effect sizes) from processes required to solve the cognitive task (serial subtraction of 7's).

Furthermore, the positive moderate correlation between the number of squat repetitions and the number of correct answers in the first set suggests that some synchronization between the motor task and the cognitive task has occurred. Speculatively, the synchronization between motor tasks and cognitive tasks could be a strategy to better cope with the cognitive demands imposed by the simultaneous solving of specific motor task (i.e., squatting) and cognitive task (i.e., serial subtraction of 7's) [47]. However, this finding should be threated cautiously as it (i) was not persistent across the second to fifth set and (ii) could not been observed regarding other parameters of cognition (i.e., total number of answers and accuracy score). Moreover, the observed DT effect cannot merely be a result of a higher physical exertion in the DT condition but rather a consequence of the execution of the low-load barbell back squat itself. This

Table 3. Overview of correlation coefficients (Spearman's Rho [r_s]) and corresponding p-values / RPE: Rating of relative perceived exertion; sERT: Self-rated experience in strength training; Reps: Number of squat repetitions; RTS: Resistance training sessions per week.

Correlation	1st set	2nd set	3rd set	4th set	5th set
Single-task condition					
RPE and total number of answers	r_s = -0.19 ($p_{corrected}$ = 1.00)	r_s = -0.13 ($p_{corrected}$ = 1.00)	r_s = -0.04 ($p_{corrected}$ = 0.84)	r_s = -0.08 ($p_{corrected}$ = 1.00)	r_s = -0.17 ($p_{corrected}$ = 1.00)
RPE and number of correct answers	r_s = -0.14 ($p_{corrected}$ = 1.00)	r_s = -0.11 ($p_{corrected}$ = 1.00)	r_s = -0.04 ($p_{corrected}$ = 0.86)	r_s = -0.08 ($p_{corrected}$ = 1.00)	r_s = -0.12 ($p_{corrected}$ = 1.00)
RPE and accuracy score	r_s = -0.30 ($p_{corrected}$ = 1.00)	r_s = -0.08 ($p_{corrected}$ = 1.00)	r_s = -0.01 ($p_{corrected}$ = 1.00)	r_s = 0.05 ($p_{corrected}$ = 1.00)	r_s = 0.14 ($p_{corrected}$ = 1.00)
Mean HR and total number of answers	r_s = -0.00 ($p_{corrected}$ = 0.99)	r_s = 0.06 ($p_{corrected}$ = 1.00)	r_s = 0.06 ($p_{corrected}$ = 1.00)	r_s = 0.13 ($p_{corrected}$ = 1.00)	r_s = 0.17 ($p_{corrected}$ = 1.00)
Mean HR and number of correct answers	r_s = -0.03 ($p_{corrected}$ = 1.00)	r_s = 0.06 ($p_{corrected}$ = 1.00)	r_s = 0.01 ($p_{corrected}$ = 0.96)	r_s = 0.08 ($p_{corrected}$ = 1.00)	r_s = 0.09 ($p_{corrected}$ = 1.00)
Mean HR and accuracy score	r_s = -0.03 ($p_{corrected}$ = 1.00)	r_s = -0.02 ($p_{corrected}$ = 0.94)	r_s = -0.31 ($p_{corrected}$ = 0.57)	r_s = -0.28 ($p_{corrected}$ = 0.56)	r_s = -0.44 ($p_{corrected}$ = 0.17)
Dual-task condition					
RPE and total number of answers	r_s = -0.23 ($p_{corrected}$ = 0.84)	r_s = -0.43 ($p_{corrected}$ = 0.15)	r_s = -0.21 ($p_{corrected}$ = 0.33)	r_s = -0.35 ($p_{corrected}$ = 0.40)	r_s = -0.21 ($p_{corrected}$ = 0.64)
RPE and number of correct answers	r_s = -0.22 ($p_{corrected}$ = 1.00)	r_s = -0.40 ($p_{corrected}$ = 0.25)	r_s = -0.11 ($p_{corrected}$ = 1.00)	r_s = -0.22 ($p_{corrected}$ = 0.93)	r_s = -0.07 ($p_{corrected}$ = 0.76)
RPE and accuracy score	r_s = -0.00 ($p_{corrected}$ = 1.00)	r_s = 0.30 ($p_{corrected}$ = 1.00)	r_s = 0.13 ($p_{corrected}$ = 1.00)	r_s = 0.34 ($p_{corrected}$ = 0.53)	r_s = -0.01 ($p_{corrected}$ = 1.00)
Mean HR and total number of answers	r_s = 0.37 ($p_{corrected}$ = 0.40)	r_s = 0.25 ($p_{corrected}$ = 0.25)	r_s = 0.32 ($p_{corrected}$ = 0.40)	r_s = 0.31 ($p_{corrected}$ = 0.28)	r_s = 0.37 ($p_{corrected}$ = 0.32)
Mean HR and number of correct answers	r_s = 0.36 ($p_{corrected}$ = 0.44)	r_s = 0.16 ($p_{corrected}$ = 0.45)	r_s = 0.28 ($p_{corrected}$ = 0.76)	r_s = 0.22 ($p_{corrected}$ = 0.59)	r_s = 0.23 ($p_{corrected}$ = 0.86)
Mean HR and accuracy score	r_s = -0.17 ($p_{corrected}$ = 1.00)	r_s = -0.23 ($p_{corrected}$ = 1.00)	r_s = 0.11 ($p_{corrected}$ = 1.00)	r_s = -0.02 ($p_{corrected}$ = 0.92)	r_s = -0.08 ($p_{corrected}$ = 1.00)
sERT and total number of answers	r_s = 0.30 ($p_{corrected}$ = 0.80)	r_s = 0.14 ($p_{corrected}$ = 1.00)	r_s = -0.08 ($p_{corrected}$ = 1.00)	r_s = 0.01 ($p_{corrected}$ = 1.00)	r_s = 0.01 ($p_{corrected}$ = 0.96)
sERT and number of correct answers	r_s = 0.23 ($p_{corrected}$ = 1.00)	r_s = 0.12 ($p_{corrected}$ = 1.00)	r_s = -0.06 ($p_{corrected}$ = 1.00)	r_s = -0.06 ($p_{corrected}$ = 1.0)	r_s = -0.04 ($p_{corrected}$ = 0.86)
sERT and accuracy score	r_s = -0.10 ($p_{corrected}$ = 1.00)	r_s = -0.19 ($p_{corrected}$ = 1.00)	r_s = -0.08 ($p_{corrected}$ = 1.00)	r_s = -0.27 ($p_{corrected}$ = 1.00)	r_s = 0.08 ($p_{corrected}$ = 0.73)
RTS and total number of answers	r_s = 0.34 ($p_{corrected}$ = 0.50)	r_s = 0.22 ($p_{corrected}$ = 1.00)	r_s = 0.08 ($p_{corrected}$ = 1.00)	r_s = 0.02 ($p_{corrected}$ = 0.91)	r_s = 0.18 ($p_{corrected}$ = 1.00)
RTS and number of correct answers	r_s = 0.29 ($p_{corrected}$ = 0.85)	r_s = 0.20 ($p_{corrected}$ = 1.00)	r_s = 0.08 ($p_{corrected}$ = 1.00)	r_s = -0.03 ($p_{corrected}$ = 0.87)	r_s = 0.11 ($p_{corrected}$ = 1.00)
RTS and accuracy score	r_s = -0.16 ($p_{corrected}$ = 1.00)	r_s = -0.20 ($p_{corrected}$ = 1.00)	r_s = -0.07 ($p_{corrected}$ = 1.00)	r_s = -0.05 ($p_{corrected}$ = 0.82)	r_s = 0.15 ($p_{corrected}$ = 1.00)
Reps and total number of answers	r_s = 0.43 ($p_{corrected}$ = 0.14)	r_s = 0.28 (p_{corr} = 0.37)	r_s = 0.51 ($p_{corrected}$ = 0.05)	r_s = 0.23 ($p_{corrected}$ = 0.28)	r_s = 0.34 ($p_{corrected}$ = 0.30)
Reps and number of correct answers	r_s = 0.44* ($p_{corrected}$ = 0.03)	r_s = 0.30 ($p_{corrected}$ = 0.12)	r_s = 0.55 ($p_{corrected}$ = 0.48)	r_s = 0.27 ($p_{corrected}$ = 0.40)	r_s = 0.24 ($p_{corrected}$ = 0.26)
Reps and accuracy score	r_s = -0.09 ($p_{corrected}$ = 1.00)	r_s = 0.14 ($p_{corrected}$ = 1.00)	r_s = 0.32 ($p_{corrected}$ = 0.66)	r_s = 0.15 ($p_{corrected}$ = 1.00)	r_s = 0.06 ($p_{corrected}$ = 0.77)

https://doi.org/10.1371/journal.pone.0226431.t003

assumption is, at least partly, supported by the absence of statistically significant correlations between RPE scores or mean HR and measures of cognitive performance. Moreover, the absence of significant associations between resistance training experience and cognitive performance suggests that the observed dual-task effect is relatively independent of an individual's expertise level in our study performing low-load barbell back squats on a Smith machine. This finding is in accordance with results of a previous study which did not report an effect of

expertise level on cognitive performance changes in the dual-task conditions [48]. However, it is also reported that experts outperform novices in challenging dual-task conditions [49]. Hence, in order to rule out whether this finding is generalizable, further research should directly compare groups with different levels of expertise in resistance training and with different levels of load.

The observation that the number of total responses was significantly higher in the fifth set as compared to the first set indicates that some learning might have occurred. The appearance of a learning effect in DT conditions (e.g., with regard to cognitive measures) is in line with previous findings [50,51] and could be attributed to the automatization of task execution which leads to the freeing of cognitive resources [50]. However, given that the differences between ST and DT remained significant even in the fifth set, the presence of a supposed emerged learning effect would not argue against the assumption that higher cognitive resources are needed to perform low-load barbell back squats on a Smith machine. To further strengthen the assumption that higher cognitive resources are required to perform resistance exercises, more research is needed that investigates whether (i) dual-task effects emerge with other cognitive tasks that target other cognitive domains (e.g., working memory by n-back task), (ii) dual-task effects occur during the performance of other resistance exercises (e.g., seated rowing), or (iii) how dual-task effects are influenced by other exercise variables (e.g., load, rest phases, movement velocity). Additionally, as older adults require more generic resources to perform a motor task (e.g., postural tasks) [13], it seems promising to clarify in future research whether the observed dual-task costs in response to resistance exercises (i.e., barbell back squat) are more pronounced in the elderly.

Limitations

While our results suggest that higher cognitive resources are necessary to perform barbell back squats, the findings need to be interpreted in light of some limitations. A drawback of this study is the abdication of kinematic analyses (e.g. by using motion capture systems) or muscle functional analyses (e.g., by using electromyography) of the barbell back squats. Such kinematic analyses or electromyographic analyses could be helpful to assess the motor-related dual-task costs and their application is recommended in further studies.

Conclusion

In conclusion, our results suggest that in our cohort the execution of low-load barbell back squats requires the recruitment of higher cognitive resources. However, since our results are neither transferable to other cognitive tasks nor other cohorts, further studies which utilize other cognitive tasks (e.g., n-back task), conduct other resistance exercises (e.g., seated rowing), investigate a potential dose-response relationship (e.g., different loads), and/or recruit further cohorts (e.g., older adults, experts in resistance training) are necessary to confirm and generalize our findings.

Acknowledgments

We thank all volunteers who have participated in our study.

Author Contributions

Conceptualization: Fabian Herold, Dennis Hamacher.

Formal analysis: Fabian Herold.

Investigation: Fabian Herold, Leonard Goldschmidt.

Methodology: Fabian Herold.

Resources: Notger G. Müller, Lutz Schega.

Supervision: Notger G. Müller.

Writing – original draft: Fabian Herold.

Writing – review & editing: Fabian Herold, Dennis Hamacher, Alexander Törpel, Notger G. Müller, Lutz Schega.

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Herold *et al. BMC Neurosci* (2021) 22:10
https://doi.org/10.1186/s12868-021-00615-6

BMC Neuroscience

RESEARCH ARTICLE Open Access

Cortical hemodynamics as a function of handgrip strength and cognitive performance: a cross-sectional fNIRS study in younger adults

Fabian Herold[1,2*], Tom Behrendt[3], Alexander Törpel[3], Dennis Hamacher[3], Notger G. Müller[1,2,4†] and Lutz Schega[3†]

Abstract

Background: There is growing evidence for a positive correlation between measures of muscular strength and cognitive abilities. However, the neurophysiological correlates of this relationship are not well understood so far. The aim of this study was to investigate cortical hemodynamics [i.e., changes in concentrations of oxygenated (oxyHb) and deoxygenated hemoglobin (deoxyHb)] as a possible link between measures of muscular strength and cognitive performance.

Methods: In a cohort of younger adults (n = 39, 18–30 years), we assessed (i) handgrip strength by a handhold dynamometer, (ii) short-term working memory performance by using error rates and reaction times in the Sternberg task, and (iii) cortical hemodynamics of the prefrontal cortex (PFC) via functional near-infrared spectroscopy (fNIRS).

Results: We observed low to moderate negative correlations ($r_p = \sim -0.38$ to -0.51; $p < 0.05$) between reaction time and levels of oxyHb in specific parts of the PFC. Furthermore, we noticed low to moderate positive correlations ($r_p = \sim 0.34$ to 0.45; $p < 0.05$) between reaction times and levels of deoxyHb in distinct parts of the PFC. Additionally, higher levels of oxyHb (r_p (35) = 0.401; $p = 0.014$) and lower levels of deoxyHb (r_p (34) = − 0.338; $p = 0.043$) in specific parts of the PFC were linked to higher percentage of correct answers. We also found low to moderate correlations ($p < 0.05$) between measures of handgrip strength and levels of oxyHb ($r_p = \sim 0.35$; $p < 0.05$) and levels of deoxyHb ($r_p = \sim -0.25$ to -0.49; $p < 0.05$) in specific parts of the PFC. However, there was neither a correlation between cognitive performance and handgrip strength nor did cortical hemodynamics in the PFC mediate the relationship between handgrip strength and cognitive performance ($p > 0.05$).

Conclusion: The present study provides evidence for a positive neurobehavioral relationship between cortical hemodynamics and cognitive performance. Our findings further imply that in younger adults higher levels of handgrip strength positively influence cortical hemodynamics although the latter did not necessarily culminate in better cognitive performance. Future research should examine whether the present findings can be generalized to other cohorts (e.g., older adults).

*Correspondence: fabian.herold@st.ovgu.de
†Notger G. Müller and Lutz Schega share the senior authorship
[1] Department of Neurology, Medical Faculty, Otto Von Guericke University, Leipziger Str. 44, 39120 Magdeburg, Germany
Full list of author information is available at the end of the article

Keywords: Cognition, Functional near-infrared spectroscopy, Handgrip strength, Cognition, Sternberg paradigm, Muscular fitness

Background

Recent reviews provide evidence that the preservation of muscular strength (e.g., due to regular resistance training) is beneficial to maintain brain health and cognitive functioning [1–4].

