Exploring Inflammatory Predictors of Depressive Response to Exercise

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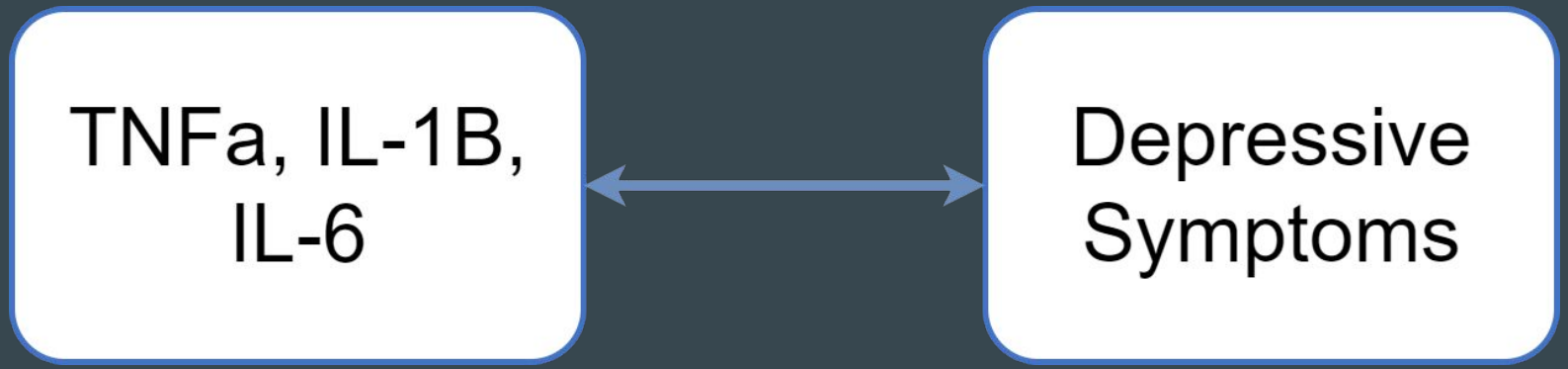
Costs of Depression

- 11% of years lived with disability globally
- Associated with cancer, cardiovascular disease, and hypertension
- 210 billion in associated costs in U.S.

Despite prevalence and impact, poorly understood

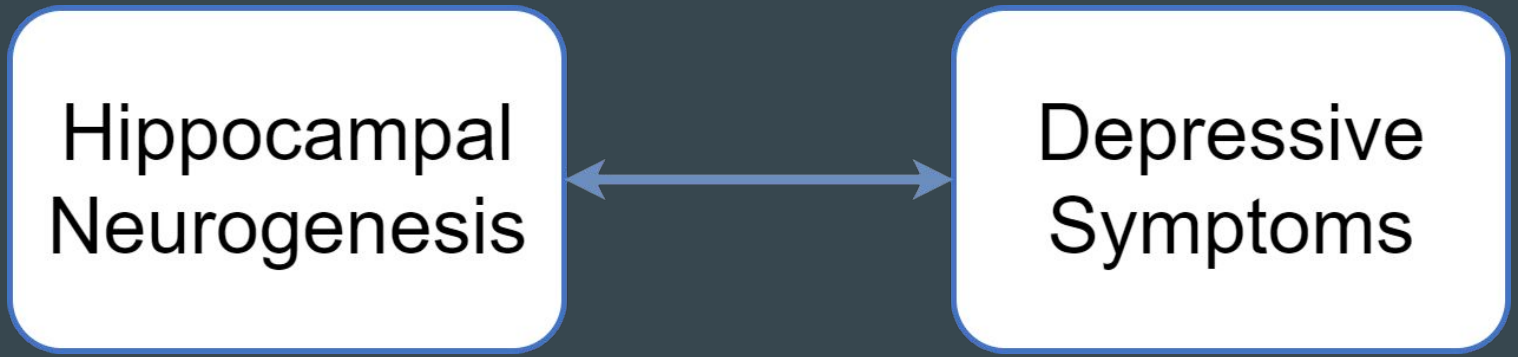
Cytokines and Depression

- Depressed patients have increased TNFa and IL-6
- Exogenous cytokine application increases depressive symptoms
- Antidepressant drugs decrease IL-1B and IL-6
- Anti-inflammatory drugs reduce depressive symptoms



