Genetic Pathways and Networks Interacting with Sports to Modify Learning and Memory in Adolescents

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Introduction

- Regular physical activity is known to improve learning, memory, and executive function through increased hippocampal volume and enhanced synaptic function especially during adolescence when brain development is most dynamic (Erickson, 2011).
- Large individual variability exists in cognitive gains from exercise → suggests genetic factors modulate these effects but the gene-environment interaction driving this variability remains incompletely understood.
- Using the Adolescent Brain Cognitive Development (ABCD) study, we conducted a genome-wide interaction study (GWIS) to identify gene-by-sports interactions influencing learning- and memory-related pathways. We integrated these results with cell-type-specific regulatory networks to pinpoint key driver genes in cognition-relevant brain regions and assessed the clinical relevance of using polygenic risk scores.

Methods

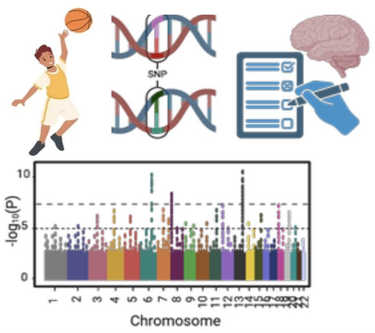
1. ABCD Cohort Data

No Sports → 1,174
Sports → 6,435

<u>To measure learning and memory performance:</u>

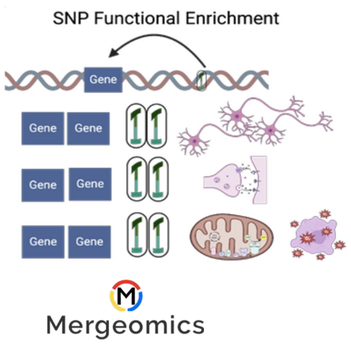
- derived 3 PCs that condensed scores from NIH Toolbox Cognitive Battery, Rey Auditory Verbal Learning Test, and Little Man Task
- used NPC3 for analysis

2. Gene-by-Sport Interaction GWAS

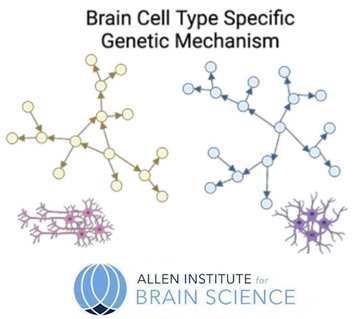


*NPC3 = B0 + B1*SNP + B2*Env + **B3*(SNP x Env)** + covariates*

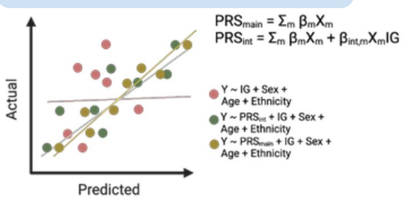
3. Marker Set Enrichment Analysis



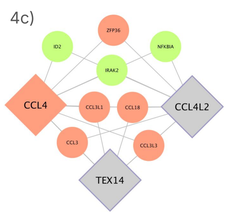
4. Key Driver Analysis



5. Polygenic Risk Score Modeling



4c)



Results

<u>SNP x Sport GWAS:</u>

- No SNPs passed the significance threshold ($p \leq 5e\text{-}08$) for the interaction term, but 15 SNPs passed a threshold of $p \leq 1e\text{-}06$

