Neuroimaging Insights Pertaining to Physical Activity Effects upon Brain Structure in Mild Cognitive Impairment and in Alzheimer’s Disease

Youshan Zhang1, *, Nicole Marcione2, Danielle Borrajo3, Julia Boudreau3, Neda Khanjani3, Yujia Zhong3

1Department of Computer Science and Engineering, Lehigh University, Bethlehem, USA
2Department of Division of Biokinesiology and Physical Therapy, University of Southern California, Los Angeles, USA
3Department of Neuroimaging and Informatics, University of Southern California, Los Angeles, USA

Email address:
yoz217@lehigh.edu (Youshan Zhang), marcione@usc.edu (N. Marcione), borrajo@usc.edu (D. Borrajo), juliabou@usc.edu (J. Boudreau), khanjani@usc.edu (S. Khanjani), yuizh@usc.edu (Yujia Zhong)

*Corresponding author

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Abstract: Alzheimer’s disease (AD) and mild cognitive impairments (MCI) are two neurological conditions that commonly affect the aging brain. These conditions cause debilitating symptoms, namely, the loss of the ability to perform activities of daily living. This prevents the patient from being able to live independently and severely decreases their quality of life. A growing treatment option involves the patient integrating physical activity (PA) into their daily lives. There is an increasing amount of evidence that supports both the psychological and anatomical improvements of MCI and AD patients that engage in PA. The different cognitive improvements measured via neuropsychological assessments complement the neuroimaging data found in current literature. Different neuroimaging modalities such as PET, MRI, fMRI and EEG all contribute to the amount of data in support of PA as a viable treatment option for people with AD and MCI. Notable improvements can be found in the hippocampal region of the brain. Other lifestyle advancements such as diet changes and sleeping habits can also have a profound effect on AD and MCI patients. Our research is important because it will lead to treatments that can delay the onset of these diseases or even aid in finding an ultimate cure.

Keywords: Alzheimer’s Disease, Mild Cognitive Impairment, Physical Activity, Neuroimaging

1. Introduction

Alzheimer’s disease (AD), named after German psychiatrist Alois Alzheimer—who first described it in 1907 [1]—is a chronic neurodegenerative condition whose initial symptoms typically appear in the sixth decade of life and whose severity gradually increases with age. It is a major type of dementia with typical symptoms ranging from memory impairment to language deficits and executive dysfunction. The onset of memory impairments is associated with the early stages of neurodegeneration—which can result in mild cognitive impairment (MCI)—while the other two classes of deficits typically appear as MCI progresses even further to AD, with debilitating symptoms such as agnosias, problem-solving difficulties, mood swings and other affective disturbances. As the patient condition worsens, social relationships may be strained or even severed, while physical function also deteriorates gradually. Around 70% of AD cases are thought to be associated with genetically inherited factors [2], while other contributors to AD vulnerability include brain damage, clinical depression and high blood pressure [3]. Individuals with AD survive for only about seven years after diagnosis [4]. As in the case of other dementias, AD is associated with continuous brain cell death and with disrupted inter-neuronal connectivity, which leads to decreases in gray (GM) and white
matter (WM) volumes, respectively. The progression of the disease is paralleled by the formation of tau-protein plaques in the brain, and differential diagnosis involves a review of the patient’s medical history in conjunction with cognitive testing, neuroimaging and blood assays to reject alternative causes for the observed symptoms. Furthermore, post mortem histopathological examination of brain tissue can provide rigorously-detailed descriptions and classifications of underlying neuropathology [2].

According to MacGill (2016), symptoms associated with AD-related cognitive decline may be classified into five important classes [5]. One of the first to manifest itself is a lessened ability to retain new information, which often results in (1) patients needing to have questions or entire sentences repeated to them, (2) their failure to locate recently-handled personal belongings, (3) missing important appointments and/or (4) being lost in familiar locations. Another important class of symptoms involves difficulties in reasoning and in exercising judgment. For instance, AD patients may be unable to evaluate personal safety risks, regulate their personal finances, take appropriate decisions or undertake routine activities. A third class of symptoms involves decreased visuospatial competence, including the inability to recognize familiar faces and spatial targets within sight, to use common appliances, etc. Fourthly, linguistic abilities may be impaired to the extent that forgetting ordinary words and making spelling errors or grammatical mistakes become common. Finally, sudden swings in behavior may occur, leading to loss of temper, to anger bursts, to loss of enthusiasm or motivation and/or to unusually obsessive behavior. Thus, AD is associated with a wide array of cognitive deficits.