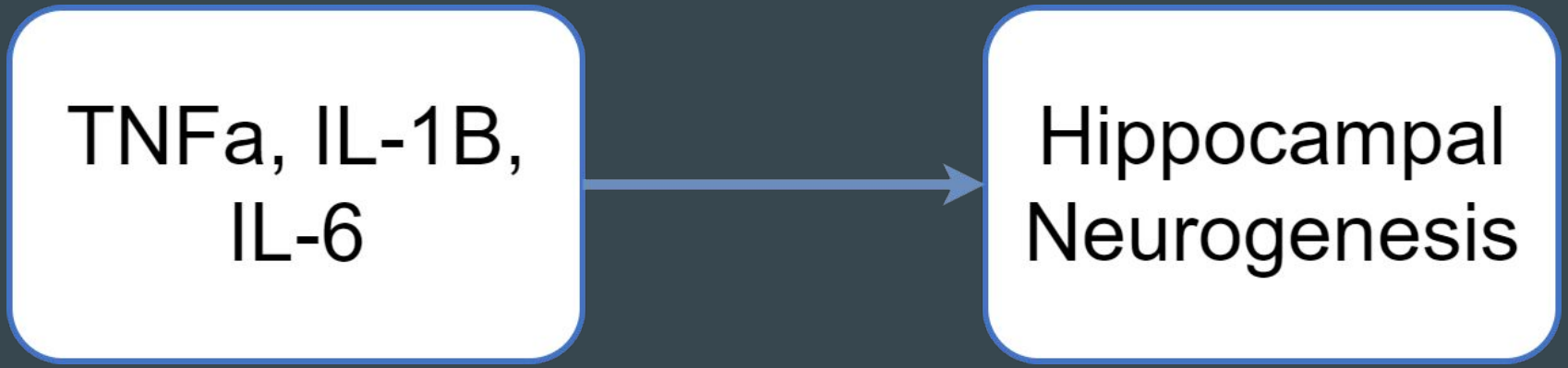
Hippocampal Neurogenesis and Depression

- Hippocampal atrophy in depressed patients
- Antidepressant drugs increase neurogenesis
  - Is neurogenesis necessary for antidepressant effects?
- Increasing neurogenesis protects against stress-induced depressive symptoms

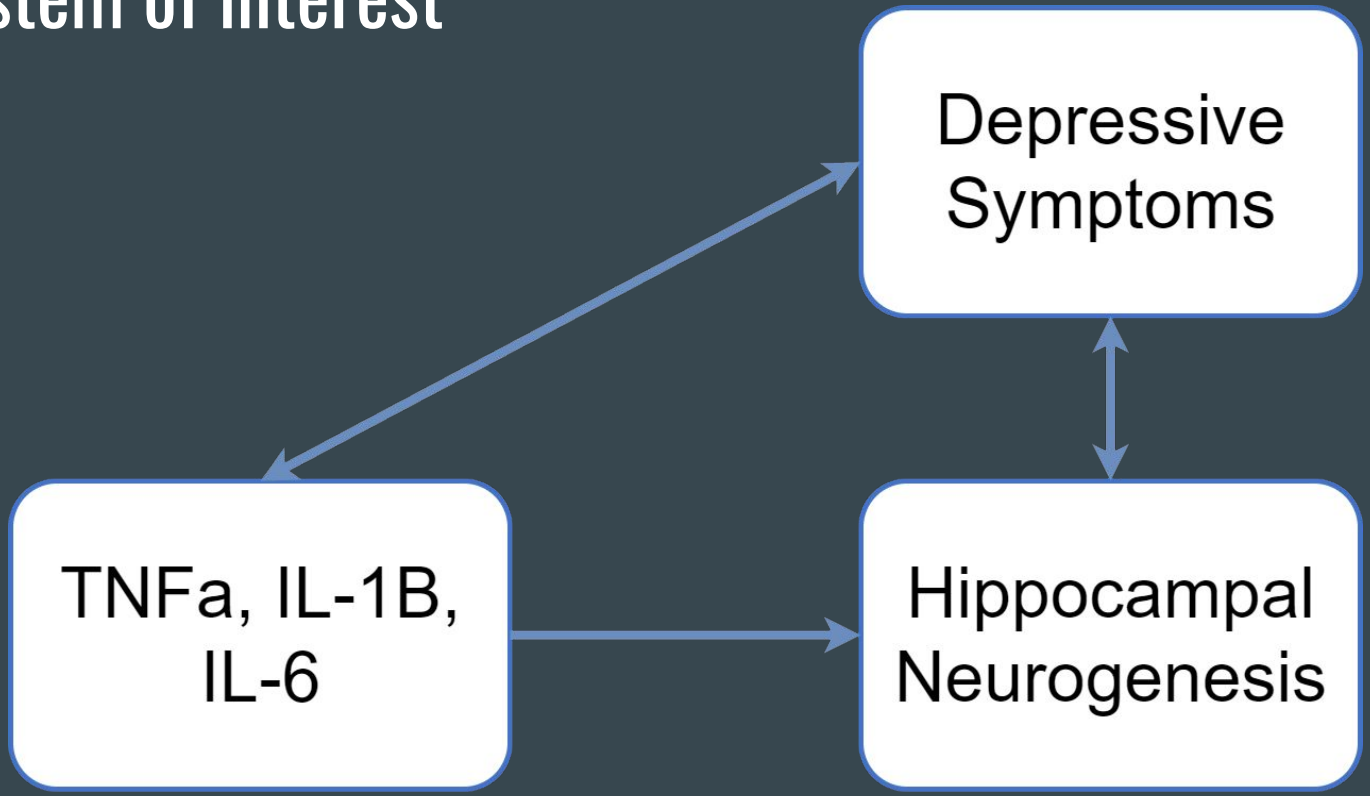


Cytokines and Neurogenesis

- IL-1B, TNFa, IL-6 decrease neurogenesis
- Blocking cytokine actions reduces depressive and anti-neurogenic effects of chronic stress



