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Review article

Does resistance training in older adults lead to structural brain changes associated with a lower risk of Alzheimer's dementia? A narrative review

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ABSTRACT

Dementia, particularly Alzheimer's Disease (AD), has links to several modifiable risk factors, especially physical inactivity. When considering the relationship between physcial activity and dementia risk, cognitive benefits are generally attributed to aerobic exercise, with resistance exercise (RE) receiving less attention. This review aims to address this gap by evaluating the impact of RE on brain structures and cognitive deficits associated with AD. Drawing insights from randomized controlled trials (RCTs) utilizing structural neuroimaging, the specific influence of RE on AD-affected brain structures and their correlation with cognitive function are discussed. Preliminary findings suggest that RE induces structural brain changes in older adults that could reduce the risk of AD or mitigate AD progression. Importantly, the impacts of RE appear to follow a dose-response effect, reversing pathological structural changes and improving associated cognitive functions if performed at least twice per week for at least six months, with greatest effects in those already experiencing some element of cognitive decline. While more research is eagerly awaited, this review contributes insights into the potential benefits of RE for cognitive health in the context of AD-related changes in brain structure and function.

1. Introduction

Dementia represents a profound decline in cognitive abilities, greatly impacting an individual's capability to live independently (American Psychiatric Association, 2022). In 2019, an estimated 57.4 million individuals worldwide were living with dementia (Nichols et al., 2022). This number is expected to increase to as much as 152.8 million by 2050. Alzheimer's disease (AD) accounts for 60–80 % of dementia cases and is therefore considered the primary cause of dementia worldwide (American Psychiatric Association, 2022). More than 2500 clinical trials for potential AD therapies have been registered since 2003 (C. K. Kim et al., 2022). These trials encompass efforts to improve cognition as well as develop and test disease-modifying therapies (Cummings et al., 2014, 2022). However, the failure rate of therapeutic candidates for AD, and dementia in general, remains notably high, with the past two decades witnessing the failures of at least 98 distinct compounds (Cummings et al., 2014; C. K. Kim et al., 2022).

Despite the FDA approving several drugs for AD treatment, they have yet to demonstrate sustained long-term benefits. Five approved drugs—tacrine, rivastigmine, donepezil, galantamine, and memantine—provide only modest symptomatic benefits without altering disease progression (McShane et al., 2019; Yiannopoulou and Papageorgiou, 2020). Two newer drugs that target amyloid-beta—Aducanumab and Lecanemab—have recently gained accelerated and full approval. However, their modest effects may not achieve clinical significance (Kepp et al., 2023; Peng et al., 2023), and concerns have emerged due to the potential risk of edema, hemorrhage, and accelerated brain atrophy (Alves et al., 2023; Kepp et al., 2023).

The lack of robust treatment approaches for AD has driven research into non-pharmacological interventions, such as physical activity, to slow cognitive-functional decline and potentially delay the onset of dementia. Such interests are well-founded, considering that at least

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30–40 % of dementia cases are attributable to modifiable risk factors such as physical inactivity (Livingston et al., 2020; Norton et al., 2014). The World Health Organization advocates for regular physical exercise in both children and adults to maintain a healthy cognitive state, including cognitive performance and mental health (Bull et al., 2020), which is substantiated by a wealth of research. An umbrella review, which examined 24 meta-analyses covering 109 primary randomized controlled trials (RCTs) with more than 11,000 healthy participants, revealed that almost all studies reported positive and significant overall effects of regular exercise on cognitive function (Ciria et al., 2023). The benefits of physical exercise, mainly of moderate-to-vigorous intensity, were notably observed in global cognitive function as well as in specific cognitive domains such as executive function (EF), complex attention, and memory (Broadhouse et al., 2020; Colcombe and Kramer, 2003; Engeroff et al., 2018; Ludyga et al., 2020; Northey et al., 2018; Rathore and Lom, 2017). These effects were also observed in carriers of autosomal dominant forms of AD and patients with mild memory or cognitive impairments (Broadhouse et al., 2020; Heyn et al., 2004; Müller et al., 2018; Suo et al., 2016).

Structured physical activity comprises at least three fundamental types of exercise with distinct physiologic demands: aerobic exercise (AE), resistance exercise (RE, also known as strength training), and coordinative exercise. Aerobic exercise involves a significant increase in oxygen consumption compared to resting levels, requiring energy expenditure to sustain an elevated heart rate and heightened oxygen intake (Diamond and Ling, 2019; McArdle et al., 2015). This category includes brisk walking, jogging, swimming, and cycling. Resistance exercise entails physical activities requiring the expression of muscular force against external resistance, such as weightlifting (McArdle et al., 2015). Coordinative exercises involve movements requiring sensory and neuromuscular control mechanisms to maintain body stability throughout each motion, including activities like gymnastics and yoga (Dunsky, 2019; Kwok et al., 2011).