It has been known for over a decade that physical activity (PA) can reduce the rate of cognitive decline in older adults [6-8]. Recently, much interest has been expressed in determining whether these same benefits can be obtained in MCI and AD patients. There is evidence to the effect that regular, long-term PA can modestly improve executive function in AD patients [9], which suggests that PA could play a role in addressing the healthcare challenges of AD. A particularly promising avenue for investigating PA effects upon brain structure and function involves the use of neuroimaging techniques to examine the relationship between PA-related improvements in cognitive function, on the one hand, and structural and/or functional brain changes, on the other hand [10][11]. Such neuroimaging studies are essential due to the substantial impact of MCI/AD upon public health and to the expected increase in the total number of MCI/AD cases as a large fraction of the population in the Western world reaches retirement age [8].

The purpose of this review is to describe and synthesize current scientific knowledge on how the brains of MCI/AD patients adapt to PA, and on how neuroimaging techniques can supplement other research to provide insights into the role of PA upon the longitudinal trajectory of MCI- or AD-related neurodegeneration. Specifically, we aim to discuss the use of structural magnetic resonance imaging (MRI), blood oxygenation level-dependent (BOLD) functional MRI (fMRI), magnetic resonance spectroscopy (MRS), diffusion tensor imaging (DTI) and positron emission tomography (PET) in conjunction with neuropsychological assessments, as well as the usefulness of these techniques for quantifying changes in cognitive function, brain structure and physiological function prompted by PA.

2. MCI/AD Demographics and Public Health Significance

Approximately 5.4 million Americans now live with diagnosed AD and this number is projected to nearly triple by 2050 to a projected 13.8 million [12]. According to the Alzheimer’s Association (alz.org), ~10 million baby boomers are expected to develop AD in the United States. Given these estimates, it is imperative to identify effective strategies which can delay and even prevent MCI/AD onset in this particularly significant population. AD patients often depend upon long-term assistance from others, which has increased the economic and clinical burden of the disease and has turned AD patient care into one of the foremost financial challenges of modern healthcare [13]. In 2016, AD and other forms of dementia cost the nation $236 billion whereas, by 2050, AD is projected to require healthcare expenditures in excess of $1 trillion, with costs to Medicare alone expected to increase by ~360% [13]. Public health concerns, along with the extraordinary costs which accompany AD patient care, highlight the tremendous importance of scientific research to the task of alleviating the burden of this disease.

Individuals with MCI have a 10-30% chance of developing AD [14], and the time period associated with MCI onset offers a critical window when interventions to stave off MCI progression to full-blown AD can be implemented. Consequently, a prominent goal among AD researchers and clinicians has been to develop strategies which might delay and even prevent the onset of the disease. Currently, there are no available medications or nutritional supplements to cure AD [15], and pharmaceutical agents have not yielded a satisfactory level of treatment efficacy. The administration of antipsychotic medications to alleviate behavioral dysfunction and dementia-related psychosis is widespread [16], though their use comes with limited benefits and with an increased risk of premature death [17]. For these and other reasons, a growing number of clinicians and healthcare policy makers have been seeking alternative strategies for AD prevention.

3. PA for Altering the Trajectory of MCI/AD

Undertaking PA, performing mentally-stimulating activities and avoiding or reversing obesity can decrease AD risk or even stall its progress. In the case of PA, it has been challenging to quantify the effects of this type of intervention because PA regimen, duration and intensity vary extensively across studies [7]. Partly for this reason, formulating a
standardized PA routine to delay the onset of MCI/AD has been an elusive goal. Investigating the effects of various PA regimens is nevertheless important because making a healthy lifestyle choice involving PA is more enjoyable to an individual if s/he has a wide array of options from which to choose. Walking is a popular exercise for AD patients [18], partly due to the advanced age and lack of physical ability in this patient group. While it is common for researchers to study the effect of aerobic PA (such as walking) as an intervention, the impact of PA routines other than walking—such as resistance training, yoga, tai chi, cycling, etc.—has also been investigated. Two important considerations which should be taken into account when formulating PA regimens for MCI/AD patients are that (1) activities often need to be kept relatively simple and (2) exercise routines may need to be fairly easy for older adults to complete without much strain.

