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How mind-body therapies might reduce pathological features of Alzheimer's disease

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Alzheimer's disease (AD) is an irreversible neurodegenerative disorder that is responsible for around 60–80% of all dementia cases and currently affects around 50 million people worldwide. As the population's life span tends to increase, current predictions suggest that by 2050, 152 million people worldwide will suffer from dementia (Balsinha, 2019). While the exact cause of AD remains obscure, various hypotheses regarding AD etiology have been described in the last decades. According to the amyloid hypothesis, the pathogenic changes related to AD start with the accumulation of amyloid-beta (Aß) in the brain. These Aß peptides form oligomers and insoluble amyloid plaques which are neurotoxic and trigger harmful downstream events such as the aggregation of the microtubule-associated protein Tau into neurofibrillary tangles, chronic inflammation, and brain atrophy.

Despite numerous clinical trials, to date no causal AD therapy exists. Therefore, preventive strategies that reduce the risk of developing AD are coming to the fore. Interestingly, the first pathological changes in the brain occur years to decades before the first AD symptoms arise. These early changes offer a time window for strategies that might delay or even prevent dementia symptoms. Mind-body therapies (MBTs) that are rooted in ancient eastern traditions and include practices such as yoga, meditation and mindfulness, have recently emerged as a complementary therapeutic approach for neurological diseases and conditions, as they can influence both brain structure and function. MBTs have the intention to build a connection between the brain, mind, body, and behavior to enhance the minds capacity which influences physical function and promotes overall health (Mooventhan and Nivethitha, 2017). How yoga and meditation practices affect the brain during aging and in neurodegenerative disorders has not yet been studied in detail, even though *Silver Yoga* or *Chair Yoga* has been created to meet special challenges of the senior population. During this type of yoga, adaptations of original yoga poses (asanas) are practiced sitting on a chair or using a chair for support. A limited number of studies with patients suffering from Mild cognitive impairment (MCI) or dementia mostly showed beneficial effects of MBTs on neuropsychiatric and cognitive outcomes. Nevertheless, the mechanistic link between the positive effect of MBTs and AD-related pathological processes is still missing, as there are no investigations on how yoga and meditation affect characteristic amyloid plaque and tau accumulation, neuron loss or brain growth factor level changes. However, various studies in patients with conditions other than dementia have shown that yoga and meditation can have a direct effect on parameters such as brain volume, brain-derived neurotrophic factor (BDNF), serotonin and cortisol levels as well as sleep quality, which directly or indirectly affect the pathogenesis of AD.

Neuron loss and subsequent grey matter atrophy displays one of the most prominent pathological features during the progression of AD. While the loss of < 1% of brain mass

per year from the early twenties on is part of normal physiological functioning, brain atrophy rates are much higher during AD progression. Surprisingly, to date there exists no study on how yoga and meditation affect grey matter volume in patients with dementia. However, studies in MCI patients have shown that these practices have specifically positive effects on hippocampal volumes, giving evidence that MBTs positively affect brain regions vulnerable to neurodegeneration (Fotuhi et al., 2016).
On a molecular level, the neurotrophin BDNF could be a key player in decreasing brain atrophy due to yoga and meditation practices. BDNF is predominantly located within neurons of the cortex and hippocampus of the brain and regulates their survival, function, and plasticity. Therefore, this neurotrophin exerts numerous neuroprotective effects in brain areas that are first affected by AD. Interestingly, BDNF serum levels are significantly lower in AD patients when compared to healthy controls and studies with healthy individuals showed that mind-body interventions such as yoga increase serum BDNF levels (Cahn et al., 2017). Therefore, it is tempting to speculate that the upregulation of BDNF due to yogic practices is, at least partly, responsible for the observed decreased grey matter volume loss that is related to these interventions in MCI patients.
Like BDNF, levels of the neurotransmitter serotonin are significantly lower under AD conditions when compared to healthy controls, and serotonin receptor expression has been shown to be decreased in various AD brain areas (Garcia-Alloza et al., 2004). While it was not clear for a long time whether changes in the serotonergic system are a cause or a product of AD-related brain changes, it is now known that these changes occur at very early stages of AD pathogenesis, as they are already present in MCI patients. Serotonin is produced in the raphe area of the brain stem and stored in raphe nuclei. Raphe nuclei project serotonergic signals to the hippocampus, the amygdala, and the prefrontal cortex, which regulate learning and memory function. While no study so far investigated the effect of MBTs on serotonin in cognitively impaired people, in healthy individuals and patients of chronic lower back pain, yoga has shown to increase serotonin plasma and serum levels (Lee et al., 2014). Interestingly, *in vitro* studies have shown that serotonin has a direct impact on the toxic amyloid beta peptides that accumulate to insoluble Aß plaques in AD brains. One study showed that serotonin destabilizes both amyloid beta oligomers and fibrils (Hornedo-Ortega et al., 2018). As oligomers and fibrils have been shown to be the neurotoxic versions of Aß, serotonin therefore might protect against Aß-induced neuronal death. Another *in vitro* study demonstrated that serotonin receptor activation induces the non-amyloidogenic processing of the amyloid beta precursor protein, leading to the secretion of a peptide variant with neuroprotective and neurotrophic properties (Shen et al., 2011). Accordingly, serotonin release upon yogic practices might affect harmful Aß species and therefore protect from their neurotoxic effects.
Sleep problems are among the lifestyle factors that are associated with a greater risk to develop dementia. Around 40% of all AD patients suffer from sleep disturbances. Already at early timepoints of disease progression, sleep problems become present and evolve simultaneously to the accumulation of cerebral amyloid beta depositions. A direct bidirectional relationship between sleep and Aß has been demonstrated in numerous studies. Just recently it was shown that only one night of sleep deprivation significantly increases the accumulation of beta amyloid in human brains (Ooms et al., 2014). One hypothesis to explain this phenomenon is an increased activity of the glymphatic system during the night. This clearing system is supposed to transport amyloid beta peptides from the interstitial fluid out of the brain to maintain a balance between its synthesis, clearance, and re-uptake. As studies in rodent models have shown that the glymphatic