Aerobic exercise has been the most well studied and has demonstrated significant brain and cognitive benefits. These benefits are commonly attributed to longer-term improvements in cardiovascular fitness (Jonasson et al., 2017; Netz, 2019), in addition to the acute cognitive benefits of exercise (Dustman et al., 1984; Mandolesi et al., 2018). Though less well studied, compelling arguments suggest that RE may provide comparable benefits to AE and that distinct mechanisms may confer them (Loprinzi et al., 2020). Given the potential of RE as an intervention to prevent or mitigate changes in brain structure and function associated with AD, this review aims to assess the impact of RE on the brain. Our focus will be on brain structures related to AD, as neurodegeneration and brain atrophy represent the most immediate substrate for cognitive impairment in AD and provide a stable indicator of neuronal loss and brain atrophy (Vemuri and Jack, 2010). The review begins by exploring the general effects of physical activity, with subsequent emphasis on the specific impact of RE on cognitive function. We then discuss vulnerable brain structures affected by AD pathology, highlighting distinctions from structural changes related to normal aging. Finally, by drawing insights from RCTs that utilized structural neuroimaging, we review effects of RE on brain structures affected by AD and how these effects align with cognitive function in older people at risk of AD.

2. Overview of physical activity and cognitive function

Physical activity confers many physiological and cognitive benefits, including improved cerebral blood flow regulation, mitigation of inflammation and oxidative stress, and promotion of neuroplasticity and neurogenesis (Chen and Nakagawa, 2023). One of the earliest signs of cognitive decline in normal aging and AD is decreased episodic memory (i.e., the ability to recall specific personal events and experiences; Nagamatsu et al., 2012). In one longitudinal study, Josefsson et al. (2012) tracked changes in episodic memory performance over 15 years in more than a thousand adults aged 35–85 years. Using a random-effects pattern-mixture model, they categorized participants into three distinct groups based on their memory changes: “maintainers” (18 %), those who exhibited age-typical decline (68 %), and “decliners” who exhibited accelerated memory decline (13 %). Intriguingly, amongst the many characteristics that were found to increase the likelihood of being a maintainer (e.g., education or not living alone), physical activity was the most significant protective factor, increasing the likelihood of maintaining memory function by 2.2-fold.

Research exploring the relationship between cognition and AE has revealed that regular AE, even at low intensity (e.g., walking), leads to increased cortical thickness and brain volume in critical brain regions like the prefrontal and temporal cortices, the hippocampus, and various gray and white matter regions in older healthy individuals (Colcombe et al., 2006; Dustman et al., 1984; Erickson et al., 2010, 2011; Jonasson et al., 2017). When examined in interventional studies, changes in brain structure or volume appear to correlate with increases in cardiovascular fitness (Erickson et al., 2011). Moreover, such increases in brain volume are also shown to be predictive of better cognitive performance, including cognitive domains such as EF and spatial memory (Colcombe and Kramer, 2003; Dustman et al., 1984; Erickson et al., 2011; Jonasson et al., 2017; Kramer et al., 1999). Cerebral angiogenesis and improved vascularization are believed to underlie some of the benefits of AE on cognition (Churchill et al., 2002). Specifically, the growth of new capillaries from preexisting vessels is hypothesized to promote neuronal cell growth and synaptogenesis (Churchill et al., 2002). In rodent studies, prolonged running induces heightened hippocampal neurogenesis and restructuring of neuronal and vascular networks, resulting in improvements in memory functions (Gao et al., 2023; Vivar et al., 2023). Exercise-induced increases in brain-derived neurotrophic growth factors (BDNF) is another proposed mechanism mediating the cognitive benefits of AE (Churchill et al., 2002; Lessmann et al., 2003; Loprinzi et al., 2020).

Recent research showing that the characteristics of an exercise significantly influences cognitive outcomes has led some authors to advance a more nuanced relationship between AE and cognitive gains (Diamond and Ling, 2019; Hillman et al., 2008; Ludyga et al., 2020). In a scoping review evaluating exercise interventions explicitly designed to enhance EF, Diamond and Ling (2019) argued that AE with minimal cognitive demands does not benefit EF. This assertion finds support in a systematic review and meta-analysis by Ludyga et al., (2020), who investigated the differential effects of exercise subtypes on cognitive function in healthy individuals. They discovered that coordinative exercise provided greater cognitive function benefits than other exercise types, and found no difference between AE, RE, and mixed exercise modalities, all of which were associated with only minor beneficial effects on cognition (Ludyga et al., 2020).

Alongside the heterogeneity of effects described in the literature, it is essential to note the uneven distribution of studies available to examine the effect of each exercise type (Diamond and Ling, 2019; Ludyga et al., 2020; Netz, 2019; Tomporowski and Pesce, 2019). For example, in their review, Diamond and Ling (2019) identified only nine studies incorporating RE interventions. In some instances, RE was designed as an active control rather than the intervention, contrasting with sixteen trials concentrating on AE as the primary intervention. Therefore, while RE displays significant promise with respect to its effects on cognitive function in general as well as prevention of cognitive decline, (Karamacoska et al., 2023; Xu et al., 2023; Zhang et al., 2023) further research is needed to determine whether specific subgroups of individuals or types of RE will receive or generate the most benefit, respectively.

