Multilevel variance components and brain volume mediation of life stress on post-traumatic stress disorder symptoms in children via regularization

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Introduction

- Exposure to traumatic events (TEs) is common (~80% of the U.S. population have experienced at least one during their lifetime [1]).
- Childhood TEs increase the risk for developing Post-Traumatic Stress Disorder (PTSD) symptoms [2].
- Previous research showed that the heritability of TEs is 53% and 38% for PTSD symptoms in non-combat exposed populations [3].
- Reduced volume in brain regions of interest (ROIs) is linked to increased risk for PTSD [4].

Aims

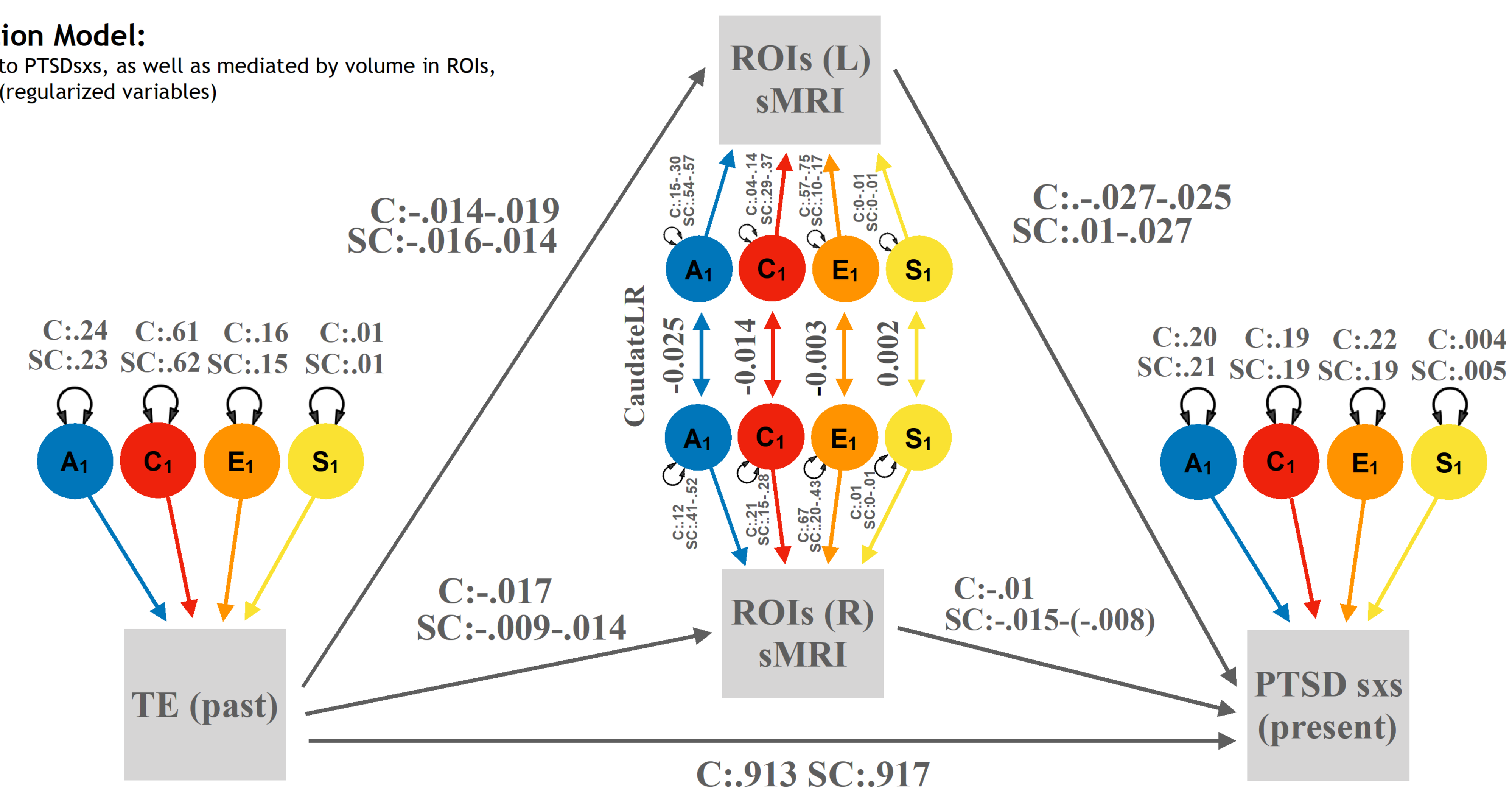
- **Aim 1:** To estimate the additive genetic **(A)**, shared **(C)** and unique **(E)** environmental, and site **(S)** variance components of the variables, via multilevel (individual, group and study) structural equation modeling.
- **Aim 2:** To assess the **mediation effects** of subcortical and cortical volume of regions of interest (ROIs), as well as the **direct effects** between traumatic events (TEs) and PTSD symptoms, via an agnostic perspective selecting the most informative ROIs using Elastic Net (EN) regularization on all subcortical and cortical ROIs.