Our system of interest

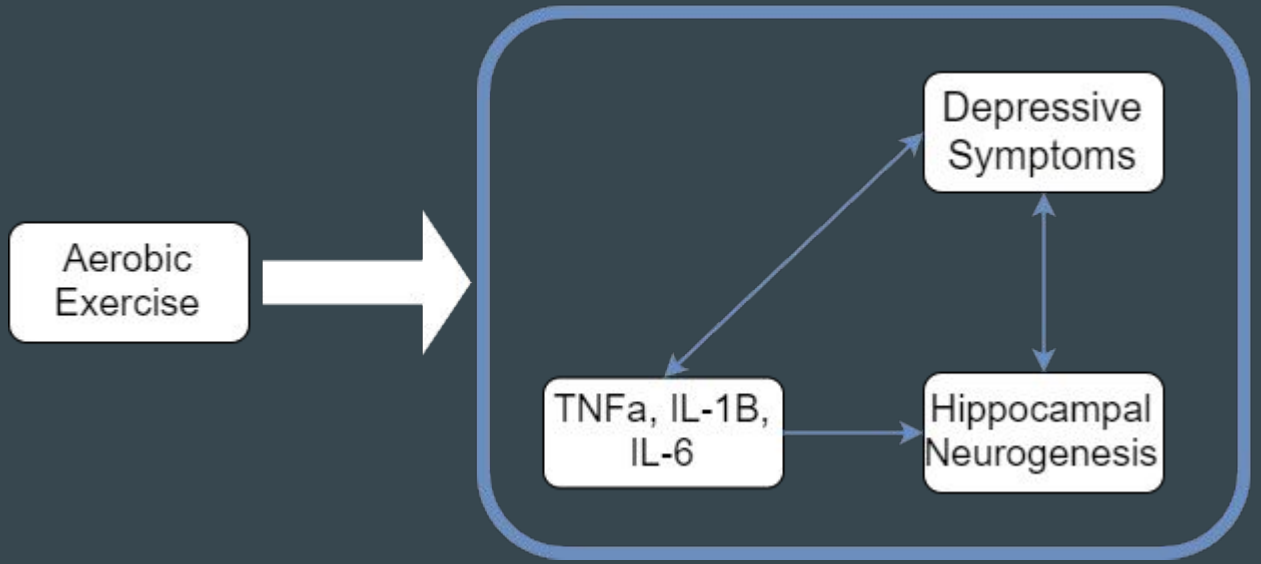


How can we better understand it?

- Hard to directly manipulate these variables
- What about manipulating the system through another variable?
  - **Aerobic exercise!**

Aerobic exercise...

- Reduces inflammation
- Increases neurogenesis
- Decreases depressive symptoms
- Easy to manipulate



Older adults as an ideal population

- Inflamed
- Sedentary
- Prevalent depression

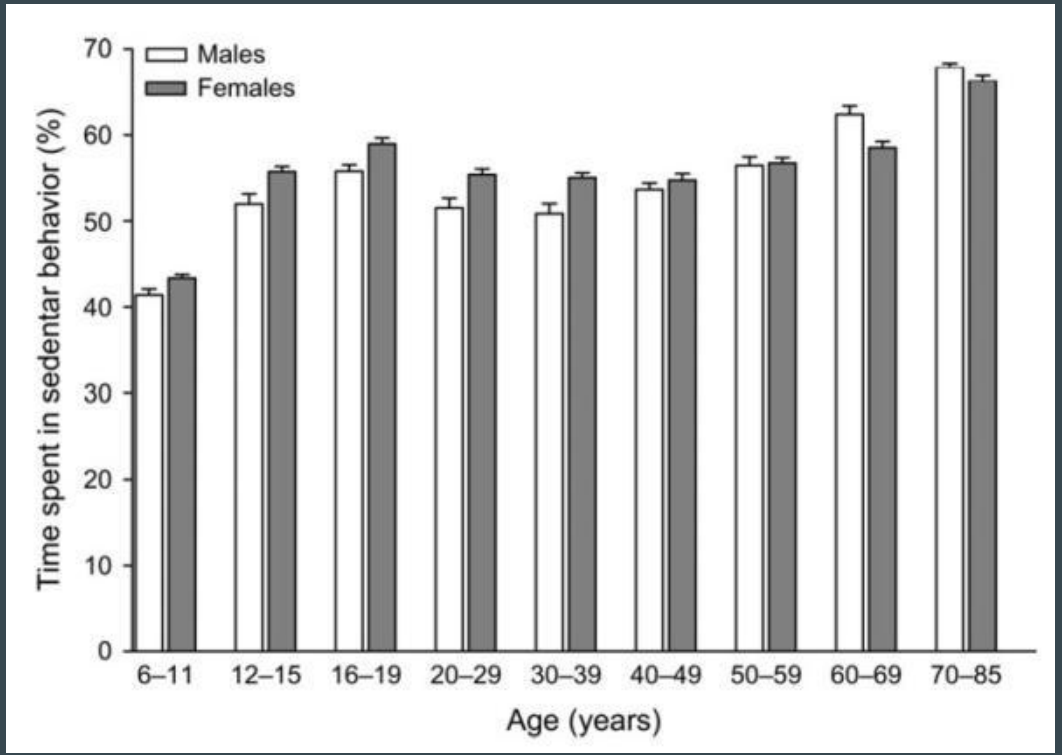
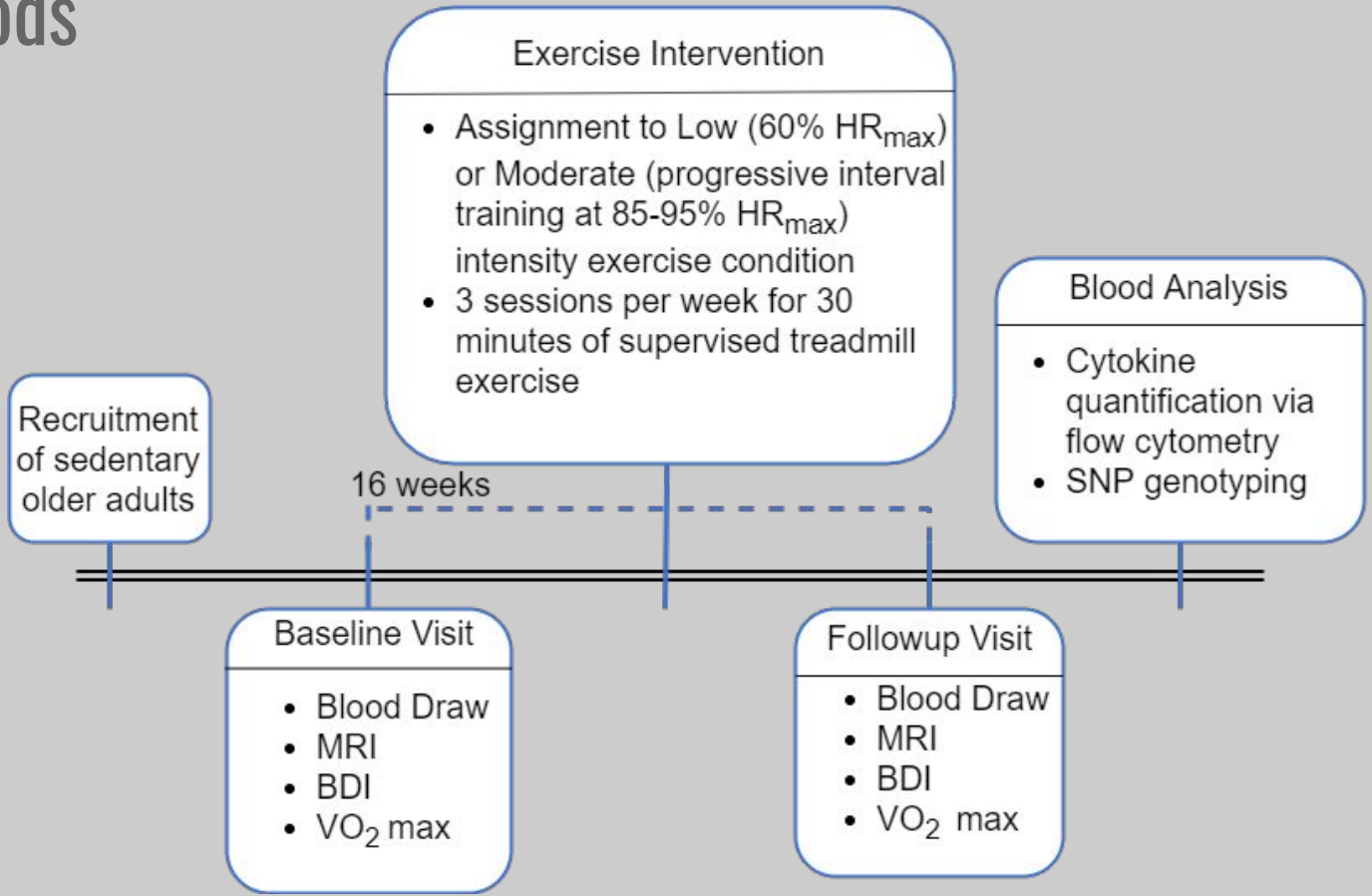