3. Overview of RE and cognitive function in older adults

Multiple factors support the potential of RE in mitigating the progression of cognitive decline and the risk of dementia. One compelling

reason lies in its ability to increase muscle mass, and research has linked low skeletal muscle mass or impaired muscle function to cognitive impairments (Oudbier et al., 2022; Storoschuk et al., 2023; Sui et al., 2021; Tessier et al., 2022; Xue et al., 2023). The few randomized interventional trials investigating the impact of RE on cognitive function are also persuasive. In the Brain Power study (Liu-Ambrose et al., 2010), one of the most comprehensive investigations to date that established the merits of long-term RE on cognitive function, Liu-Ambrose and colleagues investigated the effects of a 52-week supervised progressive and high-intensity RE program in 155 healthy, older women aged 65–75 years. Participants were randomized into one of the three groups: once-weekly RE group (RT1), twice-weekly RE group (RT2), or an active control group performing balance and tone training (BAT) twice-weekly. The RE program consisted of ten exercises utilizing free weights and a pneumatic air resistance system. In each session, participants in the RE groups were required to perform two sets of 6–8 repetitions for each exercise. The training stimulus was increased if participants completed the exercises with proper form and ease. At the end of the study, compared to the BAT active control group, both RE groups saw significant improvements in Stroop test performance, a measure of selective attention and cognitive flexibility. Further analyses showed that the effects persisted for up to one year following RE cessation (Best et al., 2015). Interestingly, the RT2 group, but not the RT1, also demonstrated improvements in memory (as assessed by Rey Auditory Verbal Learning Test) and peak muscle power (Best et al., 2015), compatible with a dose-response effect of RE on memory that was associated with improvements in muscle function.

Following the Brain Power study, the same research group examined changes in cognitive function with an RE intervention in a cohort of community-dwelling women aged 70–80 years (Nagamatsu et al., 2012). Study participants reported subjective memory complaints and were assessed as having probable mild cognitive impairment (MCI), as indicated by a Montreal Cognitive Assessment (MoCA) score of <26 out of 30. This trial, known as the "Exercise for Cognition and Everyday Living" (EXCEL) trial, utilized the same intervention protocol as Brain Power and spanned six months. By the study's conclusion, both RE groups exhibited significant improvements in the Stroop and associative memory tasks compared to the BAT control group. Between the Brain Power and the EXCEL study, a notable difference was found in the timing of improvements in Stroop task performance. Specifically, the Brain Power study demonstrated enhancements exclusively at 12 months, with no discernible improvement at six months. By contrast, participants engaging in twice-weekly RE in the EXCEL study exhibited improved Stroop task performance as early as six months into the intervention. Consequently, the authors suggested that the benefits of RE in terms of selective attention and conflict resolution might be more pronounced among individuals at higher risk for dementia, such as those of older age or with lower MMSE scores (Nagamatsu et al., 2012).

Aligning with the EXCEL trial's findings, the SMART study revealed significant enhancements in global cognition and EF with high-intensity RE (Fiatarone Singh et al., 2014). Here, 100 men and women aged 55–87 years with subjective memory complaints and MCI were randomly assigned to RE, cognitive training, or both in a 2×2 trial design with sham training in those not assigned to active RE or cognitive training. For six months, participants in the RE groups engaged in twice-weekly RE, performing three sets of 8 reps for 5–6 different exercises during each session. Notably, significant improvement in ADAS-Cog scores, a measure of global cognition, was observed exclusively among participants in the RE groups compared to non-RE groups. At baseline, the mean ADAS-Cog scores for participants in the intervention groups ranged from 8.02 to 8.79 (95 % CI: 7.02, 9.56). As a reference, the authors categorized an ADAS-Cog score of ≤5 as normal based on the mean score reported in non-cognitively impaired individuals aged 55–89. After the six-month intervention and an 18-month follow-up, only the RE groups exhibited a mean ADAS-Cog score within the normal range, i.e., 4.97 (95 % CI: 3.55, 6.38). The proportion of participants achieving a normal ADAS-Cog score after six months of RE increased from 24 % to 48 % at 18 months, compared to an increase from 20 % to 27 % with sham exercises (Fiatarone Singh et al., 2014). These findings, which appear unique to RE, suggest that this form of exercise could enhance cognitive function and reverse MCI status (Fiatarone Singh et al., 2014; Suo et al., 2016).

While the cognitive benefits of RE seem convincing, the clinical significance of these findings is debated. Diamond and Ling (2019), for example, concluded in their systematic review that RE had been the least successful approach in improving EF compared to other exercise types. In their assessment of nine RE studies, none conclusively demonstrated benefits for EF, and only two presented suggestive evidence of EF benefits. In this context, they defined *clear evidence* as a significant improvement in EF and better post-test EF performance than the control group on at least 67 % of measures, whereas *suggestive evidence* was defined as either more EF improvement or better post-test EF performance than the control group on at least 50 % of measures. Of note, the authors mentioned that four of the nine studies included RE as the active control condition rather than being the intervention group, thus precluding those studies from examining the relationship between an RE intervention and changes in EF (Diamond and Ling, 2019).

It is reasonable to speculate that RE might enhance cognitive function through distinct mechanisms from AE, particularly by fostering favorable neuroplastic adaptations (Cooper et al., 2018; Leung et al., 2015; Loprinzi et al., 2020; Suo et al., 2016). Tomporowski and Pesce (2019) proposed that, while exercise in general induces physiological adaptations in the body and brain, physical activities demanding the allocation of mental resources, such as those involved in skill acquisition, yield the largest cognitive benefits. We have also recently argued that cognitive demand such as that associated with formal education, social interaction, and skill development, is a primary driver of long-term cognitive function (Turknett and Wood, 2022). As such, some forms of RE involving controlled external pacing or precise movement ranges might therefore generate cognitive demands akin to learning a new skill or novel movement patterns that unimodal AE may not (Leung et al., 2015, 2017; Weier et al., 2012). Furthermore, muscles have been shown to secrete neurotrophic factors and myokines, such as insulin growth factor-1 and BDNF, which may promote structural and functional plasticity in brain regions such as the hippocampus and prefrontal cortex (Broadhouse et al., 2020; Cooper et al., 2018; Coutinho et al., 2022; Loprinzi et al., 2020). Though the release of myokines is not specific to RE, they provide another putative mechanism by which RE may support long-term brain structure and function, perhaps by augmenting other skill- and muscle-related adaptations that benefit cognitive function.

