The Roles of Physical Activity, Exercise, and Fitness in Promoting Resilience During Adolescence: Effects on Mental Well-being and Brain Development

Supplemental Information

Table S1. Physical activity or exercise and brain structure in children and adolescents

A) Cross-sect	tional stru	ictural morpho	metric studies			
AUTHOR	YEAR	DESIGN	PARTICIPANTS	PA or EX MEASURES	BRAIN MEASURES	BRAIN STRUCTURE RESULTS
Chaddock (1)	2010	Cross- sectional	N=49, 9-10 year olds, <ts bmi="" ii,="" nr,<br="">59% Female, USA</ts>	21 HF and 28 LF based on VO2 testing	3T MRI, structural ROIs of hippocampus and nucleus accumbens volumes	HF > LF hippocampus volumes. No difference in nucleus accumbens volumes. Bilateral hippocampal volume positively correlated with accuracy on relational memory performance. Sobel test suggested greater hippocampal volume mediated the relationship between aerobic fitness and relational memory, but not item memory
Chaddock (2)	2010	Cross- sectional	N=55, 9-10 year olds, <ts bmi="" ii,="" nr,<br="">55% Female, USA</ts>	25 HF and 30 LF based on VO2 testing	3T MRI, structural ROIs of dorsal striatum (caudate nucleus and putamen), ventral striatum (nucleus accumbens) and globus pallidus volumes	HF > LF left caudate, bilateral putamen, bilateral globus pallidus. No difference in nucleus accumbens. Also see Chaddock 2012 for how these volumes relate to Flanker performance 1 year later in subsample
Herting (3)	2012	Cross- sectional	N=34, 15-18 year- olds, TS Mid-Post, 0% Female, Healthy Weight, USA	VO2 testing	3T MRI, structural ROIs of hippocampal and whole brain volumes	Aerobic fitness was positively associated with larger hippocampal volumes. No

Chaddock- Heyman (4)	2015	Cross- sectional	N=48, 9-10 year olds, <ts bmi="" ii,="" nr,<br="">54% Female, USA</ts>	24 HF and 24 LF based on VO2 testing	3T MRI, structural ROIs of frontal (anterior, middle, superior), parietal (superior, inferior), temporal (superior, middle, inferior), and lateral occipital volumes	associations seen for global gray or white matter brain volumes HF < LF cortical thickness in the superior frontal, superior temporal, and lateral occipital
Herting (5)	2016	Cross- sectional	N=34, 15-18 year- olds, TS Mid-Post, 0% Female, Healthy Weight, USA	17 HF and 17 LF based on VO2 testing	3T MRI, structural whole brain cortical thickness, surface area, and volume	HF > LF right medial pericalcarine and cuneus and left precuneus surface areas. VO2 positively associated with left rostral middle frontal cortex volume. An interaction was seen between VO2 and BDNF genotype, with a positive association with VO2 bilateral lingual gyrus surface area in Val/Val carriers but not in Met carriers
Esteban- Cornejo (6)	2017	Cross- sectional	N=101, 8-11 year olds, Premenstrual for females, Overweight/Obese, 41% Female, Spain	ALPHA health- related fitness test battery (cardiorespiratory fitness by 20-m shuttle-run)	3T MRI, structural whole brain gray matter tissue	Higher cardiorespiratory fitness was positively related to greater gray matter volumes in premotor and SMA, hippocampus, caudate, inferior temporal gyrus, parahippocampal gyrus, and calcarine cortex
Esteban- Cornejo (7)	2019	Cross- sectional	N=101, 8-11 year olds, Premenstrual for females, Overweight/Obese, 41% Female, Spain	ALPHA health- related fitness test battery (cardiorespiratory	3T MRI, structural ROIs of right premotor cortex, right SMA and left IFG, left inferior	Higher cardiorespiratory fitness was related to total greater cortical thickness, but not surface area or ROIs of cortical