In this context, handgrip strength has been considered an important marker of health in general [5–8] and of brain health in particular [9–11]. In line with this assumption, there is accumulating evidence linking measures of handgrip strength to cognitive functioning across the human lifespan. More specifically, it has been observed that in older individuals, higher levels of handgrip strength are associated with lesser cognitive decline during aging [12–19] and with better performance in standardized cognitive tests [20–25]. Moreover, also in younger adults [26] and middle-aged adults [27] higher levels of handgrip strength were linked to higher cognitive performance. Accordingly, these findings suggest that even in younger and middle-aged adults, a certain level of (handgrip) strength is an important factor contributing to cognitive well-functioning. However, based on the low number of available studies incorporating those age groups, additional, arguably more critical investigations, are required before strong conclusions can be drawn with certainty.

Notably, none of the mentioned studies help answering the question why higher levels of handgrip strength are linked to better cognitive performance as those studies did not assess the neurophysiological correlates (e.g., cortical hemodynamics). These neurophysiological correlates (e.g., cortical hemodynamics) might mediate the relationship between handgrip strength and cognitive performance [1, 18]. The assumption that changes in cortical hemodynamics (e.g., changes in oxyHb and deoxyHb) can mediate the relationship between handgrip strength and cognitive performance emerged from studies investigating the relationships between cardiorespiratory fitness, cognitive performance and cortical hemodynamics.

In particular, these previous studies observed (i) that higher levels of cardiorespiratory fitness (e.g., objectified by maximal oxygen uptake [VO_{2max}]) are associated with better cognitive performance and higher levels of oxyHb in the PFC [28–31] as well as (ii) that cortical hemodynamics (e.g., level of oxyHb concentration) mediate, at least partly, the relationship between cardiorespiratory fitness level and cognitive performance [30–32].

To the best of our knowledge, there is currently no comparable study available that has examined the relationship between muscular strength, cognitive functioning, and cortical hemodynamics [1]. Hence, the current study aims to investigate the possible links between muscular strength (i.e., operationalized by handgrip strength), cognitive functioning (i.e., assessed by reaction times and errors in Sternberg task), and functional cortical hemodynamics (i.e., measured by fNIRS) in younger adults.

Materials and methods

Participants and study design

Thirty-nine healthy right-handed, young adults [13 female/26 male; age 24.0 ± 3.1 years; body height 174.4 ± 9.2 cm; body mass 72.7 ± 14.2 kg; body mass index (BMI) 23.7 ± 3.3 kg/m^2] with normal or corrected vision who had no history of self-reported orthopaedic, cardiovascular, psychiatric, and/or neurological diseases participated in this study.

The study was approved by the local ethics committee of the Medical Faculty of the Otto von Guericke University Magdeburg (No. 181/18) and was in accordance with the Declaration of Helsinki (1964). All participants were informed about the study procedures and provided written informed consent to participate. The participants received a compensation fee of 16 EUR.

In this cross-sectional study, the participants were asked to visit our laboratory once to assess their general participants' characteristics, to complete questionnaires on mental health, sleep quality, and regular physical activity level, to conduct selected neuropsychological tests, and to assess their handedness and maximal isometric handgrip strength. Furthermore, fNIRS was used to record the cortical hemodynamics while the participants solved the Sternberg task. All tests are described below in more detail.

Screening measures and handgrip strength testing

The mental health status was assessed by using the Becks Depression Inventory II (BDI-II) in which higher total scores indicate more serve depressive symptoms [33]. Furthermore, we evaluated sleep quality by using the Pittsburgh Sleep Quality Index (PSQI) [34]. A higher total PSQI score indicates more impaired sleep quality [34].

The regular physical activity level and the regular physical exercise level was objectified by using a

German-language questionnaire ['Bewegungs- und Sportsaktivitätsfragebogen' (BSA-F)] [35]. To rate the level of regular physical activity and the regular physical exercise, the frequency and duration for each activity or exercise needed to be stated and was added up to a single outcome value (in minutes per week).

The time to complete both parts of the Trail-Making Test (TMT A&B) was used to probe the individual performance in visual search (TMT A) and cognitive flexibility (TMT B) [36, 37]. In addition, we calculate the time difference (TMT B-A) between TMT-B and TMT-A as measure of shifting ability [38].

To determine the handedness of the participant, the Edinburgh Handedness Inventory (EHI) [39] with a cut-off value of ± 50 was used (left hander: < -50; ambidexter: between ≥ -50 and $\leq +50$; right hander: $> +50$) [40].

Handgrip strength was measured using a handhold dynamometer (DHD-1; Saehan®, South Korea) and following the recommendations provided in the Southampton protocol [41]. Accordingly, the participants were seated in a comfortable chair with their feet flat on the ground. The shoulder of the tested extremity was adducted and neutrally rotated. We advised the participants to flex the elbow of the tested extremity at 90° and maintain a neutral wrist position (i.e., thumb facing upward). The participants were asked to squeeze the hand as hard as they can for 3 s. Each participant performed three trials for each hand and after performing one trial, the hand was changed [41]. The maximal handgrip strength of the three trials of each extremity side was used for further analysis. To account for the influence of body composition, we normalized the maximal handgrip strength to the body mass index (BMI) of the participants by using following equation: normalized handgrip strength (NGS) = absolute handgrip strength (in kg)/BMI (in kg/m^2) [42, 43].

Cognitive testing

The Sternberg task which assesses short-term working memory [44] was used in this study because previous publications showed that Sternberg task induces a robust activation of the prefrontal cortex [45–50]. At the beginning of the experiment, each participant was placed in a self-selected comfortable distance to the presentation screen (mean distance to the presentation screen: 67.14 cm; standard deviation: 9.86 cm). We used PsychoPy 2 to present the Sternberg task [51–53]. As shown in Fig. 1, at the beginning of each trial an array of seven letters (i.e., the target memory set) occurred for 1.5 s on the screen and was followed by a retention period with a white fixation cross for 4 s. Afterwards, a probe letter which was flanked by two interrogation marks was shown for no more than 2 s. We asked the subjects to maintain the target memory set over the retention period in mind. When the probe letter occurred, the participants were advised to press the right cursor button (if the presented letter was included in the target memory set) or the left button (if the presented letter was not included in the target memory set) as quickly and accurately as possible.

All participants used the index finger of the right hand to press the left cursor button and middle finger of the right hand to press the right cursor button. Furthermore,

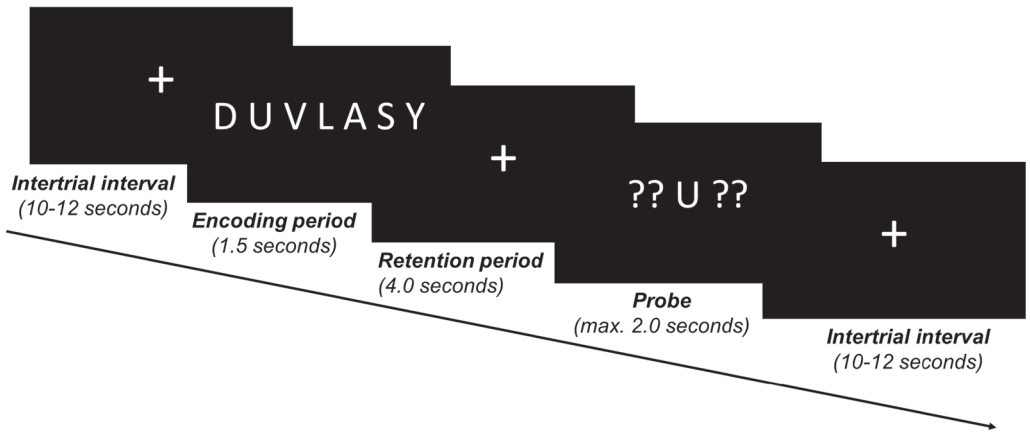

Fig. 1 Schematic illustration of a trial of the modified Sternberg task. The trial started with a white fixation cross at the middle of a black screen (first picture: "+") that was presented for a randomly varying period of time between 10 and 12 s. The fixation cross was followed by an encoding period which lasted for 1.5 s. During this period participants had to encode a string of seven letters (second picture: "DUVLASY"). After, a retention period of 4.0 s (third picture: "+") a single probe letter flanked by two questions marks on each side was shown for a maximum duration of 2.0 s (fourth picture: "?? U ??"). At this point, participants were instructed to decide as fast as possible (within the response window of 2 s) whether the probe letter had been included in the encoding period or not. Thereafter, the next trial started with an intertrial interval of 10–12 s (fifth picture: "+")

after a trial a rest period with a randomized time interval of 10 to 12 s, in which the participants looked at white fix a fixation cross, was included to diminish possible resonance effects [45, 54]. Each participant solved 24 trials and in the half of the trials the target memory set included the probe letter.

During Sternberg task, the behavioral performance for each trial (accuracy and reaction time) and cortical hemodynamics using functional near-infrared spectroscopy were recorded. We averaged accuracy and reaction time across all trials. Accuracy was expressed as accuracy score (percentage of correct answers). In addition, each participant was adequately familiarized with the Sternberg task and solved ten familiarization trials before recording cortical hemodynamics (mean accuracy score: 88.38%; standard deviation: 10.68%, mean reaction time: 1.00 s; standard deviation: 0.25 s).

During the entire duration of the Sternberg task, we measured heart rate signal using a heart rate watch and a chest strap (Polar watch V800® and chest strap H10®, Polar Electro Oy, Kempele, Finland). The heart rate signals were processed using "Kubios HRV" (Biosignal Analysis and Medical Imaging Group, University Kuopio, Finland; Version 3.0.0) [55, 56]. Artefact correction was performed for every participant separately in order to select the optimal threshold for artefact correction [56]. Possible artefacts were removed using a threshold-based filter algorithm which was set to the lowest correction level that cleans all artefacts but does not remove too many normal RR intervals [56]. In the current study, we used a low (35 s) or a medium threshold (0.25 s). Using these thresholds, all values that differ more than 0.25 s (or 0.35 s) from the average value were replaced with interpolated values estimated by a cubic spline interpolation [55–57]. After artefact correction, the HR time series was detrended by applying the smoothness-priors-based detrending approach (smoothing parameter, $\lambda = 500$) [55, 56]. For analyzing the frequency bands, the frequency ranges were selected as follows: very low frequency (VLF): 0–0.04 Hz, low frequency (LF): 0.04–0.15 Hz, and high frequency (HF): 0.15–0.4 Hz [55, 56, 58].

Functional near-infrared spectroscopy

fNIRS is a relatively new, non-invasive neuroimaging technique which is based on theory of neurovascular coupling and optical spectroscopy [54, 59, 60]. fNIRS enables the recording of changes in oxygenated hemoglobin (oxyHb) and deoxygenated hemoglobin (deoxyHb) which allows the "indirect" assessment of cortical activation. A higher cortical activation is commonly indicated by an increase on oxyHb and a decrease in deoxyHb [54, 60]. More detailed information on fNIRS can be found in the referenced literature [54, 59–66].

In the current study, we recorded changes in cortical hemodynamics at a frequency of 7.81 Hz by using a portable continuous wave fNIRS system (NIRSport™, NIRx Medical Technologies, Glen Head, New York, USA). Our fNIRS system consists of eight light sources (emitting light at wavelengths of 760 and 850 nm), eight light detectors, and a short-distance detector bundle. The fNIRS optodes were placed according to the 10–20 EEG system [67] using a standardized cap (EasyCap GmbH, Herrsching, Germany). As shown in Fig. 2, our fNIRS setup consists of 22 long source-detector separation channels (LSC; ~ 27 mm to 45 mm) and 8 short source-detector separation channels (SSC; ~ 8 mm). The LSC were used to measure changes in cortical hemodynamics while SSC were used to account for changes in extracerebral blood flow (see "fNIRS data processing"). To assign fNIRS-signals from LSC's to specific brain regions, we

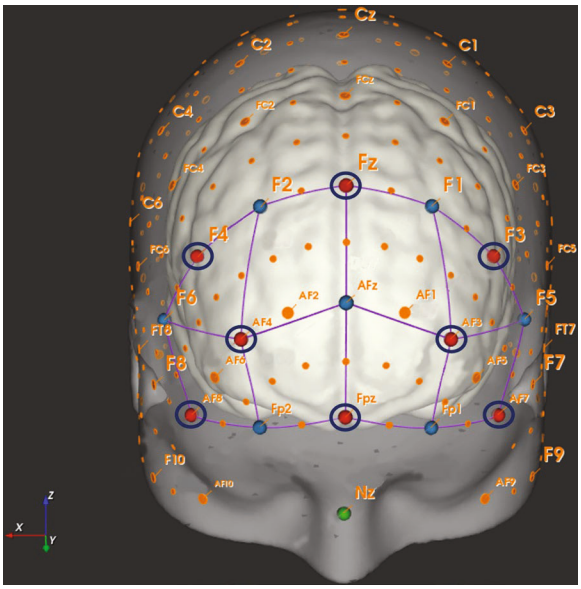

Fig. 2 Schematic illustration of the channel setup. The 'red dots' represent sources and the 'blue dots' represent detectors. A 'dark blue circle' around a detector indicates the position of a short-separation channel (SSC; 8 mm). Channels in 'purple' are combinations of distinct sources and detectors. The corresponding EEG-positions and the long-separation channel distance (LSC) between sources and detectors result in the following recorded measurement channels: Channel 1 (F4-F2; LSC: 30 mm), Channel 2 (F4-F6; LSC: 30 mm), Channel 3 (AF8-F6; LSC: 33 mm), Channel 4 (AF8-Fp2; LSC: 30 mm), Channel 5 (AF4-F2; LSC: 44 mm), Channel 6 (AF4-F6; LSC: 45 mm), Channel 7 (AF4-Fp2; LSC: 28 mm), Channel 8 (AF4-Afz; LSC: 36 mm), Channel 9 (Fpz-Fp2; LSC: 31 mm), Channel 10 (Fpz-AFz; LSC: 40 mm), Channel 11 (Fpz-Fp1; LSC: 30 mm), Channel 12 (AF3-AFz; LSC: 36 mm), Channel 13 (AF3-Fp1; LSC: 27 mm), Channel 14 (AF3-F5; LSC: 44 mm), Channel 15 (AF3-F1; LSC: 44 mm), Channel 16 (AF7-Fp1; LSC: 30 mm), Channel 17 (AF7-F5; LSC: 33 mm), Channel 18 (F3-F5; LSC: 29 mm), Channel 19 (F3-F1; LSC: 29 mm), Channel 20 (Fz-F2; 29 mm), Channel 21 (Fz-F2; LSC: 40 mm), and Channel 22 (Fz-F1; LSC: 29 mm)

performed a virtual and probabilistic spatial registration using the software fNIRS Optodes' Location Decider (fOLD) [68] and the Broadmann atlas (BA) [69]. Based on this probabilistic spatial registration, our setup covered the following cortical regions: right dorsolateral prefrontal cortex (BA 9; Channel 1, 5, and 20), right dorsolateral prefrontal cortex (BA 46; Channel 6), left dorsolateral prefrontal cortex (BA 9; Channel 15, 19, and 22), left dorsolateral prefrontal cortex (BA46; Channel 14), right frontopolar area (BA 10; Channel 4, 7, 8, and 9), left frontopolar area (BA 10; Channel 11, 12, 13, and 16), right pars triangularis of Broca's area (BA 45; Channel 2 and 3), left pars triangularis of Broca's area (BA 45; Channel 17 and 18), middle frontopolar area (BA 10; Channel 10), and middle dorsolateral prefrontal cortex (BA 9; Channel 21). More detailed information on spatial registration is provided in Additional file 1: Table S1.

fNIRS data processing

The fNIRS data were preprocessed using the software program Homer 2 (version 2.8) [70] and followed current data processing recommendations [54, 71]. At first, we used enPruneChannels function with a signal-to-noise threshold (SNR thres) of 10 to exclude to noisy channels [coefficient of variation (CV) > 10] from further analyses. In this study 1.5% of channels were excluded because they were considered as to noisy which were on average 0.36 channels per individual. Then, the raw light intensity signals were converted into changes in optical density (using hmrIntensity2OD function) [70]. Afterwards, the fNIRS time series were corrected for motion artefacts [59, 72]. For this purpose, we used the hmrMotionCorrectWavelet filtering function implemented in Homer 2 which is based on the algorithm described by Molavi and Dumont [73]. The threshold of the wavelet filter was set to 1.219 times of interquartile [74–76] that corresponds to the recommend α of 0.1 [72, 73, 77]. Following the motion artefact correction, we used a bandpass filter (hmrBandpassFilt function) with a high-pass cut-off frequency of 0.01 Hz to account for instrumental noise and low frequency drifts and a low-pass cut-off frequency of 0.09 Hz to account for cardiac oscillations and Mayer-waves [71]. Subsequently, preprocessed optical density data of both wavelengths were converted via the modified Beer–Lambert law (MBLL) into concentration changes of oxygenated hemoglobin (oxyHb) and deoxygenated hemoglobin (deoxyHb) by using the hmrOD2Conc function. The differential pathlength factor which is required in the MBLL was calculated for each individual participant using the equation provided by Scholkmann and Wolf [78].

