Cerebral changes improved by physical activity during cognitive decline: A systematic review on MRI studies

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\textbf{ABSTRACT}

Current treatment in late-life cognitive impairment and dementia is still limited, and there is no cure for brain tissue degeneration or reversal of cognitive decline. Physical activity represents a promising non-pharmacological interventional approach in many diseases causing cognitive impairment, but its effect on brain integrity is still largely unknown. Especially research of cerebral alterations in disease state that goes beyond observations of clinical improvement is crucial to understand disease processes and possible effective treatments. In this systematic review, we address the question how physical activity and fitness in mild cognitive impairment (MCI) and Alzheimer's disease (AD) influences brain architecture compared to cognitively healthy elderly. We review both interventional studies comprising aerobic, coordinative and resistance exercises and observational studies on fitness and physical activity combined with Magnetic Resonance imaging (MRI). Different MRI approaches were included such as volumetric and structural analyses, Diffusion Tensor Imaging (DTI), functional MRI and Cerebral Blood Flow (CBF). We evaluate MRI results for different exercise modalities and performed a methodological evaluation of interventional studies in cognitive decline compared to normal aging. According to our results, among 12 interventions in AD/MCI, aerobic exercise is most frequently applied (9 studies). Interventions in AD/MCI altogether reveal a higher methodological quality compared to interventions in healthy elderly (8.33 ± 2.19 vs. 6.25 ± 2.36 out of 13 points), with most frequent missing aspects related to descriptions of complications, lack of intention-to-treat and statistical power analyses. Effects of aerobic exercise and fitness seem to mainly impact brain structures sensitive to neurodegeneration, which especially comprise frontal, temporal and parietal regions, such as the hippocampal/parahippocampal region, precuneus, anterior cingulate and prefrontal cortex, which are reported by several studies. General fitness measured via an objective fitness assessment and questionnaires seems to have a more global cerebral effect, probably due to its long-term application, whereas distinct intervention effects of durations between 3 and 6 months seem to concentrate on more local brain regions as the hippocampus, which can also be influenced by region of interest analyses. There is still a lack of evidence on other or combined types of intervention modalities, such as resistance, coordinative as well as multicomponent exercise during cognitive decline, and complex interventions as dancing. Future research should examine their beneficial effect on brain integrity, since several non-MRI studies already point to their advantageous impact. As a further future prospect, combination and application of newly developed imaging methods such as metabolic imaging should be envisaged to understand physical activity and its cerebral influence under its many-sided facets.

\section{1. Introduction}

In our growing elderly population, Alzheimer's disease (AD) is the central form of dementia with a massive socio-economic impact, representing one of the most expensive diseases for our health systems (Gustavsson et al., 2011). Despite being highly relevant for our society,
medical treatment for preventing cognitive decline is still sparse (Moniz-Cook et al., 2011). Therefore, alternative forms of treatment, which can be well implemented in patients' daily routine, are gaining the attention of current research. In this context, physical activity is a viable promising low-cost, low-risk, individual and widely available option, which is already known for its reduction impact in health risks, such as cardiovascular diseases, cancer and mental health problems (Nelson et al., 2007). Accordingly, beneficial effects of exercise and fitness on cognition and brain structure have also been described and offer a promising tool for preventing cognitive decline during the aging process (Van Der Borght et al., 2009; Eadie et al., 2005; Kronenberg et al., 2003; Van Praag et al., 1999; Redila et al., 2006; Norton et al., 2014). Several randomized controlled trials (RCTs) in young, as well as elderly, healthy humans showed that physical exercise lead to an improvement in cognition, especially in spatial and executive functioning (Gates et al., 2013; Hess et al., 2014; Zheng et al., 2016). Some studies also report a reduced risk of development of dementia (Burns et al., 2008; Lautenschlager et al., 2012; 2008; Ngandu et al., 2015; Tolppanen et al., 2015; Vidoni et al., 2012b). There are further indications that physical activity might slow down progression of dementia and that cardiorespiratory fitness can help reducing the detrimental effects of cerebral amyloid on cognition in AD (Schultz, 2015) and could decrease the amount of amyloid beta 1–42 in cerebrospinal fluid (CSF) (Baker et al., 2010).

Despite such evidence of the advantageous effect of exercise in many aspects, the structural changes at the cerebral level in neurodegenerative diseases are still poorly understood, especially when comparing to cognitively healthy older adults. This understanding, however, is crucial for offering an optimized treatment adapted to disease state. In this context, MRI represents a neuroimaging tool, easy to implement in clinical routine, to further examine alterations on brain level corresponding to cognitive improvements in neurodegenerative disease. Next to structural changes, such as regional volume alterations, MRI can further serve to detect functional alterations, network shifting and even metabolic alterations in neurodegenerative disease progression (Reetz et al., 2012; Romanzetti et al., 2014). It is also able to monitor intervention effects (Hohenfeld et al., 2017) and disease progression, which makes it a most valuable biomarker. So far, longitudinal MRI studies on MCI have shown that initial degeneration focusses on substructures of the temporal lobe, spreading to the parietal lobe and finally extending to frontal lobe regions when converting to AD (Chételat et al., 2005; Whitwell et al., 2007). Recent findings via diffusion-tensor-imaging (DTI) have proved that not only gray matter, but also white matter is affected in MCI and AD, leading to changes in the connections of hippocampus (Fellgiebel et al., 2004; 2005), posterior cingulum (Fellgiebel et al., 2004; Medina et al., 2006), thalamus (Rose, 2006) and regions in the posterior white matter in MCI, also correlating with cognitive impairment. In functional MRI (fMRI) studies on MCI, there have been several discrepant results. On the one hand, studies showed decreased activity in the medial temporal lobe (MTL) in AD and their genetic-at-risk population (Johnson et al., 2006; Machulda et al., 2003; Mondadori et al., 2007; Petrella et al., 2006; Ringman and Coppola, 2013). On the other hand, other studies reported an increase of activity in temporal regions, especially in very early MCI (Kircher et al., 2007; Lenzi et al., 2011), which is discussed as a possible compensatory increase of activity brain response, reflecting recruitment of supplementary neural resources to counteract the effects of AD pathology, or could in contrary, as indicated in a pharmacological intervention study, represent a dysfunctional condition (Bakker et al., 2012).