Image Credit:

Matthews et al., 2008

Methods


Exercise Intervention
Assignment to Low (60% HR_{max}) or Moderate (progressive interval training at 85-95% HR_{max}) intensity exercise condition
3 sessions per week for 30 minutes of supervised treadmill exercise
Blood Analysis
Cytokine quantification via flow cytometry
SNP genotyping
Recruitment of sedentary older adults
16 weeks
Baseline Visit
Blood Draw
MRI
BDI
VO_2 max
Followup Visit
Blood Draw
MRI
BDI
VO_2 max

Hypotheses

Replication:

- Anti-inflammatory effects of exercise
- Increase in hippocampal volume
- Decrease in depressive symptoms

Higher intensity exercise

greater change

- At baseline, lower inflammation -> larger hippocampus, less depression
    - Larger hippocampus -> less depression

Hypotheses (cont.)

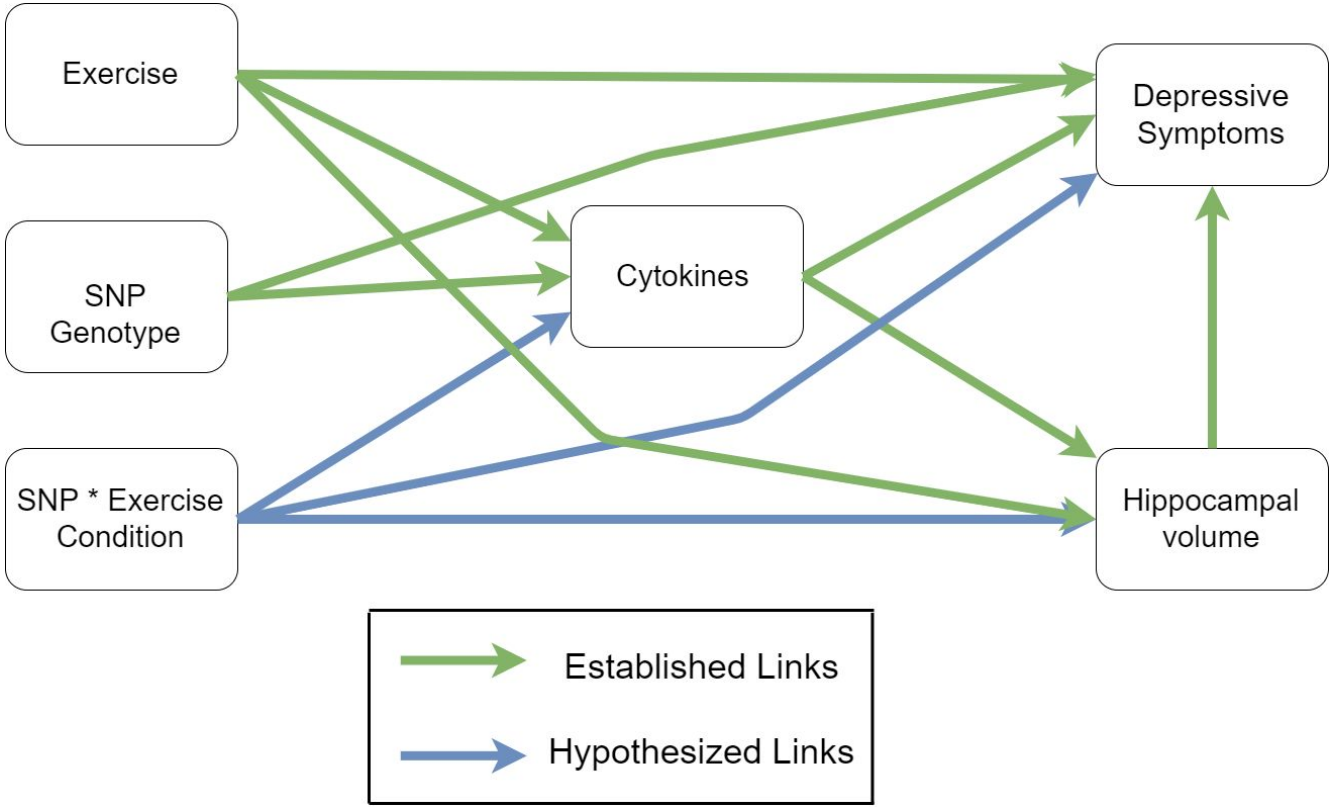
Novel:

