Breathing techniques as neuroprotective interventions in older age

Research proposal

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October 27, 2023

Abstract

Cognitive decline in older adults poses a challenge not only those affected and their close ones, but also to psychology and our society as a whole. Past research has constituted 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 protective effects 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, associated with an increased difficulty of everyday activities. 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 has 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. As such, it has become a major goal in the cognitive neurosciences of aging 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. The framework of successful aging has heavily been criticised to ignore factors such as disability or socioeconomic contexts, while stressing the importance of individual choice in making healthy lifestyle decisions (Katz & Calasanti, 2015; Stephens, 2017). We need to overcome this bias by investigating neuroprotective interventions that do not exclude vulnerable and marginalized populations such as older adults with physical disabilities. This 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 breathing techniques should not *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. A power analysis in g*power (Faul et al., 2007) for a repeated-measures ANOVA (within-between interaction, three groups, two measurements, Cohen's d=2.5, alpha = .0125, power = .80) resulted in a total sample size of n=135. To account for drop outs, I will adjust the desired sample size to n=168, which allows for an attrition rate of 20% while still maintaining a power of 80% for an effect of d= 0.25. 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, they will meet with their group 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 3 other days each week. This intervention will last for a total of 12 months for each participant. 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 or nurse will be present to react to any occurring adversities.

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) in Swedish language. 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 10 minutes 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 and variance. These measures will later be used to assess whether they are statistically related to the abovementioned outcomes of cognitive performance and structural imaging.

Statistical analysis

To 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, which has been accounted for in the power analysis.

To further analyse the mechanisms underlying potential differences in cognitive and brain changes, multiple regression analyses will be used for each outcome measure. The abovementioned physiological and biological measures (change in blood BDNF; change and variance in oxygen and CO_2 levels) will be entered as predictors for changes in episodic memory and executive functions as well as in hippocampus and PFC volume. Regarding the dependent variables, change refers to the difference between pre- and post-intervention measures.

Workplan

First, a period of nine months will be reserved for hiring a research assistant, planning the recruiting phase (design of flyers and online posts) and to further design and pilot the questionnaires and interventions that will be used in the group sessions. Also, the application for ethic approval will be submitted at the start of this period. After that, the recruitment phase will start. Each participant will receive a recruitment phone call to set up 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 the 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 10 months. The maximum size of each group will be approximately 56 participants, before participants finish the intervention after a duration of 12 months. 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 10 months, the total duration of the intervention and measurement is estimated to be roughly 2 years.

After completion of the intervention and measurement phase, preparation and analysis of data will be performed over a span of 6 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 3.5 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. Also, they will be presented on international conferences focusing on cognitive aging. Moreover, if the findings happen to show significant potential benefits of breathing techniques, it might be a good aim to also communicate these 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.

References

Almahayni, O. & Hammond, L. (2023). Does the Wim Hof method have a beneficial impact on physiological and psychological outcomes in healthy and non-healthy participants? A systematic review. *medRxiv (Cold Spring Harbor Laboratory)*. https://doi.org/10.1101/2023.05.28.23290653

Andrade, A. V., Bubu, O. M., Varga, A. W. & Osorio, R. S. (2018). The relationship between obstructive sleep apnea and Alzheimer's disease. *Journal of Alzheimer's Disease*, *64*(s1), S255–S270. https://doi.org/10.3233/jad-179936

Benussi, L., Binetti, G. & Ghidoni, R. (2017). Loss of neuroprotective factors in neurodegenerative dementias: the end or the starting point? *Frontiers in Neuroscience*, *11*. https://doi.org/10.3389/fnins.2017.00672

Blondell, S. J., Hammersley-Mather, R. & Veerman, L. (2014). Does physical activity prevent cognitive decline and dementia?: A systematic review and meta-analysis of longitudinal studies. *BMC Public Health*, *14*(1). https://doi.org/10.1186/1471-2458-14-510

Bowler, S., Green, A. & Mitchell, C. (1998). Buteyko Breathing Techniques in Asthma: A blinded Randomised Controlled trial. *The Medical Journal of Australia*, *169*(11–12), 575–578. https://doi.org/10.5694/j.1326-5377.1998.tb123422.x

