Effects of Aerobic Exercise on Structural Changes in Brain Areas Associated with Pain Processing in Older Adults

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Abstract

Brain structures such as the prefrontal cortex, insula and cingulate gyrus are known to be activated during pain processing. Furthermore, loss of brain structures, including cortical thinning, are seen in chronic pain patients, but also occur with normal aging. Interestingly, older adults also are at increased risk for developing chronic pain. Studies of cognition in older adults with dementia have shown recovery of brain structure along with improvements in cognition following moderate exercise programs. This study tested whether an aerobic exercise program would increase brain structures associated with pain processing in older adults. Four healthy older adults completed a 12-week aerobic exercise program using stationary bicycles. Structural MRI was performed before and after the exercise program. A total of 8 cortical and subcortical areas were targeted and included areas associated with pain processing and modulation (Insular, Rostral Anterior Cingulate, Caudal Anterior Cingulate, and Lateral Orbital Frontal) and others which are not associated with pain processing (Superior Temporal, Middle Temporal, Inferior Temporal, and Isthmus Cingulate). Significant post-exercise differences were found for right side Insular ($p = .009$), Rostral Anterior Cingulate ($p = .036$), Lateral Orbital Frontal ($p < .001$) and the Caudal Anterior Cingulate ($p = .029$) within the left hemisphere only.

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Introduction

Pain is a complex sensory experience that is processed at multiple levels of the neuroaxis. Nociception, the sensory system's response to harmful stimuli, begins at the site of injury and is further processed by the nervous system at higher levels (Garland, 2012). Recent technological advances have enabled noninvasive assessment of brain activity during pain testing. A meta-analysis of data from several imaging protocols, including positron emission tomography (PET), electroencephalography (EEG), and functional magnetic resonance imaging (fMRI), have indicated that common areas that are active during pain experiences include the prefrontal cortex, insula, and cingulate gyrus (Tracey & Mantyh, 2007).

Persistent, or chronic pain, is often defined as pain lasting beyond 3 months (Gibson & Lussier, 2012). The burden of persistent pain among older adults is significant; in large, community-based populations, up to 60% of adults over 65 years of age report chronic pain (Watkins, Wollan, Melton, & Yawn, 2008). Persistent pain can inhibit an individual's ability to perform daily activities.

Chronic pain has been associated with cortical thinning. Across a range of chronic pain syndromes, loss of volume in certain brain structures are seen in patients and may result in altered pain processing (Rodriguez-Raecke, Niemeier, Ihle, Ruether, & May, 2013). Compared with controls, patients with chronic pancreatitis showed decreased cortical thickness in their prefrontal cortices and insula. The thinning found in these areas correlated with the patients' clinical pain scores (Frokjaer et al., 2012). In another study, longer pain duration in knee osteoarthritis patients correlated with bilateral cortical thinning, once age effects were controlled (Alshuft, Condon, Dineen, & Auer, 2016).

Although the effects of aging on pain are not fully understood, several studies have suggested there is a general reduction in brain volume associated with aging. A comparison

between young adults and older adults revealed similar pain-related activity in areas such as the insula and cingulate, when subjected to noxious pressure stimulation. However, older adults demonstrated lower pain thresholds. Within the same study, there were significant between-group differences in brain volumetry; older adults had significantly less normalized brain parenchymal volume compared to their younger counterparts (Cole, Farrell, Gibson, & Egan, 2010). A longitudinal analysis of cortical thickness in older adults across 8 years also indicated that the cortical thinning followed an anterior-posterior gradient; in general, frontal and parietal regions showed greater rates of decline compared to temporal and occipital regions (Thambisetty et al., 2010). Farrell (2012) proposed that such age-associated reductions in brain volume likely impact pain processing and may, in part, explain why older adults also are at increased risk of developing chronic pain.