4. Combining Neuroimaging with Psychometrics to Assess PA Efficacy

Neuroimaging methods, which have been used to study the relationship between PA levels and neural integrity in AD, range from MRI [19] and MRS [20] to PET [21] and DTI [22]. In the context of our topic, one motivation for adopting a multimodal neuroimaging approach to investigate PA-related changes in MCI/AD trajectories is the fact that different neuroimaging methods provide distinct, though complementary, insights into how the brain is affected by varying PA levels. For this reason, multimodal studies offer the unique opportunity to understand the relationship between structural/functional brain changes and neuropsychological function (as assessed psychometrically) to monitor cognitive decline in MCI/AD patients [23]. Thus, neuroimaging insights pertaining to patients’ cognitive decline can complement those offered by neuropsychological testing and can additionally be quite useful because, if the latter are standardized, they often have high reliability and validity [24].

Many studies use neuropsychological assessments to gain insight into the relationship between cognitive abilities and brain health. When used in conjunction with such assessments, however, neuroimaging further allows researchers to investigate structural brain changes and abnormalities; by contrast, neuropsychological tests indicate primarily which behavioral/cognitive abilities are most vulnerable without providing insight into which neuroanatomic structures are associated with these vulnerabilities. Thus, both neuroimaging and neuropsychological evaluations are important when evaluating the efficacy of lifestyle interventions which aim to modify the trajectory of neurodegeneration in MCI/AD. Incidentally, using both approaches allows for greater accuracy in predicting the rate of MCI conversion to AD [25]. Similarly, the use of correlations between neuropsychological and neuroimaging measurements can be extended to examine the effects of PA interventions in these patients.

As expected, many studies investigating PA effects upon the mental abilities of MCI/AD patients have focused on memory, since this cognitive domain is most severely affected by many types of dementia, including AD. Specifically, cognitive improvements associated with PA often involve changes in neuropsychological variables which are descriptive of both short- and long-term memory, particularly regarding patients’ ability to orient themselves [25]. This ability can be quantified using the Mini-Mental Status Examination (MMSE), which is a commonly-used neuropsychological diagnostic examination for a variety of neurodegenerative disorders and which can also be used to rule out neurodegenerative processes in other conditions [26]. The MMSE queries patients on their physical location, on the current date and day of the week as well as on other short-term memory items pertaining to one’s ability to orient oneself. As expected, patients who fail this test are at considerable risk for being diagnosed with late MCI or AD because one’s failure to orient oneself in space and time indicates the existence of severe memory deficits which curtail the ability to perform routine activities. The rate of long-term memory loss—which is similarly affected by AD above and beyond the extent expected in normal aging—also appears to decelerate with increased PA [27].

Since there are unique cognitive deterioration patterns associated with both MCI and AD, neuropsychological assessments and neuroimaging can be used together to diagnose and differentiate MCI from AD patients [26] and additionally to provide quantitative associations between behavioral and neuroanatomical trajectories. For example, because the hippocampus is heavily involved in short-term memory encoding and retrieval, this structure has received considerable attention from neuroimaging experts whose aim is to quantify how memory decline is paralleled by changes in hippocampal volumetrics and morphometry. PA interventions have been shown to reduce the rate of atrophy in the hippocampus, which has been linked to improvements in MCI/AD patients’ ability to carry out routine activities [19]. Additionally, PA has been proposed as an intervention to decelerate the atrophy rates observed in other areas of the AD-affected brain, such as the frontal cortex and certain areas of the parietal lobe [11]. These and other studies suggest that neuroimaging and psychometric assessments should be further integrated to evaluate PA effects upon MCI/AD trajectories. Since the relationship between PA and cognitive function improvement in dementia appears to be insufficiently understood to inform patient-tailored clinical decision making, further research on this relationship could aid in designing novel PA interventions in which are personalized specifically for MCI/AD patients.

5. PA Effects Upon Brain Structure

As already stated, there is substantial evidence suggesting that PA can affect the trajectory of MCI/AD and delay the onset of these conditions [28, 29]. However, the extent and
manner in which PA intensity, duration, and frequency can alter brain structure and clinical outcome in MCI/AD has not been fully ascertained. For this reason, PA effects upon brain anatomy in MCI/AD—especially upon the hippocampal formation and upon temporal cortex—could certainly benefit from additional investigation.