Given that the effects of RE alone on cognitive function are relatively understudied, we will now discuss whether RE in older adults leads to structural brain changes that might be associated with a lower risk of AD. We will first briefly explain the trajectory of brain changes in normal aging and AD, emphasizing distinctions in structural changes between the two scenarios. Subsequently, we will explore the potential benefits of RE using brain structural neuroimaging as a proximal measure of brain changes associated with cognitive decline in AD.

4. Consequences of normal aging on brain structure

The brain undergoes continuous changes in its structure throughout the lifespan, including alterations in global and regional volume and tissue characteristics. Many of the changes that occur during adulthood become apparent after reaching the age of around 55 (Leong et al., 2017; MacDonald and Pike, 2021), though changes in functions such as EF, short- and long-term memory, and processing speed can appear much earlier (Turrini et al., 2023). It is well-documented that gross brain volume decreases over time, with an average rate ranging from 0.2 % to 0.9 % per year (Fjell et al., 2014; Leong et al., 2017). By the time individuals reach 90 years of age, their average brain weight may have

decreased by as much as 15 % from its peak (Leong et al., 2017).

Although longitudinal change with age has been observed across almost the entire cerebral cortex, the frontal and temporal lobes display the highest relative change over time, followed by the medial parietal area, which includes the precuneus and the adjacent retrosplenial and posterior cingulate cortices (Fjell et al., 2014). Other changes include decreases in hippocampal volume ranging from around 0.8–2.0 % per year, as well as associated ventricular dilation (Fjell et al., 2014; Leong et al., 2017). One potential mechanism by which brain atrophy occurs is a gradual decline in age-related glymphatic function, resulting in cellular loss and widespread hypoperfusion across the entire brain (Turrini et al., 2023), though other broad aging-related cellular changes are likely to be involved as well (López-Otín et al., 2023).

Age-related brain atrophy coincides with a decline in specific cognitive functions. Cognitive functions generally follow three patterns of age-related change: (1) decreasing across the lifespan (e.g., processing speed and EF), (2) decreasing in late life (e.g., numerical ability, spatial orientation, reasoning, mental set shifting, and inhibition), and (3) remaining relatively stable or moderately increasing over time, as seen with crystallized intelligence (e.g., semantic knowledge, emotional regulation and processing, and autobiographical and automatic memory), which typically remains intact well into a person's sixth and seventh decades (Leong et al., 2017; Salthouse, 2012; Turrini et al., 2023). Importantly, while the typical age-related declines in cognitive function are less severe than those observed in dementing illnesses, they may still hinder one's capability to execute tasks requiring flexible cognitive skills such as quick thinking, adaptability, logical reasoning, and the capacity to concentrate on specific tasks or multitask, as exemplified by activities like driving or managing air traffic control (Harada et al., 2013; Salthouse, 2012). Therefore, while this review focuses on RE in the context of AD-related brain changes, RE and other forms of exercise remain strong candidates for supporting and maintaining cognitive function across the lifespan in healthy aging.

5. Differentiating age-related cognitive decline and AD

Though there is an overlap between the cognitive changes of aging and the early stages of AD, beyond that point, these conditions diverge (Breijyeh and Karaman, 2020). In AD, cognitive decline is more severe, characterized by a faster rate of decline and broader-reaching effects on cognition, including behavioral changes and an inability to perform basic daily activities (American Psychiatric Association, 2022). Alzheimer's disease is recognized as a continuum, with three discernible neuropathological hallmarks substantiating the diagnosis: the presence of amyloid-beta peptide (Aβ) plaques, the occurrence of pathologic tau, and evidence of neurodegenerative or neuronal injuries, such as synapse loss. The AD continuum begins with preclinical AD, which may be identifiable via imaging and AD biomarkers (Bjorkli et al., 2020; K. Kim et al., 2020), though these are not particularly predictive of current or future cognitive function. As AD progresses within this continuum, cognitive decline associated with AD occurs in two main phases - first MCI, which is then followed by AD dementia.

5.1. Brain structure changes in preclinical AD

In 2011, the National Institute on Aging and Alzheimer's Association introduced the term "preclinical AD" to represent a stage of AD in individuals without overt symptoms but with the presence of pathological markers, including abnormal amyloid deposition and the presence of pathological tau (Jack et al., 2016, 2018).