Afterwards, we used the hmrDeconvHRRF_DriftSS function to account for the confounding effects of extracerebral (superficial) blood flow. This function is based on the assumptions that SSC record changes in extracerebral blood flow whereas LSC measures both change in superficial blood flow and cortical brain tissue [54, 79]. Hence, the signals of SSC can be used to regress out signals from extracerebral layers from LSC which result in an improved data quality and help to avoid "false positives" [80]. In the hmrDeconvHRRF_DriftSS function, the hemodynamic response function (HRF) is estimated by using a general linear model approach (GLM) that uses ordinary least squares [81]. As done in several previous publications [82–90], the HRF was modeled with a consecutive sequence of Gaussian functions with a standard deviation of 0.5 s and their means separated by 0.5 s over a specific regression time (used parameters in Homer 2: trange −2.0 to 20; glmSolveMethod 1; idxBasis 1; paramsBasis 0.5 and 0.5). To account for baseline drift, it was modeled using a third order polynomial fit [84, 89, 91]. Furthermore, we used the nearest SSC as static estimator for regression because the location of the SSC impacts the performance of the regression analysis substantially [92]. Following the SSC regression, we used the hmrBlockAvg function to perform a baseline correction and to calculate the block averages for oxyHb and deoxyHb changes over all trials and for each measurement channel (i.e., each LSC). In order to baseline correct our data, we used a time period of 2 s prior to stimulus onset which is a commonly utilized time period in event-related fNIRS studies (for review see [54]). The entire period of the stimulus phase was used to calculate baseline-corrected block averages (i.e., 0 to 20 s after stimulus onset).

After pre-processing with Homer 2, the baseline-corrected block averages of the time series of oxyHb and deoxyHb were exported and imported into Matlab (The Mathworks®, Natick, Massachusetts, USA). Using the exported block averages and an in-house Matlab software, we calculated the median values of oxyHb and deoxyHb for each fNIRS measurement channel across a period of 0 to 16 s after trial onset. Median values were used for further statistical analyses because they are deemed to be less influenced by potential outliers [54, 59].

Statistical analysis

The statistical analysis was performed using IBM SPSS (Statistical Package for Social Science, Version 26, Chicago, Illinois, USA). To investigate whether cortical hemodynamics (e.g., oxyHb and deoxyHb) mediate the relationship between measures of handgrip strength and measures of cognitive performance (i.e., reaction time in Sternberg task), a mediation analysis was conducted. Thereto, we assessed in the first step, normal distribution using the Shapiro–Wilk test. As the most parameters (especially fNIRS parameters)

were not normally distributed, we used non-parametric methods in the subsequent statistical analysis. In the second step, we examined the bivariate relationships (i) between measures of handgrip strength and measures of cognitive performance, (ii) between measures of cognitive performance and measures of cortical hemodynamics, and (iii) between measures of cortical hemodynamics and measures of handgrip strength by calculating non-parametric partial correlations (r_p) controlling for age and gender [93, 94]. The correlations were rated as follows: 0 to 0.19: no correlation; 0.2 to 0.39: low correlation, 0.40 to 0.59: moderate correlation; 0.60 to 0.79: moderately high correlation; ≥ 0.80: high correlation [95, 96]. The level of statistical significance was set to $\alpha = 0.05$ in correlation analysis.

In the third step, we performed a robust mediation analysis using the SPSS extension bundle "robmed" [97] and the calculated mediation model includes a three-output analyses process (Paths A–C′). In this regard, the associations between (i) the independent variable (measures of handgrip strength) and dependent variable (measures of cognitive performance)—Path C, (ii) the independent variable (measures of handgrip strength) and the mediator (measures of cortical hemodynamics)—Path A, and (iii) the mediator (measures of cortical hemodynamics) and the dependent variable (measures of cognitive performance)—Path B, were computed. Afterwards, the direct effect (Path C′) of the independent variable (e.g., measures of handgrip strength) on the dependent variable (e.g., measures of cognitive performance) was estimated by controlling for the mediator (measures of cortical hemodynamics) and the indirect effect (Path AB). To calculate the direct and indirect effects, we computed a robust mediation model [97] with bias-corrected bootstrap 95% confidence intervals (CIs) based on 5000 bootstrap resamples and entered the covariates age and gender [93, 94]. In accordance with the literature, a significant mediation was assumed if the CIs in Path AB did not include zero whereas a partial mediation was indicated if the CIs of Path C′ cross zero [98–100]. Please note a mediation analysis was only computed if two phenomena appeared: firstly, if the non-parametric partial correlation analysis (see "second step" and Tables 2 and 3) exhibited that there was a significant correlation between mediator and independent variable (or dependent variable) and secondly, if there was a correlation of at least $r_p \geq 0.2$ between mediator and dependent variable (or independent variable). We selected a threshold of $r_p \geq 0.2$ because this is deemed to be the minimum effect size that represents a "practical" significant effect [101].

Results

The general characteristics of the participants are shown in Table 1.

Correlations between measures of handgrip strength and cognitive performance in Sternberg task

The non-parametric partial correlations (controlling for the influence of age and gender) between left- and right-hand absolute handgrip strength (AHS) and reaction time in Sternberg task [left AHS: r_p (35) = − 0.278; p = 0.096/right AHS: r_p (35) = − 0.157; p = 0.354] and between left- and right-hand normalized handgrip strength (NHS) and reaction time in Sternberg task [left NHS: r_p (35) = − 0.253; p = 0.131/right NHS: r_p (35) = − 0.134; p = 0.431] did not reach statistical significance. Furthermore, we did also not observe statistically significant correlations between left- and right-hand absolute handgrip strength and correct answers in Sternberg task [left AHS: r_p (35) = 0.012; p = 0.945/right AHS: r_p (35) = − 0.045; p = 0.791] and between left- and right-hand normalized handgrip strength and correct answers in Sternberg task [left NHS: r_p (35) = 0.122; p = 0.472/right AHS: r_p (35) = 0.091; p = 0.592].

Table 1 Median and interquartile range of the screening tests in the investigated sample

Parameters	Median ± interquartile range
BDI-II (total score)	3.0 ± 6.0
Level of education (years)	15.6 ± 2.4
PSQI (total score)	4.0 ± 2.0
BSA (min per week)	PA: 236.5 ± 255.0/PE:292.5 ± 350.5
TMT A (s)	19.4 ± 6.3
TMT B (s)	42.9 ± 14.4
TMT B-A (s)	22.9 ± 11.4
EHI (total score)	83.3 ± 17.3
Mean heart rate during ST (bpm)	71.8 ± 20.2
LF/HF ratio	1.43 ± 1.51
Left/Right AHS (kg)	38.9 ± 26.2/44.1 ± 22.7
Left/Right NHS (A.U.)	1.67 ± 0.87/1.87 ± 0.78
Reaction time in ST (s)	0.94 ± 0.37
Correct answers in ST (%)	87.5 ± 12.5

AHS absolute handgrip strength, *A.U.* arbitrary unit, *BDI-II* Becks Depression Inventory II (a score of 13 and higher indicates depression [102, 103]), *bpm* beats per minute, *BSA* physical activity questionnaire, derived from German 'Bewegungs- und Sportaktivitätsfragebogen' (The World Health Organization recommends, at least, 150 min of moderate-intensity physical activity in a week for substantial health benefits [104]), *EHI* Edinburgh Handedness Inventory (a score of 50 and higher indicates right-handedness [40]), *LF/HF ratio* low-frequency/high-frequency ratio, *kg* kilogram, *min* minutes, *NHS* normalized handgrip strength (normalized to body-mass-index), *PA* physical activity, *PE* physical exercise, *s* seconds, *PSQI* Pittsburgh Sleep Quality Index (a score of 6 and higher indicates insomnia [105]), *ST* Sternberg task, *TMT* Trail Making Test

Table 2 Overview of the regional cortical changes in the concentrations of oxygenated hemoglobin (oxyHb) measured during the Sternberg task (ST) and their correlations with measures of handgrip strength and cognitive performance

Channels	Median ± IQR	Non-parametric partial correlations		
	OxyHb (µmol/L)	AHS (left/right)	NHS (left/right)	Reaction time in ST/correct answers in ST
1 (rt. DLPFC; BA9)	0.017 ± 0.028	r_p (35) = 0.179; p = 0.288/ r_p (35) = 0.241; p = 0.151	r_p (35) = 0.145; p = 0.391/ r_p (35) = 0.190; p = 0.260	*r_p (35) = − 0.417; p = 0.010/ r_p (35) = 0.401; p = 0.014*
2 (rt. Broca; BA 45)	0.013 ± 0.058	r_p (35) = 0.287; p = 0.085 /r_p (35) = 0.161; p = 0.340	r_p (35) = 0.210; p = 0.212/ r_p (35) = 0.134; p = 0.430	*r_p (35) = − 0.426; p = 0.009/* r_p (35) = 0.206; p = 0.222
3 (rt. Broca; BA 45)	0.017 ± 0.053	r_p (34) = 0.021; p = 0.905/ r_p (34) = 0.075; p = 0.663	r_p (34) = 0.036; p = 0.833 /r_p (34) = 0.108; p = 0.530	*r_p (34) = − 0.388; p = 0.019/* r_p (34) = 0.241; p = 0.156
4 (rt. FPA; BA 10)	− 0.018 ± 0.073	r_p (35) = − 0.021; p = 0.903/ r_p (35) = − 0.007; p = 0.968	r_p (35) = − 0.094; p = 0.581/ r_p (35) = − 0.061; p = 0.719	r_p (35) = − 0.170; p = 0.316/ r_p (35) = 0.249; p = 0.138
5 (rt. DLPFC; BA 9)	0.016 ± 0.052	*r_p (32) = 0.359; p = 0.037/* r_p (32) = 0.257; p = 0.143	r_p (32) = 0.225; p = 0.202/ r_p (32) = 0.147; p = 0.407	*r_p (32) = − 0.404; p = 0.018/* r_p (32) = 0.177; p = 0.317
6 (rt. DLPFC; BA 46)	0.021 ± 0.077	r_p (34) = 0.157; p = 0.360/ r_p (34) = 0.174; p = 0.310	r_p (34) = 0.087; p = 0.613/ r_p (34) = 0.161; p = 0.347	*r_p (34) = − 0.431; p = 0.009/* r_p (34) = 0.227; p = 0.182
7 (rt. FPA; BA 10)	0.012 ± 0.035	r_p (34) = 0.005; p = 0.979/ r_p (34) = 0.053; p = 0.759	r_p (34) = − 0.068; p = 0.692/ r_p (34) = 0.009; p = 0.958	r_p (34) = 0.091; p = 0.598/ r_p (34) = − 0.160; p = 0.351
8 (rt. FPA; BA 10)	0.008 ± 0.049	r_p (35) = 0.142; p = 0.402/ r_p (35) = 0.128; p = 0.451	r_p (35) = 0.013; p = 0.940/ r_p (35) = 0.008; p = 0.964	r_p (35) = − 0.299; p = 0.072/ r_p (35) = 0.145; p = 0.391
9 (rt. FPA; BA 10)	− 0.037 ± 0.043	r_p (35) = 0.135; p = 0.427/ r_p (35) = 0.108; p = 0.524	r_p (35) = 0.120; p = 0.481/ r_p (35) = 0.116; p = 0.494	r_p (35) = − 0.091; p = 0.593/ r_p (35) = 0.221; p = 0.188
10 (md. FPA; BA 10)	− 0.004 ± 0.037	r_p (35) = 0.246; p = 0.143/ r_p (35) = 0.125; p = 0.460	r_p (35) = 0.273; p = 0.102/ r_p (35) = 0.152; p = 0.370	*r_p (35) = − 0.518; p = 0.001/* r_p (35) = 0.173; p = 0.306
11 (lt. FPA; BA 10)	− 0.019 ± 0.056	r_p (35) = 0.102; p = 0.546/ r_p (35) = − 0.018; p = 0.915	r_p (35) = 0.093; p = 0.585/ r_p (35) = − 0.014; p = 0.934	*r_p (35) = − 0.416; p = 0.010/* r_p (35) = 0.045; p = 0.793
12 (lt. FPA; BA 10)	0.004 ± 0.049	r_p (35) = 0.295; p = 0.077 /r_p (35) = 0.141; p = 0.405	r_p (35) = 0.214; p = 0.205/ r_p (35) = 0.072; p = 0.672	*r_p (35) = − 0.393; p = 0.016/* r_p (35) = 0.103; p = 0.545
13 (lt. FPA; BA 10)	− 0.003 ± 0.052	r_p (34) = 0.244; p = 0.152/ r_p (34) = 0.102; p = 0.555	r_p (34) = 0.152; p = 0.375/ r_p (34) = 0.017; p = 0.923	r_p (35) = − 0.099; p = 0.566/ r_p (35) = − 0.088; p = 0.610
14 (lt. DLPFC; BA 46)	0.018 ± 0.057	r_p (34) = 0.088; p = 0.609/ r_p (34) = 0.066; p = 0.704	r_p (34) = 0.048; p = 0.782/ r_p (34) = 0.088; p = 0.611	r_p (34) = − 0.118; p = 0.492/ r_p (34) = 0.207; p = 0.225
15 (lt. DLPFC; BA 9)	0.002 ± 0.037	r_p (32) = 0.269; p = 0.125/ r_p (32) = 0.095; p = 0.593	r_p (32) = 0.242; p = 0.169/ r_p (32) = 0.060; p = 0.736	*r_p (32) = − 0.459; p = 0.006/* r_p (32) = 0.202; p = 0.251
16 (lt. FPA; BA 10)	− 0.008 ± 0.063	r_p (35) = 0.115; p = 0.498/ r_p (35) = 0.167; p = 0.322	r_p (35) = 0.115; p = 0.498/ r_p (35) = 0.171; p = 0.311	r_p (35) = 0.000; p = 1.000/ r_p (35) = 0.122; p = 0.474
17 (lt. Broca; BA 45)	0.019 ± 0.071	r_p (35) = 0.165; p = 0.329/ r_p (35) = 0.116; p = 0.493	r_p (35) = 0.165; p = 0.329/ r_p (35) = 0.173; p = 0.306	r_p (35) = − 0.230; p = 0.170/ r_p (35) = 0.133; p = 0.431
18 (lt. Broca; BA 45)	0.013 ± 0.051	r_p (35) = 0.089; p = 0.601/ r_p (35) = 0.030; p = 0.860	r_p (35) = − 0.014; p = 0.936/ r_p (35) = 0.007; p = 0.970	r_p (35) = 0.017; p = 0.922/ r_p (35) = 0.033; p = 0.844
19 (lt. DLPFC; BA 9)	0.014 ± 0.035	r_p (34) = 0.109; p = 0.527/ r_p (34) = 0.020; p = 0.908	r_p (34) = 0.021; p = 0.902/ r_p (34) = − 0.029; p = 0.868	r_p (34) = − 0.131; p = 0.445/ r_p (34) = 0.089; p = 0.606
20 (rt. DLPFC; BA 9)	0.009 ± 0.031	r_p (35) = 0.241; p = 0.151/ r_p (35) = 0.288; p = 0.084	r_p (35) = 0.154; p = 0.362/ r_p (35) = 0.243; p = 0.147	r_p (35) = − 0.042; p = 0.806/ r_p (35) = 0.234; p = 0.164
21 (md. DLPFC; BA 9)	0.003 ± 0.032	*r_p (34) = 0. 358; p = 0.032/* r_p (34) = 0.230; p = 0.178	r_p (34) = 0.228; p = 0.181/ r_p (34) = 0.088; p = 0.612	r_p (34) = − 0.315; p = 0.061/ r_p (34) = 0.299; p = 0.076
22 (lt. DLPFC; BA 9)	0.001 ± 0.029	r_p (35) = 0.110; p = 0.517/ r_p (35) = − 0.030; p = 0.860	r_p (35) = 0.092; p = 0.587/ r_p (35) = − 0.054; p = 0.752	*r_p (35) = − 0.389; p = 0.017/* r_p (35) = 0.248; p = 0.139