To investigate the relationship between PA intensity and memory function trajectories in older individuals with MCI, [28] recruited 47 MCI patients for whom (A) walking speed during exercise was measured to quantify PA intensity, and (B) the Scenery Picture Memory Test (SPMT) was administered to quantify cognitive function. Stepwise multiple linear regression was used to analyze the relationship between PA intensity and SPMT scores and MRI was used to examine the relationship between semantic memory activation and PA intensity to determine whether varying levels of PA intensity could be associated with neuroanatomical changes in brain regions involved in semantic memory storage and retrieval. The results of this study indicated that (A) increasing PA intensity was strongly correlated with improvements in short-term memory function and that (B) decreasing PA intensity was associated with faster decline in patients’ memory recall abilities. The authors also found that, when their volunteers increased their PA intensity, the rate of their motor function decline decreased as well. These findings illustrate the fact that neuroimaging should be used more widely to investigate PA effects upon memory function.

Unlike the study by Tanigawa et al.—who only used walking speed to study the effect of PA upon cognitive decline—Hoffmann et al. (2013) investigated whether aerobic PA can simultaneously improve spatial memory function and also alleviate the severity of mental health conditions in AD patients [29]. Specifically, these authors used both amyloid β (Aβ) PET and MRI to study AD-related brain pathology in a cohort of 192 patients. Additionally, the researchers obtained cerebrospinal fluid (CSF) and blood plasma samples from their patients to monitor PA effects upon AD pathology. Hoffmann et al. found that increases in aerobic PA intensity were significantly associated with increases in both the spatial memory recall abilities and the mental health of study participants, leading to the conclusion that moderate- to high-intensity aerobic PA can alleviate certain cognitive impairments associated with AD.

In a study by Yu et al. (2014), the effects of aerobic PA upon cognitive impairment and upon hippocampal volume were studied in a clinical trial with a randomized, controlled design [19]. The researchers examined the effects of a 6-month, individualized, moderate-intensity cycling intervention (20 to 50 minutes per session, 3 times a week) in 90 community-dwelling older adults mild-to-moderate AD. The study group consisted of 60 patients while the control group consisted of 30 volunteers who undertook physical stretching exercises instead of cycling. \(T_1\)-weighted structural MRI volumes were acquired from all patients using the same scanner and protocol in all patients and hippocampal volumes were then calculated. The authors found that, in AD patients, aerobic PA was significantly associated with the alleviation of memory loss severity and with the attenuation of mental health comorbidities.

The presence of the apolipoprotein E genotype (APOE) \(\varepsilon4\) allele is one of the few established risk factors for AD, and there is growing evidence to support the notion that PA is more associated with cognitive gains in those at highest genetic risk of developing AD. Indeed, the protective effects of exercise appear to be greater in APOE-\(\varepsilon4\) carriers in many studies [11] [30]. This could be because APOE-\(\varepsilon4\) carriers have substantial potential for improvement in motor ability: the APOE-\(\varepsilon4\) allele has been associated with relatively faster motor decline among older adults [31], even when controlling for cognitive status and for many other factors, such as race, body mass index, vascular risk factors and diseases. Recently, it was found that MCI patients who are APOE-\(\varepsilon4\) carriers exhibit a significantly slower average walking speed compared to non-carriers [32].

Smith et al. (2014) used a 3 T scanner to acquire \(T_1\)-weighted structural MRI volumes from 97 volunteers, used FreeSurfer software [34] to segment each brain and then investigated whether PA could affect the rate of hippocampal atrophy in AD patients [33]. Based on a self-report questionnaire regarding PA frequency and intensity, participants were assigned to one of two groups, depending on whether they habitually undertook either high or low levels of PA, respectively. AD risk status in each volunteer was defined by the presence or absence of the APOE-\(\varepsilon4\) allele and four subgroups were studied, namely low risk/high PA (N = 24), low risk/low PA (N = 34), high risk/high PA (N = 22) and high risk/low PA (N = 17). The authors found that high PA is associated with longitudinal decreases in the rate of hippocampal atrophy, particularly in individuals at increased genetic risk (APOE-\(\varepsilon4\)) for AD. The study also suggested that patients could potentially reduce hippocampal degeneration by increasing their PA levels, though the authors did not investigate the relationship between changes in PA levels and other neuroimaging variables. Future studies should aim to investigate the neural differences underlying PA effects upon cognitive and motor decline in healthy subjects as well as in MCI and AD patients, APOE-\(\varepsilon4\) carriers and non-carriers.