When taking these described brain alterations into account, several relevant questions arise when considering the effects of physical exercise on brain integrity in MCI/AD: What is the specific effect of physical exercise on the brain? Are only certain brain regions/networks responsive to physical activity, regions which are mainly affected by disease state, as described above? The aim of this systematic review is to give an overview of studies examining the brain changes detectable by MRI after physical exercise intervention of individuals with MCI and/or AD, which may support planning of future interventional studies. In the first section of this review, we describe our search methods. In a second part, we rate the quality of RCTs according to criteria from the Cochrane Library, the PEDro Scale and the Evidence-based Medicine Working Group (Forbes et al., 2008; Guyatt et al., 1993, 1994; Liu and Latham, 2009; Maher et al., 2003) introduced by Pitkälä et al., 2013. We additionally visualize the rating results, ordered by interventions, and compare cerebral changes induced by exercise between cognitively healthy older adults and patients with cognitive impairment. Finally, we discuss potential study designs and provide an outlook of future work.

2. Materials and methods

2.1. Search methods

A comprehensive search of PubMed database (https://www.ncbi.nlm.nih.gov/pubmed/) was performed from inception to and including October 2018. Reference lists of included articles and author's personal libraries were manually searched for further publications. Only articles in English were selected. The following search term composed of the relevant keywords was used for search: (“MCI” OR “Alzheimer” OR “Dementia” OR “Cognitive impairment”) AND (“Fitness” OR “Exercise” OR “Physical activity”) AND “MRI”. For comparison purposes, studies including older subjects were selected via keywords “MRI” AND (“Exercise” OR (“Fitness” OR “Fitness”) AND (“Age” OR “Elderly”) and were further searched manually in reference lists and authors' libraries. The main focus on this review lies on cerebral alterations induced by physical exercise in disease state. Studies were included when (1) the state of fitness and physical activity of subjects were examined via objective techniques or via questionnaires or via interventions, such as aerobic, resistance, coordinative training/multicomponent exercise, in (2) individuals with MCI and/or AD. We included studies where (3) MRI was performed to detect changes in cerebral structures, comprising studies using structural MRI with Voxel-based-morphometry (VBM) or similar volume analyses and cortical thickness, functional MRI and resting state MRI and connectivity analyses via DTI and cerebral blood flow (CBF). We further report on cognitive outcomes. We excluded interventions relying on specific sport arts (e.g. yoga, Thai Chi) and interventions, such as dancing, which represents a complex combination of activity, music involvement, interaction with a partner and cognition. This was done to facilitate interpretation and comparability of induced MRI alterations. We further excluded studies on vascular dementia/vascular alterations and other neurodegenerative diseases. Randomized, non-randomized controlled, and cohort study designs were included. The review was structured according to PRISMA (preferred reporting items for systematic reviews and meta-analyses) recommendations (http://www.prisma-statement.org/). A schematic flow chart of the inclusion process is given in Fig. 1.

2.2. Methodological quality

We performed an evaluation of the methodological quality of the studies using a modified rating system established by Pitkälä et al., 2013. This rating system combines criteria for randomized intervention trials developed by the Cochrane library modified by Cochrane collaborators (Forbes et al., 2008; Liu and Latham, 2009), as well as the PEDro scale, which is a tool for evaluating the methodological quality of clinical trials related to physiotherapy (Maher et al., 2003) and criteria developed by the Evidence-based Medicine Working Group (Guyatt et al., 1993, 1994). Criteria are listed according to Pitkälä and colleagues in Table 1. Each criterion represents one point. If the study fulfills only parts of the criterion or one criterion is not reported in the manuscript, zero points are given. Classification into high, medium and low quality was performed using the total rating score (high quality:
2.3. Comparison of cerebral alterations in patients Versus older adults

For a determination and comparison between groups and studies of the impact of physical activity and fitness on MCI and AD, anatomical masks of brain regions, flagged as significantly associated with exercise and fitness, using a threshold of \( p < 0.05 \), were selected from the wu-pickatlas toolbox for SPM (version 3.0.4) (Maldjian et al., 2003) and illustrated accounting for methodological quality in intervention studies or for sample size in non-intervention studies. Only studies presenting data on regional volume and/or cortical thickness were included to facilitate direct comparison between studies and subject populations. Results are reported in the results section for the different physical activity modalities. Comparisons were calculated between intervention studies, objective fitness assessment and questionnaires about physical activity. Cerebral sub-regions of superordinate brain regions affected by exercise are illustrated in respect to sample sizes and reported frequency of occurrence.

3. Results

From our literature search, a total of 23 MRI studies on physical activity and cognitive decline met inclusion criteria (Tables 3, 4, Supplementary Table 5, 6). Thirteen studies report on participants with MCI, 8 studies on participants with early AD and one study on participants with subjective memory loss. One study included both participants with AD and MCI (Raji et al., 2016). There were twelve intervention studies of different durations (range 3–6 months) and frequency (range 2–5 sessions per week). Among the intervention studies, 9 studies applied aerobic exercise, 2 applied resistance training, one applied a multicomponent exercise (Fig. 2). From the studies with aerobic exercise, two studies used combined interventions with cognitive stimulation (Anderson-Hanley et al., 2018; Köbe et al., 2016) and additional nutritional supplementation (Köbe et al., 2016). Suo et al., 2016, used a combination of progressive resistance training and cognitive stimulation. Two publications were categorized together since they examined the same sample (Frederiksen et al., 2018; van der Kleij et al., 2018). There were three publications performing analyses from the same sample pool (Chirles et al., 2017; Reiter et al., 2015; Smith et al., 2013) and Nagamatsu, 2012 and Ten Brinke et al., 2015, performed analyses from the same intervention.

Aside from intervention studies, observational studies applying objective evaluations of fitness levels were also included. In this context, objective measurement of peak VO\(_2\) consumption is a widespread technique. It represents the oxygen uptake during peak exercise (such as on a treadmill) and was used in seven of the studies in cognitive impairment. In one study, fitness was assessed by wearing a triaxial accelerometer for 2 weeks (Makizako et al., 2015).

There were three studies using questionnaires to measure physical activity, either using the Minnesota Leisure Time Physical Activity (MLTPA) questionnaire (Braskie et al., 2014; Raji et al., 2016), or the Stanford Brief Activity Survey (SBAS) (Smith et al., 2011a).

