Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. Clinical Assessment and SES Score Creation

The Philadelphia Neurodevelopmental Cohort (PNC) is a genotyped sample recruited from the Children's Hospital of Philadelphia (CHOP) pediatric network and not from psychiatric services. Enrollment criteria included: stable health; proficiency in English; physical and cognitive ability to complete interview and neurocognitive assessment; no contraindication for MRI for the randomly selected subsample $(N=1601)$ who underwent neuroimaging.¹

Clinical Assessment

A structured interview (GOASSESS), incorporating the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SAD), ² was administered.³ The frequency, duration and presence of distress or impairment caused by symptoms across psychopathology domains was measured, with algorithms providing DSM-IV diagnosis.³ Exploratory item-factor analysis extracting 4 factors (oblimin rotation) was performed on 112 clinical symptom items from the GOASSESS.⁴ This analysis produced a clean theory-consistent solution (Anxious-Misery, Fear, Externalizing, Psychosis) that facilitated the building of two confirmatory models from which scores were obtained: a correlated-traits model (4 correlated scores) and a bifactor model (4 orthogonal scores plus an overall psychopathology score, also orthogonal). The former (correlated-traits) scores were used here because they are better determined⁵ (Grice, 2001) than the bifactor scores, and their collinearity is not a problem because they are treated as correlated DVs in a repeated measures mixed model - in contrast to, for example, using the clinical variables simultaneously as IVs, in which case the bifactor model might have been appropriate

SES Score Creation

Due to the large number of participants in the PNC, we did not collect individual-level data targeting family-level SES (e.g. parental income, net worth, etc.). However, the census-based SES score correlates in the expected direction with SES-related variables such as parental education (Pearson $r = 0.52$), Caucasian race (biserial $r = 0.76$) and African-American race (biserial $r = -0.78$). Further, as shown in Moore et al. (2016), the census-based SES variable is the strongest predictor of neurocognitive performance (stronger than the effects of parent education, trauma, substance use, race, and psychopathology *combined*). For more information on the methods used here, see Moore et al. (2016).

eMethods 2. Neurocognitive Assessment, Neuroimaging, and Neuroimaging Data Processing Details Neurocognitive Assessment

The Penn Computerized Neurocognitive Battery (CNB) was administered concomitantly with the clinical assessment. The CNB provided measures of accuracy and response time for Executive Function (attention, abstraction and mental flexibility, working memory), Episodic Memory (verbal, facial, spatial), Complex Cognition (language reasoning, spatial processing, non-verbal reasoning) and Social Cognition (emotion identification, emotion differentiation, age differentiation).5,6 Each test provides measures of accuracy and response time. Here we measure efficiency, which provides four factor scores corresponding to these domains.⁷ **Neuroimaging**

MRIs were acquired on a 3T Siemens TIM Trio whole-body single scanner at the Hospital of the University of Pennsylvania.¹ Structural imaging used a magnetization-prepared, rapid acquisition gradient-echo (MPRAGE) T1-weighted image (TR 1810 ms; TE 3.51 ms; FOV 180x240 mm; matrix 192x256; 160 slices; slice thickness/gap 1/0 mm; TI 1100 ms; flip angle 9 degrees; effective voxel resolution of 0.93 x 0.93 x 1.00 mm). Image quality procedures were applied for all modalities.⁸ Parameters for this study include: brain volume; gray matter density (GMD); diffusion tensor imaging (DTI)-based mean diffusivity (MD) for the whole brain and fractional anisotropy (FA) for white matter tracts; cerebral blood flow (CBF); resting state fMRI (rsfMRI) measures of regional homogeneity (ReHo) and amplitude of low frequency fluctuations (ALFF).