Aside from neurodegeneration in the hippocampus, cortical atrophy is another hallmark of AD. Reiter et al. (2015) explored the effect of PA upon cortical thickness using whole-brain \(T_1\)-weighted MRI volumes acquired using a spoiled gradient echo (SPGR) sequence [35]. The authors found that increases in PA levels were associated with atrophy rate decreases in the inferior and superior frontal cortices. Additional PA effects upon cortical structure have been found in studies where dietary interventions were also used; these findings are discussed in the following section.

6. Diet, PA, and Brain Structure

Aside from PA, diet is another modifiable lifestyle factor which may play a role in the AD progression. Higher levels
of PA and omega-3 fatty acid consumption have both been independently associated with better cognitive performance in healthy adults [36]. Diets which are low in omega-3 fatty acids have been linked to delayed brain development [37-41] and, in late life, to increased risk for AD [42]. Relatively high levels of docosahexaenoic acid (DHA) – the most abundant omega-3 fatty acid in neural tissue – in blood and high self-reported DHA intake have been associated with better executive function in middle age [43][44]. DHA mediates this effect by regulating ion pump and channel activity [45] and neurotransmitter release [46][47], thereby modulating neural signaling and brain activity in general [48]. Increasing omega-3 fatty acid intake has also been shown to enhance the production of glutamate, dopamine, acetylcholine, and serotonin [47], leading to better working memory, processing speed and cognitive flexibility in middle-aged adults [43]. A recent review of the literature suggests that higher intake of omega-3 fatty acids improves cognitive performance by enhancing neural efficiency and by decreasing the total amount of neural activity required to complete cognitive tasks [48].

Low intake of omega-3 fatty acids, which is characteristic of the typical American diet (US Department of Agriculture, 2014) has also been linked to an increased risk for developing AD [42]. As such, dietary supplementation has been proposed as a potential therapeutic intervention in AD. Despite all of the above, the effects of fatty acid intake upon neurocognitive function appear to be less clearly established than the effects of PA, with many studies yielding only limited evidence or showing variable domain-specific effects [42]. Omega 3 fatty acids and PA may exert similar biological effects, such as improving cardiovascular health [52][53], so it is quite reasonable to wonder whether omega-3 fatty acid consumption might have a moderating effect upon the neurocognitive benefits achieved through PA. A recent study by Leckie et al., for example, showed that higher levels of omega-3 fatty acid intake can actually offset the deleterious effect of low PA levels, thereby essentially mimicking the effect of engaging in more exercise [54]. It may be the case that a diet rich in omega-3 fatty acids can help mitigate the drawbacks of a more sedentary lifestyle in older adults with MCI/AD who have low ability to engage in PA, perhaps to the extent that dietary changes can play a more substantial role than PA in this group.

Theresa et al. (2016) used a randomized interventional design to examine the effects of combining omega-3 fatty acid supplementation with aerobic PA and with cognitive stimulation (target intervention) in MCI patients (N = 22, 8 females) [55]. T₁-weighted MRI volumes acquired at 3 T were used to quantify intervention-related changes in various areas of the cortex, including frontal, parietal, temporal and cingulate regions. A total of 13 patients completed a cycling training routine in conjunction with omega-3 fatty acid intake (target intervention) while the other 9 patients did not undergo the aerobic PA routine though they did participate in the omega-3 fatty acid intake experiment. Study results showed statistically significant differences between the two groups, namely (1) accelerated rates of GM volume decrease in the frontal, parietal and cingulate cortices of control patients and (2) relatively-slower rates of GM atrophy in the study group, leading to the conclusion that omega-3 fatty acid intake, when combined with aerobic PA, can decelerate cortical atrophy in MCI patients.

7. Effects of PA Upon BOLD Activity

Whereas structural MRI studies have observed brain adaptations in response to PA in individuals with MCI or AD (as detailed in the previous section), there is a dearth of literature examining such adaptations using fMRI. An extensive search of scholarly databases yielded only several studies on this topic. In one of these [56], whole-brain fMRI was used to measure semantic memory in 17 MCI subjects (78.7 ± 7.5 years old, mean ± standard deviation) and 18 healthy control volunteers (76 ± 7.3 years old) who participated in a 12-week treadmill walking intervention. The intervention was repeated four times per week for 30 minutes, with an additional 10 minutes of warm-up and cool-down. Both groups improved their VO₂ max, a measure of aerobic fitness. Participants completed an fMRI famous-name discrimination task and a neuropsychological test battery before and after the study, and post-intervention performance on a list-learning task was found to be significantly better after the study in MCI participants compared to control volunteers. fMRI measurements showed relative decreases in BOLD responses following semantic memory recruitment, along with improved episodic memory performance. In light of this, the authors posited that PA may improve neuronal communication efficiency as well as cognitive function in the study group of older adults with MCI. However, there was no follow-up of neuropsychological assessments to investigate their relationship to BOLD signal changes, such that caution is needed when interpreting these results.