				fitness by 20-m shuttle-run)	temporal gyrus, right parahippocampal gyrus and right superior temporal gyrus, and occipital/ calcarine thickness and surface area	thickness. This association was also mediated by fat mass index
Esteban- Cornejo (8)	2019	Cross- sectional	2 samples: ActiveBrains: N=100, 8-11 year olds, Premenstrual for females, Overweight/obese, 40% Female Spain; FITKids2: N = 142, 7-9 year olds, <ts ii,<br="">36% Overweight/Obese, 55% Female, USA</ts>	ActiveBrains: ALPHA health- related fitness test battery (cardiorespiratory fitness by 20-m shuttle-run); FIT Kids2: VO2 testing	3T MRI, structural whole brain white matter volume	ActiveBrains: Higher cardiorespiratory fitness was positively related to white matter volume in the inferior fronto-opercular gyrus and inferior temporal gyrus. Overweight/Obese FIT Kids2: cardiorespiratory fitness was positively related to inferior temporal gyrus, cingulate gyrus, middle occipital gyrus, and fusiform gyrus. Normal Weight FIT Kids2: No association between cardiorespiratory fitness and white matter volume
Gorham (9)	2019	Cross- sectional	N=4191, 9-11 year olds, TS NR, BMI NR, 48% Female, USA	Caregiver-report on the Sports and Activities Involvement Questionnaire for 23 sports	3T MRI, structural ROIs of hippocampus volumes	Team and structured sports involvement was associated correlated with hippocampal volume in both boys and girls. Hippocampal volume also interacted with sex to predict depressive symptoms, with a negative relationship in boys, and served as a partial mediator for the relationship between involvement in sports and depressive symptoms in boys
Ruotsalainen (10)	2019	Cross- sectional	N=60, 12-16 years old, TS Range: 1.5-	Hip accelerometers	3T MRI, structural subcortical ROIs:	Cardiorespiratory fitness was negatively related to the left

	5.0, BMI Range	MVPA and	putamen, pallidum,	superior frontal cortex volume
	15.7–31.1, 67%	maximal 20-m	caudate, nucleus	and positively related to the left
	Female, Finland	shuttle run test	accumbens,	pallidum. No associations with
			thalamus	MVPA
			and hippocampus	
			volumes. Cortical	
			ROIs: paracentral	
			lobule, postcentral	
			gyrus,	
			posterior cingulate	
			cortex, precentral	
			gyrus, superior	
			frontal gyrus,	
			lateral orbitofrontal	
			cortex, anterior	
			cingulate cortex,	
			middle frontal gyrus,	
			and medial	
			orbitofrontal cortex	
STUDY DESIGN is based on MRI portion	on of the study. Abbrevia	tions: HF=high-fit; L	F=low-fit; TS=Tanner	Stage; BMI=Body Mass Index;
NR=not reported				

A) Cross-sec	tional DT	I Studies				
AUTHOR	YEAR	DESIGN	PARTICIPANTS	PA or EX MEASURES	BRAIN MEASURES	BRAIN STRUCTURE RESULTS
Chaddock- Heyman (11)	2014	Cross-sectional	N=24, 9-10 year olds, <ts 38%<br="" bmi="" ii,="" nr,="">Female, USA</ts>	12 HF and 12 LF based on VO2 testing	3T MRI, diffusion tensor imaging (4 b0, 30-directions at b=1000 s/mm2) & TBSS and tracts ROIs from JHU	HF > LF FA in corpus callosum, superior corona radiata (SCR), and superior longitudinal fasciculus (SLF)
Herting (12)	2014	Cross-sectional	N=34, 15-18 year- olds, TS Mid-Post, 0% Female, Healthy Weight, USA	17 HF and 17 LF based on VO2 testing	3T MRI, diffusion tensor imaging (6 b0, 30-directions at b=1000 s/mm2) & TBSS and tractography	HF > LF streamline number in tracts of bilateral corticospinal tract (CST) and genu of the corpus callosum (CC). VO2 was negatively associated with FA in portions of the left CST in all subjects
Rodriguez- Ayllon (13)	2019	Cross-sectional	N=103, 8-11 year olds, TS NR, Overweight/Obese, 41% Female, Spain	Hip and wrist accelerometers for 7 days; self- report on Youth Activity Profile- Spain	3T MRI, diffusion tensor imaging (1 b0, 30-directions at b=1000 s/mm2) & tractography	Self-reported total physical activity as well as objective measurements of total, light, and MVPA were positively correlated with total whole brain FA. Objectively measured total activity was negatively correlated with whole brain RD. No associations with either self- reported or objective measurements of physical activity were found with MD or AD
Rodriguez- Ayllon (14)	2020	Cross-sectional	N=2532, 10 year olds, TS NR, BMI Mean 17.36+/-2.50, 50% Female, The Netherlands	Caregiver-report about the number of days per week and duration per day their child	3T MRI, diffusion tensor imaging (b0 NR, 30-directions at b=1000 s/mm2) & tractography	Total physical activity was postively associated with global FA and negatively with MD. Follow-up analyses showed this association was seen when

