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Combined omega-3 fatty acids, aerobic exercise and cognitive stimulation prevents decline in gray matter volume of the frontal, parietal and cingulate cortex in patients with mild cognitive impairment

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ABSTRACT

Previous studies in older adults suggested beneficial effects of omega-3 fatty acid (FA) supplementation, aerobic exercise, or cognitive stimulation on brain structure and function. However, combined effects of these interventions in patients suffering from mild cognitive impairment (MCI) are unknown. Using a randomized interventional design, we evaluated the effect of combined omega-3 FA supplementation, aerobic exercise and cognitive stimulation (target intervention) versus omega-3 FA supplementation and non-aerobic exercise (control intervention) on cognitive function and gray matter volume in patients with MCI. Moreover, we analyzed potential vascular, metabolic or inflammatory mechanisms underlying these effects. Twenty-two MCI patients (8 females; 60–80 years) successfully completed six months of omega-3 FA intake, aerobic cycling training and cognitive stimulation (n = 13) or omega-3 FA intake and non-aerobic stretching and toning (n = 9). Before and after the interventions, cognitive performance, magnetic resonance imaging of the brain at 3 T (n = 20), intima-media thickness of the internal carotid artery and serum markers of glucose control, lipid and B-vitamin metabolism, and inflammation were assessed. Intervention-related changes in gray matter volume of Alzheimer's disease (AD)-related brain regions, i.e., frontal, parietal, temporal and cingulate cortex were examined using voxel-based morphometry of high resolution T1-weighted images.

After the intervention period, significant differences emerged in brain structure between groups: Gray matter volume decreased in the frontal, parietal and cingulate cortex of patients in the control intervention, while gray matter volume in these areas was preserved or even increased after the target intervention. Decreases in homocysteine levels in the target intervention group were associated with increases in gray matter volume in the middle frontal cortex ($p = 0.010$). No significant differences in cognitive performance or other vascular, metabolic and inflammatory parameters were observed between groups. This pilot study provides preliminary evidence that omega-3 FA intake combined with aerobic exercise and cognitive stimulation prevents atrophy in AD-related brain regions in MCI patients, compared to omega-3 FA intake plus the control condition of stretching and toning. These promising findings should now be validated in a larger interventional trial.

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with devastating impact on daily activities and independent living (Sperling et al., 2011). No effective pharmacological treatment has been identified to date (Eshkoor et al., 2015). In this situation, non-pharmacological interventions like nutritional supplementation (Gomez-Pinilla, 2008; Hooijmans et al., 2012), physical activity (Colcombe et al., 2006; Erickson et al., 2011) and cognitive stimulation (Rebok et al., 2014; Sitzer et al., 2006) receive increasing attention, although no definite conclusions can be drawn so far. For example, in healthy older adults, a previous interventional trial demonstrated beneficial effects of omega-3 FA intake on brain structure and function (Witte et al., 2014a), while others did not observe significant positive effects (Dangour et al., 2010; van de Rest et al., 2008). In patients with

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mild cognitive impairment (MCI) but not in those with dementia, omega-3 FA supplementation showed a significant improvement in short- and long-term memory function, and global cognition (Chiu et al., 2008; Freund-Levi et al., 2006; Lee et al., 2013). Moreover, there are currently no published studies investigating the effect of omega-3 FA on brain structure in MCI patients.

Exercise intervention in healthy older adults has frequently been demonstrated to increase cognitive function (Albinet et al., 2010; Erickson et al., 2011; Ruscheweyh et al., 2011), yet other trials showed minimal or no effects (Blumenthal and Madden, 1988; Madden et al., 1989). Notably, several imaging studies provide evidence that exercise training increases volume of brain regions that are vulnerable to age-related and disease-related atrophy, i.e., hippocampus, frontal, temporal and cingulate cortex, and induces neuroprotective cascades, such as increased concentration of serum brain-derived neurotrophic factor (BDNF) (Colcombe et al., 2006; Erickson et al., 2011; Ruscheweyh et al., 2011). First evidence also points towards beneficial effects of physical exercise intervention on cognitive performance (Suzuki et al., 2012) and gray matter structure (Suzuki et al., 2013) in MCI patients; however, large-scale studies are still missing.

Regarding cognitive stimulation, first interventional trials in humans have suggested beneficial effects on memory functions, attention, speed, and reasoning in healthy older adults (Ball et al., 2002; Rebok et al., 2014) and MCI patients (Forster et al., 2011; Kurz et al., 2009), a finding not replicated in other studies though (Slegers et al., 2009; Vidovich et al., 2015). Moreover, memory training led to increased gray matter volume in supramarginal, entorhinal, inferior temporal and inferior frontal regions in healthy adults and patients with subjective memory complaints (Engvig et al., 2014). In sum, lifestyle interventions as described above seem promising for healthy aging; however, the exact impact is still a matter of debate.