In AD patients, PA has been found to have beneficial effects upon functional brain connectivity. Taubert et al. (2011) used structural MRI and fMRI to study brain connectivity longitudinally in 14 AD patients who underwent a six-week PA training routine [57]. In the study group, the results of the study showed a bilateral increase in functional network centrality associated with supplementary and pre-supplementary motor areas (SMAs and pre-SMAs, respectively) and with the right ventral premotor cortex (VPMC) across three weeks of training. The observed changes in internal functional connectivity between the left SMA/pre-SMA and the mPL (medial parietal lobe) were interpreted as being in agreement with previous findings on microstructural alterations in underlying WM fiber tracts and on functional connectivity increased observed in tandem with increases in local GM densities. In the 14 control volunteers without AD, however, there were no statistically significant changes in connectivity between cortical areas, leading the authors to propose that the observed decreases in the rate of GM atrophy were associated with beneficial functional connectivity alterations in the regions examined. The overall
conclusion of the study was that PA could bring about improvement in cognitive function in both AD and MCI by means of altering both structural and functional brain connectivity.

An fMRI study by Eyre et al. (2016) used yoga as the PA intervention and recruited participants with MCI who were randomly assigned to either a yoga group (N = 14; 67.1 ± 9.5 years old) or to a control group (N = 11; 67.8 ± 9.7 years old) [58]. The participants in the control group were assigned to a memory enhancement training (MET) protocol. Neuropsychological assessments of verbal memory and visuospatial function were obtained, and clinical depression scores were also measured using the Geriatric Depression Scale. Subsequent analysis focused on four functional networks related to long-term memory, namely the default-mode network (DMN, which includes the precuneus, anterior and posterior cingulate cortex as well as medial frontal cortex), the posterior DMN (precuneus, lateral parietal cortex and the hippocampus), the language processing network (involving, among others, Broca’s and Wernicke’s areas) and the superior parietal network. Resting-state fMRI results showed that improved verbal memory was positively correlated with increased functional connectivity across the DMN and the language network. No significant effects were identified in the posterior DMN. Increased activity in the superior parietal network was negatively correlated with improved memory recall. Participants in the yoga group also exhibited significantly improved depression scores and visuospatial memory function.

It has been posited that advanced age is associated with decreased WM tract integrity [59][60] and with the disruption of WM connections (including those which form the DMN). Some researchers have also proposed that functional impairments of the DMN depend upon the extent of WM tract discontinuity [61], with high levels of functioning being associated with high integrity of white matter networks. This indicates that using fMRI in conjunction with DTI could prove valuable for evaluating both functional and structural responses to PA in older adults, particularly since the DMN is associated with cognitive functions which include memory and planning [61]. Further investigation of decreased WM anatomical connectivity is merited in both healthy aging populations, as well as patients with MCI and AD [62].

8. Insights from PET

There is a wide range of biomarkers which can help to distinguish healthy subjects from MCI patients, on the one hand, and MCI from AD patients such as Aβ (1-42) and T-tau levels, on the other hand [63]. The neurodegenerative processes which lead to MCI and AD are accompanied by complex biochemical changes which ultimately result in brain pathology. Such changes may be detectable by monitoring patients’ cerebrospinal fluid (CSF), though the invasiveness of this strategy prohibits its use in most MCI/AD patients. An indirect way to measure and quantify the extent to which brain metabolism changes due to MCI/AD-related neurodegeneration is PET, which involves the use of radioactive tracers to quantify various aspects of brain metabolism. Two of the most common tracers used to study MCI/AD patients are the Pittsburgh compound-B (PiB) [64] and 18F-fluorodeoxyglucose (FDG) [65]. Like CSF biomarkers, PET can provide substantial insight into the neuropathological changes occurring in MCI/AD patients.