On the left hand of the table, median ± interquartile range (IQR) of concentrations of oxyHb are displayed. On the right hand of the table, non-parametric correlations (controlled for age and gender) between oxyHb and absolute handgrip strength (AHS), normalized handgrip strength (NHS), reaction time and percentage of correct answers in the ST are shown. Significant correlations are presented in italic

BA broadman area, *DLPFC* dorsolateral prefrontal cortex, *FPA* frontopolar area, *lt.* left, *md.* middle, r_p partial correlation controlling for age and gender, *rt.* right, *ST* Sternberg task

Table 3 Overview of the regional cortical changes in the concentrations of deoxygenated hemoglobin (deoxyHb) measured during the Sternberg task (ST) and their correlations with measures of handgrip strength and cognitive performance

Channels	Median ± IQR	Non-parametric partial correlations		
	DeoxyHb (µmol/L)	AHS (left/right)	NHS (left/right)	Reaction time in ST/correct answers in ST
1 (rt. DLPFC; BA9)	0.001 ± 0.005	r_p (35) = − 0.197; p = 0.243/ r_p (35) = − 0.182; p = 0.280	r_p (35) = − 0.232; p = 0.167/ r_p (35) = − 0.245; p = 0.144	r_p (35) = 0.198; p = 0.240/ r_p (35) = − 0.276; p = 0.099
2 (rt. Broca; BA 45)	0.000 ± 0.015	r_p (35) = − 0.299; p = 0.072/ r_p (35) = − 0.180; p = 0.286	r_p (35) = − 0.204; p = 0.225/ r_p (35) = − 0.133; p = 0.434	*r_p (35) = 0.343; p = 0.038/* r_p (35) = − 0.142; p = 0.401
3 (rt. Broca; BA 45)	− 0.002 ± 0.011	r_s (34) = − 0.071; p = 0.680/ r_p (34) = − 0.203; p = 0.234	r_p (34) = − 0.088; p = 0.609/ r_p (34) = − 0.227; p = 0.183	r_p (34) = 0.262; p = 0.122/ r_p (35) = − 0.199; p = 0.245
4 (rt. FPA; BA 10)	0.000 ± 0.023	r_p (35) = − 0.301; p = 0.070/ r_p (35) = − 0.191; p = 0.258	r_p (35) = − 0.294; p = 0.077/ r_p (35) = − 0.224; p = 0.182	r_p (34) = 0.172; p = 0.307/ r_p (35) = − 0.095; p = 0.574
5 (rt. DLPFC; BA 9)	0.000 ± 0.015	*r_p (32) = − 0.442; p = 0.009/ r_p (32) = − 0.385; p = 0.025*	*r_p (32) = − 0.454; p = 0.007/ r_p (32) = − 0.390; p = 0.023*	*r_p (32) = 0.441; p = 0.009/* r_p (32) = − 0.236; p = 0.179
6 (rt. DLPFC; BA 46)	− 0.006 ± 0.019	r_p (34) = − 0.040; p = 0.818/ r_p (34) = − 0.112; p = 0.514	r_p (34) = 0.005; p = 0.977/ r_p (34) = − 0.088; p = 0.610	*r_p (34) = 0.459; p = 0.005/* r_p (34) = − 0.275; p = 0.105
7 (rt. FPA; BA 10)	0.003 ± 0.012	*r_p (34) = − 0.379; p = 0.023/ r_p (34) = − 0.420; p = 0.011*	*r_p (34) = − 0.339; p = 0.043/ r_p (34) = − 0.368; p = 0.027*	r_p (34) = 0.306; p = 0.070/ r_p (34) = − 0.177; p = 0.300
8 (rt. FPA; BA 10)	0.002 ± 0.013	*r_p (35) = − 0.363; p = 0.027/ r_p (35) = − 0.429; p = 0.008*	*r_p (35) = − 0.347; p = 0.035/ r_p (35) = − 0.434; p = 0.007*	r_p (35) = 0.150; p = 0.376/ r_p (35) = − 0.113; p = 0.504
9 (rt. FPA; BA 10)	0.002 ± 0.014	r_p (35) = − 0.200; p = 0.234/ r_p (35) = − 0.199; p = 0.239	r_p (35) = − 0.252; p = 0.133/ r_p (35) = − 0.218; p = 0.194	r_p (35) = 0.244; p = 0.145/ r_p (35) = − 0.113; p = 0.507
10 (md. FPA; BA 10)	0.001 ± 0.009	*r_p (35) = − 0.340; p = 0.039/* r_p (35) = − 0.306; p = 0.066	r_p (35) = − 0.213; p = 0.205/ r_p (35) = − 0.188 p = 0.265	r_p (35) = 0.031; p = 0.856/ r_p (35) = 0.047; p = 0.781
11 (lt. FPA; BA 10)	0.002 ± 0.012	r_p (35) = − 0.194; p = 0.251/ r_p (35) = − 0.132; p = 0.437	r_p (35) = − 0.072; p = 0.670/ r_p (35) = − 0.021; p = 0.904	r_p (35) = 0.164; p = 0.331/ r_p (35) = − 0.085; p = 0.618
12 (lt. FPA; BA 10)	0.002 ± 0.010	*r_p (35) = − 0.390; p = 0.017/* r_p (35) = − 0.264; p = 0.115	r_p (35) = − 0.263; p = 0.116/ r_p (35) = − 0.131; p = 0.438	r_p (35) = 0.147; p = 0.385/ r_p (35) = 0.048; p = 0.776
13 (lt. FPA; BA 10)	0.002 ± 0.011	*r_p (34) = − 0.436; p = 0.008/* r_p (34) = − 0.326; p = 0.052	*r_p (34) = − 0.396; p* = 0.017/ r_p (34) = − 0.252; p = 0.137	r_p (34) = − 0.163; p = 0.341/ r_p (34) = 0.018; p = 0.916
14 (lt. DLPFC; BA 46)	− 0.003 ± 0.025	r_p (34) = − 0.263; p = 0.122/ r_p (34) = − 0.270; p = 0.112	r_p (34) = − 0.240; p = 0.159/ r_p (34) = − 0.312; p = 0.064	r_p (34) = 0.101; p = 0.557/ *r_p (34) = − 0.338; p = 0.043*
15 (lt. DLPFC; BA 9)	0.002 ± 0.017	*r_p (32) = − 0.409; p = 0.016/* r_p (32) = − 0.326; p = 0.060	*r_p (32) = − 0.493; p = 0.003z/ r_p (32) = − 0.411; p = 0.016*	r_p (32) = 0.127; p = 0.474/ r_p (32) = − 0.027; p = 0.879
16 (lt. FPA; BA 10)	0.001 ± 0.021	r_p (35) = − 0.206; p = 0.222/ r_p (35) = − 0.207; p = 0.219	r_p (35) = − 0.097; p = 0.570/ r_p (35) = − 0.073; p = 0.667	r_p (35) = − 0.027; p = 0.872/ r_p (35) = 0.003; p = 0.986
17 (lt. Broca; BA 45)	− 0.003 ± 0.017	r_p (35) = − 0.151; p = 0.373/ r_p (35) = − 0.210; p = 0.213	r_p (35) = − 0.188; p = 0.264/ r_p (35) = − 0.244; p = 0.145	r_p (35) = 0.020; p = 0.905/ r_p (35) = − 0.021; p = 0.901
18 (lt. Broca; BA 45)	0.002 ± 0.009	r_p (35) = 0.281; p = 0.092/ r_p (35) = 0.296; p = 0.075	r_p (35) = 0.293; p = 0.078/ r_p (35) = 0.263; p = 0.116	r_p (35) = − 0.055; p = 0.746/ r_p (35) = − 0.130; p = 0.445
19 (lt. DLPFC; BA 9)	0.001 ± 0.008	r_p (34) = − 0.123; p = 0.474/ r_p (34) = − 0.181; p = 0.291	r_p (34) = − 0.080; p = 0.645/ r_p (34) = − 0.168; p = 0.327	r_p (34) = − 0.154; p = 0.371/ r_p (34) = 0.067; p = 0.698
20 (rt. DLPFC; BA 9)	0.000 ± 0.011	r_p (35) = − 0.226; p = 0.179/ r_p (35) = − 0.277; p = 0.097	r_p (35) = − 0.185; p = 0.272/ *r_p (35) = − 0.328; p = 0.048*	r_p (35) = − 0.053; p = 0.756/ r_p (35) = − 0.022; p = 0.898
21 (md. DLPFC; BA 9)	0.003 ± 0.010	r_p (34) = − 0.276; p = 0.103/ r_p (34) = − 0.230; p = 0.178	r_p (34) = − 0.315; p = 0.061/ r_p (34) = − 0.325; p = 0.053	r_p (34) = − 0.029; p = 0.869/ r_p (34) = − 0.113; p = 0.511
22 (lt. DLPFC; BA 9)	0.002 ± 0.009	r_p (35) = − 0.155; p = 0.359/ r_p (35) = − 0.085; p = 0.618	r_p (35) = − 0.144; p = 0.395/ r_p (35) = − 0.103; p = 0.545	r_p (35) = − 0.073; p = 0.666/ r_p (35) = 0.003; p = 0.984

On the left hand of the table, median ± interquartile range (IQR) of concentrations of deoxyHb are displayed. On the right hand of the table, non-parametric partial correlations (controlled for age and gender) between deoxyHb and absolute handgrip strength (AHS), normalized handgrip strength (NHS), reaction time and percentage of correct answers in the ST are shown. Significant correlations are presented in italic

BA broadman area, *DLPFC* dorsolateral prefrontal cortex, *FPA* frontopolar area, *lt.* left, *md.* middle, r_p partial correlation controlling for the influence of age and gender, *rt.* right, *ST* Sternberg task

Correlations between measures of handgrip strength, measures of cognitive performance, and measures of cortical hemodynamics

The results of the partial correlation analysis (controlling for the influence of age and gender) between measures of handgrip strength, cognitive performance, and cortical hemodynamics are shown in Table 2 (oxyHb) and Table 3 (deoxyHb).

With regard to oxyHb, we observed a low positive correlation between the level of oxyHb in right dorsolateral prefrontal cortex (DLPFC) and middle DLPFC (Ch. 5 and Ch. 21) and left AHS. Furthermore, we found moderate negative correlations between level of oxyHb in specific channels of frontopolar area (FPA) and DLPFC and reaction time, and a moderate positive correlation between level of oxyHb in right DLPFC (Channel 1) and percentage of correct answers in Sternberg task (for a detailed overview see Table 2). Hence, better cognitive performance (e.g., faster reaction time and higher percentage of correct answers) is linked to higher levels of oxyHb (indicating, in general, a higher cortical activation) in distinct parts of the PFC.

With regard to deoxyHb, we observed low to moderate positive correlations between the level of deoxyHb in right FPA and left and right DLPFC and AHS and NHS (for a detailed overview see Table 3). Furthermore, we found a moderate positive correlation between level of deoxyHb in right Borca area (Channel 2) and right DLPFC (Channel 5 and 6) and reaction time in Sternberg task. In addition, we noticed a low and negative correlation between the level of deoxyHb in left DLPFC (Channel 14) and percentage of correct answers in Sternberg task. Collectively, better cognitive performance (e.g., faster reaction time and higher percentage of correct answers) is associated with lower levels of deoxyHb (indicating, in general, a higher cortical activation) in distinct parts of the PFC.

Mediation analysis

The results of the mediation analysis for the channels which meet our criteria to conduct mediation analysis (see 'Statistical analysis') are shown in Table 4.

Regarding Path A, we found that left AHS significantly predict [$\beta = 0.001$ (0.000); z (39) = 2.189; $p = 0.029$] the amplitude of oxyHb in Channel 2 (right Broca; BA 45) and that left AHS significantly predict [$\beta = 0.000$ (0.000); z (38) = − 2.180; $p = 0.029$] the amplitude of deoxyHb in Channel 7 (right FPA; BA 10), although the beta coefficient are very small (i.e., tending towards zero). As shown in Table 4, all other regressions of Path A did not reach statistical significance ($p \geq 0.05$).