3.1. Methodological quality

Methodological quality was rated for all intervention studies (Table 2). Quality of studies in cognitive decline mostly ranged between moderate and high values. Among the most frequent missing points was the lack of description on complications during intervention, missing intention-to-treat analyses and lack of statistical power analyses and description. From all intervention studies in disease state, Suzuki et al., 2013 had the highest sample size with MRI (n = 100) in their multicomponent exercise intervention, followed by Morris et al., 2017 with 68 participants undergoing MRI in an aerobic exercise intervention, with both studies being of high methodological quality. When comparing studies on cognitive decline.
with studies on cognitively healthy elderly via students’ t-test, the quality was higher in the patients’ group (t(30) = 2.48; p = 0.019; 8.33 ± 2.19 points vs. 6.25 ± 2.36 points), primarily considering missing descriptions of randomization and blinding, description of complications during intervention, dropouts and statistical power analyses. When comparing intervention studies using aerobic exercise, which represented the majority, the higher methodological quality of studies in cognitive decline compared to healthy controls became even more prominent (t(21) = 3.95; p = 0.00073, 8.33 ± 1.87 points vs. 5.33 ± 1.69 points).

3.2. MRI results by type of intervention in interventional studies

3.2.1. MRI results induced by aerobic exercise

There are nine intervention studies using aerobic exercise as intervention (Table 3). One of the central regions of interest (ROI) targeted in these studies is the hippocampus, as a structure which is early affected in AD. One study reported a direct increase in hippocampal volume in a group of MCI after 6 months intervention of aerobic exercise (Ten Brinke et al., 2015), which was not observed in their resistance training part, though. Two other studies found no direct hippocampal increase after intervention but detected an association between fitness increase and exercise load with hippocampal volume in AD (Morris et al., 2017; Frederiksen et al., 2018 and van der Kleij et al., 2018). The latter study further examined hippocampal CBF and did not find an increase of CBF induced by their 16-week aerobic exercise intervention. In contrast to their findings, Burdette et al., 2010, in a very small sample with subjective cognitive impairment (SCI), detected an increase of CBF in hippocampus and even a stronger connectivity between hippocampus and anterior cingulate. The authors interpreted the increase of connectivity between these two regions as a possible neuropsychological change in executive processes, as the anterior cingulate cortex (ACC) is involved in episodic memory tasks requiring cognitive control (de Chastelaine et al., 2007; Kompus et al., 2009; Fleck et al., 2006). Unfortunately, no corresponding cognitive outcomes are reported in these studies.

However, not only the hippocampus seems to be related to fitness effects: In a 12-week treadmill walking program by Reiter et al., 2015, 14 individuals with MCI and 15 controls demonstrated a significant association between changes in fitness and cortical thickness in several mainly parietal regions. MCI subjects showed even stronger effects in the left insula and left superior temporal gyrus compared to the healthy controls. A possible explanation might be that previous studies suggest a vulnerability of these structures to neurodegeneration (Xie et al., 2012) which might mean they are able to compensate more under intervention when compared to controls. This leads to the conclusion, however, that such structures would be potential targets for future interventions. In the same sample, Smith et al., 2013 performed an fMRI famous name discrimination paradigm and reported a decrease in semantic memory related fMRI activation both in MCI participants and cognitively intact older adults after intervention, reflecting a possible reduced neural workload and an improved neural efficiency. MCI patients also showed new areas of activation compared to controls as in frontal, occipital and temporal regions, which was discussed as reflecting the recruitment of new neural circuits in the context of cognitive improvement. Accordingly, the study by Chirles et al., 2017 reported after the same intervention an increased connectivity in ten regions, comprising the frontal, temporal, parietal and insular lobes in the MCI group compared to the control group during resting state fMRI.

There were also studies combining aerobic exercise with other types of intervention: One study applied aerobic exercise, cognitive stimulation and Omega-3-Fat acid supplementation and reported preserved or increased gray matter volume in frontal, parietal and cingulate cortex after intervention (Köbe et al., 2016). However, no cognitive impact was found and the individual contributions of each of the intervention components cannot be separated. Similarly, a study by Anderson-Hanley et al., 2018 combined exercise with a mental task (during a videogame pedaling exercise with scoring compared to a virtual reality biking tour) in 14 subjects with MCI. Exercise dose was associated with changes in gray matter volume in ACC and prefrontal cortex (PFC), but both conditions led to an improvement in verbal and executive memory.

3.2.2. MRI results induced by resistance training

Only two studies applied resistance training in cognitive decline (Nagamatsu, 2012; Suo et al., 2016; see also Table 3). In the first study, 86 women with probable MCI defined by subjective memory complaints and reduced scores on Montreal Cognitive Assessment (MoCA)
Table 2
Evaluation of quality criteria in intervention studies among people with cognitive impairment (A) and cognitively healthy elderly (B) in descending order of total scoring: + = fulfills criteria; − = does not fulfill criteria; ± = fulfills criteria only partly; ? = cannot be concluded from the study report.