The entorhinal cortex (EC) is one of the selectively vulnerable regions in AD. In earlier attempts to differentiate the stages of AD, Braak et al. (2006) illustrated that lesions marked by the accumulation of hyperphosphorylated tau are evident in the transentorhinal and EC regions during the initial stages of AD even before symptoms appear (Braak et al., 2006). The EC is associated with memory, lying in a critical path of neural systems that connect the neocortex and the hippocampus (Maass et al., 2014, 2015). In normal aging, the total number of neurons in the EC, estimated to be around 7 million, as well as neuronal densities and volumes, remains stable between the ages of 60 and 90 (Gómez-Isla et al., 1996; Trillo and Gonzalo, 1992). However, neuronal loss in the EC is evident early in the AD process. Even individuals with very mild cognitive decline have nearly one-third fewer neurons in some areas of the EC compared to a normally-aging control group (Gómez-Isla et al., 1996).

The cholinergic white matter pathway (CWMP), involved in attention and memory, is another region susceptible to AD-related degeneration. Integrity of the CWMP appears to deteriorate progressively from the early stages of MCI to full-blown AD dementia (Braak et al., 2006; Nemy et al., 2023). The CWMP consists of a substantial population of cholinergic neurons originating from the nucleus basalis of Meynert (NBM) within the basal forebrain. This pathway extends in two distinct bundles of cholinergic fibers that connect to the cerebral cortex and amygdala (Selden et al., 1998). Recent research has shown that in the initial phases of the AD continuum, the cingulum, a pathway traversed by one of the CWMPs, exhibits significant increases in mean diffusivity (MD) values, indicating reduced white matter (WM) tract integrity (Nemy et al., 2023; Selden et al., 1998). In particular, increased MD is observable in the retrosplenial and posterior cingulate regions among individuals reporting subjective cognitive decline compared to their cognitively healthy counterparts (Nemy et al., 2023). This suggests an early regional vulnerability of posterior cholinergic WM in the preclinical stage of AD.

Finally, neurodegeneration of the hippocampus, which is highly associated with memory, is another pathological hallmark of AD. However, prior studies have shown that the hippocampus is relatively spared at the early preclinical stage, only showing subtle lesions in the later phases of preclinical AD or at the threshold for clinical detection of dementia (Braak et al., 2006; Gómez-Isla et al., 1996). In addition to these conventional brain structural changes, other brain abnormalities, such as the presence of white matter lesions (WMLs), may elevate the risk of developing AD. Lesions in the WM can indicate pathological occurrences, including tissue rarefaction associated with loss of myelin and axons (Debette and Markus, 2010). Although WMLs are common among older individuals, they are associated with an increased risk of incident AD in the general population (Debette and Markus, 2010).

5.2. Brain structure changes in mild cognitive impairment (MCI)/ prodromal AD

MCI represents the transitional stage between cognitively healthy individuals and those with dementia. In 2013, the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) developed the term "mild neurocognitive disorder" (mild NCD) to describe MCI (American Psychiatric Association, 2022). The clinical criteria for mild NCD include (i) evidence of cognitive decline in one or more cognitive domains (e.g., complex attention, EF, learning and memory, language, perceptual-motor skills, and social cognition) obtained from reports from the client, an informant, or a clinician, or from objective testing; (ii) preserved functional independence; (iii) that the cognitive impairments do not occur exclusively during episodes of delirium; and (iv) the cognitive deficits cannot be better explained by another condition (e.g., depression). MCI is sometimes referred to as prodromal AD (American Psychiatric Association, 2022). Although the onset of MCI can occur at any age, a comprehensive analysis indicated that it typically first manifests at age 73 for women and 70 for men (Hale et al., 2020). For individuals aged 75 or older, an estimated 60–65 % of those with MCI are expected to progress to develop dementia, with the highest conversion rates observed during the initial 18 months of observation (Busse et al., 2006).

In MCI, neurodegeneration extends beyond what is typically observed in the preclinical stage of AD, such as an increased lesion

density in the transentorhinal and EC regions (Braak et al., 2006). Killiany et al. (2000) found that individuals with possible AD (clinical dementia rating, CDR = 0.5) who progressed to AD within three years of follow-up exhibited a 36 % smaller EC volume compared to controls who maintained normal cognition (CDR = 0) throughout the three years of assessment. At this stage, lesions in the transentorhinal and EC also extend to the occipitotemporal lobe and the hippocampus, including the CA1 and the subiculum subregion (Braak et al., 2006). Accelerated hippocampal atrophy is also consistently observed (Driscoll et al., 2009; Leong et al., 2017), with estimated annual atrophy rates reaching 2.8 % for stable MCI and 3.7 % for those progressing to AD, compared to 0.8 %-2.0 % observed in elderly controls (Apostolova et al., 2012).

In MCI, the degenerating integrity of the CWMP also progresses beyond that of preclinical AD, with elevated MD values detected in the rostral anterior cingulate, extending beyond the areas seen in preclinical AD subjects where heightened MD values were limited to the posterior cingulate (Nemy et al., 2023). Possibly due to the extensive CWMP degeneration, noticeable decreases in NBM volume occur in prodromal AD (Nemy et al., 2023). It is worth noting that at this phase, CWMP integrity, but not NBM volume, correlates significantly with memory and attention (Nemy et al., 2020).

5.3. Alzheimer's dementia

Dementia is the most severe stage of cognitive decline. The DSM-V now includes "dementia" within the broader condition of "major NCD" (American Psychiatric Association, 2022). The first occurrence of AD dementia typically arises at the age of 83 for women and 79 for men (Hale et al., 2020). Though sharing similar diagnostic criteria with MCI, individuals at this stage typically lose their ability to live independently and may require assistance with multiple or all basic life activities, depending on the severity. The DSM categorizes dementia severity into three stages: mild, moderate, and severe. In the mild stage, individuals may face difficulties with instrumental daily activities like managing household chores and finances. In the moderate stage, challenges typically arise in performing basic daily activities, such as eating and dressing independently. In the severe stage, individuals become entirely reliant on others for survival (American Psychiatric Association, 2022).