Regarding the B path, we observed that level of oxyHb in Channel 2 (right Broca; BA 45), Channel 5 (right DLPFC; BA 9), and Channel 10 (middle FPA; BA 10) significantly predict reaction time in Sternberg task (for detailed overview see Table 4). Furthermore, the level of deoxyHb in Channel 5 (right DLPFC; BA 9) predict the reaction time in Sternberg task, whereas level of deoxyHb in Channel 14 (left DLPFC; BA 46) predict the percentage of correct answers in Sternberg task. The other regressions of Path B, which are shown in Table 4, did not reach statistical significance ($p \geq 0.05$).

Regarding path AB and C, we found a significant direct effect of left AHS on reaction time in Sternberg task [$\beta = -0.004$ (0.002); z (39) = − 2.175; $p = 0.030$; oxyHb—Channel 2], although the beta coefficient is very small. However, as the 95% CI for the indirect path included zero, a full mediation effect of the level of oxyHb of Channel 2 (right Broca; BA 45) could not be assumed. Furthermore, we observed a statistically significant direct effect of left AHS [$\beta = -0.005$ (0.002); z (39) = − 2.369; $p = 0.018$; deoxyHb—Channel 2] and left NHS [$\beta = -0.098$ (0.049); z (39) = − 2.083; $p = 0.037$; deoxyHb—Channel 2] on reaction time in Sternberg task, but with very small beta coefficients. A full mediation effect of deoxyHb of Channel 2 (right Broca; BA 45) could not be assumed because the 95% CI crossed zero. No other direct or indirect effects were observed to be statistically significant (for detailed overview see Table 4). Taken together, neither oxyHb nor deoxyHb can be considered significant mediators of the relationship between measures of handgrip strength and cognitive performance.

Discussion

The current study investigated the relationship between measures of handgrip strength, cognitive performance, and cortical hemodynamics. Thereto, we assessed handgrip strength via a handheld dynamometer and recorded cortical hemodynamics during a standardized cognitive test (Sternberg task) using fNIRS.

We observed that a higher cortical activation (objectified by higher level of oxyHb and lower levels of deoxyHb) of distinct parts of the PFC (e.g., FPA and DLPFC; see Tables 2 and 3) is associated with better cognitive performance. This finding is in accordance with the literature reporting that, at least in older adults, a higher level of oxyHb in the PFC during the cognitive testing is associated with better cognitive performance [106]. In this regard, it was also observed that after an acute bout of physical exercise [107–110] and during physical exercise [111], higher levels of oxyHb in distinct parts the PFC (e.g., FPA and DLPFC) are linked to better cognitive performance. In line with these previous observations, our findings buttress the assumption of a

Table 4 Mediation models

Independent variable (x)/ mediator (m)/dependent variable (y)	Path A	Path B	Path AB (indirect effect)	Path C (direct effect)
oxyHb				
Right AHS/Ch. 1/CA in ST	β = 0.000 (0.000); z (39) = 1.828; p = 0.068	β = 64.051 (52.713); z (39) = 1.498; p = 0.134	β = 0.025; CI [− 0.008 to 0.095]	β = − 0.003 (0.075); z (39) = − 0.234; p = 0.815
Left AHS/Ch. 2/RT in ST	*β = 0.001 (0.000); z (39) = 2.189; p = 0.029*	*β = − 1.854 (0.636); z (39) = − 2.948; p = 0.003*	β = − 0.002; CI [− 0.005 to 0.000]	*β = − 0.004 (0.002); z (39) = − 2.175; p = 0.030*
Left NHS/Ch. 2/RT in ST	β = 0.016 (0.011); z (39) = 1.537; p = 0.124	*β = − 1.954 (0.710); z (39) = − 2.801; p = 0.005*	β = − 0.032; CI [− 0.097 to 0.003]	β = − 0.082 (0.050); z (39) = − 1.862; p = 0.063
Left AHS/Ch. 5/RT in ST	β = 0.001 (0.000); z (36) = 1.694; p = 0.090	*β = − 3.004 (1.158); z (36) = − 2.523; p = 0.012*	β = − 0.002; CI [− 0.007 to 0.000]	β = − 0.002 (0.003); z (36) = − 0.680; p = 0.497
Left NHS/Ch. 5/RT in ST	β = 0.014 (0.011); z (36) = 1.271; p = 0.204	*β = − 3.076 (1.056); z (36) = − 2.857; p = 0.004*	β = − 0.042; CI [− 0.150 to 0.012]	β = − 0.038 (0.061); z (36) = − 0.661; p = 0.509
Left AHS/Ch. 10/RT in ST	β = 0.000 (0.000); z (39) = 1.315; p = 0.188	*β = − 4.091 (1.362); z (39) = − 3.008; p = 0.003*	β = − 0.002; CI [− 0.007 to 0.001]	β = − 0.003 (0.003); z (39) = − 1.230; p = 0.219
Left NHS/Ch. 10/RT in ST	β = 0.010 (0.010); z (39) = 1.237; p = 0.216	*β = − 4.087 (1.290); z (39) = − 3.190; p = 0.001*	β = − 0.041; CI [− 0.170 to 0.016]	β = − 0.062 (0.062); z (39) = − 0.998; p = 0.318
Left AHS/Ch. 12/RT in ST	β = 0.001 (0.000); z (39) = 1.445; p = 0.148	β = − 1.949 (1.757); z (39) = − 1.213; p = 0.225	β = − 0.001; CI [− 0.005 to 0.001]	β = − 0.004 (0.003); z (39) = − 1.157; p = 0.247
Left NHS/Ch. 12/RT in ST	β = 0.009 (0.009); z (39) = 0.661; p = 0.509	β = − 2.101 (1.747); z (39) = − 1.310; p = 0.190	β = − 0.018; CI [− 0.101 to 0.010]	β = − 0.075 (0.066); z (39) = − 1.211; p = 0.226
Left AHS/Ch. 15/RT in ST	β = 0.001 (0.000); z (36) = 1.557; p = 0.119	β = − 2.227 (1.656); z (36) = − 1.587; p = 0.112	β = − 0.002; CI [− 0.007 to 0.000]	β = − 0.002 (0.003); z (36) = − 0.533; p = 0.594
Left NHS/Ch. 15/RT in ST	β = 0.018 (0.009); z (36) = 1.761; p = 0.078	β = − 2.253 (1.592); z (36) = − 1.685; p = 0.092	β = − 0.041; CI [− 0.135 to 0.005]	β = − 0.040 (0.075); z (36) = − 0.553; p = 0.580
Left AHS/Ch. 21/RT in ST	β = 0.000 (0.000); z (38) = 1.758; p = 0.079	β = − 1.781 (1.357); z (38) = − 1.473; p = 0.141	β = − 0.001; CI [− 0.003 to 0.000]	β = − 0.004 (0.003); z (38) = − 1.483; p = 0.138
Left NHS/Ch. 21/RT in ST	β = 0.007 (0.006); z (38) = 0.987; p = 0.324	β = − 1.878 (1.461); z (38) = − 1.389; p = 0.165	β = − 0.013; CI [− 0.065 to 0.012]	β = − 0.082 (0.069); z (38) = − 1.285; p = 0.199
deoxyHb				
Left AHS/Ch. 2/RT in ST	β = 0.000 (0.000); z (39) = − 1.581; p = 0.114	β = 6.522 (5.036); z (39) = 1.562; p = 0.118	β = − 0.001; CI [− 0.006 to 0.000]	*β = − 0.005 (0.002); z (39) = − 2.369; p = 0.018*
Left NHS/Ch. 2/RT in ST	β = − 0.003 (0.003); z (39) = − 1.189; p = 0.235	β = 6.710 (6.091); z (39) = 1.362; p = 0.173	β = − 0.019; CI [− 0.134 to 0.010]	*β = − 0.098 (0.049); z (39) = − 2.083; p = 0.037*
Left AHS/Ch. 5/RT in ST	β = 0.000 (0.000); z (36) = − 1.944; p = 0.052	*β = 6.349 (3.104); z (36) = 2.037; p = 0.042*	β = − 0.002; CI [− 0.006 to 0.000]	β = − 0.002 (0.003); z (36) = − 0.662; p = 0.508
Right AHS/Ch. 5/RT in ST	β = 0.000 (0.000); z (36) = − 1.480; p = 0.139	*β = 6.989 (2.621); z (36) = 2.689; p = 0.007*	β = − 0.002; CI [− 0.006 to 0.000]	β = − 0.001 (0.003); z (36) = − 0.198; p = 0.843
Left NHS/Ch. 5/RT in ST	β = − 0.007 (0.005); z (36) = − 1.626; p = 0.104	*β = 6.473 (3.060); z (36) = 2.183; p = 0.029*	β = − 0.042; CI [− 0.169 to 0.011]	β = − 0.046 (0.031); z (36) = − 0.415; p = 0.678

Table 4 (continued)

Independent variable (x)/ mediator (m)/dependent variable (y)	Path A	Path B	Path AB (indirect effect)	Path C (direct effect)
Right NHS/Ch. 5/RT in ST	β = − 0.005 (0.005); z (36) = − 1.417; p = 0.156	*β = 6.965 (2.587); z (36) = 2.788; p = 0.005*	β = − 0.034; CI [− 0.147 to 0.009]	β = − 0.028 (0.064); z (36) = − 0.083; p = 0.934
Left AHS/Ch. 5/CA in ST	β = 0.000 (0.000); z (36) = − 1.922; p = 0.055	β = − 133.058 (117.670); z (36) = − 1.223; p = 0.222	β = 0.039; CI [− 0.022 to 0.198]	β = 0.001 (0.089); z (36) = − 0.202; p = 0.840
Right AHS/Ch. 5/CA in ST	β = 0.000 (0.000); z (36) = − 1.483; p = 0.138	β = − 136.131 (119.154); z (36) = − 1.262; p = 0.207	β = 0.030; CI [− 0.019 to 0.170]	β = − 0.006 (0.091); z (36) = − 0.410; p = 0.682
Left NHS/Ch. 5/CA in ST	β = − 0.007 (0.005); z (36) = − 1.609; p = 0.108	β = − 113.039 (115.465); z (36) = − 1.047; p = 0.295	β = 0.737; CI [− 0.752 to 4.501]	β = 0.912 (1.683); z (36) = 0.520; p = 0.603
Right NHS/Ch. 5/CA in ST	β = − 0.005 (0.005); z (36) = − 1.400; p = 0.161	β = − 117.697 (117.911); z (36) = − 1.064; p = 0.287	β = 0.568; CI [− 0.669 to 3.706]	β = 0.691 (1.649); z (36) = − 0.345; p = 0.730
Left AHS/Ch. 7/RT in ST	*β = 0.000 (0.000); z (38) = − 2.180; p = 0.029*	β = 4.306 (11.759); z (38) = 0.416; p = 0.677	β = − 0.001; CI [− 0.009 to 0.006]	β = − 0.005 (0.004); z (38) = − 1.147; p = 0.251
Left NHS/Ch. 7/RT in ST	β = − 0.005 (0.004); z (38) = − 1.841; p = 0.066	β = 5.213 (7.642); z (38) = 0.739; p = 0.460	β = − 0.026; CI [− 0.174 to 0.070]	β = − 0.091 (0.065); z (38) = − 1.507; p = 0.132
Left AHS/Ch. 14/CA in ST	β = 0.000 (0.000); z (38) = − 1.535; p = 0.125	*β = − 160.626 (75.764); z (38) = − 2.060; p = 0.039*	β = 0.065; CI [− 0.008 to 0.262]	β = 0.015 (0.072); z (38) = 0.237; p = 0.813
Left NHS/Ch. 14/CA in ST	β = − 0.007 (0.007); z (38) = − 1.327; p = 0.185	*β = − 154.613 (75.744); z (38) = − 1.994; p = 0.046*	β = 1.151; CI [− 0.384 to 5.134]	β = 0.945 (1.521); z (38) = 0.851; p = 0.395

Significant paths are presented in italic

AHS absolute handgrip strength, *CA in ST* percentage of correct answers in Sternberg task, *Ch.* channel, *CI* 95% confidence intervals, *deoxyHb* deoxygenated haemoglobin, *NHS* normalized handgrip strength (normalized to body-mass-index), *RT* reaction time in Sternberg task, *ST* Sternberg task

positive neurobiobehavioural relationship between cortical hemodynamics and cognitive performance.

Furthermore, we noticed that a higher level of handgrip strength is linked to a higher level of cortical activation (objectified by higher level of oxyHb and lower levels of deoxyHb) in distinct parts of the PFC (see Tables 2 and 3). In the literature, it was observed that a higher level of cardiorespiratory fitness is positively correlated with the magnitude of the oxyHb in the PFC in older adults [112] and negatively correlated with magnitude of deoxyHb in right and left PFC in younger adults [113]. Consequently, our finding supports the general notion that a certain level of muscular strength (e.g., achieved by a regular resistance training) is beneficial for brain health (e.g., cortical hemodynamics) in younger adults [1, 2]. Whether a training-induced increase in (handgrip) strength of younger adults can improve brain health remains speculative because the majority of the available studies in this field of research has focused on older adults [1–3]. By saying that, there is also some evidence available suggesting that training interventions have a limited ability to change measures of handgrip strength in adults [114, 115] although this finding is not universal [116]. Moreover, it is hypothesized that baseline values of (handgrip) strength (e.g., obtained prior to a resistance training) might be a more appropriate indicator regarding health-related outcomes as compared to training-induced changes [117, 118]. Hence, the practical implications of our findings are currently not fully clear which, in turn, calls for further research broaden our knowledge in this direction.

We did not find statistical indices providing compelling evidence that in our cohort of younger adults measures of cortical hemodynamics mediate the relationship between handgrip strength and cognitive performance (see Table 4). The absence of a mediation effect could be related to the absence of a significant correlation between measures of handgrip strength and cognitive performance. The lack of such a correlation contradicts the findings of a previous study [26]. Presumably, these contrary findings are related to the different cognitive tests which have been used. In the study of Choudhary et al. [26], a simple reaction time task was employed whereas we have probed short-term working memory performance with the Sternberg task [44, 45] which is well-established in the field of exercise-cognition science [119–124]. Hence, our findings suggest that handgrip strength is associated with measures of cortical hemodynamics, but that this

relationship might not strictly culminate in a superior cognitive performance, at least in our cohort of younger adults. In turn, the absence of a relationship between level of handgrip strength and cognitive functioning suggests that in younger adults, there might be other factors than the level of handgrip strength being important for superior cognitive performance.