| Study                        | Randomization described and acceptable | Valid definition of diagnosis | Inclusion and exclusion criteria described | Adequate statistical power described with power analyses | Valid measurements and outcome measures | Baseline characteristics in groups described and groups comparable | Drop-out described and included in analysis | Intention to treat analysis | Comparison of differences in changes between the groups in outcome variables | Blinding used | Description of intervention | Compliance described | Complications described | Total score |
|------------------------------|----------------------------------------|-------------------------------|-------------------------------------------|--------------------------------------------------------|----------------------------------------|-------------------------------------------------------------|-----------------------------|-----------------------------|-------------------------------------------------|---------------|-----------------------------|---------------------|------------------------|-------------|
| A)                           |                                        |                               |                                           |                                                        |                                        |                                                             |                             |                             |                                                |               |                             |                     |           |              |
| Morris et al., 2017          | +                                      | +                             | +                                        | +                                                      | +                                      | +                                                           | −                           | +                          | +                                              | +             | +                          | +                   |             | 12           |
| Suzuki et al., 2013          | +                                      | +                             | +                                        | +                                                      | +                                      | +                                                           | ?                           | +                          | +                                              | +             | +                          | +                   |             | 12           |
| Ten Brinke et al., 2015      | +                                      | −                             | +                                        | +                                                      | ±                                      | +                                                           | +                           | +                          | +                                              | +             | +                          | +                   |             | 11           |
| Smith et al., 2013           | −                                      | +                             | −                                        | +                                                      | +                                      | ±                                                           | −                           | +                          | +                                              | +             | +                          | −                   |             | 8            |
| Reiter et al., 2015          | −                                      | +                             | −                                        | +                                                      | +                                      | −                                                           | −                           | +                          | +                                              | −             | +                          | −                   |             | 8            |
| Frederiksen et al., 2018; van der Kleij et al., 2018 | +                                      | +                             | −                                        | +                                                      | +                                      | ±                                                           | −                           | +                          | +                                              | −             | +                          | −                   |             | 8            |
| Suo et al., 2016             | +                                      | +                             | −                                        | +                                                      | +                                      | ±                                                           | +                           | +                          | +                                              | −             | −                          | −                   |             | 8            |
| Burdette et al., 2010        | −                                      | −                             | +                                        | −                                                      | +                                      | −                                                           | −                           | +                          | +                                              | +             | +                          | −                   |             | 7            |
| Köbe et al., 2016            | −                                      | +                             | −                                        | +                                                      | +                                      | ±                                                           | −                           | +                          | −                                              | −             | +                          | −                   |             | 7            |
| Chirles et al., 2017         | −                                      | +                             | −                                        | +                                                      | +                                      | −                                                           | −                           | +                          | +                                              | ±             | −                          | −                   |             | 7            |
| Anderson-Hanley et al., 2018 | ±                                      | −                             | +                                        | ±                                                      | +                                      | ±                                                           | −                           | +                          | ?                                              | +             | +                          | −                   |             | 7            |
| Nagamatsu, 2012              | ±                                      | −                             | −                                        | +                                                      | +                                      | ±                                                           | −                           | +                          | +                                              | ±             | +                          | −                   |             | 5            |
| B)                           |                                        |                               |                                           |                                                        |                                        |                                                             |                             |                             |                                                |               |                             |                     |           |              |
| Liu-Ambrose et al., 2010     | +                                      | +                             | +                                        | +                                                      | +                                      | +                                                           | ?                           | +                          | +                                              | +             | +                          | −                   |             | 12           |
| Liu-Ambrose et al., 2012     | +                                      | +                             | −                                        | +                                                      | +                                      | −                                                           | −                           | +                          | +                                              | +             | +                          | −                   |             | 9            |
| Best et al., 2015            | −                                      | ±                             | +                                        | −                                                      | +                                      | +                                                           | +                           | +                          | +                                              | −             | +                          | −                   |             | 9            |
| Nishiguchi et al., 2015      | +                                      | +                             | ±                                        | +                                                      | +                                      | ?                                                           | −                           | +                          | +                                              | −             | +                          | +                   |             | 9            |
| Matura et al., 2017          | ±                                      | +                             | +                                        | +                                                      | +                                      | ±                                                           | −                           | +                          | +                                              | +             | +                          | −                   |             | 9            |

(continued on next page)
| Study                               | Randomization described and acceptable | Valid definition of diagnosis | Inclusion criteria described | Adequate statistical power described | Valid measurements and outcome measures | Baseline characteristics in groups described and groups comparable | Drop-out included in analysis | Intention to treat analysis | Comparison of differences in changes between the groups in outcome variables | Blinding used | Description of intervention | Compliance described | Complications described | Total score |
|------------------------------------|----------------------------------------|-------------------------------|----------------------------|--------------------------------------|----------------------------------------|--------------------------------------------------------------------------------|-----------------------------|-----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|---------------|-----------------------------|---------------------|------------------------|-------------|
| Chapman et al., 2013              | −                                      | +                             | −                          | +                                    | +                                      | +                                                                              | ?                           | +                          | +                                                                                                                                                  | +            | +                          | −                   | −                      | 8           |
| Ruscheweyh et al., 2011           | −                                      | +                             | +                          | −                                    | +                                      | +                                                                              | −                           | −                          | + ±                                                                                                                                   | +            | −                          | −                   | −                      | 6           |
| Maass et al., 2015                | −                                      | +                             | ±                          | −                                    | +                                      | +                                                                              | −                           | −                          | + ?                                                                                                                                   | −            | −                          | −                   | −                      | 6           |
| Kleemeyer et al., 2016            | −                                      | +                             | ±                          | +                                    | +                                      | ±                                                                              | −                           | −                          | ± ?                                                                                                                                   | +            | ±                          | −                   | −                      | 6           |
| Godde and Voelcker-Rehage, 2017   | −                                      | +                             | +                          | −                                    | +                                      | +                                                                              | −                           | −                          | − +                                                                                                                                   | −            | −                          | −                   | −                      | 6           |
| Colcombe et al., 2006             | +                                      | ±                             | ±                          | −                                    | +                                      | +                                                                              | −                           | −                          | + ?                                                                                                                                   | +            | −                          | −                   | −                      | 5           |
| Erickson et al., 2011             | −                                      | ±                             | +                          | ±                                    | +                                      | +                                                                              | −                           | −                          | + ?                                                                                                                                   | +            | ±                          | −                   | −                      | 5           |
| Voss et al., 2010                 | −                                      | +                             | ±                          | −                                    | +                                      | ±                                                                              | −                           | −                          | + ?                                                                                                                                   | +            | +                          | −                   | −                      | 5           |
| Voss et al., 2013a                | −                                      | +                             | +                          | −                                    | +                                      | +                                                                              | −                           | −                          | + ?                                                                                                                                   | +            | −                          | −                   | −                      | 5           |
| Tamura et al., 2015               | −                                      | +                             | ±                          | +                                    | ±                                      | ±                                                                              | ±                           | −                          | + ?                                                                                                                                   | −            | −                          | −                   | −                      | 5           |
| Nagamatsu et al., 2016            | −                                      | +                             | ±                          | −                                    | ±                                      | +                                                                              | −                           | −                          | + ?                                                                                                                                   | +            | −                          | −                   | −                      | 5           |
| Rosano et al., 2017               | ±                                      | ±                             | ±                          | −                                    | +                                      | +                                                                              | −                           | −                          | + ?                                                                                                                                   | ±            | +                          | −                   | −                      | 5           |
| Holzschneider et al., 2012        | −                                      | +                             | ±                          | −                                    | +                                      | ±                                                                              | −                           | −                          | + ?                                                                                                                                   | +            | −                          | −                   | −                      | 4           |
| Fledin et al., 2017; Jonasson et al., 2016 | −                                      | +                             | ±                          | +                                    | ±                                      | ±                                                                              | −                           | −                          | + ?                                                                                                                                   | ±            | −                          | −                   | −                      | 4           |
| Colcombe et al., 2004             | −                                      | ±                             | ±                          | −                                    | +                                      | ±                                                                              | −                           | −                          | + ?                                                                                                                                   | ±            | −                          | −                   | −                      | 2           |
Table 3
Overview of intervention studies in cognitive impairment.