- Larger increase in hippocampus -> larger decrease in depression
- Changes in inflammation, exercise condition, changes in hippocampal volume predict changes in depression

Exploratory hypotheses

- Attempt to understand genetic component to depression, individual variation in depressive responses.
- Examination of 3 SNPs (rs16944, rs1800797, rs1800629) involved in cytokine regulation, depression, or both

Generally, people with SNP genotypes that increase cytokine expression will have higher depression and smaller hippocampi at baseline. Exercise by SNP genotype interactions will influence hippocampal and depressive responses to the exercise intervention.


Exercise
SNP Genotype
SNP * Exercise Condition
Cytokines
Depressive Symptoms
Hippocampal volume
Established Links
Hypothesized Links

Subjects

	LICT	MICT+IT
N	55	60
Age (M±St. Dev.)	68.89 ± 1.61	68.28 ± 1.39
%Female	56.36	61.67
%White	92.7	93.3
BDI (M±St. Dev.)	8.61 ± 5.96	7.58 ± 6.92
Hippocampal Volume / ICV	0.0049 ± 0.00074	0.0051 ± 0.00092
	rs16944	
% A/A	5.5	16.7
%A/G	36.36	38.33
%G/G	41.82	35
%Undetermined	16.36	15
	rs1800629	
% A/A	3.6	1.67
%A/G	20	23.33
%G/G	67.27	70
%Undetermined	9	5
	rs1800797	
% A/A	18.18	20.5
%A/G	38.18	23.08
%G/G	24.54	43.57
%Undetermined	9.1	12.8