Given that previous studies have reported that cortical hemodynamics (e.g., level of oxyHb) are a significant mediator of the relationship between cardiorespiratory fitness and cognition in older adults [30–32], it seems to be promising to investigate if measures of cortical hemodynamics mediate the relationship between handgrip strength and cognitive performance in a cohort of older individuals. This idea is supported by the findings suggesting an association between higher levels of handgrip strength and lesser cognitive decline in older age [12–18]. In this regard, it is also recommended that future studies should aim to assess further fitness dimensions (e.g., muscular fitness, cardiorespiratory fitness, and motor fitness) because it was observed that changes in different fitness dimensions influence the brain differently [125–127].

Limitations

Despite our presented findings are interesting, this study has limitations which warrant further discussion. Firstly, even if we have account for the confounding influence of superficial blood flow by a short-separation channel regression, it is recommended that future studies should consider to quantify additional physiological parameters (e.g., blood pressure, respiration rate, skin conductance) to assess the influence of systemic physiological changes more comprehensively (also referred to as 'systemic physiological augmented fNIRS' [128–133]) which, in turn, can reduce the risk of 'false positive' findings in fNIRS studies [80]. Secondly, although the sample size in the current study is in the range of comparable investigations [30], it is relatively small. In this context, it is also important to acknowledge that our findings are not generalizable because we only included young right-handed individuals in order to avoid laterality effects. Thirdly, we did not perform multiple comparison adjustments. However, there is an ongoing discussion about when and how it would be necessary to adjust for multiple comparisons [134–136] and it is stated that in exploratory studies, multiple comparison adjustments are not strictly required [135]. Fourthly, as the findings of our cross-sectional study are based on correlational analyses, it is not possible to derive strong (causal) conclusions. Cognizant of these limitations, further cross-sectional and interventional studies with a larger sample size are necessary to confirm (or rebut) our findings and to investigate whether those are generalizable to other cohorts (e.g., older adults without and with cognitive impairments).

Conclusion

In summary, our findings show promising evidence for a positive neurobehavioral relationship between cortical hemodynamics and cognitive performance. Moreover, we complement the existing literature by adding that in younger adults higher levels of handgrip strength are linked to more pronounced cortical hemodynamics which imply that muscular strength influences brain health positively. However, our work also showed that in younger adults such a positive effect on a parameter of brain health does not necessarily benefit cognitive performance as we did not find convincing evidence for a relationship between handgrip strength and cognitive performance or that cortical hemodynamics mediate this relationship. Considering that such relationships might change as function of age and disease, further research should aim to investigate whether our findings are also generalizable to different cohorts (e.g., older adults) and whether different fitness dimensions influence cognitive performance and cortical hemodynamics differently.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12868-021-00615-6.

Additional file 1: Table S1. Detailed overview of the probe placement which shows the exact position of the sources and detectors in the 10–20 EEG system, the MNI coordinates (X, Y, Z), the corresponding anatomical landmarks (e.g., dorsolateral prefrontal cortex) and the distance between sources and detectors. Please note that this output was generated by using the fOLD-software [68]

Abbreviations

AHS: Absolute handgrip strength; A.U.: Arbitrary unit; BA: Broadman area; bpm: Beats per minute; BDI-II: Becks Depression Inventory II; BMI: Body mass index; BSA-F: "Bewegungs- und Sportaktivitätsfragebogen"; CA: Correct answers; Ch.: Channel; CI: Confidence interval; cm: Centimeter; CRF: Cardiorespiratory fitness level; CV: Coefficient of variation; deoxyHb: Deoxygenated hemoglobin; DLPFC: Dorsolateral prefrontal cortex; EEG: Electroencephalography; EHI: Edinburgh Handedness Inventory; fNIRS: Functional near-infrared spectroscopy; fOLD: FNIRS Optodes' Location Decider; FPA: Frontopolar area; GLM: General linear model; HF: High frequency; HRF: Hemodynamic response function; IQR: Interquartile range; kg: Kilogram; LF: Low frequency; LSC: Long-separation channel; lt.: Left; MBLL: Modified Beer–Lambert law; md.: Middle; mm: Millimeter; NHS: Normalized handgrip strength; oxyHb: Oxygenated hemoglobin; PA: Physical activity; PE: Physical exercise; PFC: Prefrontal cortex; PSQI: Pittsburgh Sleep Quality Index; r_p: Partial correlation coefficient; RT: Reaction time; s: Seconds; SSC: Short-separation channels; ST: Sternberg task; TMT: Trail Making Test; VLF: Very low frequency; VO_{2max}: Maximal oxygen uptake.

Acknowledgements

We would like to thank all volunteers who have participated in this study.

Authors' contributions

Conceptualization: FH; methodology: FH; software: FH and TB; validation: FH and TB; formal analysis: FH; investigation; FH and TB; resources: NGM and LS;

data curation: FH and TB; writing—original draft: FH; writing—review and editing: FH, TB, AT, DH, NGM, and LS; visualization: FH; supervision: NGM and LS; project administration: FH and TB. All authors read and approved the final manuscript.

Funding
Open Access funding enabled and organized by Projekt DEAL.

Availability of data and materials
The public sharing of the data from this trial has been restricted by the local Research Ethics Committee in order to protect participants' privacy. Data are therefore only available on reasonable request from the corresponding author.

Ethics approval and consent to participate
The study was approved by the local ethics committee of the Medical Faculty of the Otto von Guericke University Magdeburg (181/18) and it was in accordance with the Declaration of Helsinki (1964). All participants were informed about the study procedures and provided written informed consent to participate.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
[1] Department of Neurology, Medical Faculty, Otto Von Guericke University, Leipziger Str. 44, 39120 Magdeburg, Germany. [2] Research Group Neuroprotection, German Center for Neurodegenerative Diseases (DZNE), Leipziger Str. 44, 39120 Magdeburg, Germany. [3] Institute III, Department of Sport Science, Otto Von Guericke University Magdeburg, Zschokkestr. 32, 39104 Magdeburg, Germany. [4] Center for Behavioral Brain Sciences (CBBS), Brenneckestraße 6, 39118 Magdeburg, Germany.

Received: 16 June 2020 Accepted: 1 February 2021
Published online: 15 February 2021

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Brief Report

A Link between Handgrip Strength and Executive Functioning: A Cross-Sectional Study in Older Adults with Mild Cognitive Impairment and Healthy Controls

Fabian Herold [1,2,*], Berit K. Labott [1,3], Bernhard Grässler [3], Nicole Halfpaap [3], Corinna Langhans [3], Patrick Müller [1,4], Achraf Ammar [3], Milos Dordevic [1,2,4], Anita Hökelmann [3] and Notger G. Müller [1,2,4,5]

1 Department of Neurology, Medical Faculty, Otto von Guericke University, 39120 Magdeburg, Germany; berit.labott@med.ovgu.de (B.K.L.); patrick.mueller@dzne.de (P.M.); milos.dordevic@dzne.de (M.D.); notger.mueller@uni-potsdam.de (N.G.M.)
2 Research Group Degenerative and Chronic Diseases, Movement, Faculty of Health Sciences Brandenburg, University of Potsdam, 14476 Potsdam, Germany
3 Institute III, Department of Sport Science, Otto von Guericke University Magdeburg, 39104 Magdeburg, Germany; bernhard.graessler@ovgu.de (B.G.); nicole.halfpaap@ovgu.de (N.H.); corinna.langhans@ovgu.de (C.L.); achraf1.ammar@ovgu.de (A.A.); anita.hoekelmann@ovgu.de (A.H.)
4 Research Group Neuroprotection, German Center for Neurodegenerative Diseases (DZNE), 39120 Magdeburg, Germany
5 Center for Behavioral Brain Sciences (CBBS), 39118 Magdeburg, Germany
* Correspondence: fabian.herold@fgw-brandenburg.de

Citation: Herold, F.; Labott, B.K.; Grässler, B.; Halfpaap, N.; Langhans, C.; Müller, P.; Ammar, A.; Dordevic, M.; Hökelmann, A.; Müller, N.G. A Link between Handgrip Strength and Executive Functioning: A Cross-Sectional Study in Older Adults with Mild Cognitive Impairment and Healthy Controls. *Healthcare* **2022**, *10*, 230. https://doi.org/10.3390/healthcare10020230

Academic Editors: Rafał Stemplewski and Janusz Maciaszek

Received: 1 December 2021
Accepted: 21 January 2022
Published: 26 January 2022

Abstract: Older adults with amnestic mild cognitive impairment (aMCI) who in addition to their memory deficits also suffer from frontal-executive dysfunctions have a higher risk of developing dementia later in their lives than older adults with aMCI without executive deficits and older adults with non-amnestic MCI (naMCI). Handgrip strength (HGS) is also correlated with the risk of cognitive decline in the elderly. Hence, the current study aimed to investigate the associations between HGS and executive functioning in individuals with aMCI, naMCI and healthy controls. Older, right-handed adults with amnestic MCI (aMCI), non-amnestic MCI (naMCI), and healthy controls (HC) conducted a handgrip strength measurement via a handheld dynamometer. Executive functions were assessed with the Trail Making Test (TMT A&B). Normalized handgrip strength (nHGS, normalized to Body Mass Index (BMI)) was calculated and its associations with executive functions (operationalized through z-scores of TMT B/A ratio) were investigated through partial correlation analyses (i.e., accounting for age, sex, and severity of depressive symptoms). A positive and low-to-moderate correlation between right nHGS (rp (22) = 0.364; $p = 0.063$) and left nHGS (rp (22) = 0.420; $p = 0.037$) and executive functioning in older adults with aMCI but not in naMCI or HC was observed. Our results suggest that higher levels of nHGS are linked to better executive functioning in aMCI but not naMCI and HC. This relationship is perhaps driven by alterations in the integrity of the hippocampal-prefrontal network occurring in older adults with aMCI. Further research is needed to provide empirical evidence for this assumption.

Keywords: MCI; hippocampal-prefrontal network; handgrip strength; exercise cognition; aging; brain health

1. Introduction

Handgrip strength was found to be an important marker of health in general [1–4] and brain health in particular [5–7]. Indeed, a stronger handgrip has been linked to superior cognitive performance in younger adults [8], in middle-aged adults [9], and in older adults [10–18]. Furthermore, in older adults, higher levels of handgrip strength are associated with lesser cognitive decline during aging [19–26]. In sum, these studies suggest that a relationship between measures of handgrip strength and cognitive performance

exists. Hence, handgrip strength may be a clinically useful marker to identify individuals at high risk of developing mild cognitive impairment (MCI) [27,28], and/or dementia (e.g., Alzheimer's Disease) [29,30].

However, the majority of the mentioned studies used rather global measures of cognitive performance (e.g., Mini-Mental State Examination (MMSE)) [19,20,22,24–26] while the empirical evidence regarding the association of handgrip strength with specific cognitive domains (e.g., executive functions) is not exhaustive. Interestingly, there is some evidence that executive functions, especially task switching and cognitive flexibility, are compromised in older individuals with amnestic MCI (aMCI) [31–33]. Importantly, older adults with aMCI who in addition to their memory deficits suffer from a frontal-executive dysfunction have a higher risk of developing dementia compared to older adults with aMCI with additional visuospatial or language dysfunction [34].

To allow a timely initiation of interventions aiming to lower the burdens of neurological disorders (e.g., dementia), an early identification of adults being at a high risk of developing them (e.g., older adults with aMCI and executive dysfunction) is mandatory. Notably, in the literature, the hypothesis that motoric measures (e.g., handgrip strength) and higher-order cognitive functions (e.g., executive functions) share a set of common neural substrates (e.g., frontal cortex, hippocampus) was proposed [5]. Accordingly, motoric measures (e.g., handgrip strength) might be a valuable and easily applicable parameter to identify adults at higher risk of developing neurological disorders such as MCI [27,28] and/or dementia [29,30]. In this context, and with regard to the idea of shared neural substrates, there is evidence in the literature (i) that the hippocampus is involved in memory and executive functions in adults [35–37] and (ii) that handgrip strength is related to the (right) hippocampal volume in healthy adults and in adults with a major depressive disorder [38]. These findings suggest that the hippocampus could be, among other brain structures such as the frontal cortex, a neural substrate that is shared by higher-order cognitive functions (i.e., executive functions) and motoric measures (i.e., handgrip strength). Moreover, there is evidence that the hippocampal volume is influenced by the subtype of MCI as it was observed that older adults with aMCI have a lower hippocampal volume as compared to older adults with naMCI [39]. Whether such a difference in the shared neural substrate (e.g., hippocampal volume) is also mirrored in behavioral performance (i.e., the relationship between measures of executive functions and handgrip strength) has not been extensively studied. Again, an early recognition of adults being at high risk of developing dementia (e.g., older adults with aMCI and executive dysfunction) is essential to initiate appropriate interventions, and thus the investigation of possible relationships between measures of handgrip strength and executive functioning in older adults with different subtypes of MCI is of great practical relevance. Hence, this study aims to investigate the relationships between measures of handgrip strength (i.e., assessed with a handheld dynamometer) and executive functioning (i.e., operationalized as performance in Trail Making Test (TMT)) in older adults with different subtypes of MCI (amnestic and non-amnestic) and healthy older adults. Based on the available evidence [10–16,19–25], we hypothesize that positive correlations between measures of HGS and executive functioning exist, and that the magnitude of the associations might be a function of the cognitive status of the older adults.

2. Materials and Methods

2.1. Participants

In the current study, older adults with aMCI, naMCI, and healthy controls (HC) were recruited as part of a larger project (MyFit study [40]) through advertisements in local newspapers, flyers, posters, word of mouth, and by using existing databases. After recruitment, the individuals were screened for eligibility based on the following inclusion criteria: (i) 50 to 80 years old, (ii) native German-speaking, and (iii) able to manage everyday activities independently. Individuals who had poor or uncorrected vision/hearing or color weakness/blindness, and/or suffer from (a) severe psychiatric disorders (e.g.,

bipolar disorder) or depression (assessed via the Geriatric Depression Scale (GDS; 15 items; cut-off score $\geq$ 6) [41]), (b) severe orthopaedic diseases (e.g., a bone fracture in last six months, herniated vertebral disc), (c) severe muscular diseases (e.g., myositis, tendovaginitis), (d) severe cardiovascular diseases (e.g., heart insufficiency), (e) severe endocrinologic diseases (e.g., manifest hypothyroidism or hyperthyroidism, insulin dependent diabetes mellitus type II, BMI > 30), (f) neurological diseases other than MCI (e.g., stroke, epilepsy, Multiple Sclerosis), (g) major injury or had major surgery in the last six months, and/or use neuroleptics, narcotic analgesics, benzodiazepines, or psychoactive medications, and/or consume illegal intoxicants and/or have an alcohol abuse, and (h) are pregnant were excluded.

As shown in Figure 1, three participants of the MCI groups and three participants of the HC group were excluded from the analysis due to the severity of depressive symptoms. Due to diseases of the hands, three participants from the MCI group were also excluded. Furthermore, only right-handers were included in the analysis who were determined by the short version (10 items) of the Edinburgh Handedness Inventory [42] (EHI; cut-off score $\geq$50 indicated right-handedness; <50 to >$-$50 indicate ambidextrous handedness; ≤ -50 indicated left-handedness [43]). Hence, due to left-handedness, six participants in the MCI groups and four participants in the HC group were excluded from the analysis (see Figure 1).