Table S2. Physical activity or exercise and white matter microstructure in children and adolescents

Ruotsalainen (15)	2020	Cross-sectional	N=59, 12-16 years old, TS Range: 1.5- 5.0, BMI Range 14.6– 31.1, 66% Female, Finland	engages in: (i) walking or cycling to/from school, (ii) outdoor play, and (iii) sports Hip accelerometers for 7 days and maximal 20-m shuttle run test	3T MRI, diffusion tensor imaging (10 b0, 30-directions at b=1000 s/mm2) & TBSS with ROIs of the body and genu of corpus callosum (CC), the bilateral superior corona radiata (SCR), the bilateral superior longitudinal fasciculus (SLF) and the bilateral uncinate fasciculus (UF)	looking at outdoor play or sports participation. No association was found between total physical activity and FA within individual tracts. Negative associations seen between total physical activity and MD in almost all individual tracts Cardiorespiratory fitness was positively related to FA and negatively related to MD, AD, and RD in the SCR and the CC. No associations with MVPA. FA in the CC and right SCR moderated the relationship between cardiorespiratory fitness and working memory
B) RCT DTI	Studies				••••	
AUTHOR	YEAR	DESIGN	PARTICIPANTS	PA or EX MEASURES	BRAIN MEASURES	BRAIN STRUCTURE RESULTS
Krafft (16)	2014	RCT	N=18, 8-11 year olds, TS NR, Sedentary/Overweight, 50% Female, USA	Both groups were offered an after school program every school day for ~8 months. EX group	3T MRI, diffusion tensor imaging (3 b0, 30-directions at b=1000 s/mm2) & tractography of the superior	No significant group by time interaction seen, but a time by group by attendance interaction. EX group showed an effect with attendance and change in the right SLF (FA/RD) and a trend for the left SLF FA. The control

				participated in 40 min of instructor-led aerobic activities (e.g., tag or jump rope) (N=10). CON group participated in instructors led sedentary activities (e.g., art and board games) daily (N=8).	longitudinal fasciculus (SLF)	group did not show significant relationships between attendance and change in SLF
Schaeffer (17)	2014	RCT	N=18, 8-11 year olds, TS NR, Sedentary/Overweight, %Female NR, USA	Both groups were offered an after school program every school day for ~8 months. EX group participated in 40 min of instructor-led aerobic activities (e.g., tag or jump rope) (N=10). CON group participated in instructors led sedentary activities (e.g., art and board games) daily (N=8).	3T MRI, diffusion tensor imaging (3 b0, 30-directions at b=1000 s/mm2) & tractography of the uncinate fasciculus (UF)	Groups did not differ at baseline. From baseline to posttest, EX group showed greater positive change in bilateral FA of the UF when compared to the control group. EX also showed greater negative change in RD of the left UF. No significant correlations were found between changes in measures of white matter integrity (FA and RD) and measures of fatness or fitness (BMI, percent body fat, and VO2 peak)

Chaddock- Heyman (18)	2018	RCT	N=143, 7-9 year olds, <ts bmi<br="" ii,="" pre-test="">average of 19.0 and 18.7 for the EX and control group, 51% Female</ts>	9-month, 2-hr after school EX program (FIT Kids, N=76) or waitlist CON group (N=67). EX group spent 30–35 min of sustained MVPA and up to 90 min of intermittent MVPA.	3T MRI, diffusion tensor imaging (2 b0, 30-directions at b=1000 s/mm2) & TBSS and tracts ROIs from JHU	EX group had increased FA, decreased RD, and no change in AD in the genu of the corpus callosum (CC) from pre- to posttest. No changes seen in the waitlist control group		
	STUDY DESIGN is based on MRI portion of the study. Abbreviations: HF=high-fit; LF=low-fit; TS=Tanner Stage; BMI=Body Mass Index; NR=not reported; FA=fractional anisotropy; MD=mean diffusivity; RD=radial diffusivity; AD=axial diffusivity; TBSS=tract based spatial							