In AD dementia, neurodegeneration becomes widespread across brain regions including the frontal, parietal, and occipital cortex (Braak et al., 2006). The rate of atrophy accelerates significantly, with AD patients experiencing a gross brain volume atrophy rate of up to 4.7 % per year (Chan et al., 2001). Additionally, the shrinkage rate of the hippocampus doubles compared to that observed in normal aging, with an annual atrophy rate of 3.5–4.0 % per year (Apostolova et al., 2012). Within the EC, subjects with AD dementia have also been documented to have up to 90 % fewer neurons, particularly in layer II, which represents the part that provides excitatory input to the hippocampus (Gómez-Isla et al., 1996). Furthermore, the compromised integrity of the CWMP further extends from the rostral anterior cingulate to the dorsal anterior cingulate, temporal, and prefrontal areas (Nemy et al., 2023). A summary of the differences in brain structural changes seen in aging versus AD is shown in Table 1.

6. Impact of RE on AD-associated brain structures

Having described the trajectory of brain structure changes in AD, we will now explore how those same structures respond to RE interventions as documented in RCTs. The key findings of relevant studies are summarized in Table 2.

Two studies, the Brain Power study and the SMART study (Table 2), employed neuroimaging to assess the impact of RE on the brain. The Brain Power study (Liu-Ambrose et al., 2010) utilized structural magnetic resonance imaging (MRI) to measure the whole brain volume of individuals enrolled in the trial. Following 52 weeks of RE, both intervention groups—whether engaging RE once or twice weekly—exhibited an unexpected decrease in brain volume compared to the control group (BAT), which showed no change. Interestingly, this reduction in brain volume coincided with improvements in cognitive function, to which the authors tentatively postulated that lower brain volumes may be attributed to decreases in pathological plaque burden. Subsequent neuroimaging analyses were then conducted to examine changes in distinct brain regions, including the hippocampal, gray matter (GM), and white matter (WM) volume, as well as the presence of WMLs (Best et al., 2015; Bolandzadeh et al., 2015). In one analysis, Best et al. (2015) obtained available baseline MRI scans of 88 out of the original 155 participants and then conducted follow-up MRIs with them one year after the intervention. At follow-up, only those who engaged in RE twice a week displayed preserved cortical WM volume, which further supports the RE dose-response hypothesis. Apart from the cortical WM, however,

Table 1
Summary of structural changes seen in aging vs. AD.

	Normal aging	AD		
		Pre-clinical	Prodromal (MCI)	Dementia
Brain structural changes	• Gradual shrinkage across entire cerebral cortex, especially in the frontal and temporal lobe (Fjell et al., 2014) • Annual atrophy rate: 0.2 %-0.9 % (Beason-held and Horwitz, 2002; Fjell et al., 2009).	• Presence of lesions in highly vulnerable brain regions (e.g., transentorhinal and EC, hippocampus, and cholinergic WM pathway) (Braak et al., 2006; Nemy et al., 2023). • Annual atrophy rate: 0.5 %-4.7 % (Chan et al., 2001; Fjell et al., 2009).		
Notable AD-associated subregions				
Hippocampus	• Stable until ~60 years (Fjell et al., 2014) • Annual atrophy rate: 0.79 %-2.0 % (Fjell et al., 2014; Leong et al., 2017).	• No apparent difference in atrophy rate compared to control (Nemy et al., 2023).	• Annual atrophy rate: 2.8 % if stable; 3.7 % if transitioning to AD (Apostolova et al., 2012).	• Annual atrophy rate: 3.5 %-4.0 % (Apostolova et al., 2012).
Entorhinal cortex	• Total number of neurons, neuronal densities and volumes remain stable between 60 and 90 years (Gómez-Isla et al., 1996; Trillo and Gonzalo, 1992). • ~7 million neurons (Gómez-Isla et al., 1996).	• One-third fewer EC neurons in subjects with very mild cognitive impairment (Gómez-Isla et al., 1996).	• 36 % smaller EC volume in individuals who are at risk of converting to AD (Killiany et al., 2000).	• Up to 90 % fewer neurons in some EC regions (Gómez-Isla et al., 1996).
Cholinergic WM pathway (from basal membrane)	• No data.	• ↓ WM integrity in posterior cingulate and retrosplenial regions (Nemy et al., 2023).	• ↓ WM integrity extends to rostral anterior cingulate (Nemy et al., 2023). • ↓ NBM volume (Nemy et al., 2023).	• ↓ WM integrity includes dorsal anterior cingulate, temporal, and prefrontal areas (Nemy et al., 2023). • ↓ NBM volume (Nemy et al., 2023).

EC: entorhinal cortex; WM: white matter; NBM: nucleus basalis of Meynert

Table 2
Summary of structural neuroimaging-based RCTs on the impact of RE on brain structures.