| Study | Included sample size | Mean age in years (SD) | Description of sample | Intervention/Content | Duration in weeks | Frequency per week | Session duration (min) | Outcome measures MRI and cognition | Results |
|-------|----------------------|------------------------|------------------------|----------------------|-------------------|-------------------|----------------------|----------------------------------|---------|
| Burdette et al., 2010 | 11 SCI | 74.0 (2.5) | I: AT (mainly walking); C: stretching | Supervised treadmill walking of moderate intensity | 16 | 4 | Total of 150 min/week | Postinterventional structural MRI, ASL, Resting state | I: Increase of hippocampal CBF; Increase of hippocampal connectivity | Not performed | N | 7 |
| Smith et al., 2013 | 35 (17 MCI, 18 HC), 34 with MRI | MCI 78.7 (7.5), HC 76.0 (7.3) | I: Omega-3 FA, aerobic exercise, cognitive stimulation; C: Omega-3 FA, stretching and toning | Supervised treadmill walking of moderate intensity | 12 | Gradual increase to 4 sessions | 30 | fMRI: Familiar Name Discrimination Task; Neuropsychology: MRI | I: Increase in GM volume in middle frontal cortex, frontal pole, angular cortex, precuneus, post. Cingulate cortex | Improved learning on the AVLT in MCI and HC | N | 8 |
| Köbe et al., 2016 | 22 MCI, 13 in intervention, 9 in control condition; 20 with MRI | 70 (7.2) in intervention | I: Omega-3 FA, aerobic exercise, cognitive stimulation; C: Omega-3 FA, stretching and toning | Supervised treadmill walking of moderate intensity | 24 | 2 | 45 | MRI: Carotid int. media; SNP genotyping; Serology; Anthropometrics | Association between larger fitness and changes of CT in bilat. Insula, precentr. Gyri, precuneus, post. Cingulate cortex, inf. + sup. Frontal cortices and temporal gyrus in MCI | No effect on cognitive results | N | 7 |
| Reiter et al., 2015 (see also Smith et al., 2013) | 30 (14 MCI, 16 HC) | MCI 78.85 (7.5), HC: 75.87 (6.90) | Supervised treadmill walking of moderate intensity | Supervised moderate AT vs. stretching and toning | 12 | Gradual increase to 4 sessions | 30 | MRI: Carotid int. media; SNP genotyping; Serology; Anthropometrics | Association between larger fitness and changes of CT in bilat. Insula, precentr. Gyri, precuneus, post. Cingulate cortex, inf. + sup. Frontal cortices and temporal gyrus in MCI | See Smith et al., 2013 | N | 8 |
| Ten Brinke et al., 2015 | 86 MCI (all F) | AT 76.07 (3.43); RT 73.75(3.72); BAT 75.46 (3.93) | Supervised moderate AT vs. stretching and toning | Supervised moderate AT vs. stretching and toning | 24 | 3–5 | Total of 150 min/week | MRI: Carotid int. media; SNP genotyping; Serology; Anthropometrics | Association between change in cardiorespiratory fitness with bilateral hippoc. Volume | Association between increased left hippoc. Volume and reduced verbal memory | N | 11 |
| Morris et al., 2017 | 68 with probable AD | 72.9 (7.7) | Supervised moderate AT vs. stretching and toning | Supervised moderate AT vs. stretching and toning | 24 | 3–5 | Total of 150 min/week | MRI: Carotid int. media; SNP genotyping; Serology; Anthropometrics | Association between change in cardiorespiratory fitness with bilateral hippoc. Volume | Association between change in cardiorespiratory fitness with bilateral hippoc. Volume | N | 12 |
| Chirkes et al., 2017 (see Smith et al., 2013) | 32 (16 MCI, 16 HC) | MCI 79.6 (6.8), HC 76.1 (7.2) | Supervised treadmill walking of moderate intensity | Supervised treadmill walking of moderate intensity | 12 | Gradual increase to 4 sessions | 30 | MRI: Carotid int. media; SNP genotyping; Serology; Anthropometrics | Increased functional connectivity of PCC/precuneus; Postcentral gyrus with decreased connectivity in HC | See Smith et al., 2013 | N | 7 |
| Anderson-Hanley et al., 2018 | 14 MCI for 6 months analysis (46 in 3 months analysis) | 78.1 (9.9) | Supervised treadmill walking of moderate intensity | Supervised treadmill walking of moderate intensity | 24 | Gradual increase from 2 to at least 3–5 sessions | 45 | MRI: Carotid int. media; SNP genotyping; Serology; Anthropometrics | Association between greater exercise dose and increasing PFC and ACC; Inverse correlation between verbal memory errors and BLFPC volume | I: Improvement in immediate verbal memory, self-report of everyday cognitive function + physical ability | N | 7 |
| Frederiksen et al., 2018; van der Kleij et al., 2018 | 41 (mild to moderate AD) | I: 67.8 (7.7); C: 69.8 (7.7) | Supervised aerobic exercise of moderate-to-high intensity | Supervised aerobic exercise of moderate-to-high intensity | 16 | 3 | 60 | MRI: Carotid int. media; SNP genotyping; Serology; Anthropometrics | Positive correlation of exercise load with hippocampal volume change and frontal CT | Association between volume changes in frontal CT and mental speed + attention | N | 8 |
| Nagamatsu, 2012 | 77 with MCI (RT = 26, AT = 24, BAT = 27), 22 with MRI | 74.9 (3.5) | RT, AT, BAT | fMRI during associative memory | 24 | 2 | 60 | MRI: Carotid int. media; SNP genotyping; Serology; Anthropometrics | No effect on CBF | Improvement of RT group during Stroop and associative memory test | N | 5 |