system is more active during sleep, sleep disturbances might diminish the efficient clearance of Aß (Xie et al., 2013). Studies in individuals with subjective cognitive decline as well as healthy older adults and individuals with other medical conditions than dementia have repeatedly shown that MBTs have a positive effect on sleep. Therefore, the cerebral clearance of beta amyloid and less toxic Aß species production might be promoted by an improved night sleep due to yogic practices in dementia patients.
Next to sleep disturbances, persistent high levels of the steroid hormone cortisol are associated with an increased risk to develop dementia. In AD patients, cortisol plasma concentrations have repeatedly shown to be dysregulated. After crossing the blood brain area, cortisol activates glucocorticoid receptors in various areas of the brain, with the hippocampus being particularly responsive as it contains a high concentration of these receptors. As demonstrated in both humans and animal models, an increased secretion of cortisol and its downstream signaling events is associated with an abnormal accumulation of Aß, resulting in synaptic dysfunction and neurodegenerative processes. The exact molecular mechanism behind the increased amyloid deposition due to stress remains elusive, however, initial studies showed that Aß production is stimulated by cortisol (Dong and Csernansky, 2009). In dementia patients, no study has investigated the relationship between stress levels and disease progression yet. However, other individuals with chronic stress that practiced yoga and meditation showed a measurable decrease in cortisol levels as well as lower subjective stress levels, depression, and anxiety (Danucalov et al., 2013). Accordingly, AD patients might benefit from yogic practices by a downregulation of cortisol levels and subsequent decrease of cortisol induced Aß production and deposition.
In summary, here we propose that yoga and meditation practices might act as a barrier for neurodegenerative processes and diminish the progression of AD by affecting specific pathological characteristics of the disease (Figure 1). Studies with healthy individuals and patients with conditions other than dementia clearly show that yogic practices can have positive effects on sleep, stress levels, BDNF and serotonin levels as well as brain volume. As both *in vitro* and/or *in vivo* studies have shown that sleep, stress levels and serotonin directly act on Aß, it is tempting to speculate that yoga and meditation might slow down disease progression in AD patients. Clearly, both long- and short-term clinical studies with dementia patients are necessary to proof this hypothesis and to clarify the relationship between MBTs and the molecular pathways implicated in AD progression.