PET studies aiming to quantify the effect of PA upon the brains of MCI/AD patients have allowed scientists to quantify some of the biochemical changes associated with these conditions. Cellular metabolism in the brain is substantially differently from cellular metabolism elsewhere, such that the effects of PA upon the brain are markedly different from its effects upon the rest of the body. Because glucose is the main source of energy in the brain, small changes to its biochemistry can have substantial effects upon PET signatures. In a study by Gobbi et al. (2015), it was found that PA could change regional brain glucose metabolism (rBGM) in brain regions mediating cognition such as the anterior cingulate, inferior and medial frontal gyri, in the precentral gyrus, in anterior entorhinal cortex and in the cerebellum. These authors studied 40 subjects with a mean age of 70.3 (SD: 5.4) years [21]. All subjects had an initial MMSE score of 27.4 (SD: 1.7), participated in an aerobic training program for 24 weeks, and had their rBGM measured using FDG-PET both before and after a PA intervention. The cardiopulmonary exercise test (CET) was used to measure cardiovascular parameters and the AD Assessment Scale-cognitive (ADAScog) was used as a comprehensive neuropsychological battery to assess cognitive dysfunction. The results of the study showed that, after the PA intervention, there were decreases in ADAScog scores associated with improvements in cognitive function in MCI subjects. PET showed rBGM decreases after PA in the dorsal anterior cingulate cortex (dACC), left anterior entorhinal cortex (ETC), left precentral gyrus (PCG), left inferior frontal gyrus (IFG), and left substantia nigra. However, rBGM increased after PA in right retrosplenial cortex (RSC), posterior cingulate cortex (PCC), in the ventral posterior cingulate region (PCR), in the right gyrus rectus, left medial frontal gyrus and in the right posterior lobe of the cerebellum. The pattern of relative rBGM differences in response to PA is not well understood; some studies suggested that the strong connectivity between the dorsal posterior cingulate cortex (dPCC) and dorsalateral prefrontal cortex may play a role [66], while others pointed out that the brain areas in question are known as strategic cognitive areas [67][68]. In addition, rBGM reduction has been frequently observed in AD [69][70], for example, decreases in the metabolic rate of glucose in the parieto-temporal, frontal and posterior cingulate cortices have been useful for predicting AD onset [71]. Thus, because these areas play an important role in AD pathology, metabolic changes in such regions may be useful for evaluating the effect of PA on AD patients in future studies.
PA has been shown to have a greater effect upon glucose metabolism in APOE-ε4 carriers than in non-carriers [72]. APOE-ε4 carriers who were more physically active were found to have higher glucose metabolism in the temporal lobe, while those carriers who were less physically active had higher glucose metabolism in the frontal and parietal lobes [72]. Though increased metabolism in the inferior temporal cortex and decreased metabolism in the middle and superior frontal gyri and in the right inferior parietal lobe were correlated with PA in APOE ε4 carriers, this effect was not observed in non-carriers [73], suggesting that the relationship between PA and brain metabolism requires further study.

In a study by Liang et al. (2010), PiB PET was used to map and quantify the relationship between Aβ concentrations and PA levels in the prefrontal cortex, gyrus rectus, precuneus and in the lateral aspect of the temporal lobe. This study involved healthy older adults aged 55 to 88 whose progression of aging was monitored over ~6 months. Both tau and p-tau proteins were collected from the volunteers’ CSF and their concentrations were measured using an enzyme-linked immunosorbent assay. It was found that subjects who exercised less had increased levels of PiB-labeled Aβ compared to physically-active subjects [20]. Increases in PiB metabolism measured by PET were found significantly more often in subjects who were more likely to develop AD later in life. Similarly, a team of researchers who used FDG–PET, CSF biomarkers and structural MRI found that PET allowed them to reliably predict MCI-to-AD conversion rates [74], thereby illustrating the usefulness of this technique for studying PA effects upon conversion rates.