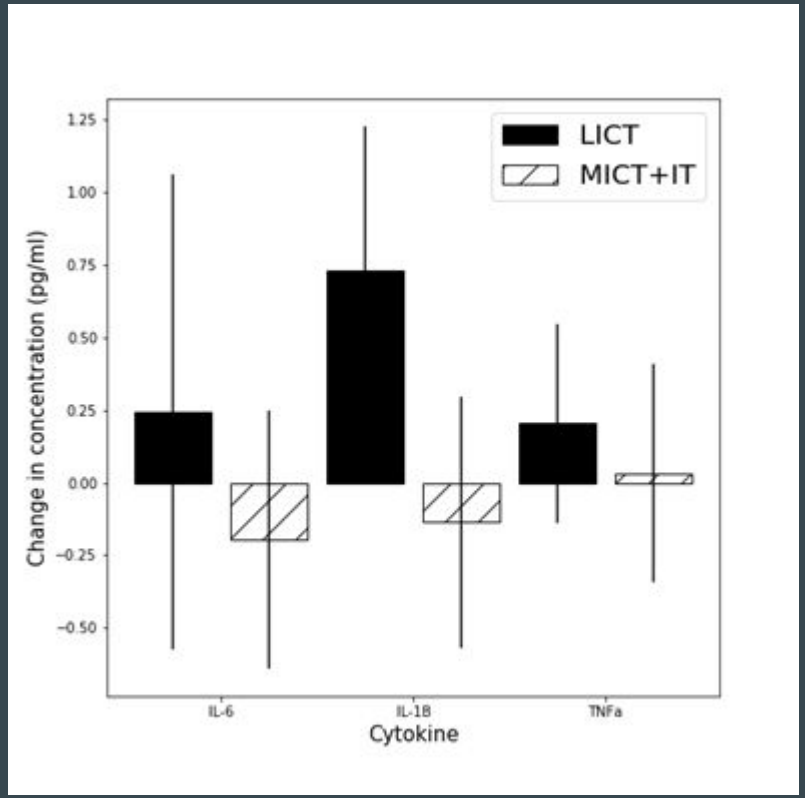
Results and Discussion

Baseline relationships

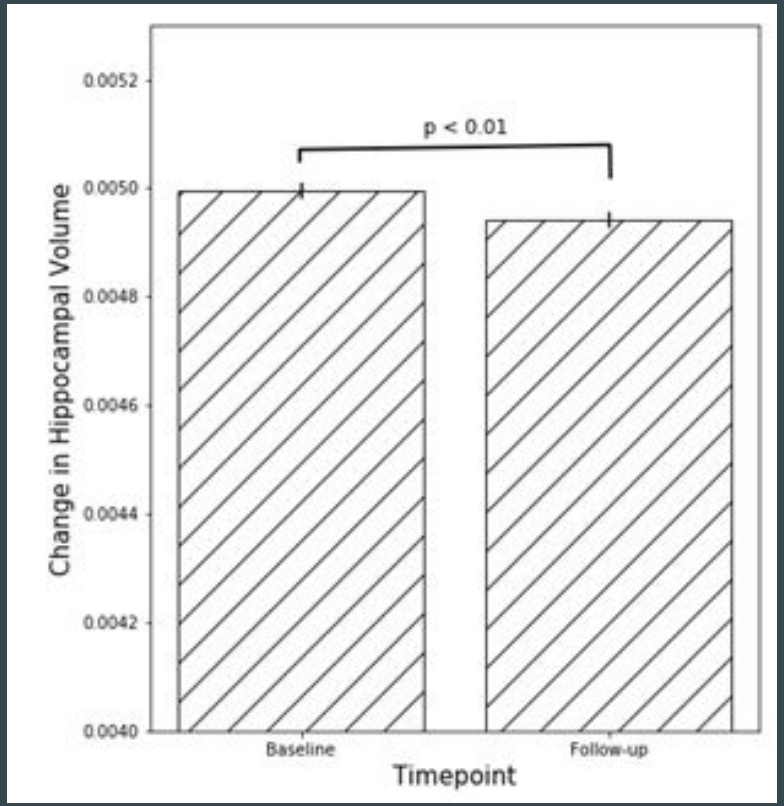
	IL-1β	IL-6	TNFα	Hippocampal Volume
IL-6	0.53***			
TNFα	0.72***	0.75***		
Hippocampal Volume	-0.11	-0.03	-0.02	
BDI	-0.04	0.21*	0.06	-0.01

Note. * indicates $p < 0.05$, *** indicates $p < 0.001$

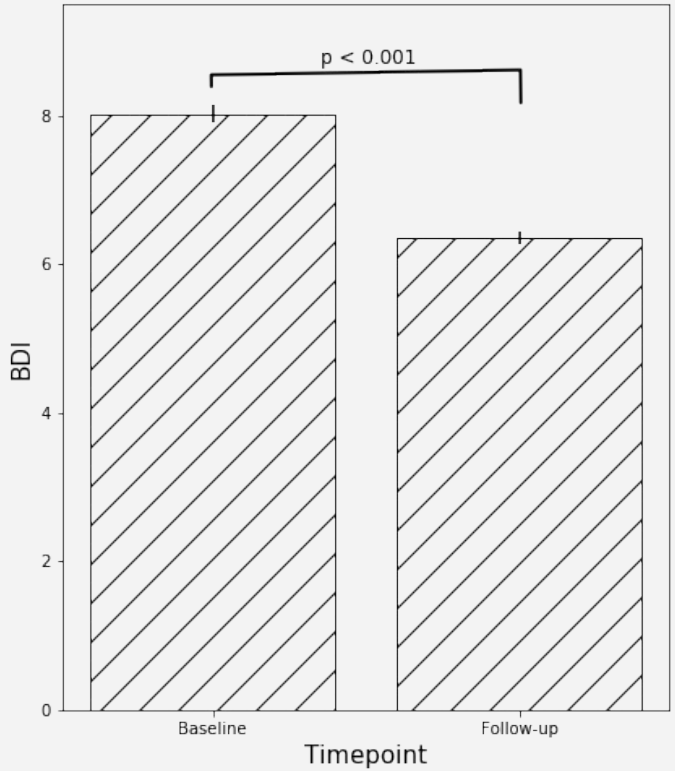
No exercise regulation of cytokines



Decreases in hippocampal volume after intervention



Decrease in BDI after intervention



Do these variables change together?

	IL-1β	IL-6	TNFα	Hippocampal Volume
IL-6	0.17^			
TNFα	0.65***	0.34***		
Hippocampal Volume	0.05	0.06	-0.06	
BDI	0.1	-0.08	0.12	-0.13