Neuroimaging data processing details

Structural

We evaluated volume and gray matter density utilizing the MPRAGE sequence. To parcellate the brain into anatomically-defined regions, we used an advanced multi-atlas labeling approach. Specifically, 24 young adult T1-weighted volumes from the OASIS data set⁹ that were manually labeled by Neuromorphometrics, Inc. were registered to each subject's T1-weighted volume using the topperforming SyN diffeomorphic registration.^{10,11} These label sets were synthesized into a final parcellation using joint label fusion.¹² Volume was determined for each lobe using the intersection between the lobe created and a prior driven gray matter cortical segmentation from the ANTs cortical thickness pipeline as described below. Density estimates were calculated within each parcel as described below. To avoid registration bias and maximize sensitivity to detect regional effects that can be impacted by registration error, a custom adolescent template and tissue priors were created using data from 140 PNC participants, balanced for age and sex. Structural images were then processed and registered to this custom template using the ANTs cortical thickness pipeline.¹³ This procedure includes brain extraction, N4 bias field correction,¹³ Atropos tissue segmentation,¹⁴ and SyN diffeomorphic registration method.^{10,11} Finally, gray matter density was calculated using Atropos,¹⁴ with an iterative segmentation procedure that is initialized using 3-class K-means segmentation. This procedure produces both a discrete 3-class hard segmentation as well as a probabilistic gray matter density map (soft segmentation) for each subject. Gray matter density was calculated within the intersection of this 3-class segmentation and the subject's volumetric parcellation.¹⁵ Images included in the final analysis passed a rigorous quality assessment procedure as previously detailed.⁸

Diffusion

Diffusion data were skull stripped by generating a brain mask for each subject by registering a binary mask of a standard image (FMRIB58_FA) to each subject's brain using FLIRT.¹⁶ When necessary, manual adjustments were made to this mask. Next, eddy currents and movement were estimated and corrected using FSL's eddy tool.¹⁷⁻¹⁹ Eddy is an improvement upon the typical eddy/motion correction used as part of FSL's Diffusion Tool Box.²⁰ This tool simultaneously models the effects of diffusion eddy current and head movement on DTI images in order to reduce the amount of resampling and is an improvement of the standard FSL eddy correct tool.^{17,18} Next, the diffusion gradient vectors were rotated to adjust for motion using the 6-parameter motion output generated from eddy. Then, the B0 field map was estimated and distortion correction was applied to the DTI data using FSL's FUGUE.²¹ Finally, the diffusion tensor was modeled and metrics (FA and MD) were estimated at each voxel using FSL's DTIFIT. Registration from native space to a template space was completed using DTI-TK.^{22,23} First, DTI output files from DTIFIT were converted to DTI-TK format. Next, a template was generated from the tensor volumes using 14 representative diffusion data sets that were considered "Excellent" from the PNC sample. One individual from each of the 14 ages (age range 8-21) was randomly selected. These 14 DTI volumes were averaged together to create an initial template. Next, data from the 14 subjects were registered to this template in an iterative manner. Unlike standard intensity-based registration algorithms, this process utilizes the full tensor information in an attempt to best align the underlying white matter tracts using iterations of rigid, affine and diffeomorphic registration leading to the generation of a successively refined template. Ultimately, one high-resolution refined template was created and used for registration of the remaining diffusion datasets. All DTI maps were then registered (rigid, affine, diffeomorphic) to the high-resolution study-specific template using DTI-TK. Whole brain analysis was performed using a customized implementation of tract-based spatial statistics (TBSS).²⁴ FA and MD values were computed using a study specific white matter skeleton. Then, standard regions of interest (ROI; ICBM-JHU White Matter Tracts; Harvard-Oxford Atlas) were registered from MNI152 space to the study-specific template using ANTs registration.¹⁰ Mean diffusion metrics were extracted from these ROIs using FSL's 'fslmeants'. Images included in this final analysis had passed a stringent quality assessment procedure as previously detailed.¹⁹

Resting State BOLD

Task-free functional images were processed using a top-performing pipeline for removal of motion-related artifact.²⁵ Preprocessing steps included (1) correction for distortions induced by magnetic field inhomogeneities using FSL's FUGUE utility, (2) removal of the 4 initial volumes of each acquisition, (3) realignment of all volumes to a selected reference volume using MCFLIRT¹⁶ (4) removal of and interpolation over intensity outliers in each voxel's time series using AFNI's 3DDESPIKE utility, (5) demeaning and removal of any linear or quadratic trends, and (6) co-registration of functional data to the high-resolution structural image using boundary-based registration.²⁶ The artifactual variance in the data was modelled using a total of 36 parameters, including the 6 framewise estimates of motion, the mean signal extracted from eroded white matter and cerebrospinal fluid compartments, the mean signal extracted from the entire brain, the derivatives of each of these 9 parameters, and quadratic terms of each of the 9 parameters and their derivatives. Both the BOLD-weighted time series and the artifactual model time series were temporally filtered using a first-order Butterworth filter with a passband between 0.01 and 0.08 Hz.

