Changes in TNF-α, IL-6, and IL-18 Predict Depression Following a 16-Week Exercise Intervention in Older Adults

Benjamin Morris[1], Timothy Helmuth, B.A.[1], Gregory Giordano, M.S.[1], Angela Bryan, Ph.D.[1]
[1]University of Colorado, Boulder, Department of Psychology and Neuroscience

Abstract

After a 16-week exercise intervention, depressive symptoms in sedentary older adults decreased ($t(75) = 2.79, p < 0.01, d = 0.297$) in a manner predicted by a composite of changes in peripheral plasma concentrations of the cytokines TNF-α, IL-6, and IL-18, and baseline depressive symptoms ($R^2adj. = 0.535, F(3,41) = 17.81, p < 0.001$).

Introduction

Exercise is well-documented to alleviate depressive symptoms, but each hypothesis explaining these effects lacks conclusive backing in humans. One such hypothesis concerns exercise regulation of cytokines, a family of signaling proteins involved in regulating the body's innate inflammatory response. Recent research has indicated a bidirectional relationship between pro-inflammatory cytokines and depressive symptoms, noting depressive symptoms in patients undergoing interferon therapies[1] and elevation of cytokines Tumor Necrosis Factor alpha (TNF-α) and Interleukin (IL) 6 in depressed patients[2].

Findings that chronic elevation of central serotonin levels bolstered hippocampal neurogenesis in adult rats[3] suggest a mechanism for cytokine alteration of depressive symptoms, as cytokines such as TNF-α reduce serotonin availability in the brain through disruption of serotonin synthetic pathways[4] and upregulation of serotonin transporters[5], while impaired neurogenesis and hippocampal atrophy are in turn linked to depression[6]. This leads to the hypothesis (Fig. 1) that exercise normalizes cytokine levels and in turn serotonin networks, increasing neurogenesis and hippocampal volume while reducing depressive symptoms.

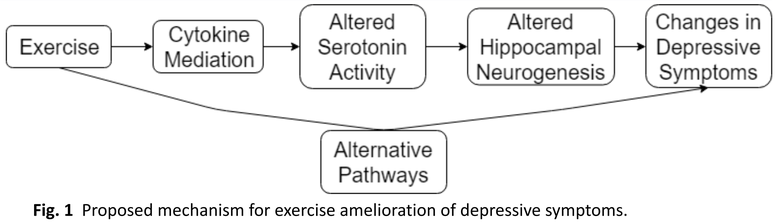

Fig. 1 Proposed mechanism for exercise amelioration of depressive symptoms.

Over 16 weeks, sedentary older adults conducted three 40-minute sessions of supervised treadmill exercise per week. Participants were assigned to either a low intensity (LI) or moderate intensity (MI) exercise group (Fig. 2). Pre- and post-intervention, depressive symptoms were assessed using the Beck Depression Inventory (BDI) and blood samples were collected to measure peripheral plasma concentrations of 13 cytokines. A younger control group, which did not participate in the exercise intervention, was used to represent baseline 'healthy' levels of cytokines.

Specific Hypotheses

1. Exercise will moderate cytokine concentrations in older adults towards the concentrations seen in younger adults
2. Changes in depression will be associated with changes in cytokines that disrupt serotonin systems and with age, as older adults will have greater cytokine dysregulation
3. MI exercisers will have greater decreases in depressive symptoms than LI exercisers

Methods

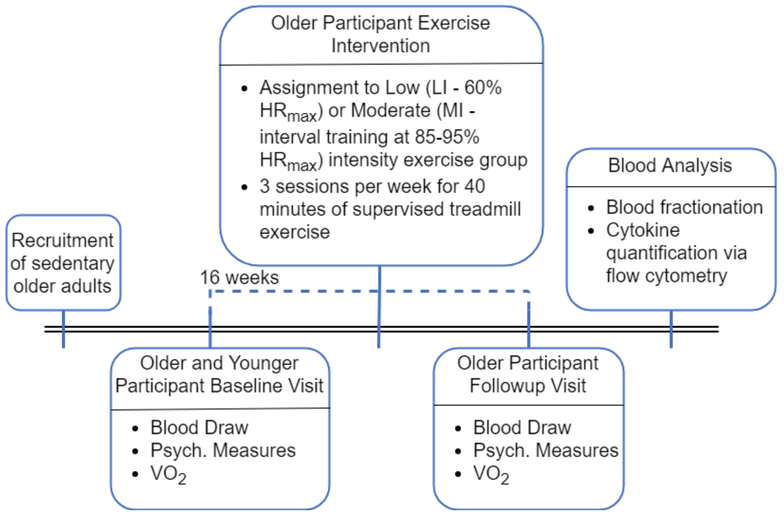

Fig. 2 Summary of methods.

Results

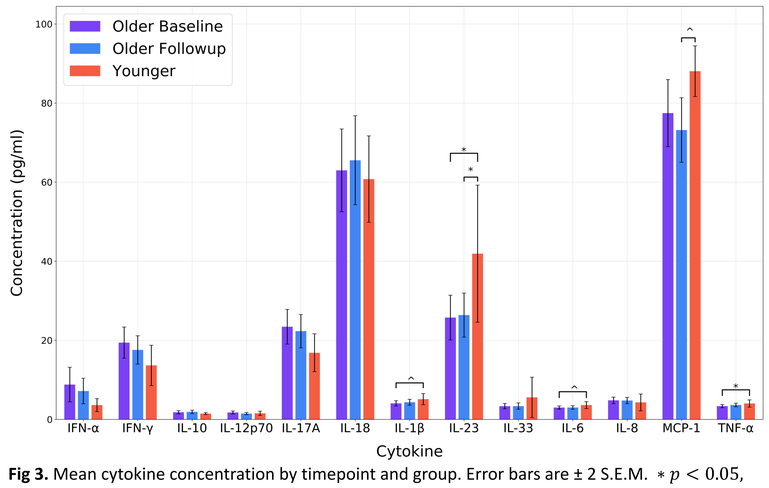

Fig 3. Mean cytokine concentration by timepoint and group. Error bars are ± 2 S.E.M. $* p < 0.05$, $\hat{} p < 0.10$, Tukey HSD by cytokine