(continued on next page)
Table 3 (continued)

| Study | Description of sample | Description | Intervention/Component | Duration in weeks | Session frequency per week | Session duration (min) | Outcome measures MRI and cognition |
|-------|-----------------------|-------------|-----------------------|-------------------|---------------------------|------------------------|-----------------------------------|
| Soo et al., 2016 | 86 MCI (79 with MM) | MCI | PRT; CCT; CT; stretching, Tonning | 26 | 2 | 90 | Increase in CT of PC in all regions of cortex, the right lingual, occipital-fusiform gyrus and the right frontal pole, during the encoding and recall of associations. In a study conducted by Soo et al., 2016, 100 older subjects with MCI were randomized to four intervention arms encompassing progressive resistance training (PRT) and computerized cognitive training (CCT). PRT led to improvement in global cognition and increased gray matter in the posterior cingulate. Interestingly, Soo et al. did not find an additional therapeutic benefit from combining resistance and cognitive training. |
| Suzuki et al., 2013 | 100 (50 amnestic MCI 75.8 (6.1) C: 74.8 (7.4) C) | MCI, 50 other MCI | PRT; CCC; CCT+ | 24 | 2 | 90 | Neurophysiology, Neuropsychology. |}

Abbreviations: ACC = Anterior Cingulate Cortex, AD = Alzheimer's Disease, ADAS-Cog = Alzheimer's Disease Assessment Scale – Cognitive Subscale, aMCI = amnestic Mild Cognitive Impairment, ASL = Arterial Spin Labelling, AT = Aerobic Training, AVLT = Rey Auditory Verbal Learning Test, BAT = Balance and Tone Training, BDNF = Brain-Derived Neurotrophic Factor, C = Control condition, CBF = Cerebral Blood Flow, CCT = Computerized Cognitive Training, CT = Cortical Thickness, DLPFC = Dorsolateral Prefrontal Cortex, DM = Developmental Motoric, F = Female, GM = Gray Matter, H = Healthy, PA = Physical activity, PC = Posterior Cingulate, PCC = Posterior Cingulate Cortex, PFC = Prefrontal Cortex, PRT = Progressive Resistance Training, RT = Resistance Training, SCI = Subjective Cognitive Impairment, SD = Standard Deviation, SNP = Single Nucleotide Polymorphism, VEGF = Vascular Endothelial Growth Factor, VSRAD = voxel-based specific regional analysis system for Alzheimer's disease, WM = white matter, WMS-LM = Wechsler Memory Scale –Logical Memory, Y = Yes.

Fitness status was associated with whole brain, white matter (Burns et al., 2008; Honea et al., 2009; Vidoni et al., 2012a). Fitness status was associated with whole brain, white matter (Burns et al., 2008; Honea et al., 2009; Vidoni et al., 2012a). Fitness status was associated with whole brain, white matter (Burns et al., 2008; Honea et al., 2009; Vidoni et al., 2012a). Fitness status was associated with whole brain, white matter (Burns et al., 2008; Honea et al., 2009; Vidoni et al., 2012a). Fitness status was associated with whole brain, white matter (Burns et al., 2008; Honea et al., 2009; Vidoni et al., 2012a). Fitness status was associated with whole brain, white matter (Burns et al., 2008; Honea et al., 2009; Vidoni et al., 2012a). Fitness status was associated with whole brain, white matter (Burns et al., 2008; Honea et al., 2009; Vidoni et al., 2012a). Fitness status was associated with whole brain, white matter (Burns et al., 2008; Honea et al., 2009; Vidoni et al., 2012a).
| Study | Description of sample | Content | Results |
|-------|-----------------------|---------|---------|
| Burns et al., 2008 | 121 (64 HC, 57 early AD) | pVO2 via treadmill test | No difference in neuropsychological or executive performance between levels of fitness in AD. |
| Honea et al., 2009 | 117 (56 HC, 61 early AD) | pVO2 via treadmill test | Association between fitness and increased progression of dementia severity. |
| Smith et al., 2011a | 18 aMCI (9 high PA, 9 low PA) | pVO2 via treadmill test | Increased activation in left caudate in High-PA aMCI. |
| Vidoni et al., 2012a | 90 (37 early AD, 53 HC) | pVO2 over 2 years via treadmill test | Association between fitness and increased progression of dementia severity. |
| Vidoni et al., 2013 | 34 (18 HC, 16 early AD) | pVO2 via treadmill test | Association between fitness and increased white matter integrity in right IFOF. |
| Perea et al., 2016 | 37 ADCE | pVO2 in cardio-pulm. exercise test | Association between fitness and increased white matter integrity in right IFOF. |
| Raj et al., 2016 | 87 (52 MCI or AD) | pVO2 via treadmill test | Association between fitness and increased white matter integrity in right IFOF. |
| Takajo et al., 2016 | 35 HC | pVO2 via treadmill test | Association between fitness and increased white matter integrity in right IFOF. |
| Pard et al., 2017 | 81 (56 HC, 25 MCI) | VO2max | Association between fitness and increased white matter integrity in right IFOF. |
| Makizako et al., 2015 | 310 MCI | Triaxial accelerometer for 2 weeks | Association between moderate PA and hippocampal volume. |

**Abbreviations**: ACC = Anterior Cingulate Cortex, AD = Alzheimer’s Disease, aMCI = amnestic mild cognitive impairment, ADH = alcoholism, SCF = Cerebrospinal Fluid, DTI = Diffusion-Tensor Imaging, PA = Physical Activity, PASE = Physical Activity Scale for the Elderly, PPT = Physical performance test, MD = Mean diffusivity, RD = Radial diffusivity, WM = White Matter.
A) Intervention Studies

B) Fitness

C) Physical Activity

Brain Regions Affected by Interventions

Brain Regions Affected by Fitness

Brain Regions Affected by Physical Activity

(caption on next page)
et al., 2008) and gray matter volume (Honea et al., 2009), with higher correlations in cognitive decline when compared to healthy aging, a finding where a possible higher heterogeneity in the AD group could be discussed. Vidoni et al., 2012a, report that in early AD, baseline fitness was associated with a more severe disease progression. Another study examining volume effects, as well as white matter integrity, was conducted by Teixeira et al., 2016. They found an association of aerobic fitness with gray matter morphology in frontal brain areas and integrity of tracts connecting frontal, temporal, occipital and parietal areas via DTI. These results are in line with findings by Perea et al., 2016 and baseline data from Vidoni et al., 2012a. Similarly, DTI studies in older healthy adults showed especially effects on interconnections with frontal regions vulnerable to aging processes (Johnson et al., 2012; Abe et al., 2002; Nusbaum et al., 2001).