MOST PATHWAYS MAPPED BROADLY TO SYNAPTIC FUNCTION, DEVELOPMENTAL PROCESSES, AND CELLULAR SIGNALING

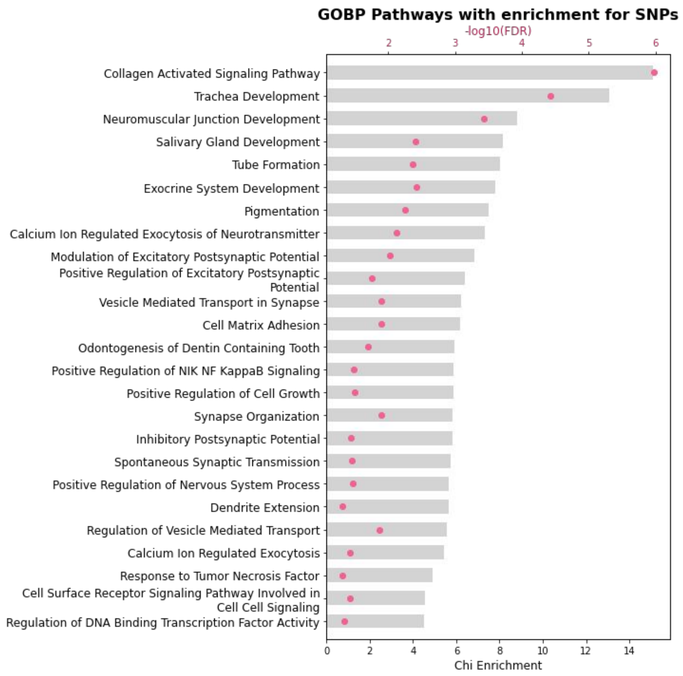
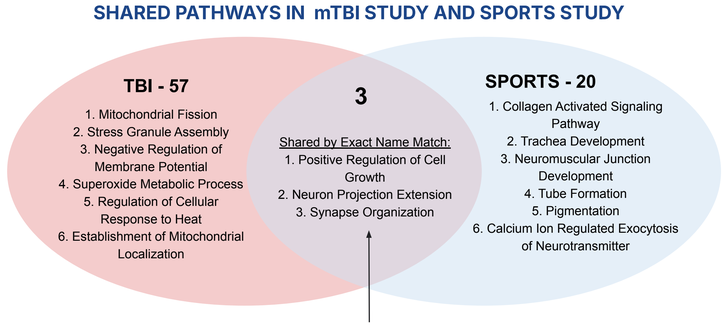


Figure 1. GOBP Pathways that were enriched for the GWAS SNPs with stronger associations. 24 pathways showed significant enrichment (FDR < 0.05).

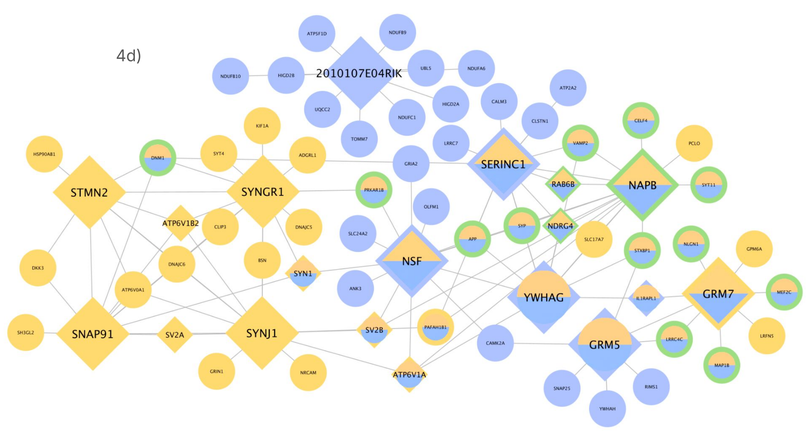
SHARED PATHWAYS IN mTBI STUDY AND SPORTS STUDY



<u>Significant Pathways with 30% gene overlap and the Top Odds Ratio Using Fisher's Exact:</u>
1. Positive Regulation of Cell Growth, Developmental Growth, and Axon Extension
2. Neuron Projection Extension, Axon Extension, and Developmental Growth
3. Dendrite Extension, Developmental Growth, Cell Growth
4. Modulation of Excitatory Postsynaptic Potential, Regulation of Trans Synaptic Signaling
5. Odontogenesis of Dentin Containing Tooth, Amelogenesis

Figure 3. Venn Diagram of Enriched Pathways in the mTBI study (red) and Sports study (Blue)

4d)