Note. ^ indicates $p < 0.1$, *** indicates $p < 0.001$

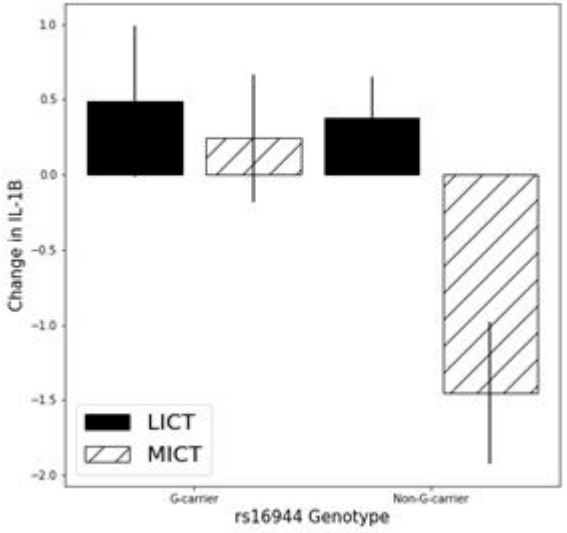
Exploratory Analyses

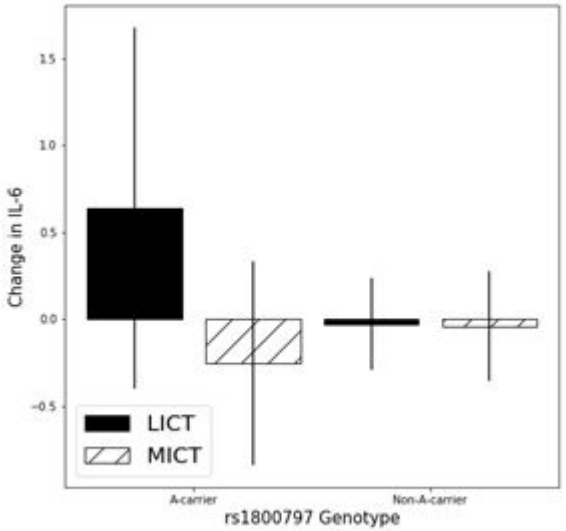
Baseline differences by genotype

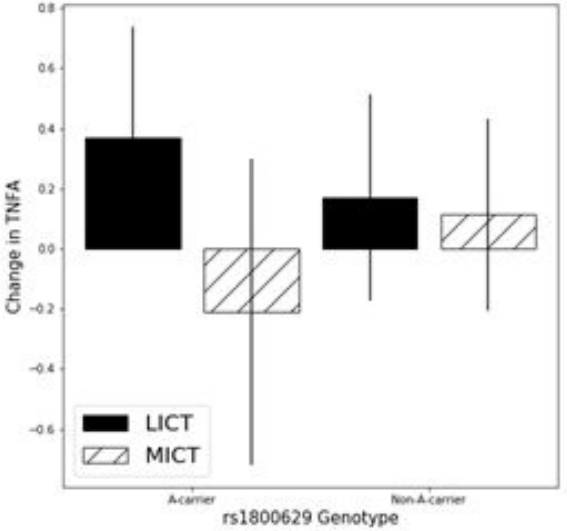
	rs16944		rs1800629		rs1800797	
	G-carrier	Non-G-carrier	A-carrier	Non-A-carrier	A-carrier	Non-A-carrier
IL-1β	4.02 ± 3.72	5.51 ± 3.49				
TNFα			3.66 ± 3.16	3.29 ± 2.27		
IL-6					4.1 ± 2.08	3.5 ± 2.63
BDI	8.52 ± 6.8	7.6 ± 4.4	9.93 ± 7.67^	7.41 ± 5.85^	8.57 ± 6.6	7.56 ± 6.13
Hippocampal Volume/ICV	0.0050 ± 0.00085	0.0048 ± 0.00093	0.0052 ± 0.00095	0.0049 ± 0.0078	0.0050 ± 0.00077	0.0050 ± 0.00095