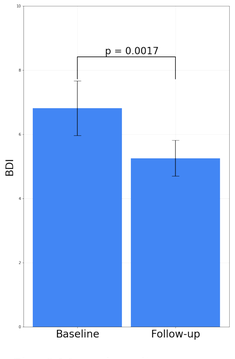

Fig. 4 Mean baseline vs. follow-up BDI. Error bars are ± 2 S.E.M

Table 1. OLS Multiple linear regression predicting follow-up BDI response from a composite of serotonin-disrupting cytokines, age, and baseline depressive symptoms ($R^2adj. = 0.535, F(3,41) = 17.81, p < 0.001$)

	Coeff.	Std. Error	t	$P(\geq \mid t \mid)$
(Intercept)	-10.09	7.4518	-1.354	0.183
Cytokine Composite	0.1607	0.076	2.107	0.041*
Age	0.1704	0.110	0.1549	0.129
Baseline BDI	0.64	0.098	6.533	7.56×10^{-8}*
	* $\rightarrow p < 0.05$			

Discussion

With the exception of IL-10, no statistically significant differences were found in peripheral cytokine concentrations or BDI at baseline across gender, race, ethnicity, or exercise condition.

Overall, post-intervention peripheral cytokine concentrations trended towards the concentrations present in the younger controls (Fig. 3). While only IL-23 ($p < 0.05, d = 0.51$) and TNF-α ($p < 0.05, d = 0.48$) differed significantly between older adults and the younger controls at baseline, younger/older group differences in TNF-α were erased at follow-up. Using the younger adults as a 'healthy' control, this suggests that regular exercise can moderate some age-related inflammation.

Further, both exercise groups had moderately reduced BDI scores at follow-up (Fig. 4) ($t(75) = 2.79, p < 0.01, d = 0.297$). However, LI exercisers experienced greater reductions in depressive symptoms than MI exercisers ($p < 0.05$, $\mu_{LI} = -2.53 \pm 1.46$, $\mu_{MI} = -0.56 \pm 1.27$).

To examine whether changes in serotonin-altering cytokines and age were associated with changes in depressive symptoms, an OLS multiple linear regression was constructed (Table 1). Due to high correlations between cytokines involved in serotonin regulation (namely TNF-α, IL-6, and IL-18), a composite variable was created as the mean concentration of these cytokines. Although it was predicted that aging increases cytokine dysregulation, and thus that exercise's normalizing influence would result in greater reductions in BDI for older participants, age was not a significant predictor of follow-up BDI. The cytokine composite variable, however, was a significant predictor of follow-up BDI ($p < 0.05$), indicating that elevation of these cytokines, which deplete serotonin availability in the brain, are associated with worsened depression following an exercise intervention.

To further ascertain the nature of cytokines' role as an intermediary between exercise and anti-depressive effects, analysis of changes in hippocampal volume from structural MRI and of alterations to pro-inflammatory/anti-inflammatory cytokine ratios could be conducted.

Acknowledgements

This work was supported by NIH/NIA grant 1R01AG043453 and funding from the University of Colorado's Biological Sciences Initiative and Undergraduate Research Opportunity Program.

References

1. Cotler SJ, Wartelle CF, Larson AM, Gretch DR, Jensen DM, Carithers RL. Pretreatment symptoms and dosing regimen predict side-effects of interferon therapy for hepatitis C. 2000 [accessed 2019 Jan 11];7(3):211–7. http://www.ncbi.nlm.nih.gov/pubmed/10849263
2. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctôt KL. A Meta-Analysis of Cytokines in Major Depression. 2010 [accessed 2019 Jan 11];67(5):446–457. https://www.sciencedirect.com/science/article/pii/S0006322309012293. doi:10.1016/J.BIOPSYCH.2009.09.033
3. Malberg JE, Eisch AJ, Nestler EJ, Duman RS. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. 2000 [accessed 2019 Apr 4];20(24):9104–10. http://www.ncbi.nlm.nih.gov/pubmed/11124987. doi:10.1523/JNEUROSCI.20-24-09104.2000
4. Fujigaki H, Saito K, Fujigaki S, Takemura M, Sudo K, Ishiguro H, Seishima M. The Signal Transducer and Activator of Transcription 1α and Interferon Regulatory Factor 1 Are Not Essential for the Induction of Indoleamine 2,3-Dioxygenase by Lipopolysaccharide: Involvement of p38 Mitogen-Activated Protein Kinase and Nuclear Factor-κB Pathways, and Synergistic Effect of Several Proinflammatory Cytokines. 2006 [accessed 2019 Jan 12];139(4):655–662. http://www.ncbi.nlm.nih.gov/pubmed/16672265. doi:10.1093/jb/mvj072
5. Zhu C-B, Blakely RD, Hewlett WA. The Proinflammatory Cytokines Interleukin-1beta and Tumor Necrosis Factor-Alpha Activate Serotonin Transporters. 2006 [accessed 2019 Jan 16];31(10):2121. http://www.nature.com/doifinder/10.1038/sj.npp.1301029. doi:10.1038/sj.npp.1301029
6. Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. Hippocampal atrophy in recurrent major depression. 1996 [accessed 2019 Apr 4];93(9):3908–13. http://www.ncbi.nlm.nih.gov/pubmed/8632988