Cortical thickness changes are associated with changes in cognition (Jiang et al., 2016). Studies of cognition in older adults at-risk for or with dementia have shown improvements in cognition, and thus, recovery of brain structure, following moderate exercise programs (Larson et al., 2006; Lautenschlager et al., 2008). Another study analyzed the combined effects of exercise and education on cortical thinning. Longer duration of exercise was significantly correlated with greater cortical thickness globally (Lee et al., 2016). Although exercise alone was not an isolated variable, the study suggests another link between exercise intervention and increased cortical thickness.

The objective of this study is to assess whether an aerobic exercise program would increase brain structures associated with pain processing in older adults, given the correlations between cortical thinning, chronic pain, and aging, and the recovery of brain structure following exercise intervention. This study will help elucidate how chronic pain could be treated with cortical structure recovery in pain processing areas within the brain.

Aims and Hypotheses:

Aim 1: Examine the effects of a 12-week aerobic exercise intervention on pain processing, specifically via comparison of cortical thickness of pain association areas and non-pain association areas pre- and post-intervention.

- Hypothesis 1.1: Specificity in structural changes in the brain areas associated with pain processing following aerobic exercise intervention
- Hypothesis 1.2: Increased cortical and subcortical regions will occur in areas associated with pain processing (Insular, Rostral Anterior Cingulate, Caudal Anterior Cingulate, and Lateral Orbital Frontal)
- Hypothesis 1.3: No changes in areas not associated with pain processing (Superior Temporal, Middle Temporal, Inferior Temporal, and Isthmus Cingulate)

Methods

Participants

The University of Florida Institutional Review Board (IRB) approved this study (IRB#201601373). Four healthy older adults (mean = 63, SD = 6.9, with a range of 55-73), 2 males and 2 females, completed the fMRI portion of this study. Participants were recruited using posted advertisements and radio ads around the community. All participants must be physically inactive (follow no structured exercise) and obtain clearance by either their primary physician or the study's physician.

Procedure

Participants attended four pre-exercise sessions. The sessions included: an informed consent/pain testing orientation, a psychophysical pain testing session, a biomarker testing session, and an MRI session.

Brain imaging involved resting state (RS)-fMRI to assess baseline functional connectivity among regions of the brain involved in pain processing. Voxel-based morphometry was further used to assess regional gray matter volume. Following MRI, mean cortical thickness estimates for the automated parcellations of regions of interest over the left hemisphere and right

hemispheres were extracted from within FreeSurfer and exported to SPSS software for further statistical analysis.

Participants then engaged in a 12-week aerobic exercise intervention, exercising 3 times each week. Participants wore heart rate monitors to ensure that they stayed within their target heart rate. Each exercise session included a warm-up and cool down period for supervised stretching. Exercise time started initially at 20 minutes per session and increased 3-5 minutes each week to a maximum of 40 minutes. Initial baseline goal was for subjects to comfortably exercise for 20 minutes at a rate of perceived exertion (RPE) of 11-14. Intensity level of the exercise was individualized for each participant, gradually increasing from 30-40% of heart rate reserve (HRR) to a 60% of HRR maximum intensity.

Following completion of the exercise program, the participant underwent the same pre-exercise sessions, excluding the orientation session.

Apparatus

Participants performed the exercise intervention on stationary bikes that had adjustable exercise intensity levels. Borg's Rate of Perceived Exertion (RPE) scale was used to rate participants' level of physical exertion during the exercise intervention. Responses ranged from 6 (no exertion at all) to 20 (maximal exertion).

Structural fMRI was performed using a Philips 3.0T whole-body clinical MRI system, located at the UF CTSI Human Imaging Core facility at the McKnight Brain Institute.

Measures and Statistical Methods

The independent measure of this study was administration of the exercise program. The dependent measures of this study were structural measures of four cortical and subcortical regions associated with pain processing (Insular, Rostral Anterior Cingulate, Caudal Anterior Cingulate, and Lateral Orbital Frontal) and four regions not associated with pain processing (Superior Temporal, Middle Temporal, Inferior Temporal, and Isthmus Cingulate). Both right and left hemispheres were considered. Statistical significance in structural changes in cortical

and subcortical regions following the aerobic exercise program was tested using SPSS statistical program using General Estimating Equations. This procedure accounts for the correlations in region size pre- and post-exercise for each set of measurements within each participant.