Note. ^ indicates $p < 0.1$

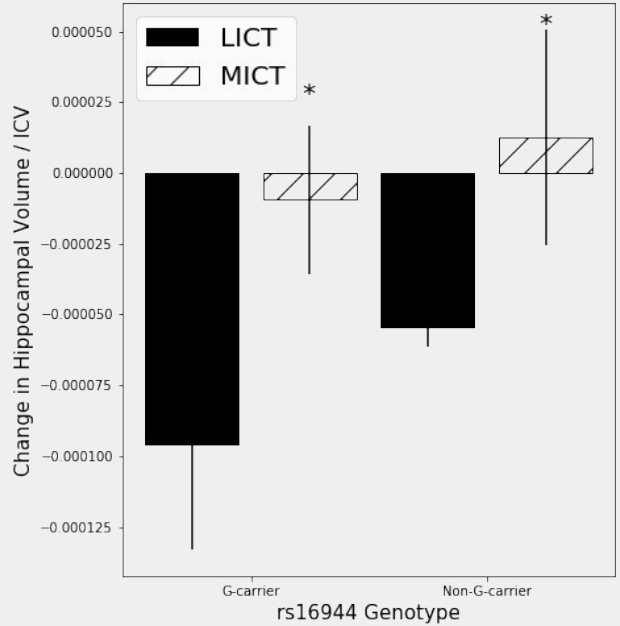
No SNP regulation of cytokines

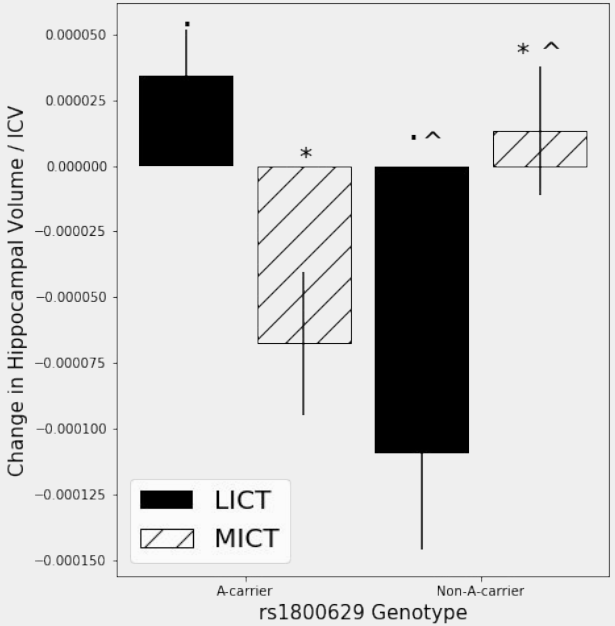


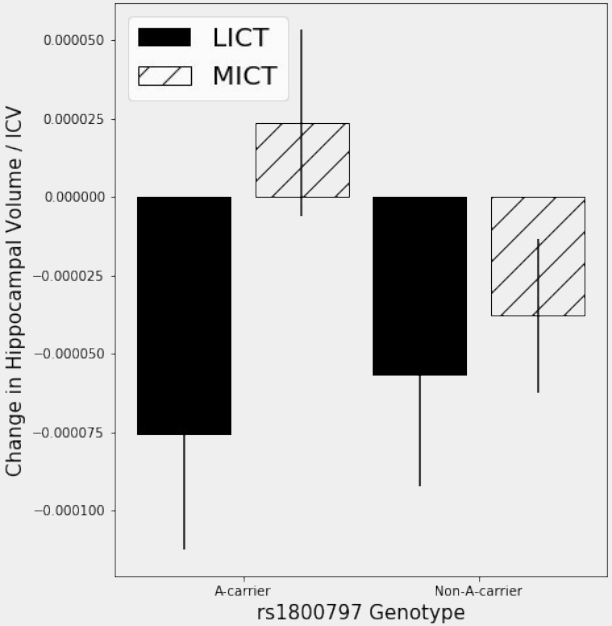




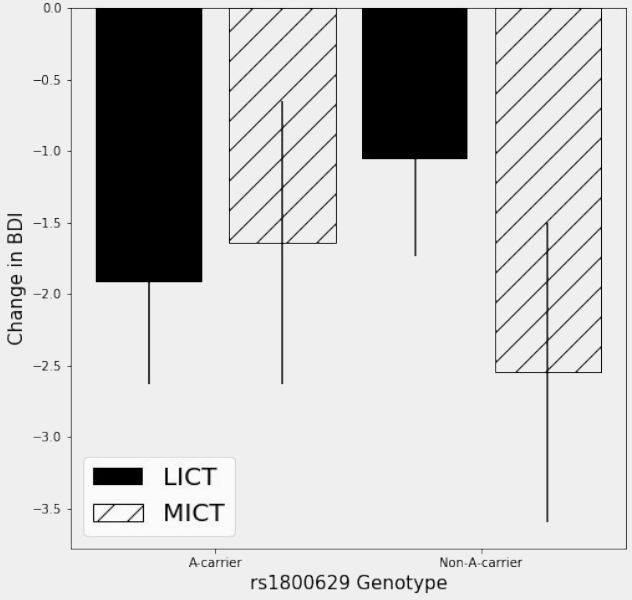
SNP x Exercise Interactions on hippocampal volume

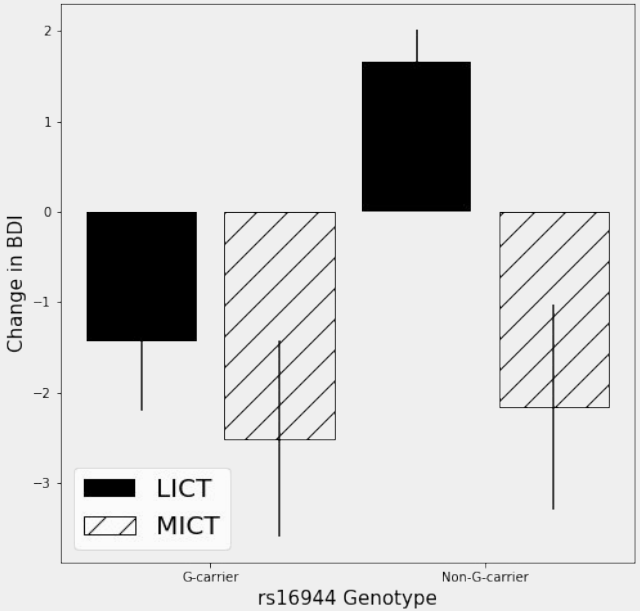


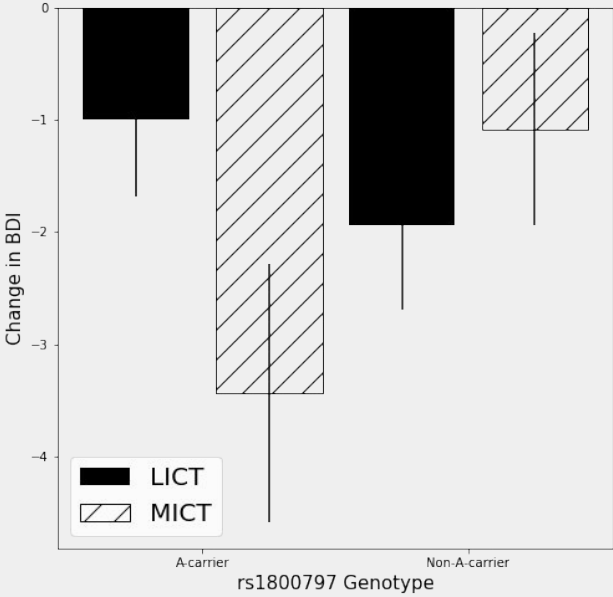




No SNP x exercise condition effects on BDI







Conclusions

- No evidence of pro-inflammatory cytokines influencing depressive symptoms through mediation of hippocampal neurogenesis
- Replication of IL-6 as a biomarker for depression and exercise alleviation of depressive symptoms
- Possible protective main effect of MICT+IT exercise on hippocampal atrophy
- Rs1800629 A-carrier status as protective against hippocampal atrophy in LICT exercise

Limitations and Further directions

- Non-clinical sample
- Age-matched sedentary control

- More sensitive measurements (central cytokines, CBV vs. structural MRI)
- Larger sample sizes

Acknowledgements

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Questions?