Study		Subjects	Intervention/Control	Duration/ Follow-up	Brain Structure Measured	Key Findings
Brain Power Study	(Liu-Ambrose et al., 2010)	155 community- dwelling women; 65–75 years; MMSE score >23; No RE in the last 6 months.	Intervention groups: (1) RT1: 1x/week (2) RT2: 2x/week RT protocol: • 60 minutes per session. • Two sets of 6–8 reps for each exercise. • Mix of free weights and machine. • Exercises: biceps curls, triceps extension, seated rowing, latissimus dorsi pull-down exercises, leg presses, hamstring curls, calf raises, mini squats, mini lunges, lunge walks. • Training stimulus increases if participants complete the exercises with proper form and ease. Control group: (1) BAT: 2x/week BAT protocol: Tai chi based forms, i.e., crane, tree pose, tandem stand, tandem walking, and single leg stance.	12 months/ 2 years.	Whole brain volume.	• ↑ selective attention and conflict resolution, but not set shifting and working memory in both RT groups. • ↓ whole brain volume in RT groups, no change in BAT.
	(Best et al., 2015)	88 of 155 participants with available baseline MRIs.			Hippocampus and cortical GM and WM.	• No effect on cortical GM or hippocampal volume. • ↓ cortical WM atrophy in RT2 but not RT1 or BAT.
	(Bolandzadeh et al., 2015)	54 of 155 participants who demonstrated evidence of WMLs.			WMLs.	• ↓ WMLs progression in RT2 but not RT1.
SMART Trial	(Suo et al., 2016)	100 MCI individuals (68 females); 55–87 years; Non-demented, non-depressed; MMSE score of 24–28; Subjective memory complaints; CDR = 0 or 0.5.	Intervention groups: (1) PRT+CCT. (2) PRT+sham CCT. PRT protocol: • 2x/week, 90 minutes per session. • 3 sets of 8 reps for each exercise. • Exercises: Chess press, leg press, seated row, standing hip abduction, knee extension. CCT protocol: • computer-based exercises targeting memory, executive function, attention and speed of information processing. Control group: (1) Sham PRT+ sham CCT. Sham PRT + CCT Protocol: • 2x/week. • Stretching and seated calisthenics + watching documentary videos.	6 months	Hippocampus, PCC, and WMLs.	• PRT only did no increase cortical thickness but ↓ PCC atrophy. • PRT reversed progression of WMLs. • No beneficial effects on hippocampus volume.
	(Broadhouse et al., 2020)			26 weeks/ 18 months	Hippocampus subfields.	• Slower atrophy rates in left subiculum, CA1, and dentate gyrus compared to control. • No effects on the right hippocampus.

CA1: cornu Ammonis 1; CCT: computerized cognitive training; CDR: Clinical Dementia Rating; GM: gray matter; MMSE: mini-mental state examination; MRI: magnetic resonance imaging; PCC: posterior cingulate cortex; PRT: progressive resistance training; RE: resistance exercise; RT: resistance training; WM: white matter; WML: white matter lesions.

RE did not significantly impact cortical GM or hippocampal volume across all groups. In a separate study, Bolandzadeh et al. (2015) investigated the influence of RE on the progression of WMLs, focusing specifically on Brain Power participants with pre-existing WMLs at baseline. Likewise, their analysis revealed that engaging in RE twice a week, but not once a week, for 12 months reduced the progression of WMLs.

The SMART trial also performed similar investigations, examining the impact of RE on the hippocampus, the posterior cingulate (PC) cortex, and WMLs in individuals with MCI (Broadhouse et al., 2020; Suo et al., 2016). Suo et al. (2016) assessed changes in whole hippocampal volume, PC cortical thickness, and WMLs at baseline and the end of the 6-month intervention, whereas Broadhouse et al. (2020) evaluated hippocampal changes 12 months after the intervention ceased i.e., at the 18-month time point. Their findings showed that bi-weekly RE sessions for six months not only preserved but also augmented PC cortical thickness while simultaneously reversing WML progression (3.4 % regression compared to 3.0 % progression in non-RE groups) (Suo et al., 2016). In addition, while no significant effects on overall hippocampus volume were seen at the 6-month time point, the RE group exhibited a slower rate of atrophy in the left hippocampus, specifically in the subiculum, CA1, and dentate gyrus, at 18 months compared to control (Broadhouse et al., 2020).

Drawing on findings from both Suo et al. (2016) and Broadhouse et al. (2020), the latter identified several significant observations in their study: (i) At six months, increased PC cortical thickness was observed in study participants assigned to the RE groups. However, this effect, which was particularly prominent in the left PC, was transient, and diminished at 18 months (12 months post-intervention). At this point, however, greater hippocampal network connectivity was seen; (ii) RE group members who showed the greatest increases in PC cortical thickness post-intervention had less subiculum and dentate gyrus atrophy at 18 months, although the correlation was weak; (iii) Functional neuroimaging revealed strengthened connectivity between the PC and the hippocampus, to which they proposed that the preservation of these hippocampal subfields results from upregulated hippocampal-PC functional connectivity — a change previously identified as unique to RE (Suo et al., 2016). At this point, the critical question is whether these changes in brain structure align with cognitive function, and whether RE-driven changes in structure mitigate the risk of AD-dementia.