Results

Our analyses focused primarily on the mean and standard deviation of volumetric changes of the cortical and subcortical brain regions pre- and post-exercise intervention, and considered both the right and left hemispheres. Wald Chi-Squared tests were conducted to determine if pre- and post-exercise volumetric changes were significantly different from zero. The results found significant differences in the areas of the brain associated with pain processing, at four of the eight hypothesized pain repeated regions. Significant pre- post-exercise differences were found for right side Rostral Anterior Cingulate (Wald Chi-square = 4.393, df = 1, $p = .036$), right Lateral Orbital Frontal (Wald Chi-square = 13.506, df = 1, $p < .001$), right Insular (Wald Chi-square = 6.840, df = 1, $p = .009$), and left Caudal Anterior Cingulate (Wald Chi-square = 4.764, df = 1, $p = .029$). Significant differences were not seen for right Caudal Anterior Cingulate, left Rostral Anterior Cingulate, left Caudal Anterior Cingulate, or left Lateral Orbital Frontal (all at $p > .15$; see Table 1).

No significant differences in volumetric changes were found in the non-pain processing regions of the brain (all at $p > .15$; see Table 2).

Discussion

The study's objective was to examine whether an aerobic exercise program would increase brain structures associated with pain processing in older adults. Our hypotheses were mostly supported; overall, specificity in structural changes was observed in the brain areas associated with pain processing following the exercise intervention. Significant pre- post-exercise differences were indicated in the areas associated with pain processing, with lateralization of the right hemisphere for three of the four areas. For the areas not associated

with pain processing, no significant differences were found in either hemisphere. The recovery of pain-processing areas could partly be explained with discussion of neurotrophins. Exercise likely increases brain-derived neurotropic factors (BDNF), an important tropic hormone involved in cellular development and central nervous system plasticity (Alomari, Khabour, Maikano, & Alawneh, 2015; Schmolesky, Webb, & Hansen, 2013).

Behavioral and clinical data suggest that pain is perceived differently in the two cortical hemispheres. Our results revealed generally greater cortical structure increases on the right side of the brain, consistent with previous studies that suggest that several regions of pain processing are lateralized toward the right hemisphere (Hsiehacd, Hannerzb, & Ingvara, 1996; Symonds, Gordon, Bixby, & Mande, 2005). Pain processing is related to attention; it requires an "alerting system" to alert an organism to stimuli. A right-lateralized pain processing system is consistent with a right-lateralized attention system (Corbetta & Shulman, 2002).

This study has several limitations. Participants missed some exercise sessions; nonetheless, all four participants attended at least 80% of the targeted 36 sessions. A fifth participant failed to complete the exercise program, resulting in a final sample size of 4. Subsequently, the study was also limited by its small sample size. Increasing the sample size could have resulted in stronger associations between increased brain areas and the exercise program.

Despite these limitations, the study contributes to the literature by recognizing aerobic exercise intervention may be linked to increased brain structures in certain pain-processing areas and has implications for treatment of chronic pain. Our results yielded moderate to large effect sizes (0.6-1.8) for the data that revealed significant differences. Our results are consistent with earlier experimental studies that modest levels of exercise are associated with recovery of brain structures in persons at-risk for dementia (Larson et al., 2006; Lautenschlager et al., 2008). Future studies are needed to investigate how other relevant pain and psychosocial biomarkers within persons with chronic pain can also be affected by exercise.