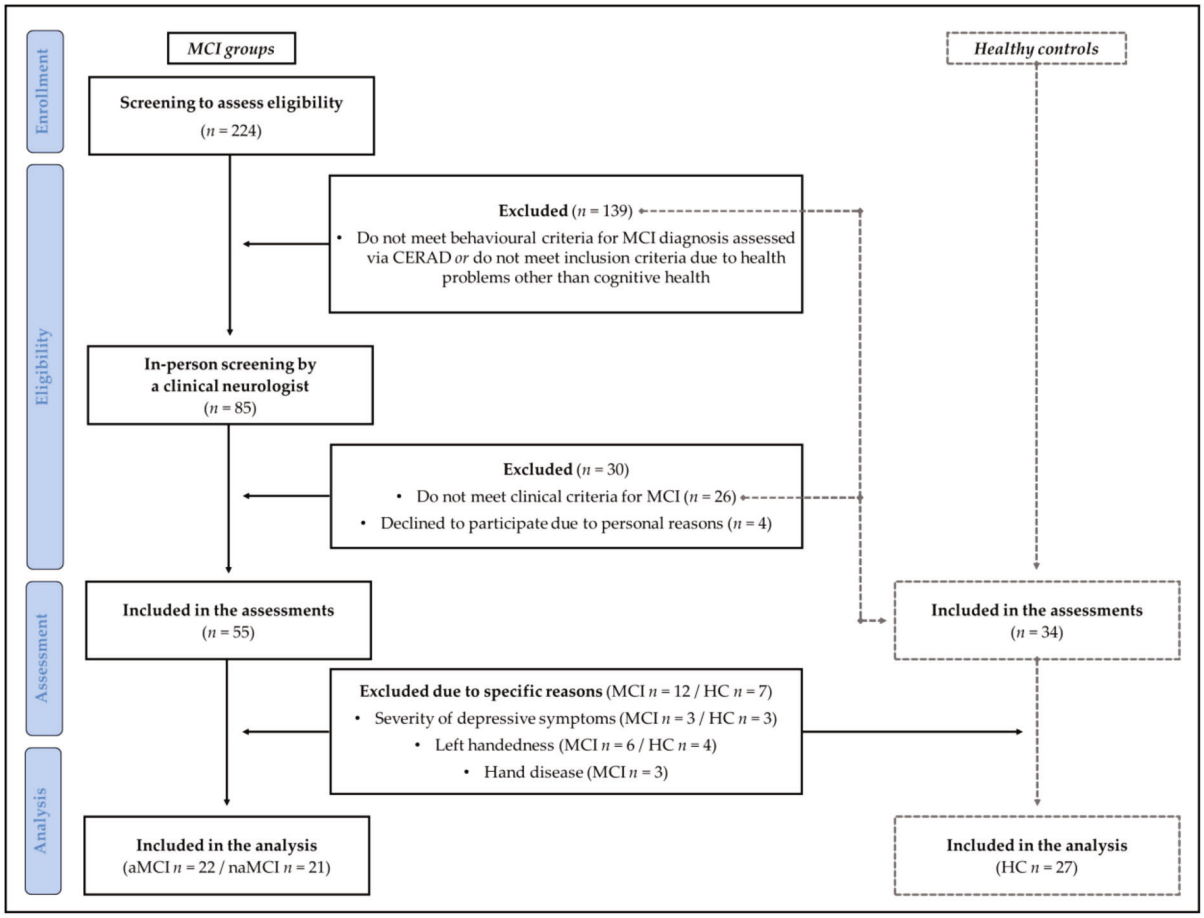

Figure 1. Flow diagram that schematically depicts the selection processes (from screening to assess eligibility to the final inclusion in the statistical analysis) and the reasons for exclusion. aMCI: amnestic mild cognitive impairment; CERAD: Alzheimer's Disease Consortium to Establish a Registry test battery; HC: healthy controls; naMCI: non-amnestic mild cognitive impairment.

To identify older adults with MCI the general recommendations of Winblad et al. [44] and Peterson et al. [45], who define MCI as cognitive performance below the age-appropriate level without symptoms indicating the presence of manifest dementia (DSM IV, ICD 10) were followed. Accordingly, individuals with MCI were characterized by (i) the preservation of basic activities of daily living and minimal impairment in complex instrumental functions, (ii) a self and/or informant-reported impairment on objective cognitive tasks, and/or (iii) evidence of decline over time on objective cognitive tasks [44]. To screen for these criteria, the Alzheimer's Disease Consortium to Establish a Registry (CEARD) Plus test battery was used [46] and mild cognitive impairment was operationalized by an under average performance (i.e., a performance below −1.5 SD in the age, sex, and education-adjusted z-value) in at least one subtest of the CEARD Plus test battery while minimum performance in the MMSE as part of the CERAD was set at 24 and above (to exclude cases of dementia) [47]. As recommended [44], participants meeting these criteria were referred to an experienced neurologist who verified (or refuted) the diagnosis of MCI. Furthermore, the neurologist performed a standard clinical examination thereby ensuring that handgrip strength was not influenced by diseases such as polyneuropathy or myopathy. Participants not meeting the clinical criteria of MCI were allocated to the HC group if they wanted to participate further (see Figure 1).

The performance (i.e., saving score) of the delayed recall trial of the Wordlist and Figure episodic memory test (included in the CERAD test battery) were used as criteria to differentiate between aMCI and naMCI. In accordance with the recommendations in the literature, participants with a performance below −1.5 SD in the age, sex, and education-adjusted z-value in at least one of these two cognitive subtests of the CERAD test battery were classified as aMCI [48]. Please note that this study is part of a larger project (MyFit study [40]) and in the current study we performed the analysis of selected and secondary outcome measures of this larger trial. Thus, no additional sample size calculation was performed as the available data of participants who had been recruited for the MyFit study were used (see reference [40] for more detailed information and sample size calculation of the MyFit study).

2.2. Assessment of Cognitive Performance and Handgrip Strength

As the data presented in this study were collected in the context of a larger project (MyFit project [40]), the participants were asked to visit our laboratory several times as described elsewhere [40]. In this study, the parameters of interest were executive functioning (assessed via Trail Making Test) and handgrip strength (assessed with a handheld dynamometer (Trailite TL-LSC100, LiteXpress GmbH, Ahaus, Germany), and thus only these measures are reported in more detail.

The Trail Making Test (TMT A and B) is part of the CERAD Plus test battery. It was conducted as described in [49]. While the TMT A probes visual search performance, the TMT B assesses cognitive flexibility [50–52]. In TMT A, a series of 25 encircled numbers has to be connected in ascending order [50,53]. In TMT B, 25 encircled numbers and letters have to be connected in an alternating and ascending order (e.g., 1 with A, then 2, then B) [50,53]. With respect to the aim of our study, the performance measures of TMT A and TMT B (time needed to complete the task) were used to calculate the ratio (TMT B/A) as a measure of the individual shifting ability [54,55]. This ratio was proposed to reflect executive functioning better than other performance measures obtained via the TMT (e.g., time to complete TMT A) [49,56].

Maximal handgrip strength was assessed based on the Southampton protocol [57]. The participants (i) were seated in a comfortable chair with their feet flat on the ground, (ii) were advised to adduct their shoulders and remain them neutrally rotated, (iii) were asked to flex the elbow of the tested extremity at 90° while maintaining a neutral wrist position (i.e., thumb facing upward), and (iv) were asked to squeeze the hand as hard as they could for three seconds to assess their handgrip strength [57]. Each participant conducted three trials for each hand and was asked to change the hand after performing one trial [58–60]. The

best trial (i.e., the trial with the highest absolute handgrip strength) of three trials of each extremity side was used to calculate the normalized handgrip strength. Maximal handgrip strength was normalized to the body mass index (BMI) of the participants to account for the influence of anthropometric factors (e.g., body mass and body height) as carried out in [58,59]. The normalized handgrip strength (nHGS) for each hand was calculated as follows: normalized handgrip strength (nHGS) = absolute handgrip strength (in kg)/BMI (in kg/m^2) [58,59,61]. The nHGS was used for further statistical analysis.

Prior to the assessment, participants were briefed about the experimental procedure and informed of possible risks and benefits associated with the study. All participants provided written consent to participate and received financial compensation. All study procedures were in accordance with the latest version of the Declaration of Helsinki, had been approved by the local Ethics Committee of the Medical Faculty of the Otto von Guericke University Magdeburg (reference number: 83/19) and were pre-registered in ClinicalTrials.gov (NCT04427436 on the 10 June 2020).

2.3. Statistical Analysis

The statistical analysis was performed using JAMOVI (version 2.2.2 current) [62]. Non-parametric tests (i.e., Kruskal–Wallis and Dwass–Steel–Critchlow–Fligner (as post-hoc tests)) were applied to compare MCI groups and HC group concerning age, body height, body mass, BMI, educational level, GDS, nHGS (left and right), and TMT performance (operationalized through z-score of TMT B/A ratio). With regard to the Kruskal–Wallis test, epsilon square (ε^2) was calculated as a measure of effect size and rated as follows: $\geq$0.01 to <0.6: small effect; $\geq$0.06 to <0.14: medium effect; $\geq$0.14: large effect [63].

Non-parametric partial correlation coefficients (i.e., Spearman's rho [r_p]; accounting for age, sex, and severity of depressive symptoms) were calculated to investigate possible relationships between executive functions and nHGS. Furthermore, the GDS score was used as a covariate since a relationship between measures of HGS and severity of depressive symptoms was reported in older adults [64]. Based on previous studies [10–16,19–25], one-tailed significance tests were used for the correlational analyses as a positive relationship between nHGS and executive functioning is assumed. The partial correlation coefficient r_p was rated as follows: <0.19: no correlation; $\geq$0.20 to $\leq$0.39: low correlation; $\geq$0.40 to $\leq$0.59: moderate correlation; $\geq$0.60 to $\leq$0.79: moderately high correlation; $\geq$0.8: high correlation [65,66].

In addition, the cocor package (one-tailed significance test) was used to compare the correlation coefficients between older adults with aMCI, naMCI, and HC [67].

For all statistical tests, the level of significance was set to $\alpha = 0.05$.

3. Results

The general characteristics of the participants are shown in Table 1 (see also Table S1 in the Supplementary Material for further information). We observed a significant effect of group concerning body height (χ^2 (df = 2; n_{aMCI} = 22, n_{naMCI} = 21, n_{HC} = 27) = 10.547, p = 0.005, ε^2 = 0.153), body mass (χ^2 (df = 2; n_{aMCI} = 22, n_{naMCI} = 21, n_{HC} = 27) = 6.446, p = 0.040, ε^2 = 0.093), GDS (χ^2 (df = 2; n_{aMCI} = 22, n_{aMCI} = 21, n_{HC} = 27) = 6.975, p = 0.031, ε^2 = 0.101) and MMSE (χ^2 (df = 2; n_{aMCI} = 22, n_{aMCI} = 21, n_{HC} = 27) = 23.700, $p \leq$ 0.001, ε^2 = 0.343). The post-hoc tests concerning body height show that aMCI (W (n_{aMCI}= 22, n_{HC} = 27) = −3.630, p = 0.028) and naMCI (W (n_{naMCI} = 21, n_{HC} = 27) = −4.063, p = 0.011) were taller than HC. However, the post-hoc tests concerning the comparison of the groups with respect to body mass did not reach statistical significance although the difference between naMCI and HC was marginally non-significant (W (n_{naMCI} = 21, n_{HC} = 27) = −3.310, p = 0.051).

Table 1. Overview of the general characteristics of the participants.

General Characteristics of the Participants	Median ± Interquartile Range (Minimum to Maximum)		
	aMCI (*n* = 22)	**naMCI (*n* = 21)**	**HC (*n* = 27)**
Female/Male (n)	14/8	9/12	19/8
Age (years)	69 ± 9 (60 to 81)	71 ± 8 (56 to 80)	68 ± 10 (54 to 83)
Body height (cm)	171.0 ± 11.0 * (150.0 to 184.0)	173.0 ± 13.0 # (159.0 to 189.0)	165.0 ± 9.5 (156.0 to 179.0)
Body mass (kg)	72.0 ± 15.0 (61.0 to 93.0)	77.0 ± 8.0 (54.4 to 94.4)	67.0 ± 22.5 (50.0 to 94.0)
BMI (kg/m^2)	24.1 ± 4.2 (20.9 to 29.1)	25.8 ± 1.6 (21.4 to 28.5)	24.7 ± 5.9 (19.3 to 31.0)
Educational level (years)	15 ± 4 (11 to 20)	15 ± 3 (11 to 18)	15 ± 3 (12 to 18)
GDS (total score)	1.5 ± 3.0 (0.0 to 4.0)	2.0 ± 2.0 # (0.0 to 5.0)	1.0 ± 1.5 (0.0 to 3.0)
EHI (score)	100.0 ± 23.3 (52.9 to 100.0)	100.0 ± 0.0 (73.3 to 100.0)	100.0 ± 21.1 (53.9 to 100.0)
nHGS left/right (a.u.)	1.05 ± 0.76/1.12 ± 0.62/ (0.75 to 2.24/0.78 to 2.03)	1.37 ± 0.51 [a]/1.43 ± 0.70 (0.84 to 2.20/0.79 to 2.23)	1.12 ± 0.33/1.21 ± 0.42 (0.47 to 1.75/0.66 to 1.89)
TMT B/A (z-score)	−0.18 ± 1.20 (−2.13 to 2.07))	−0.47 ± 0.89 (−1.43 to 1.76)	−0.32 ± 0.74 (−2.18 to 1.84)
MMSE (points)	27.0 ± 1.8 * (25.0 to 30.0)	27.0 ± 2.0 # (24.0 to 30.0)	28.0 ± 1.0 (27.0 to 30.0)

[a] Please note that values of nHGS left in the naMCI group were based on $n = 20$ since the data of one participant in the naMCI was not used to calculate median, interquartile range and minimum to maximum due to drop hand symptomatic in the left (non-dominant) hand. * indicates significant differences between aMCI and HC; # indicates significant differences between naMCI and HC. a.u.: arbitrary unit; BMI: Body Mass Index; EHI: Edinburgh Handedness Inventory (cut-off score ≥ 50 indicated right-handedness; <50 to >−50 indicate ambidextrous handedness; ≤−50 indicated left-handedness [43]); GDS: Geriatric Depression Scale (cut-off score ≥ 6 [41]); MMSE: Minimal Mental State Examination; nHGS: normalized handgrip strength; TMT: Trail Making Test.

With respect to GDS, the post-hoc tests show that the GDS score was higher in naMCI as compared to HC (W ($n_{naMCI} = 21$, $n_{HC} = 27$) = −3.780, $p = 0.021$). The post-hoc test concerning MMSE score revealed that aMCI (W ($n_{aMCI} = 22$, $n_{HC} = 27$) = 6.198, $p \leq 0.001$) and naMCI (W ($n_{naMCI} = 21$, $n_{HC} = 27$) = 5.457, $p \leq 0.001$) performed worse than HC but there was no difference between aMCI and naMCI (W ($n_{aMCI} = 22$, $n_{naMCI} = 21$) = −0.834, $p = 0.826$). No other between-group comparison was statistically significant (i.e., age, BMI, educational level, nHGS of left and right hand, and z-score of TMT B/A).

