Breathing Techniques as Neuroprotective Interventions in Older Age: Research Proposal

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Abstract

Cognitive decline in aging poses a challenge not only to medicine and psychology but to our society as a whole. Past research has led to a growing arsenal of interventions that effectively delay and reduce cognitive decline. However, it remains a problem to which extent interventions such as aerobic physical exercise can be integrated into the life of our most vulnerable populations. The study proposed here aims to investigate the potential use of breathing exercises on cognitive change and associated brain changes in older adults. Breathing exercises have been utilised for millennia in cultures across the world, but their potential has been ignored in western science until recently. In this study, a one-year intervention program will be set up to test the effectiveness of Buteyko and Wim Hof breathing in a population of healthy older adults. The effects of each technique on cognition (episodic memory and executive functions) and brain measures (hippocampal and PFC volume) will be evaluated in a longitudinal design. Potential mediating mechanisms (physiological and chemical) will also be investigated. This study will contribute not only to our understanding of cognitive and brain aging, but also explore new territories of possible interventions.

Background / Purpose

Cognitive decline and neurodegeneration are two of the most prevalent problems amongst older adults (Deary et al., 2009). Even normal cognitive aging can result in significant decreases of cognitive functions. Theories in the cognitive neurosciences, for example the theory of brain maintenance (Nyberg et al., 2012), highlight the importance of neuroprotection to reduce cognitive decline and therefore enable successful aging. Neuroprotection encompasses those mechanisms and strategies that defend the central nervous system from disease and degeneration (Rehmann et al., 2019).

One of the most promising lifestyle factors that reduce cognitive decline is (aerobic) physical activity. Its effectiveness is documented in systematic reviews and meta-analyses and is widely accepted (Blondell et al., 2014; Sofi et al., 2010). However, physical exercise requires abilities that especially older adults might lack. In general, people with physical disabilities will struggle to implement physical exercise into their daily life (Brawley et al., 2003; Forberger et al., 2017). This leads to the question, whether the effects of aerobic physical exercise can at least partially be mimicked by a less demanding form of exercise. This study proposes breathing exercises as a potential candidate.

This study will investigate whether the implementation of regular breathing exercises can have a beneficial effect on brain aging and cognitive change in older adults. Over millennia, breathing techniques have been developed to enhance physical and mental well-being. Despite this long history, their effects on human physiology have scarcely been investigated within the natural sciences. Amongst the multitude of different techniques, two have gained notable attention lastly. One is the Buteyko technique. This technique goes back to the Russian physiologist Konstantin Buteyko and consists of nasal, slow and reduced breathing with intermittent periods of breath holding (Bruton & Lewith, 2005). Studies that incorporated the Buteyko technique have so far focused on its beneficial effects on asthma (Bowler et al., 1998; Vagedes et al., 2021). It appears plausible that this technique might also have beneficial effects on brain aging. For example, slow breathing increases the levels of blood CO_2, which has been discussed to have neuroprotective functions (Yang et al., 2016; Wang et al., 2019). Increased blood CO_2 has been shown to widen blood vessels and to increase cerebral blood flow (Glodzik et al., 2013), a potentially neuroprotective mechanism that is impaired in Alzheimer's disease (Glodzik et al., 2013). Furthermore, CO_2 has anti-inflammatory effects (Galganska et al., 2021) that might also decrease inflammatory processes involved in neurodegeneration. In general, the training of nasal breathing can have beneficial effects. For example, nasal breathing helps to reduce sleep apnea (Friedman et al., 2000; Suzuki & Tanuma, 2020), a condition that has been associated with increased risk for Alzheimer's disease (Andrade et al., 2018) and other forms of cognitive dysfunctions (Pan & Kastin, 2014). Another breathing technique has gained popularity under the name "Wim Hof breathing". This technique incorporates the alternation between voluntary hyperventilation and holding of the breath. Studies have demonstrated strong acute physiological effects of this technique, for example on heart rate, blood CO_2 and oxygen levels (Citherlet et al., 2021). I have already described the potential benefits of increased CO_2 levels above. Additionally, I argue that the physiological changes induced by Wim Hof breathing might tap mechanisms through which physical exercise triggers BDNF release. For example, studies have found that BDNF expression is not only elevated in reaction to physical activity, but also under intermittent moderate hypobaric hypoxia (Semenov & Belyakov, 2022). As Citherlet and colleagues (2021) demonstrate, Wim-Hof breathing induces short term hypoxia. Also, a recent review suggests that Wim Hof breathing shows promising anti-inflammatory effects (Almahayni & Hammond, 2023). In total, it seems plausible that Buteyko and Wim Hof breathing induce physiological changes similar enough to those of physical exercise, and that the preventative and neuroprotective effects of physical exercise can at least partially be recreated by application of these techniques.