In the earlier part of the Brain Power study, Liu-Ambrose et al. (2010) reported significant improvements in Stroop test performance and memory among participants who engaged in RE for 52 weeks. Additionally, they observed functional changes in cortex regions linked to selective attention and conflict resolution, which are essential

components of EF (Liu-Ambrose et al., 2012). However, subsequent correlational analyses (Best et al., 2015; Bolandzadeh et al., 2015) failed to find any significant correlation between concurrent changes in EF and memory with either cortical WM volume or the progression of WMLs. These findings suggest that changes in brain structure and function in response to RE were at least partly uncoupled.

The SMART study, on the other hand, unveiled a significant association between changes in cognitive function and hippocampal structure. Specifically, Broadhouse et al. (2020) identified the rate of atrophy in the subiculum and CA1 as significant predictors for ADAS-cog and EF, respectively. Of note, the rate of subiculum atrophy emerged as a more robust predictor for ADAS-cog compared to age and education. Importantly, even when considering the potential effects of other factors such as post-training physical activity, individual fitness levels (for example, peak oxygen uptake, overall strength, and general physical activity), the reduction in brain atrophy in certain regions (namely CA1, subiculum, and dentate gyrus) was still significantly greater in the resistance exercise (RE) group compared to the control group. This suggests that the maintenance of brain structure associated with RE is not likely due to other physical activities done outside of the RE program or to general improvements in fitness. Based on their findings, Broadhouse et al. (2020) proposed that RE has a direct and prolonged impact on preserving the hippocampal subfields most vulnerable to degeneration in older individuals at risk of dementia, which may ultimately preserve or enhance cognitive function.

The collective findings from the studies conducted so far allow for several hypotheses. Firstly, that RE follows a dose-response effect, whereby significant benefits on the brain manifest following a consistent RE regimen lasting at least 6 months and involving a minimum of two weekly sessions. Notably, such benefits may last for months or even years after discontinuation of RE (Best et al., 2015; Bolandzadeh et al., 2015; Broadhouse et al., 2020). Secondly, that the outcomes of RE could be influenced by modifiers like sex, education level, and other inter-individual differences such as genetic risks and baseline health (Ludyga et al., 2020). For instance, the Brain Power study, which exclusively involved healthy women, observed cognitive benefits only after 12 months of training. This finding contrasts with the results of Cassilhas et al. (2007), who reported cognitive improvements in men after six months of RE, suggesting a potential influence of sex on the impact of RE. Thirdly, we can hypothesize based on the available results that RE may selectively preserve or enhance cognitive function by reversing specific pathologies or enhancing resilience in AD-associated areas (Ciria et al., 2023). Baseline cognitive function may also modify the effects, as several trials have consistently shown that the structural changes associated with RE, such as slower atrophy and reversed WMLs in AD-associated brain structures, appear more prevalent in participants with established cognitive impairments (Broadhouse et al., 2020; Nagamatsu et al., 2012; Suo et al., 2016).

7. Conclusion and future directions

In conclusion, RE in older adults appears to induce structural brain changes associated with a reduced risk or slower progression of brain structural and functional alterations associated with AD. The available evidence suggests that RE exhibits a dose-response effect on reversing relevant pathological changes or increasing resilience in AD-associated areas. This effect may be influenced by individual characteristics such as sex and baseline health. Given the scarcity of trials utilizing structural neuroimaging for outcome measures, further research is needed to validate these associations. The ongoing 'LIve active Successful Ageing (LISA) study,' initiated in 2014, is exploring the immediate and long-term effects of two distinct 1-year RE interventions (high intensity vs. moderate intensity) on brain MRI and cognitive function. This study, involving moderately aged individuals close to retirement age (62–70 years), aims to track the effects for up to 10 years (Eriksen et al., 2016). The results of this study will hopefully provide additional insights into the influence of exercise intensity, particularly RE, on AD-associated brain structures, and are eagerly anticipated.

Considering that the EC and CWMP are among the most vulnerable brain regions to AD, exhibiting signs of degeneration long before MCI becomes detectable, future studies should consider measuring these regions in RE trials. This is especially relevant for trials focusing on RE interventions to prevent the progression of cognitively normal individuals to MCI and AD. Notably, the measurement of EC provides high accuracy (93–98 %) in distinguishing between normal individuals and patients with prodromal AD who eventually develop dementia (Killiany et al., 2000, 2002).

Overall, it appears that there is significant potential for RE to delay the development of AD dementia or even reverse MCI conditions, at least if implemented early in the disease continuum and practiced consistently. However, there remain many open questions around RE interventions for AD prevention and treatment, including the optimal dose, intensity, time for implementation to maximize the clinical benefits, and the relationship between structural changes and functional improvements. Hence, more robust studies are needed to comprehensively address these uncertainties. However, based on the currently-available evidence, we cautiously suggest that RE may reverse relevant pathological structural changes and improve associated cognitive functions if performed at least twice per week for at least six months, with greatest effects in those already experiencing some element of cognitive decline.

Declaration of Competing Interest

L.N. is the founder and owner of NeuroAthletics. J.T. is the founder of Brainjo, a company that creates educational programs for adult learners, and President of Physicians for Ancestral Health. G.L. is the founder and owner of Muscle Centric Medicine™. T.R.W. is a paid scientific advisor for Hintsa Performance, Sidekick Health, Thriva LLC, and Rewire Fitness, and is a founding trustee and Treasurer of the British Society of Lifestyle Medicine.

Data availability

No data was used for the research described in the article.

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