References

Alomari, M. A., Khabour, O. F., Maikano, A., & Alawneh, K. (2015). Vascular function and brain-derived neurotrophic factor: The functional capacity factor. *Vascular Medicine, 20*(6), 518-526. doi:10.1177/1358863X15598390

Alshuft, H. M., Condon, L. A., Dineen, R. A., & Auer, D. P. (2016). Cerebral Cortical Thickness in Chronic Pain Due to Knee Osteoarthritis: The Effect of Pain Duration and Pain Sensitization. *PLoS ONE, 11*(9), e0161687. https://doi.org/10.1371/journal.pone.0161687

Cole, L. J., Farrell, M. J., Gibson, S. J., & Egan, G. F. (2010). Age-related differences in pain sensitivity and regional brain activity evoked by noxious pressure. *Neurobiology of Aging, 31*(3), 494-503. doi:10.1016/j.neurobiolaging.2008.04.012

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience, 3*(3), 201-215. doi:10.1038/nrn755

Farrell, M. J. (2012). Age-Related Changes in the Structure and Function of Brain Regions Involved in Pain Processing. *Pain Medicine, 13*(2), S37-43. doi:10.1111/j.1526-4637.2011.01287.x.

Frokjaer, J. B., Bouwense, S. A. W., Olesen, S. S., Lundager,F. H., Eskildsen, S. F., Goor, H. V.,…Drewes, A. M. (2012). Reduced Cortical Thickness of Brain Areas Involved in Pain Processing in Patients With Chronic Pancreatitis. *Clinical Gastroenterology and Hepatology, 10*(4), 434-438. https://doi.org/10.1016/j.cgh.2011.11.024

Garland, E. L. (2012). Pain Processing in the Human Nervous System: A Selective Review of Nociceptive and Biobehavioral Pathways. *Prim Care, 39*(3), 561-571. doi:10.1016/j.pop.2012.06.013

Gibson, S. J., & Lussier, D. (2012). Prevalence and Relevance of Pain in Older Persons. *Pain Medicine, 13*(2), 23-26. https://doi.org/10.1111/j.1526-4637.2012.01349.x

Hsiehacd, J., Hannerzb, J., & Ingvara, M. (1996). Right-lateralised central processing for pain of

nitroglycer-induced cluster headache. *Pain, 67*(1), 59-68. https://doi.org/10.1016/0304-3959(96)03066-7

Jiang, L., Cao, X., Li, T., Tang, Y., Li, W. Wang, J.,…Li, C. (2016). Cortical Thickness Changes Correlate with Cognition Changes after Cognitive Training: Evidence from a Chinese Community Study. *Frontiers in Aging Neuroscience, 8*(118). doi:10.3389/fnagi.2016.00118

Larson, E. B., Wang, L., Bowen, J. D., McCormick, W. C., Teri, L. Crane, P., & Kukull, W. (2006). Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Annals of Internal Medicine, 144*(2), 73-81. doi:10.7326/0003-4819-144-2-200601170-00004

Lautenschlager, N. T., Cox, K. L., Flicker, L., Foster, J. K., van Bockxmeer, F. M., Xiao, J.,…Almeida, O. P. (2008). Effect of Physical Activity on Cognitive Function in Older Adults at Risk for Alzheimer Disease. *Journal of the American Medical Association, 300*(9), 1027-1037. doi:10.1001/jama.300.9.1027

Lee, J. S., Shin, H. Y., Kim, H. J., Jang, Y. K., Jung, N., Lee, J.,…Seo, S. W. (2016). Combined effects of physical exercise and education on age-related cortical thinning in cognitively normal individuals. *Scientific Reports, 6,* 24284. DOI:10.1038/srep24284

Symonds, L. L., Gordon, N. S., Bixby, J. C., & Mande, M. M. (2005). Right-Lateralized Pain Processing in the Human Cortex: An fMRI Study. *Journal of Neurophysiology, 95*(6), 3823-3830. doi 10.1152/jn.01162.2005