There was only one fMRI study using a Stroop paradigm. Vidoni et al., 2013, examining 18 control individuals and 16 early AD patients, reported that fitness was associated with increased middle frontal, superior parietal lobe and decreased anterior cingulate activity in control subjects, but not in AD subjects. The authors discussed a possible diminished fitness effect due to the diagnosis of AD and refer to Nagamatsu, 2012 where improvement in the Stroop task, as well as during associative memory, with increased activity in lingual and temporal regions was positively correlated with improved memory.

In one study with a large sample of 310 MCI subjects fitness was assessed during 2 weeks via a triaxial accelerometer (Makizako et al., 2015). Interestingly, only moderate physical activity, but not intensive physical activity, was associated with hippocampal volume. This is in agreement with findings by Geda et al., 2010, where moderate, but not light or vigorous exercise, performed in midlife or late life was associated with a reduced risk of MCI.

### 3.3.2. Subjective assessment of cardiorespiratory fitness

There were three studies only using questionnaires for evaluating physical activity in subjects with MCI and/or Alzheimer’s disease (Braskie et al., 2014; Raji et al., 2016; Smith et al., 2011a). In Smith et al., 2011a, higher leisure time physical activity, according to the Stanford Brief Activity Survey (SBAS), was associated with an increased activation in the left caudate during a famous name discrimination fMRI task. The authors discussed the involvement of the caudate, not only as a reflection of motor function, but also in the augmentation and facilitation of cognitive processes (see also Croson et al., 2007; Haeger et al., 2015) and its involvement in the progression of MCI (Hakama et al., 2010). This is in concordance with findings from Verstynen et al., 2012, where higher cardiorespiratory fitness predicted better cognitive flexibility in older cognitively healthy adults, through greater gray matter volume in the dorsal striatum.

In Braskie et al., 2014, 43 controls and 39 subjects with AD completed the Minnesota Leisure Time Physical Activity (MLTPA) questionnaire, the walking questionnaire, and performed a whole brain volume analysis at year 9 compared to baseline. They stated that physical activity was associated with greater whole brain volume. Lower physical activity was also associated with a higher risk of developing AD in later age. Another study using the MLTPA was performed with a larger sample by Raji et al., 2016, where 876 subjects were examined, among those 213 subjects with either MCI or AD. For the whole sample, higher physical activity was associated with increased bifrontal, bitemporal and biparietal volumes, whereas in the MCI or AD group, higher physical activity was positively associated with left hippocampal volume and the cerebellar vermis.

### 3.3.3. Comparison of structural MRI alterations induced by observational studies

When comparing fitness effects between cognitive decline and physiological aging it seems that the main focus of fitness in cognitive decline lies on hippocampal and other temporal structures for both groups. (Fig. 3B). Similar to intervention studies, especially frontal, temporal and parietal regions are influenced by fitness. Furthermore, fitness seems to have global effects on gray, white matter and even whole brain volumes, which might be due to the fact that fitness is developed over longer periods compared to relatively short interventions, where there is possibly a more concentrated and regional effect due to the restricted time of application. Fig. 3C shows the comparison of regions influenced by physical activity assessed via questionnaires in the patient group versus the control group where most regions are reported in the temporal lobe. However, there is still a lack of studies applying questionnaires for evaluating physical activity in the context of MRI alterations during cognitive decline. Therefore, the interpretation has to be done with caution and more studies on physical activity assessment combined with MRI are needed.

### 4. Discussion

The aim of this review is to present an overview of MRI studies on exercise in MCI and AD to patients to define the impact of physical activity on brain architecture. We compared different physical activity modalities, both in patients and in cognitively healthy elderly. Altogether, 23 studies with a total of 2268 subjects with MRI on cognitive impairment were included in this review which used different methods concerning the type of intervention and how fitness was objectively assessed. We subdivided the studies based on the design into a) interventional studies and b) observational studies. Altogether, interventional studies in cognitive decline were of higher methodological quality than studies on cognitively healthy elderly. Here, the lack of description on complications such as injuries during intervention is a very important issue in intervention studies in elderly patients. Furthermore, intention-to-treat analyses are crucial for evaluation of possible future efficient therapeutic intervention methods. Another common issue is the lack of statistical power analyses and description which is still very important given also the relatively small sample sizes in the interventions. Most intervention studies during cognitive decline applied aerobic exercise. When quantitatively analyzing and visualizing the effects of aerobic exercise on brain volume and cortical thickness between patients’ group and cognitively healthy elderly, the main influence of aerobic exercise in disease state seems to be on distinct temporal, frontal and parietal brain regions. The effects on frontal brain regions matches neuropsychological findings of the positive impact of aerobic exercise mainly on executive functions (Camnisch et al., 2017; Farina et al., 2014), which might be due to the vulnerability of brain regions involved in executive functioning during aging (Baker et al., 2018; Scherder et al., 2005). This is supported by several studies showing effect of higher physical fitness on larger frontal brain volume (Bugg and Head, 2011; Golcombe et al., 2003, 2006; Erickson et al., 2010; Fiell et al., 2010; Gordon et al., 2008; Rusciewey et al., 2011; Weinstein et al., 2012) which was not found in young adults (Peters et al., 2009). These findings are also in concordance...
with studies suggesting that individuals with cognitive impairment activate additional frontoparietal regions during executive tasks compared to cognitively healthy subjects (Rosano et al., 2005; Vidoni et al., 2013; Yetkin et al., 2006; Kaufmann et al., 2008).