Methods

- TEs and PTSD variables: Measured using the KSADS for DSM-5 [5]. A count-level variable was created for each one. The PTSD symptoms variable only considered those with at least one TE (others coded as missing).
- Volume (mm^3) of ROIs was assessed using structural magnetic resonance imaging (sMRI).
- Subjects (N=11,869, M_{age}=9.92, SD=0.62, F=47.86%, M=52.14%; $twinN$=1729, mzN=774, dzN=985, M_{age}=10.11, SD=0.56, F=50.03%, M=49.97%) came from the ABCD study, a U.S. nationwide representative sample. Zygosity was determined with pi-hat values (MZ=.89-1.0, DZ=.4-.6).
- All variables were residualized based on age, sex, race, type of scanner and subcortical or cortical brain volume.
- Cross-validation and regularization were performed under EN mixing parameter alpha (.75-.85) to: 1) estimate penalization lambda values that restrict the fit within the minimal increase of MSE, and 2) prevent extreme shrinkage due to possible correlation and selection of ROIs under high penalization.
- Multiple testing was accounted for by adjusting the number of effective tests based on the eigenvalues of the correlation matrices [6].
- R, OpenMx [7], mxregsem [8] and glmnet [9] were used for the analysis.

Results

Multilevel Mediation Model:
Unidirectional from TEs to PTSDsxs, as well as mediated by volume in ROIs, cortical and subcortical (regularized variables)



Results

- Six cortical (see Table 1) destrieux and desikan ROIs (N=258) with mediation effects estimates > 0.0003 (0.00033-0.00042), and six subcortical (see Table 1) ROIs (N=42) with mediation effects > 0.0002 (0.00024-0.0016) were retained after EN-regularized mediation model fits and used for the **multilevel mediation cortical and subcortical fits.**
- Consistently the **unidirectional (uniDir)** model from TEs to PTSDsxs directly as well as indirectly through the ROIs had the best fit explaining the data parsimoniously compared to the more complex models.
- The mediation effects paths of all ROIs (N=300) **contained zero** in each **CI lower bound.**

Table 1.Paths and variance components estimates and standard errors (SEs) of multilevel subcortical and cortical model fits:

	Cortical | Name	Est.	SE	Subcortical | Name	Est.	SE
Paths	TEs->medialOrbitoFronL	0.01	0.01	TEs->subcorticalGrayVolume	-0.01	0.01
	TEs->middletemporalR	-0.02	0.01	TEs->cerebellumCortexL	-0.02	0.01
	TEs->cingulAntL	0.02	0.01	TEs->whiteMatterL	0.01	0.01
	TEs->parietInfSupramarL	-0.01	0.01	TEs->caudateR	0.01	0.01
	TEs -> subcallosalL	0.02	0.01	TEs -> caudateL	0.01	0.01
	TEs -> collatTransvAntL	-0.01	0.01	TEs -> lateralVentricleR	-0.01	0.01
	TEs -> PTSDsxs	0.91	0.02	TEs -> PTSDsxs	0.92	0.02
	medialOrbitoFronL->PTSDsxs	0.02	0.01	subcorticalGrayVolume->PTSDsxs	0.01	0.02
	middletemporalR->PTSDsxs	-0.01	0.01	cerebellumCortexL->PTSDsxs	0.02	0.01
	cingulAntL->PTSDsxs	0.02	0.01	whiteMatterL->PTSDsxs	0.03	0.01
	parietInfSupramarL->PTSDsxs	-0.03	0.01	caudateR->PTSDsxs	-0.02	0.03
	subcallosalL->PTSDsxs	0.01	0.01	caudateL->PTSDsxs	0.01	0.03
	collatTransvAntL->PTSDsxs	-0.03	0.01	lateralVentricleR->PTSDsxs	-0.01	0.01
Additive Genetic	Va_TEs	0.24	0.02	Va_TEs	0.23	0.02
	Va_medialOrbitoFronL	0.30	0.06	Va_subcorticalGrayVolume	0.62	0.03
	Va_middletemporalR	0.12	0.06	Va_cerebellumCortexL	0.54	0.03
	Va_cingulAntL	0.29	0.05	Va_whiteMatterL	0.57	0.03
	Va_parietInfSupramarL	0.20	0.06	Va_caudateR	0.52	0.04
	Va_subcallosalL	0.19	0.06	Va_caudateL	0.54	0.03
	Va_collatTransvAntL	0.15	0.06	Va_lateralVentricleR	0.41	0.05
	Va_PTSDsxs	0.20	0.06	Va_PTSDsxs	0.21	0.06
Shared Env.	Vc_TEs	0.61	0.02	Vc_TEs	0.62	0.02
	Vc_medialOrbitoFronL	0.04	0.04	Vc_subcorticalGrayVolume	0.27	0.03
	Vc_middletemporalR	0.21	0.03	Vc_cerebellumCortexL	0.37	0.03
	Vc_cingulAntL	0.14	0.03	Vc_whiteMatterL	0.31	0.03
	Vc_parietInfSupramarL	0.08	0.03	Vc_caudateR	0.28	0.03
	Vc_subcallosalL	0.10	0.03	Vc_caudateL	0.29	0.03
	Vc_collatTransvAntL	0.10	0.03	Vc_lateralVentricleR	0.15	0.03
	Vc_PTSDsxs	0.19	0.04	Vc_PTSDsxs	0.19	0.04
Unique Env.	Ve_TEs	0.16	0.01	Ve_TEs	0.15	0.01
	Ve_medialOrbitoFronL	0.65	0.04	Ve_subcorticalGrayVolume	0.11	0.01
	Ve_middletemporalR	0.67	0.04	Ve_cerebellumCortexL	0.10	0.01
	Ve_cingulAntL	0.57	0.04	Ve_whiteMatterL	0.11	0.01
	Ve_parietInfSupramarL	0.71	0.04	Ve_caudateR	0.20	0.02
	Ve_subcallosalL	0.71	0.05	Ve_caudateL	0.17	0.01
	Ve_collatTransvAntL	0.75	0.04	Ve_lateralVentricleR	0.43	0.03
	Ve_PTSDsxs	0.22	0.03	Ve_PTSDsxs	0.22	0.03
Site	Vs_TEs	0.01	0.00	Vs_TEs	0.01	0.00
	Vs_medialOrbitoFronL	0.01	0.00	Vs_subcorticalGrayVolume	0.01	0.00
	Vs_middletemporalR	0.01	0.00	Vs_cerebellumCortexL	0.00	0.00
	Vs_cingulAntL	0.01	0.00	Vs_whiteMatterL	0.00	0.00
	Vs_parietInfSupramarL	0.00	0.00	Vs_caudateR	0.00	0.00
	Vs_subcallosalL	0.00	0.00	Vs_caudateL	0.00	0.00
	Vs_collatTransvAntL	0.00	0.00	Vs_lateralVentricleR	0.00	0.00
	Vs_PTSDsxs	0.00	0.00	Vs_PTSDsxs	0.00	0.00