Thambisetty, M., Wan, J., Carass, A., An, Y., Prince, J. L., & Resnick, S. M. (2010). Longitudinal changes in cortical thickness associated with normal aging. *NeuroImage, 52*(4), 1215-1223. https://doi.org/10.1016/j.neuroimage.2010.04.258

Tracey, I., & Mantyh, P. W. (2007). The Cerebral Signature for Pain Perception and Its Modulation. *Neuron Review, 55,* 377-391. doi:10.1016/j.neuron.2007.07.012

Rodriguez-Raecke, R., Niemeier, A., Ihle, K., Ruether, W., & May, A. (2013) Structural Brain

Changes in Chronic Pain Reflect Probably Neither Damage Nor Atrophy. *PLoS ONE, 8*(2), e54475. doi:10.1371/journal.pone.0054475

Watkins, E. A., Wollan, P. C., Melton, L. J., & Yawn, B. P. (2008). A population in pain: report from the Olmsted County health study. *Pain Med, 9*(2), 166-174. doi: 10.1111/j.1526-4637.2007.00280.x.

Table 1
Mean and Standard Deviations of Pain Processing Region Volume

Brain Region	Pre-volume (in sq. mm)	Post-volume (in sq. mm)	Δ in volume	Effect size	P. value
	Mean (SD)	Mean (SD)	Mean (SD)		
Insular (RH)	2.73 (0.11)	2.81 (0.11)	0.11 (0.13)	0.8	.009*
Insular (LH)	2.87 (0.11)	2.84 (0.13)	-0.02 (0.07)	-0.3	.400
Rostral Anterior Cingulate (RH)	2.73 (0.25)	2.89 (0.16)	0.16 (0.17)	0.9	.036*
Rostral Anterior Cingulate (LH)	2.65 (0.21)	2.68 (0.18)	0.03 (0.05)	0.6	.168
Caudal Anterior Cingulate (RH)	2.45 (0.13)	2.52 (0.16)	0.07 (0.12)	0.6	.184
Caudal Anterior Cingulate (LH)	2.53 (0.11)	2.58 (0.15)	0.07 (0.12)	0.6	.029*
Lateral Orbital Frontal (RH)	2.51 (0.10)	2.57 (0.09)	0.07 (0.04)	1.8	<.001*
Lateral Orbital Frontal (LH)	2.52 (0.08)	2.52 (0.10)	0.00 (0.04)	0.0	.912

Notes. RH = Right hemisphere, LH = Left hemisphere
Effect size for Δ in volume calculated as change in region volume / SD for change
* Significant at the p<0.05 level

Table 2
Mean and Standard Deviations of Non-Pain Processing Region Volume

Brain Region	Pre-volume (in sq. mm)	Post-volume (in sq. mm)	Δ in volume	Effect size	P. value
	Mean (SD)	Mean (SD)	Mean (SD)		
Superior Temporal (RH)	2.72 (0.12)	2.76 (0.08)	0.04 (0.07)	0.5	.101
Superior Temporal (LH)	2.64 (0.08)	2.65 (0.05)	0.01 (0.03)	0.3	.315
Middle Temporal (RH)	2.69 (0.11)	2.73 (0.13)	0.03 (0.06)	0.5	.176
Middle Temporal (LH)	2.69 (0.09)	2.69 (0.05)	0.01 (0.05)	0.2	.641
Inferior Temporal (RH)	2.56 (0.17)	2.61 (0.14)	0.06 (0.11)	0.5	.178
Inferior Temporal (LH)	2.56 (0.21)	2.58 (0.16)	0.02 (0.06)	0.3	.359
Isthmus Cingulate (RH)	2.32 (0.10)	2.34 (0.11)	0.01 (0.03)	0.3	.205
Isthmus Cingulate (LH)	2.36 (0.09)	2.38 (0.19)	0.02 (0.10)	0.2	.724

Notes. RH = Right hemisphere, LH = Left hemisphere
Effect size for Δ in volume calculated as change in region volume / SD for change
* Significant at the p<0.05 level