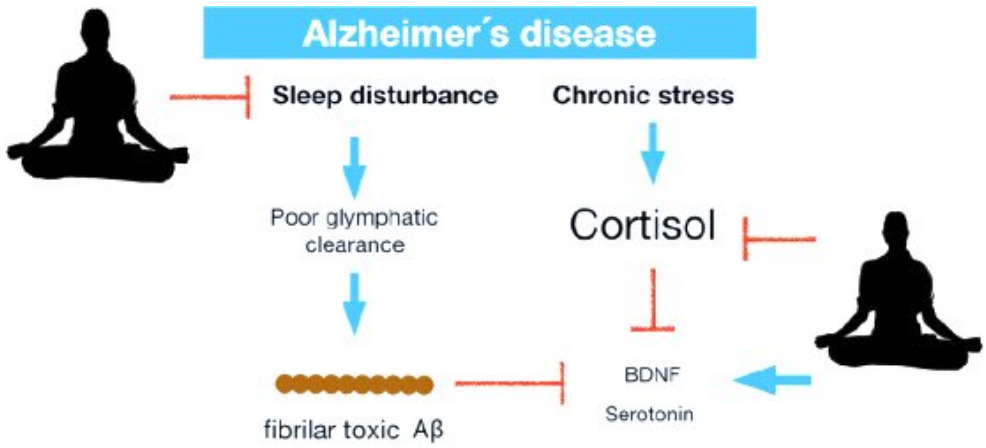

Figure 1
Mind-body therapies could reduce Alzheimer's disease progression.
By reducing chronic stress, yoga practice leads to reduced cortisol levels, and increase in BDNF and serotonin levels. Simultaneously, yoga practice improves sleep, potentially promoting glymphagtic clearance of Aß. See text for details. Aß: Amyloid-beta; BDNF: brain-derived neurotrophic factor.
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Go to:
Footnotes

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Go to:
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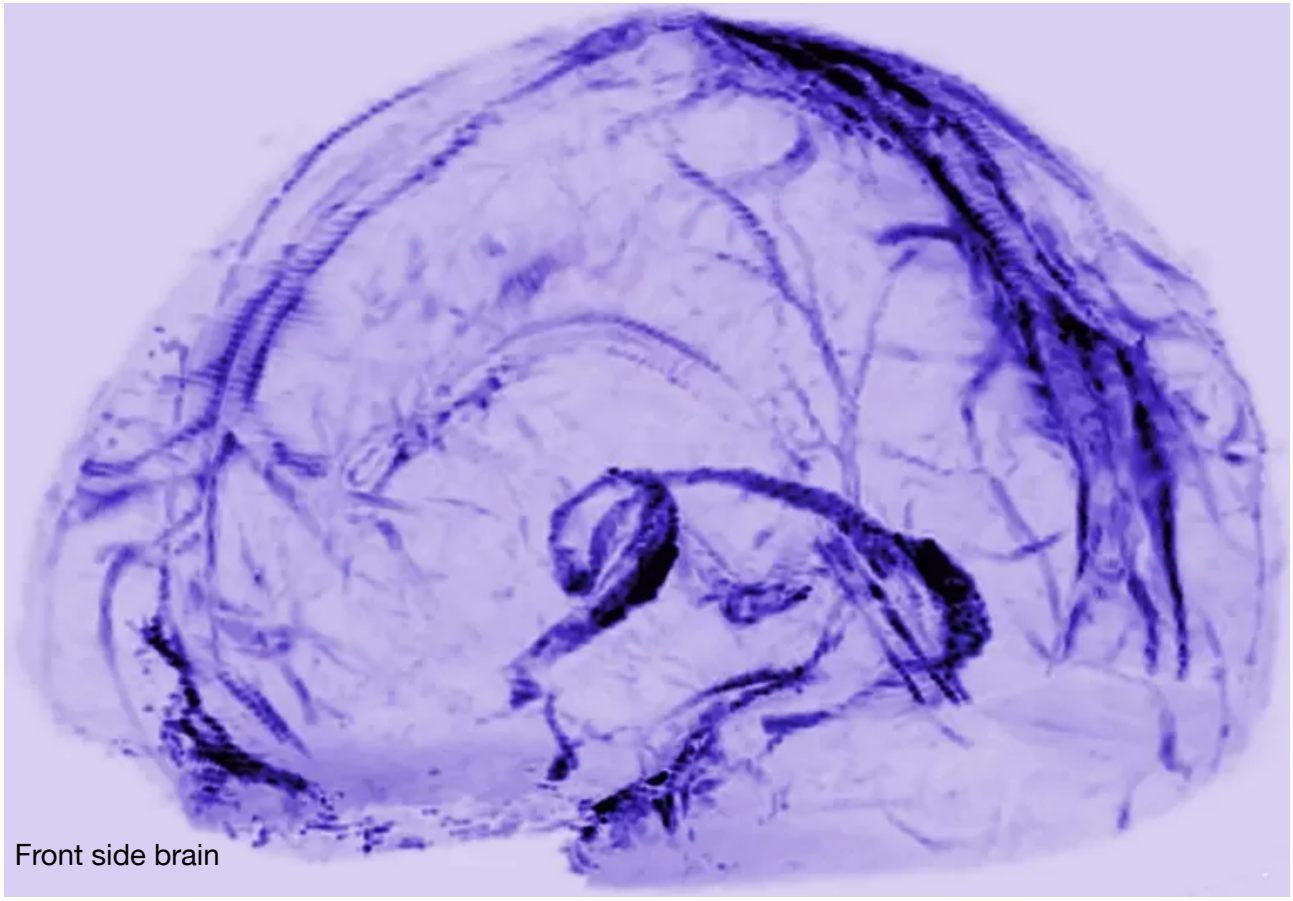
Glymphagtic system in the brain