Caudate ACES correlations: Va_caudateL-R:-0.025, SE:0.023; Vc_caudateL-R:-0.014, SE: 0.021; Ve_caudateL-R:-0.003,SE:0.009, Vs_caudateL-R:0.002, SE:0.0012

Table 2. Confidence Intervals (CIs) of mediation effect paths

Cortical	lbound	estimate	ubound	Subcortical	lbound	estimate	ubound
medialOrbitoFronL	-0.00047	0.00023	0.00140	caudateL	-0.00093	0.00015	0.00144
middletemporalR	-0.00059	0.00017	0.00123	caudateR	-0.00164	-0.00023	0.00014
cingulAntL	-0.00020	0.00048	0.00185	cerebellumCortexL	-0.00103	-0.00025	0.00008
parietInfSupramarL	-0.00061	0.00022	0.00137	whiteMatterL	-0.00017	0.00037	0.00128
subcallosalL	-0.00063	0.00016	0.00126	lateralVentricleR	-0.00030	0.00007	0.00063
collatTransvAntL	-0.00039	0.00039	0.00169	subcorticalGrayVol	-0.00062	-0.00005	0.00027

Discussion

- On the multilevel models, each with six ROIs for subcortical and cortical, **additive genetic factors** accounted for 41-62% of the variance in the **subcortical** model, as opposed to 12-30% in the **cortical** model. **Shared environmental factors** accounted for the highest proportion of the variance in TEs (61-62%). The model was able to detect small **site** variances, particularly those of neuroimaging variables (<.009, SE<.0035). Among lateralized ROIs, left hemisphere variables showed higher mediation effect estimates than those from the right hemisphere and were more frequently selected.
- ROIs with the highest estimates for mediation effects after regularization are associated with **learning, semantic memory, memory processing, and perception of emotions**.
- All the **mediation effects paths** contained zero in each **CI lower bound**, pointing to that if small mediating influences from volume in brain ROIs exist, they are **indistinguishable from zero.**
- **For 10 year-old children**, there is **no evidence of the meditational role of volume from the ROIs** indirectly influencing the impact of TEs on PTSD symptoms. However, ROIs on the group with the highest mediation effect estimates and CI lower bounds such as **caudate nucleus** and **lateral ventricles** are consistent with changes of volume in ROIs associated with PTSD in previous research mostly assessing adults.
- **TEs highly predicted PTSD symptoms (.91-.92) in children.** Higher count of TEs elevated the risk for developing increased count of PTSD symptoms.
- *Limitations*: Measurement of trauma and PTSD symptoms is very skewed (lower endorsement of TEs, reduced information and lower power under these conditions). Causal inference is based on cross-sectional twin data. Non-twin subjects might be influencing C and heritability estimates.
- *Future directions*: Fit longitudinal model. Estimate molecular heritability and polygenic scores for PTSD, substance use risk and neuroimaging variables.

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The ABCD study

- The Adolescent Brain Cognitive Development (ABCD) study is a longitudinal assessment of brain development and health in children in the U.S. Visit: abcdstudy.org

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