AUTHOR	YEAR	DESIGN	PARTICIPANTS	PA or EX MEASURES	BRAIN MEASURES	BRAIN FUNCTION RESULTS
Voss (19)	2011	Cross-sectional	N=36, 9-10 years-old, <ts 53%<br="" bmi="" ii,="" nr,="">Female, USA</ts>	18 HF and 18 LF based on VO2 Max	3T MRI; Flanker fMRI	Incongruent > Congruent (Inhibition contrast). LF>HF: greater activation of brain regions associated with attentional control and inhibition including precentral and postcentral gyrus, insular/operculum, middle frontal gyrus (MFG)
Chaddock (20)	2012	Cross-sectional	N=32, 9-10 year olds, <ts 50%<br="" bmi="" ii,="" nr,="">Female, USA</ts>	14 HF and 18 LF based on VO2 Max	3T MRI; Flanker task, fMRI	Congruent or Incongruent Congruent or Incongruent > Congruent NR. During Incongruent Trials, HF > LF: greater activation of bilateral middle frontal gyrus (MFG), anterior cingulate (ACC), supplementary motor area (SMA), left superior parietal lobe (SPL) during the first half, but no difference between groups at the end of the latter end of the task
Herting (21)	2013	Cross-sectional	N=34, 15-18 year-olds, TS Mid-Post, 0% Female, Healthy Weight, USA	17 HF and 17 LF based on VO2 Max	3T MRI; Verbal Associative Learning task fMRI	High Confidence Remembered vs. Forgotten Contrasts. Group differences were seen in brain activity despite absence of performance differences. LF > HF: less activation in superior frontal gyrus (SFG), but greater activiation in bilateral hippocampus. HF > LF:

Table S3. Physical activity or exercise and brain activity, intrinsic resting-state, and cerebral blood flow in children and adolescents

B) RCT fMI	PI task stu	dies				deactivation in posterior cingulate (PCC). HF youth showed a strong negative coupling in BOLD response between the hippocampus and default mode network (DMN) brain regions during successful memory encoding (vs. baseline), whereas LF youth showed positive coupling
AUTHOR	YEAR	DESIGN	PARTICIPANTS	PA or EX MEASURES	BRAIN MEASURES	BRAIN FUNCTION RESULTS
Davis (22)	2011	RCT	N=20, 7-11 year olds, TS NR, 40% Female, Sedentary/Overweight, USA	Groups included 13 ± 1.6 weeks of an EX program (N=11) or CON group (N=9). EX group participated in either a low or high dose (20 vs. 40 min.) of instructor-led aerobic activities (N=13). No program provided to CON group.	3T MRI; Anti- saccade task fMRI	Exact contrast NR, Increased bilateral prefrontal cortex (PFC) activity and reduced posterior parietal cortex activity during antisaccade task
Chaddock- Heyman (23)	2013	RCT	N=23, 8-9 year olds, TS <ii, bmi<br="" pre-test="">average of 18.4 and 19.3 for the EX and control group, 57% Female, USA</ii,>	9-month, 2-hr after school EX program (FIT Kids, N=14) or waitlist CON group (N=9). EX group received	3T MRI; modified Flanker task with no-go trials, fMRI. Regions of interest included right anterior prefrontal cortex (PFC) and	Mean percent signal change (versus fixation) was extracted for incongruent, neutral, and NoGo conditions. Incongruent > Congruent NR. PA > Control decreases in brain activity in right anterior PFC from pre-test