Research question

The proposed study will investigate whether regular exercise of Buteyko breathing and Wim Hof breathing has beneficial effects on the level of brain aging and associated cognitive decline in older adults.

Relevance in relation to societal / human needs

Cognitive decline in older age has become a major health care issue (Deary et al., 2009). Due to increased longevity in industrialized countries and demographic changes, this problem becomes increasingly prevalent and concerning. The negative effects of cognitive decline on the well-being of older adults have been widely demonstrated (Allerhand et al., 2014; Barrios et al., 2012). Thus, it is of major importance to investigate potential factors and mechanisms that foster brain maintenance and successful aging. Physical exercise has been recognized as the most effective preventative life-style factor, alongside nutrition and cognitive / social activities (Polidori et al., 2010). However, aerobic exercise can pose difficulties and dangers of injuries for older people. Also, we must not overlook older people with physical disabilities. To investigate neuroprotective interventions that do not exclude these vulnerable populations has to be of utmost importance in Sweden, a country that explicitly set the support of people with disabilities as a national goal (Regeringskansliet, 2017). However, not only people who are not able to practice physical exercise might benefit from the findings. While I do not want to suggest that breathing techniques should replace physical exercise, there could be complementary benefits for anyone who is willing to practice these techniques. For example, breathing techniques do not require a phase of regeneration and they do not impose such dangers as falling or muscular damage. They can be performed in many contexts either sitting or lying down. Thus, the findings would be applicable and relevant for a wide population, and a further step towards integrating neuroprotective strategies into everyday life.

Study Design

Participants

The number of n=400 participants is based on a power analysis in g*power (Faul et al., 2007) for a repeated-measures ANOVA (three groups, two measurements, Cohen's d=3.5, alpha = .0125, power = .80). Participants in the age of 65-70 years that have no symptoms of dementia or other forms of pathological cognitive decline will be recruited via flyers at hospitals and primary care units in the area of Västra Götaland and over a social media campaign that addresses both potential participants and their relatives. Before the first intervention, cognitive tests will be performed to exclude participants that have results associated with pathological cognitive impairment. Also, EKGs will be recorded during low to moderate physical activity to exclude participants with heightened risk of cardiovascular diseases. Participants excluded through these procedures will be referred to healthcare professionals for further guidance.

Study design

On the first date, all participants undergo a battery of cognitive tests (episodic memory, executive functions), an EKG and a general neuropsychological test. Hence, participants with signs of pathological cognitive decline or physical risks will be excluded from this study and referred to a healthcare professional. Included participants will then come to a second visit, on which a structural MRI image of the brain is taken. Then, participants will be randomly assigned to one of three groups. The first group will be an active control group. Here, participants will meet in weekly sessions to perform 30 minutes of guided mindfulness meditation. In the second group, a Buteyko technique intervention will be implemented. Participants will be taught the foundations of this technique (slow nasal breathing, breath holding) in a first session. After that, the group meets on a weekly basis to perform this technique for a duration of 30 minutes. In the third group, participants will be exposed to weekly guided sessions of Wim Hof breathing. Participants of all groups will be asked to repeat the practice teached in their group on at least 4 other days each week. This intervention will last for a total of 12 months. After this period, participants will again undergo testing with the cognitive test battery used on the first session. Also, structural MRI images will be taken after the last intervention session. Biological and physiological measures will be taken on a final individual intervention session during, before and after performance of the trained technique. In all training sessions, a medical doctor will be present to react to any occurring adversities.