Studies that compared assessment of single lifestyle factors with assessment of combined lifestyle patterns found higher predictive power of the latter for cognitive performance (Floel et al., 2008; Kraft, 2012; Shea and Remington, 2015). Therefore, combined interventional approaches might exert synergistic effects on brain structure and function, and thus exceed the impact of each individual intervention, a hypothesis so far mainly derived from animal models (Chytrova et al., 2010; Wu et al., 2008). Omega-3 FAs constitute more than 30% of the membrane phospholipid composition, regulating membrane structure, fluidity and signal-transduction (Gomez-Pinilla, 2008). Moreover, omega-3 FAs modulate gene expression patterns that influence homocysteine/B-vitamin pathways (Huang et al., 2013), activate energy-generating mechanisms involved in glucose and lipid metabolism (Jump, 2002), and facilitate BDNF-mediated synaptic plasticity (Akbar et al., 2005). Physical activity is also known to lower plasma homocysteine (Randeva et al., 2002; Vincent et al., 2003), to regulate glucose homeostasis (Boule et al., 2005) and to enhance BDNF release, promoting synaptic plasticity, cell survival and proliferation (Erickson et al., 2011). Both omega-3 FA and physical activity have been shown to beneficially modulate dopamine production and D2 receptor function (Davis et al., 2010; Speelman et al., 2011), ß-amyloid deposition (Oksman et al., 2006; Yuede et al., 2009) and anti-inflammatory pathways (Kiecolt-Glaser et al., 2012; Pinto et al., 2012). Hence, given these partly overlapping but also divergent molecular and cellular associations that may optimize integrity of neuronal cell membranes and myelin sheaths, and promote neurogenesis and brain plasticity, combining both interventions may show additive or multiplicative benefits on brain function and structure in the aging brain (Bamidis et al., 2014). Furthermore, these interventions would then optimize the neural substrate necessary for cognitive stimulation to induce long-term changes in cognitive performance and brain structure. Supporting this hypothesis, it has been shown in humans that combined exercise and cognitive stimulation intervention leads to a greater improvement of cognitive function (Fabre et al., 2002) and stronger neuroplastic effects measured via electroencephalogram (Styliadis et al., 2015) compared to each single intervention and a control condition; but see discussion in Shatil (2013) and Leckie et al. (2014). Moreover, functional connectivity changes are induced by combined cognitive, psychological, and physical intervention in healthy older adults compared to low control cognitive stimulation (Zheng et al., 2015).

So far, the effects of a combined approach of nutritional supplementation, physical activity and cognitive stimulation have not been tested in patients with MCI. Our main objective was to investigate if a combined lifestyle intervention would exceed the beneficial effects of a single lifestyle intervention on brain structure and function. Based on our previous positive results for omega-3 FA supplementation alone (Witte et al., 2014a), we aimed to boost these effects with the addition of aerobic physical exercise and cognitive stimulation. In a pilot study we evaluated the effects of a combination of all three intervention strategies on brain structure and function in patients with MCI, compared to omega-3 FA supplementation plus the control condition of stretching and toning. These analyses represent the primary outcome of the study. To further elucidate underlying mechanisms, we conducted exploratory analyses and evaluated markers of atherosclerosis, i.e., intima-media thickness of the internal carotid artery, and serum markers of glucose control, lipid and B-vitamin metabolism, and inflammation.

Material and methods

Study participants

Patients (aged 60–80 years) with MCI were recruited in Berlin (memory clinic of the Department of Neurology of the Charité University Hospital and Neurology specialist practice) and Frankfurt am Main (Institute of General Practice), Germany. MCI patients (amnestic; single and multiple domain) were diagnosed according to Mayo criteria based on a subjective cognitive complaint and an objective memory impairment in standardized tests (performing at least 1.5 SD below age- and education-specific norm in relevant subtests (Total Word List, Delayed Recall Word/Figures, MMSE) of the CERAD-Plus test battery (Morris et al., 1989)), relatively preserved general cognition, no impairment in activities of daily living, and no dementia (Petersen et al., 1999). Exclusion criteria comprised severe untreated medical, neurological or psychiatric disease and brain pathologies identified in the magnetic resonance imaging (MRI) scan, no right-handedness (Oldfield, 1971), non-fluent German language abilities, BMI <18 kg/m^2 or >35 kg/m^2 and intake of dietary supplements containing fish oil before starting the trial. Furthermore, patients with attendance less than 50% of physical training sessions and self-reported misses of capsule intake >5 times/week over the entire intervention period were excluded from analysis. Psychiatric comorbidity was monitored using the Beck's Depression Inventory (BDI; (Kuhner et al., 2007)) and the State-Trait Anxiety Inventory (STAI X1; (Laux et al., 1981)).

Seventy-two MCI patients were screened for study eligibility by telephone, of which 27 failed to meet inclusion criteria. The remaining 45 were invited for baseline medical examination and MRI assessment. From this group, 10 patients had to be excluded either due to a pathological MRI finding ($n = 1$) or due to comorbidities ($n = 9$; cardiac arrhythmia, Parkinson's disease, Polycythemia vera, depression). Nine patients (target intervention $n = 6$; control intervention $n = 3$) did not complete the intervention due to time constraints ($n = 9$). In total, 26 MCI patients completed the current study. Of these, four patients (target intervention $n = 2$; control intervention $n = 2$) had to be excluded because they did not meet the criteria for minimal attendance (i.e., 50%) of the exercise/sham training over the six months, leaving 22 patients for per-protocol analysis (see flowchart Fig. 1). Dropouts ($n = 23$) and successful completers ($n = 22$) did not differ with regard to baseline assessments (all ps > 0.05).