Brawley, L. R., Rejeski, W. J. & King, A. C. (2003). Promoting Physical activity for Older adultsThe Challenges for Changing Behavior. *American Journal of Preventive Medicine*, *25*(3), 172–183. https://doi.org/10.1016/s0749-3797(03)00182-x

Bruton, A. & Lewith, G. (2005). The Buteyko Breathing Technique for Asthma: A review. *Complementary Therapies in Medicine*, *13*(1), 41–46. https://doi.org/10.1016/j.ctim.2005.01.003

Buchman, A. S., Yu, L., Boyle, P. A., Schneider, J. A., De Jager, P. L. & Bennett, D. A. (2016). Higher brain*BDNF*gene expression is associated with slower cognitive decline in older adults. *Neurology*, *86*(8), 735–741. https://doi.org/10.1212/wnl.0000000000002387

Citherlet, T., Von Roten, F. C., Kayser, B. & Guex, K. (2021). Acute effects of the Wim Hof breathing method on repeated sprint ability: a pilot study. *Frontiers in sports and active living*, *3*. https://doi.org/10.3389/fspor.2021.700757

Deary, I. J., Corley, J., Gow, A. J., Harris, S. E., Houlihan, L. M., Marioni, R. E., Penke, L., Rafnsson, S. B. & Starr, J. M. (2009). Age-associated cognitive decline. *British Medical Bulletin*, *92*(1), 135–152. https://doi.org/10.1093/bmb/ldp033

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, *39*, 175-191.

Forberger, S., Bammann, K., Bauer, J., Böll, S., Bolte, G., Brand, T., Hein, A., Koppelin, F., Lippke, S., Meyer, J., Pischke, C. R., Voelcker-Rehage, C. & Zeeb, H. (2017). How to tackle key challenges in the promotion of physical activity among older adults (65+): the AEQUIPA Network approach. *International Journal of Environmental Research and Public Health*, *14*(4), 379. https://doi.org/10.3390/ijerph14040379

Friedman, M., Tanyeri, H., Lim, J., Landsberg, R., Vaidyanathan, K. & Caldarelli, D. D. (2000). Effect of improved nasal breathing on obstructive sleep apnea. *Otolaryngology-Head and Neck Surgery*, *122*(1), 71–74. https://doi.org/10.1016/s0194-5998(00)70147-1

Gałgańska, H., Jarmuszkiewicz, W. & Gałgański, Ł. (2021). Carbon dioxide inhibits COVID-19-type proinflammatory responses through extracellular signal-regulated kinases 1 and 2, novel carbon dioxide sensors. *Cellular and Molecular Life Sciences*, *78*(24), 8229–8242. https://doi.org/10.1007/s00018-021-04005-3

Glodzik, L., Randall, C., Rusinek, H. & De Leon, M. J. (2013). Cerebrovascular reactivity to carbon dioxide in Alzheimer's disease. *Journal of Alzheimer's Disease*, *35*(3), 427–440. https://doi.org/10.3233/jad-122011

Hänninen, T., Hallikainen, M., Koivisto, K., Partanen, K., Laakso, M. P., Riekkinen, P. & Soininen, H. (1997). Decline of frontal lobe functions in subjects with age-associated memory impairment. *Neurology*, *48*(1), 148–153. https://doi.org/10.1212/wnl.48.1.148

Huang, T., Larsen, K. T., Ried-Larsen, M., Møller, N. C. & Andersen, L. B. (2013). The effects of physical activity and exercise on brain-derived neurotrophic factor in healthy humans: a review. *Scandinavian Journal of Medicine & Science in Sports*, *24*(1), 1–10. https://doi.org/10.1111/sms.12069

Katz, S., & Calasanti, T. (2015). Critical Perspectives on Successful Aging: Does It "Appeal More Than It Illuminates"? The Gerontologist, 55(1), 26–33. https://doi.org/10.1093/geront/gnu027

Nyberg, L., Lövdén, M., Riklund, K., Lindenberger, U. & Bäckman, L. (2012). Memory aging and brain maintenance. Trends in Cognitive Sciences, 16(5), 292–305. https://doi.org/10.1016/j.tics.2012.04.005