Analytical methods

Outcome measures

Cognitive performance. Cognitive performance will be assessed on two domains: episodic memory performance and executive functions. Episodic memory will be assessed using a word recall test (Nyberg et al., 2007). Executive functions will be assessed using the FAB-Swe questionnaire (Pellas & Damberg, 2021), a screening for executive functions that has been validated in a Swedish population. It includes items on working memory, autonomy and mental flexibility, amongst others.

Structural MRI scans. Previous research has identified multiple measures that can be extracted from structural MRI images that are associated with cognitive decline in aging. In this study I will for simplicity's sake focus on two measures that have proven especially reliable. One is hippocampus volume. Volume of the hippocampus will be extracted using voxel-based morphometry (VBM). This approach has been used in many studies and the volume of the hippocampus has shown to correlate with episodic memory performance (Petersen et al., 2000). The other measure extracted from structural MRI will be volume of the prefrontal cortex (PFC), which has also been associated with memory (Hanninen et al., 1997) and executive functions (Peng & Raz, 2014).

Physiological / biological measurements. The last training session of each participant will be an individual session. During this session, multiple measurements will be conducted. Before and after practice of the trained technique, blood samples will be taken and analysed for blood levels of brain derived neurotropic factor (BDNF). BDNF is a neurotrophin that is known to have a major contribution to synaptic plasticity and the survival and differentiation of neurons (Benussi et al., 2017). It has been demonstrated to be released during aerobic physical activity (Huang et al., 2013) and is closely related to brain changes associated with cognitive performance in older adults (Buchmann et al., 2016). These blood samples will thus give an insight into the acute effects of each intervention on the expression of BDNF. Additionally, blood levels of oxygen and carbon dioxide will be assessed throughout the performance of the technique using an oximeter and a capnometer. Both Buteyko and Wim Hof breathing have shown strong effects on the relationship of these blood gases. From these measures, maximum and minimum concentrations of oxygen and carbon dioxide will be extracted as well as mean saturation and its variance. These measures will later be used to assess whether they show a relationship with the abovementioned outcomes of cognitive performance and structural imaging.

Statistical analysis

To assess group differences in cognitive change and brain atrophy, repeated-measures one-way ANOVAs will be performed. For each ANOVA, treatment is the categorical independent variable (control group, Buteyko, Wim-Hof). As both structural imaging and cognitive testing are performed pre- and post-intervention, these two time-points are included in the analysis to account for within-subject changes over the period of interventions. ANOVAS will be performed for the outcome measures of episodic memory, executive functions, hippocampus volume and PFC volume. The critical value for significance testing will be adjusted to $p=.0125$ to account for multiple testing.

To further test the mechanisms underlying potential differences in cognitive and brain changes, a path-analysis will be used. In this model, the beforementioned physiological and biological measures will be entered as predictors for the dependent variables of cognitive change (changes in episodic memory, executive functions) and brain change (changes in hippocampus and PFC volume).

Workplan

First, a period of six months will be reserved for planning the recruiting phase (design of flyers and online posts) and to further design and pilot the interventions that will be used in the group sessions. After that, the recruitment phase will start. Each participant will have a recruitment phone call, a scheduled date each for cognitive/neuropsychological assessment and for acquisition of the MRI image. The date of the cognitive assessment will also be used for informed consent.

The recruitment will be conducted as a rolling start, as the assessments and imaging do not allow for more than 4 participants per week to enter the study. Groups will reach their full size after approximately 12 months. The maximum size of each group will be approximately 65 participants, as after the first year as a participant leaves the group another enters anew. After the intervention, assessment of cognitive abilities, biological / physiological measures and structural brain images will be performed on separate dates. As the last participants will enter the study after approximately 24 months, the total duration of the intervention and measurement is estimated to be roughly 3 years.

After completion of the intervention and measurement phase, preparation and analysis of data will be performed over a span of 3 months, before the results are written up and submitted over a span of another 3 months. Thus, the total time span before results will be submitted is estimated to be 4 years.

Utilisation and communication of results

The results are supposed to be published in a scientific journal that focuses on the biological basis of aging and cognition. Moreover, if the findings happen to show significant potential benefits of breathing techniques, it might be a good aim to also communicate this as preliminary findings outside of the research community. For example, they might be communicated through social media and interviews to motivate people to engage in practicing these techniques. However, it must be stated clearly that these findings are only a first hint and that they should be seen with caution until they have been replicated in independent samples.

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