Another brain region sensitive to aerobic exercise is the hippocampus, as one of the central regions affected by AD pathology (Fjell and Walhovd, 2010). The responsiveness of temporal substructures to exercise might be explained by their vulnerability to neurodegeneration. In contrast, cognitively healthy subjects seem to be more globally responsive, which might be explained by a higher neuroplasticity of the healthy aging brain compared to disease state, as shown by our illustrations in the results part of this manuscript.

Results are comparable when referring to objective fitness assessment via pVO2 and accelerometers. Volume of frontal brain regions in disease state seems to be again more responsive to fitness than in cognitively elderly healthy subjects. For assessment of physical activity via questionnaires, there is a small number of studies on individuals with MCI and AD (Braskie et al., 2014; Raji et al., 2016; Smith et al., 2011a). For coordinative and resistance training, as well as multicomponent exercise, there were not enough studies for a direct comparison. In theory, coordinative training demands higher cognitive processes such as attention during balance, eye-hand and leg-arm orientation, as well as spatial orientation or reactions to stimuli. Dancing combines both physical activity with coordinative parts, as well as cognitive activity and social interaction. Not only do elderly with a long-life experience of dancing exhibit increased cognitive performance in fluid intelligence and attention (Kattenstroth et al., 2010, 2013), but dancing also seems to help rehabilitation in neurological disorders, such as Parkinson’s disease and stroke (McGill et al., 2014) and seems to play a preventive role against dementia (Verghese et al., 2003). In a study on cognitively healthy elderly and MCI, subjects with a life-time experience of dance performed better in learning and memory tasks, but showed a trend-level thinner cortex (Porat et al., 2016). More studies on this intervention form are needed to draw conclusions on brain architecture. The effect of resistance training is still poorly understood. In MCI and AD patients, only one study by Nagamatsu, 2012 performed an fMRI associative memory task and in Ten Brinke et al., 2015, resistance training showed no effect on hippocampus but their sample was also small. Interestingly, Suo et al. showed promising results with a positive effect of resistance training on posterior cingulate, whose affection represents an early biomarker in AD, and an increased connectivity of the hippocampus. Another critical point is that it stays unclear if effects of resistance training are gender-specific (Best et al., 2015) since studies on cognitive decline with MRI have mainly focused on female subjects so far (Nagamatsu, 2012; Ten Brinke et al., 2015). Interventions with coordinative and resistance training should therefore move more into focus of research to understand their beneficial effects on brain structure in disease state. Furthermore, an increase of multicomponent intervention studies should be aspired to benefit from the various advantages of different activity forms. There are already indications from studies in mice that the combination of exercise and cognitive enrichment increases protective effects against synaptotoxicity of amyloid in the hippocampus (Nichol et al., 2008). In humans, comparison of aerobic exercise, with and without addition of a cognitive task during exercise, showed an improved cognitive performance in MCI in case of combination (Sacco et al., 2015). Additionally, and related to environmental enrichment, social engagement seen as a protective factor against cognitive decline (Barnes et al., 2004) should be considered in group interventions.

In a further recently published review on the influence of physical activity on AD biomarkers, the authors did not state a clear association between hippocampal volume and physical activity in most of their included studies and also on other AD biomarkers as amyloid beta 1–42, phosphorylated tau, total tau in CSF and FDG- and Amyloid-PET (Frederiksen et al., 2019). In comparison to our review, their focus was on observational studies, though. The authors also discussed the partly low quality and quantity of the observational studies. Our review focuses on overall cerebral alterations induced by exercise interventions and physical activity with a main focus on neurodegeneration detected via MR imaging. Since the spectrum of Alzheimer’s continuum is very complex (Jack et al., 2018), more studies are needed to draw conclusions on modification on other biomarkers than MRI in AD.

There are several limitations which need to be considered when interpreting the results of the presented studies on physical activity and cognitive decline. One factor is the risk of reporting and observer bias when focus is put on a priori defined ROIs and not on whole brain analyses, which can especially occur in studies with small sample sizes. Another of the major problems is the large etiological heterogeneity in individuals with MCI, which may account for some of the discrepancy in results. As a risk state for developing dementia (Gauthier et al., 2006) MCI is considered an important timepoint for intervention. There are however individuals with MCI who eventually reverse back into a normal cognitive status. MCI encompasses a variety of etiologies as depression, polymedication and prodromal phases of neurodegenerative diseases. It might even be possible, that effects of different forms of exercise are mediated through different pathways. Some studies point to the assumption that neurogenesis and neuroprotection observed in exercise could be mediated by increases in neurotrophins as Brain-derived-neurotrophic-factor (BDNF) (Erickson et al., 2011; Ruscheweyh et al., 2011; Voss et al., 2013b) and Insulin-like-Growth-Factor (IGF-1) (Cotman et al., 2007). There are indications that increases of neurotrophins and their neuronal effects might result from different exercise modalities (Tsai et al., 2019) but this aspect is still under current research. The exact understanding of underlying cerebral processes might help us in developing new therapeutic concepts in the future.

5. Conclusion

Based on this systematic review in MCI and AD, both physical intervention and observed basal increased fitness status can mediate structural and functional brain alterations, with a main focus on regions sensitive to neurodegeneration during cognitive decline. We did not find an association between rate of whole intervention duration, session duration, frequency of sessions and number of affected brain regions in structural MRI. However, reported whole intervention and session durations as well as frequencies are in concordance with so far recommended values (Blankevoort et al., 2010; Dougherty et al., 2016; Pitkälä et al., 2013). Due to the lack of sufficient studies on resistance training and coordinative training in disease state, more MRI studies of high methodological quality on these modalities should be performed. Furthermore, future studies should aim to include etiologically clearly defined disease groups. According to our results, three further important questions need to be addressed in the future: A) Do intervention effects in cognitive decline persist after ceasing the intervention and for how long? B) Could intervention via exercise inhibit or slow down conversion from MCI to dementia state? C) Since new neuroimaging methods can help to detect even subtle effects on brain integrity and metabolism in very early stages of AD, future research should focus on newly developed imaging methods as e.g. metabolic imaging via MRI and/or PET or ultra-high-field imaging to better understand the influence of physical activity on brain integrity and neurodegeneration and to facilitate the observation of possible long-term effects in longitudinal studies.

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