				at least 70- minutes of MVPA. No program provided to CON group.	the anterior cingulate cortex (ACC)	to post-test for incongruent, where as the activation patterns in this frontal region in the wait-list control group remained unchanged. No differences in ACC between groups for incongruent trials. PA > Control also showed shorter reaction time for both incongruent trials and neutral trials at post-test relative to pre-test
Krafft (24)	2014	RCT	N=43, 8-11 year olds, TS NR, 65% Females, Sedentary/Overweight, USA	Both groups were offered an after school program every school day for ~8 months. EX group participated in 40 min of instructor-led aerobic activities (e.g., tag or jump rope) (N=24). CON group participated in instructors led sedentary activities (e.g., art and board games) daily (N=19).	3T MRI; Anti- saccade & Flanker fMRI	Both groups showed improved task performance on antisaccade and flanker tasks. Group differences in brain changes were seen even in the absence of performance differences. Antisaccade vs. fixation contrast: From baseline to post-test, the exercise group decreased activation in bilateral precentral gyrus, medial frontal gyrus (MFG), paracentral lobule, postcentral gyrus, superior parietal lobule (SPL), inferior parietal lobule (IPL), and anterior cingulate cortex (ACC); right inferior frontal gyrus (IFG) and insula; and left precuneus. In all of these regions, the exercise group showed a pattern of decreasing activation over time, while the control group showed the opposite pattern (i.e. increasing activation over time).

C) Resting-S	State fMR					Incongruent vs. congruent Flanker contrast: bilateral superior frontal gyrus (SFG), medial frontal gyrus (MFG), cingulate gyrus, and anterior cingulate cortex (ACC); and left inferior frontal gyrus (IFG) and insula. In all regions in this contrast, the exercise group showed increased activation over time, while the control group showed decreased activation
AUTHOR	YEAR	DESIGN	PARTICIPANTS	PA or EX	BRAIN	BRAIN FUNCTION
normon		DESIGN		MEASURES	MEASURES	RESULTS
Krafft (25)	2014	RCT	N=22, 8-11 year olds, TS NR, Sedentary/Overweight, 67% Female, USA	Both groups were offered an after school program every school day for ~8 months. EX group participated in 40 min of instructor-led aerobic activities (e.g., tag or jump rope) (N=13). CON group participated in instructors led sedentary activities (e.g., art and board	3T MRI; resting state eyes-closed fMRI; Independent component analysis (ICA) to look at default, salience, cognitive control#, motor networks	Less resting-state correlations in EX vs. Control group between the default mode network (DMN) and the occipital, cuneus, superior temporal, and posterior cingulate (PCC); Less resting- state correlations in EX vs. Control group between the cognitive control network with and cerebellum, posterior cingulate (PCC), precuneus and less motor network connectivity with the cuneus but more connectivity between the motor network and medial frontal gyrus (MFG)

				games) daily (N=9).		
D) Cerebral Blood Flow						
AUTHOR	YEAR	DESIGN	PARTICIPANTS	PA or EX	BRAIN	BRAIN FUNCTION
				MEASURES	MEASURES	RESULTS
Chaddock- Heyman (26)	2016	Cross-sectional	N=73, 7-9 year olds, TS <ii, 56%<br="" bmi="" nr,="">Female, USA</ii,>	VO2 Max	3T MRI, pseudo- continuous Arterial Spin Labeling (pcASL). Regions included hippocampus and brainstem	Higher aerobic fitness predicted greater cerebral blood flow (CBF) in the hippocampus when controlling for age, sex, and average hippocampal volume but no association seen between aerobic fitness and CBF in brainstem
STUDY DESIGN is based on MRI portion of the study. Abbreviations: HF=high-fit; LF=low-fit; TS=Tanner Stage; BMI=Body Mass Index;						
NR=not reported						
# Overlaps with frontoparietal network defined in the current manuscript						

Box 1: Key remaining questions regarding physical activity, exercise, and neurobiological mechanisms of resilience for mental health in adolescence.

- 1. Are there critical windows where exercise may confer larger and/or more long-term benefits than others (i.e. childhood and adolescence vs. adulthood)? Are these effects different by sex or pubertal stage?
- 2. Are PA and exercise effects specific to the proposed large-scale functional connectivity networks involving the PFC (i.e. frontoparietal, default mode, and corticolimbic systems)? How do potential changes in these networks contribute to mental health resilience?
- 3. How do various types, intensities, and frequencies of PA and exercise (i.e. aerobic vs. resistance training; high-intensity vs. low-intensity, cognitively demanding vs. mindfulness regiments) influence brain structure, function, and their associated cognitive control processes related to both internalizing and externalizing symptoms and risk for mental health disorders in adolescence?

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