Nyberg, L., Nilsson, L., Olofsson, U. & Bäckman, L. (1997). Effects of division of attention during encoding and retrieval on age differences in episodic memory. *Experimental Aging Research*, *23*(2), 137–143. https://doi.org/10.1080/03610739708254029

Pan, W. & Kastin, A. J. (2014). Can sleep apnea cause Alzheimer's disease? *Neuroscience & Biobehavioral Reviews*, *47*, 656–669. https://doi.org/10.1016/j.neubiorev.2014.10.019

Pellas, J. & Damberg, M. (2021). Assessment of executive functions in older adults: translation and initial validation of the Swedish version of the Frontal Assessment Battery, FAB-SWE. *Applied Neuropsychology: Adult*, 1–5. https://doi.org/10.1080/23279095.2021.1990929

Peng, Y. & Raz, N. (2014). Prefrontal cortex and executive functions in Healthy adults: A Meta-analysis of Structural Neuroimaging studies. *Neuroscience & Biobehavioral Reviews*, *42*, 180–192. https://doi.org/10.1016/j.neubiorev.2014.02.005

Petersen, R. C., Jack, C. R., Xu, Y., Waring, S. C., O'Brien, P. C., Smith, G. E., Ivnik, R. J., Tangalos, E. G., Boeve, B. F. & Kokmen, E. (2000). Memory and MRI-based hippocampal volumes in aging and AD. *Neurology*, *54*(3), 581. https://doi.org/10.1212/wnl.54.3.581

Polidori, M. C., Nelles, G. & Pientka, L. (2010). Prevention of Dementia: Focus on lifestyle. *International Journal of Alzheimer's Disease*, *2010*, 1–9. https://doi.org/10.4061/2010/393579

Rehman, M. U., Wali, A. F., Ahmad, A., Shakeel, S., Rasool, S., Ali, R., Rashid, S. M., Madkhali, H., Ganaie, M. A. & Khan, R. (2019). Neuroprotective Strategies for neurological disorders by natural products: an update. *Current Neuropharmacology*, *17*(3), 247–267. https://doi.org/10.2174/1570159x16666180911124605

Regeringskansliet. (2017). *Nationellt mål och inriktning för funktionshinderspolitiken*. Regeringskansliet. https://www.regeringen.se/rattsliga-dokument/proposition/2017/05/prop.-201617188/

Semenov, Д. Г. & Belyakov, A. V. (2022). BDNF and senile cognitive decline. *Neuroscience and Behavioral Physiology*, *52*(2), 287–296. https://doi.org/10.1007/s11055-022-01236-0

Sofi, F., Valecchi, D., Bacci, D., Abbate, R., Gensini, G. F., Casini, A. & Macchi, C. (2010). Physical activity and risk of Cognitive Decline: A Meta-analysis of Prospective studies. *Journal of Internal Medicine*, *269*(1), 107–117. https://doi.org/10.1111/j.1365-2796.2010.02281.x

Stephens, C. (2017). From success to capability for healthy ageing: Shifting the lens to include all older people. Critical Public Health, 27(4), 490–498. https://doi.org/10.1080/09581596.2016.1192583

Suzuki, M. & Tanuma, T. (2020). The effect of nasal and oral breathing on airway collapsibility in patients with obstructive sleep apnea: Computational fluid dynamics analyses. *PLOS ONE*, *15*(4), e0231262. https://doi.org/10.1371/journal.pone.0231262

Vagedes, J., Helmert, E., Kuderer, S., Vagedes, K., Wildhaber, J. H. & Andrasik, F. (2021). The Buteyko Breathing Technique in Children with asthma: a randomized controlled pilot study. *Complementary Therapies in Medicine*, *56*, 102582. https://doi.org/10.1016/j.ctim.2020.102582

Wang, Y., Li, T., Cao, H. & Yang, W. (2019). Recent advances in the neuroprotective effects of medical gases. *Medical gas research*, *9*(2), 80. https://doi.org/10.4103/2045-9912.260649

Yang, W., Zhang, X., Wang, N., Tan, J., Fang, X., Wang, Q., Tao, T. & Li, W. (2016). Effects of acute systemic hypoxia and hypercapnia on brain damage in a RAT model of Hypoxia-Ischemia. *PLOS ONE*, *11*(12), e0167359. https://doi.org/10.1371/journal.pone.0167359