We observed a positive low-to-moderate correlation between left nHGS (r_p (22) = 0.420, $p = 0.037$) and right nHGS (r_p (22) = 0.364, $p = 0.063$) with executive functioning (i.e., operationalized via z-score of TMA B/A ratio) in the aMCI group (see Figure 2a). In addition, in aMCI, we did not observe a significant difference between the correlation coefficients of the left hand (i.e., reaching statistical significance) and the right hand (i.e., slightly missed to reach statistical significance) with executive functioning ($p > 0.05$) using the cocor package [67].

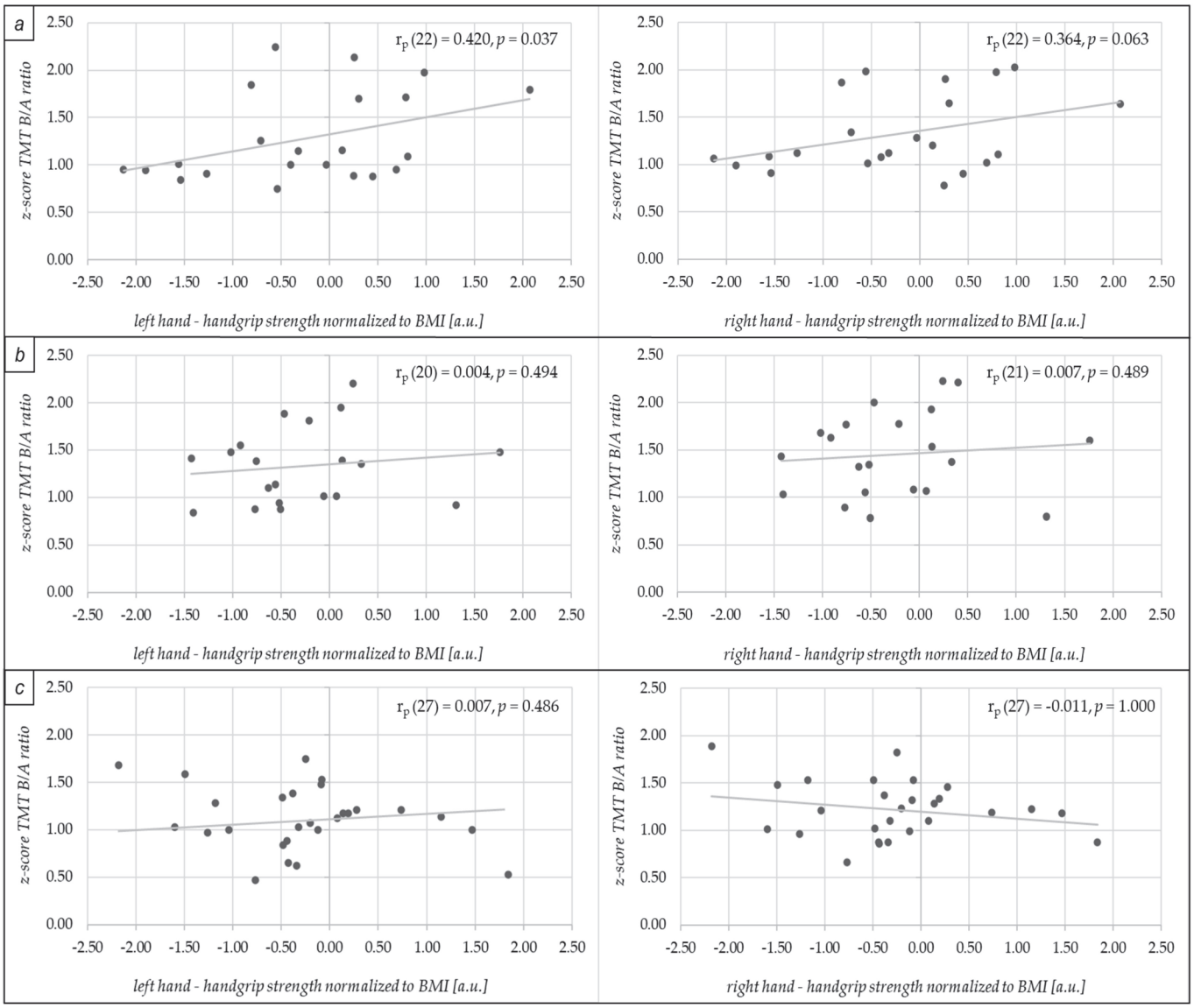

Figure 2. Scatter plots displaying the correlations between normalized handgrip strength (nHGS) of the left hand and right hand and z-scores of TMT B/A ratio (reflecting executive functioning) in the older individuals with amnestic mild cognitive impairment (aMCI) in (**a**), for older adults with non-amnestic mild cognitive impairment (naMCI) in (**b**) and healthy older controls (HC) in (**c**). The handgrip strength was normalized to the Body Mass Index to account for the influence of anthropometrics on handgrip strength [58,59]. a.u.: arbitrary unit; BMI: Body Mass Index; r_p: partial correlation coefficient (accounting for age, sex, and severity of depressive symptoms [via scores in Geriatric Depression Scale]); TMT: Trail Making Test.

As shown in Figure 2b,c, no significant correlations were observed between nHGS and executive functioning in the naMCI group (left nHGS (r_p (20) = 0.004, p = 0.494); right nHGS (r_p (21) = 0.007, p = 0.489)) and in the HC group (left nHGS (r_p (27) = 0.007; p = 0.486); right nHGS (r_p (27) = −0.011, p = 1.000)). Furthermore, there were no between-group differences with respect to the comparison of aMCI and naMCI concerning the correlation coefficients of left nHGS (z = 1.329, p = 0.092) and right nHGS (z = 1.139, p = 0.127) with executive functioning. Furthermore, no group differences between aMCI and HC were observed regarding the correlation coefficients of left nHGS (z = 1.435, p = 0.076) and right nHGS (z = 1.278, p = 0.101) with executive functioning. In addition, there were also no between-group differences with respect to the comparison of naMCI and HC concerning

the correlation coefficients of left nHGS (z = −0.010, $p = 0.496$) and right nHGS (z = 0.058, $p = 0.477$) with executive functioning.

4. Discussion

This study investigated possible links between measures of handgrip strength and executive functioning in older adults with different subtypes of MCI and HC. We observed that in aMCI, stronger nHGS was associated with better performance in executive functions (operationalized by the z-score of the TMT B/A ratio) but not in naMCI and/or in HC, although there were no between-group differences concerning the correlation coefficients. This observation is, at least partly, in line with previous studies reporting a comparable relationship between cognitive performance and handgrip strength in older adults with diabetes [68] and in older adults with MCI and dementia [69]. However, in the study of Hesseberg et al. [69], MCI patients were not further classified into amnestic or non-amnestic subtypes. Given that there are significant differences between older adults suffering from aMCI and naMCI (i) with respect to the conversion rates to dementia (i.e., conversion rate to AD is higher in aMCI as compared to naMCI [70,71]), (ii) with respect to brain changes (e.g., lower cortical thickness in entorhinal cortex, the fusiform gyrus, the precuneus and the isthmus of the cingulate gyrus [72] and hippocampal volume [39] in aMCI as compared to naMCI), and (iii) with respect to motoric measures (e.g., slower gait speed, especially in dual-task conditions, in aMCI as compared to naMCI [73]), a differentiation between different subtypes of MCI, as performed in this study, is favorable.

The absence of a correlation in the naMCI and HC group in the present study is perhaps related to the fact that in these groups the neural substrates that are important for handgrip strength and executive functioning (i.e., operationalized by TMT performance) are better preserved. In the literature, there is considerable evidence that executive functions in general [74,75], and the execution of TMT in particular [76–81], rely on the integrity of the prefrontal cortex (PFC). Accordingly, the absence of a correlation in the naMCI and HC groups might reflect that the PFC is (more) intact in these two groups.

Following this line of interpretation, the moderate and positive correlation in the aMCI group might indicate that integrity of the PFC is compromised in individuals with a relatively low handgrip strength whereas, vice versa, a relative high handgrip strength signifies better integrity of the PFC in aMCI. In line with this assumption, there is evidence that higher handgrip strength is linked to (i) more pronounced task-related cortical hemodynamics in the PFC in younger adults [60] and (ii) superior white matter integrity in the frontal cortex in older adults [82]. These findings suggest that higher handgrip strength is linked to better integrity of the frontal cortex although future research is needed to buttress this assumption empirically [60,83]. Notably, there is evidence that the integrity of the frontal cortex is compromised in individuals with aMCI encompassing (i) alterations in task-related PFC activation [84–86], (ii) changes in gray matter integrity in frontal brain areas [87], and (iii) cortical thinning in frontal brain areas [34] in older adults with aMCI compared to HC. Moreover, it was observed that brain alterations in the frontal cortex (e.g., in white matter) in older adults with MCI correlate with performance changes in executive functioning (e.g., TMT B) [88]. Thus, a higher nHGS in older adults with aMCI might reflect better preservation of these neural correlates (e.g., frontal cortex) in these individuals which, in turn, allows for better performance in tasks probing executive functioning (e.g., TMT B). This assumption nicely fits with the idea that handgrip strength shares specific neural correlates with higher-order cognitive functions (e.g., of the frontal cortex) [5] and with the evidence showing that in older adults with aMCI motoric measures (i.e., gait speed) are correlated with the grey matter volume of frontal cortical regions [89]. In this context, it seems reasonable to speculate that such associations are not only driven by changes in the PFC but rather by alterations of a complex hippocampal-prefrontal network given the evidence that the hippocampus is involved in executive functioning in adults [35–37] and that handgrip strength is related to the (right) hippocampal volume in healthy adults and in adults with a major depressive disorder [38]. Vice versa, there is also evidence that the PFC

is involved in memory processes (for review see [90,91]), which supports the idea that the relationship between measures of handgrip strength and executive functioning becomes evident especially in individuals with impaired memory function such as older adults with aMCI. However, future research is warranted to confirm this assumption empirically by applying neuroimaging techniques [60,83].

Given that individuals with aMCI, and especially those with executive dysfunctions [34,92,93], have a relatively high risk of developing AD [70,71,94–96], the difference in the association of nHGS and executive functioning between aMCI and naMCI could be of high clinical relevance (even if the comparison of those correlations did not reach statistical significance in this study), as it suggests that in individuals with aMCI a relatively high level of (handgrip) strength can indicate preserved executive functions and, therefore, a lower risk of conversion to dementia. Of course, the latter assumption needs to be verified in a long-term study.

In addition, we observed that the correlation between nHGS and executive functioning reached statistical significance concerning the left hand but not concerning the right hand (see also Figure 2a). However, given the finding (i) that there is no statistically significant difference between both correlation coefficients ($p > 0.05$) and (ii) that the correlation between nHGS of the right hand with executive functioning was close to reaching statistical significance ($p = 0.063$), this finding should not be overinterpreted. Although this cross-sectional study does not allow us to elucidate causal relationships underlying the association of handgrip strength and cognitive performance (i.e., executive functioning), our finding fits with the available evidence suggesting that resistance training can be a beneficial intervention strategy to improve brain structure and function in both healthy adults [83,97–100] and in older adults with MCI [101–103]. Based on our findings, future research should investigate whether older adults with different subtypes of MCI (e.g., aMCI vs. naMCI) would benefit differently from resistance training interventions.

In summary, our findings suggest that in older adults with aMCI, higher levels of nHGS are associated with a better performance in executive functioning. This relationship is possibly caused by alterations in brain networks that accompany aMCI such as the PFC (e.g., hippocampal-prefrontal network). However, to confirm these assumptions future studies are needed that investigate the associations between measures of handgrip strength, cognitive performance (e.g., executive functions), and their neural correlates (e.g., functional cortical hemodynamic changes in the PFC) [60,83].

5. Limitations

There are some limitations of the current study that need to be acknowledged. Firstly, the sample size was relatively small and only right-handed individuals were included in the analysis. Secondly, not all core components of executive functioning (e.g., inhibition and working memory) were assessed. Thirdly, no multiple comparison adjustments were performed. In this context, there is an ongoing discussion about when and how it is necessary to adjust for multiple comparisons [104–106] and it is stated that in exploratory studies, multiple comparison adjustments are not strictly required [105]. Hence, our findings should be interpreted cautiously, and further research with larger sample sizes is needed in order to confirm (or refute) our findings. Furthermore, additional research that considers changes on multiple levels of analysis (e.g., changes on molecular and cellular level, changes on functional and structural brain level, and socioemotional changes) is also necessary to deepen our knowledge about neurobiological mechanisms driving the relationships between measures of handgrip strength and cognitive performance [83].

6. Conclusions

The findings of the current study suggest that higher levels of nHGS are related to better executive functioning in aMCI but not in naMCI and in HC. Based on the available evidence, we hypothesize that this relationship may be driven by alterations in the integrity

of the hippocampal-prefrontal network occurring in older adults with aMCI. However, further research is needed to provide direct empirical evidence for this assumption.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/healthcare10020230/s1, Table S1: Overview of the general characteristics of the participants.

Author Contributions: Conceptualization: F.H., B.G., M.D., C.L., N.H., A.H. and N.G.M.; methodology: F.H.; software: F.H.; validation: F.H.; formal analysis: F.H.; investigation: F.H., B.K.L., B.G., C.L. and N.H.; resources: A.H. and N.G.M.; data curation; F.H., B.K.L. and N.H.; writing—original draft: F.H.; writing—review and editing: F.H., B.K.L., B.G., C.L., N.H., P.M., A.A., M.D., A.H. and N.G.M.; visualization: F.H.; supervision: N.G.M.; project administration: F.H., B.K.L., B.G., C.L., N.H., A.H. and N.G.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research was supported by joint project "Autonomy in Old Age" (AiA) funded by the European Regional Development Fund (grant number: ZS/2018/08/94206 and grant number: ZS/2019/07/99755). The authors are solely responsible for the work and the funders had no role in the preparation of the manuscript, the analysis of the studies, and the decision to publish.

Institutional Review Board Statement: This study was approved by the local ethics committee of the Medical Faculty of the Otto von Guericke University Magdeburg (MD083/19), was prospectively registered (NCT04427436), and was conducted in accordance with principles stated in the latest version of the Declaration of Helsinki.

Informed Consent Statement: We informed all participants about the study procedures, and they gave written informed consent to participate.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available in order to protect participants' privacy.

Acknowledgments: We would like to thank all volunteers who have participated in this study. Furthermore, we acknowledge the financial support for the Article Processing Charges provided by Deutsche Forschungsgemeinschaft (DFG, German Research Foundation)—grant number 491466077.

Conflicts of Interest: The authors declare no conflict of interest.

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