9. Sleep and Brain Structure in MCI/AD

Both the quality and the quantity of sleep decrease during typical aging [75]-[76]. For example, complaints about sleep are more common in older adults [77]-[78] and may involve excessive daytime sleepiness, trouble falling or staying asleep, etc. Some sleep characteristics, such as excessive daytime sleepiness and frequent awakenings, are predictive of cognitive decline [77]. Older people are also less sensitive to light, which is a fundamental zeitgeber allowing humans to synchronize their sleep-wake cycle to the Earth’s 24-hour light-dark cycle. Sleep disruptions in adults with AD are similar to those observed in healthy aging adults but tend to be more extreme and to progress faster [78]. Sleep disruptions also increase as AD severity increases [79]. Nighttime sleep in AD is repeatedly interrupted by bouts of restlessness and by active periods of wakefulness, whereas daytime activities are routinely broken up by sleep intrusions [80]. As AD progresses, behavioral sleep-wake rhythms become more irregular [81]-[82]. The suprachiasmatic nucleus (SCN), which is a neural neuroanatomic structure involved in the control of the mammalian biological clock, decreases in volume with age, and it has been shown through MRI that SCN atrophy rates are twice as fast in AD when compared to an age-matched control subject [83].

There is growing evidence of a bidirectional relationship between sleep and AD pathology [84]. The onset of AD neuropathology occurs much earlier than that of cognitive symptoms and can be identified in the pre-clinical stage of the disease if neuroimaging techniques are employed during early neurodegeneration. Recent evidence suggests that, similar to Aβ pathology, sleep disturbances actually emerge prior to cognitive symptomology in AD by several years [85]. Individuals in this stage of AD—who are cognitively normal but exhibit Aβ plaques—have lower sleep quality, duration, and efficiency, and these effects are still significant even after adjusting for age, sex and for the presence of the APOE-ε4 allele [84]. Animal models have established the bidirectional relationship between AD pathology and disrupted sleep: sleep reduction begins as amyloid plaques begin to accumulate in the hippocampus and cortex, and major sleep disruptions appear once plaques are widespread [86]. Sleep phenotype has been established as a potential sensitive early biomarker of the disease [87] and electroencephalography (EEG) recordings aimed at investigating sleep phenotype have been shown to carry a high prediction accuracy (95%) for conversion from MCI to AD [88]. EEG has been around for over 100 years and is relatively inexpensive, particularly when compared to the advanced neuroimaging techniques necessary in identifying Aβ pathology and is thus more readily available to smaller clinics and research groups.

In a manner analogous to that of the SCN, exercise may also hold potential to serve as a circadian entrainment signal or zeitgeber [89]. Specifically, it has been found that short-term exercise increases sleep duration and alters sleep architecture [90]. Because physical exercise promotes neuroplasticity and protects cognitive function [91]-[92], PA routines have been proposed as potential interventions for inducing or protecting both of these phenomena in older adults at risk for AD [93]-[94]. Sleep may also play a moderating role in how exercise affects cognitive function in older adults [95], so the complex relationship between exercise, sleep, and cognitive function in older adults at risk for or diagnosed with AD should be further explored by future research.

10. Conclusion

AD is a public health epidemic whose far-reaching worldwide effect will only continue to grow. The annual costs of both treatment and caregiving are extraordinary and show no signs of slowing down. For this reason, it is critical to find additional approaches to prevent or delay the onset of MCI/AD. Multiple lines of evidence elaborated on in this review indicate that PA can improve neurological and mental health outcomes in both MCI and AD patients. This review aimed to highlight the most important findings in the existing neuroimaging literature concerning the effects of PA upon brain structure in both MCI and AD. Through the use of neuroimaging, both structural and physiological adaptations due to PA can be quantified and used in conjunction with neuropsychological assessments.

One significant strength of our paper is that we addressed PA
effects upon MCI and AD in details, and by reviewing several pieces of evidence which are cited from different articles, it indicated that PA increases neural efficiency, improves cognitive function, and decelerated brain volume loss. Also, we find that neuroimaging biomarkers have been promising in developing new ways to measure cognitive improvements due to PA. However, there are several weaknesses in this paper. The first is that we only explored the effects of PA upon MCI and AD, we need to investigate more aspects other than PA, such as medications, gene expressions, and surgeries. Besides, we did not explore how PA can slow down or prevent the MCI and AD. Future studies should aim to investigate the neural differences underlying PA effects upon cognitive and motor decline in healthy subjects as well as in MCI and AD patients, APOE-e4 carriers and non-carriers. There is a need for researchers to formulate a standardized PA routine to delay the onset of MCI/AD. The relationship between PA and cognitive function improvement in dementia appears to be insufficiently understood to inform best practices in patient-tailored clinical care, investigating this relationship further could aid in designing novel PA interventions that can be personally tailored for those with MCI/AD. Future research should focus on devising ways to integrate distinct neuroimaging modalities to provide more comprehensive understanding of how MCI/AD can be slowed down or even prevented through PA.

References