NPC3 DISTRIBUTIONS FOR SNPS IN ENRICHED PATHWAYS REVEAL SIGNIFICANT DIFFERENCES BETWEEN SPORTS AND NON-SPORTS GROUPS

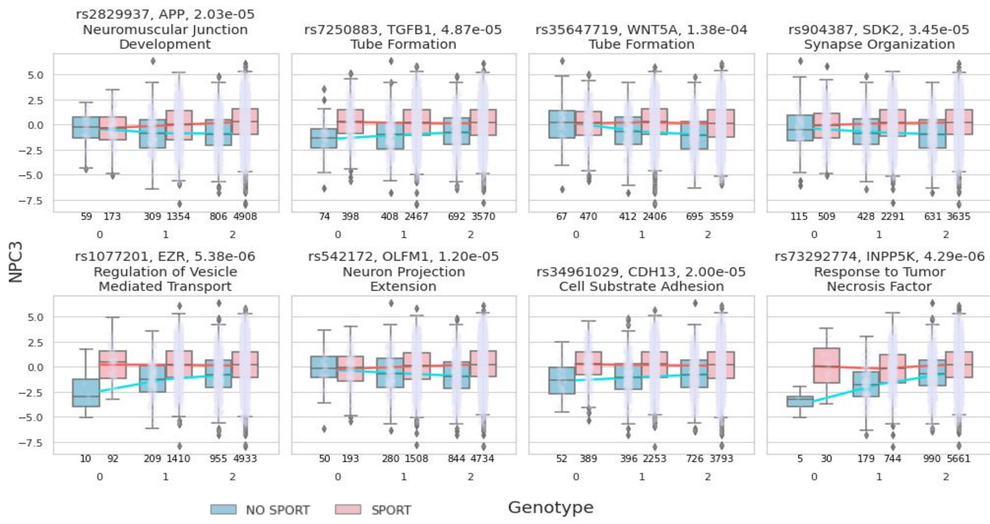


Figure 2. Learning and memory score (NPC3) distributions for SNPs in GO pathways. The count of individuals in each sports group and genotype is shown below each boxplot. Trendlines for each group show significant differences in directionality across genotype for the two groups.

CELL-TYPE-SPECIFIC NETWORK ANALYSIS REVEALS KEY REGULATORS AND NETWORKS GOVERNING NEURONAL REPAIR PATHWAYS

Sports Key Drivers

4a)

	Anterior Cingulate Cortex		Frontal Pole Secondary Motor Cortex		Hippocampus				Prelimbic Infralimbic Orbital Cortex		TOTAL
	EXC	INH	EXC	INH	EXC	INH	MICRO	OLIGO	EXC	INH	
RAB6B	1	1	0	1	1	1	0	0	0	1	6
NAPB	1	1	1	1	0	1	0	0	1	0	6
NSF	1	1	1	1	0	0	0	0	1	0	5
NDRG4	1	1	0	1	0	1	0	0	0	1	5
PSAP	0	1	0	1	1	1	0	0	0	1	5

4b)

mTBI x Sports Overlapping Key Drivers (Intersection)

	Anterior Cingulate Cortex			Frontal Pole Secondary Motor Cortex			Hippocampus				Prelimbic Infralimbic Orbital Cortex			TOTAL
	EXC	INH	OLIGO	EXC	INH	OLIGO	EXC	INH	MICRO	OLIGO	EXC	INH	OLIGO	
NSF	1	1	0	1	0	0	0	0	0	0	0	0	0	3
NAPB	1	0	0	1	0	0	0	0	0	0	0	0	0	2
NDRG4	1	1	0	0	0	0	0	0	0	0	0	0	0	2

Figure 4. (a) Table of common key drivers found after overlaying MSEA genes with Allen Institute Brain Networks and (b) shared key drivers found in both the mTBI <u>and</u> sports study (EXC = excitatory, INH = inhibitory, MICRO = microglia, OLIGO = oligodendrocyte) Most key drivers were associated with the pathways Synapse Organization and Vesicle Mediated Transport in the Synapse across various except for the (c) hippocampal microglia which had key drivers associated with the Tumor Necrosis Factor pathway. Key drivers are shown as diamonds. (d) depicts shared key drivers in mTBI (yellow) and sports (blue) in Anterior Cingulate Cortex excitatory cells.

Conclusion

- We hypothesize that sports participation interacts with genetic variation to influence learning and memory through pathways like collagen activated signaling, tube formation, and synapse organization.
- Genes known to be involved in learning and memory (eg. APP, TGFB1, WNT5A, CDH13, INPP5K) and novel learning/memory candidates (eg. SDK2, EZR, OLFM1) demonstrated significant differences in NPC3 scores in the two groups
- Hippocampal microglia CCL4/TNF signaling suggests a role in neuroinflammation.
- Overlap with mTBI gene networks highlights shared key drivers (eg. NAPB, NSD, NDRG4) for cognitive resilience and repair.

References & Acknowledgements

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- Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. Proceedings of the National Academy of Sciences [Internet]. 2011 Jan 31;108(7):3017–22. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3041121/