Voxelwise regional homogeneity $(ReHo^{27})$ is equivalent to Kendall's coefficient of concordance, was computed over the timeseries in each voxel's local neighborhood. ReHo can thus be used as an estimate of the homogeneity of each neighborhood's activation pattern. Because spatial smoothing intrinsically elevates ReHo estimates by elevating spatial autocorrelation, Kendall's W was computed only on unsmoothed data. Each voxel's neighborhood was defined to include the 26 voxels adjoining its faces, edges, and vertices. The voxelwise homogeneity map was subsequently smoothed using a Gaussian kernel with FWHM of 6mm in SUSAN to improve the signal-to-noise ratio.²⁸ Finally regional ReHo values were then averaged across the anatomically derived subject specific

segmentation. Subjects included in this analysis had low motion as measured by mean frame wise displacement, specifically mean relative frame wise displacement less then 2.5 mm.

Functional connectivity among brain regions is primarily attributable to correlations between low-frequency fluctuations in regional activation patterns. The voxelwise amplitude of low-frequency fluctuations $(ALFF²⁷)$ was computed as the sum (discretised integral) over frequency bins in the low-frequency (0.01-0.08Hz) band of the voxelwise power spectrum, computed using a Fourier transform of the time-domain of the voxelwise signal. ALFF was calculated on data smoothed in SUSAN using a Gaussian-weighted kernel with 6mm FWHM.

Perfusion (CBF)

ASL data were pre-processed using standard tools included with FSL.²¹ Following distortion correction using the B0 map with FUGUE, the first four image pairs were removed, the time series was realigned in MCFLIRT,¹⁶ the skull was removed with BET,²⁹ and the image was smoothed at 6mm FWHM using SUSAN.²⁸ CBF was quantified from control-label pairs using ASL Toolbox.³⁰ As prior,¹ the T1 relaxation parameter was modeled on an age- and sex-specific basis.³¹ This model accounts for the fact that T1 relaxation time differs according to age and sex, and has been shown to enhance the accuracy and reliability of results in developmental samples.³² The CBF image was co-registered to the T1 image using boundary-based registration,²⁶ and regional CBF values were averaged within each parcel. Subjects included in this analysis had low motion as measured by mean framewise displacement, specifically mean relative framewise displacement less than 2.5 mm.

Age classification by brain parameters

To examine whether SES and TSEs relate to accelerated brain maturation, brains were classified as either adult (18+) or adolescent $($ <18). Classification models were built using extremely randomized trees³³ as implemented in sci-kit learn version 0.80.³⁴ Models were trained using all lobular regional parameter estimates in a normative cohort within each gender. Normative cohorts were derived from participants who were identified as having benign SES backgrounds, and reporting no TSEs. Prior to building the model, race effects were removed from the data. Finally, age was predicted on all subjects and proportions of subjects identified as adults were tested within preidentified age bins (10-11,12-13,14-15,16-17, and 18+) using z-tests for proportions.

eTable 2. Demographics for the 4 Groups Contrasted in Figures

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eTable 4. Results of Logistic Regression Analysis on the Main Demographic and Trauma Factors With Proportion of Individuals at Each Age Bracket That Has Reached Puberty According to the Pubic Hair Item of the Tanner Scale

eTable 5. Results of the MMRM on the Main Demographic and Trauma Factors With Cognitive Domain Scores as Dependent Measures

more accurate and faster (lower RT) performance; interaction between SES and trauma are non-significant for both models. Factors involved with SES or TSE are in red and significant effects bolded.

Factors involved with SES or TSE are in red and significant effects (FDR corrected) bolded. P values are FDR-Corrected.

eTable 8. Results of Logistic Regression Analysis on the Main Demographic and Trauma Factors With Proportion of Individuals at Each Age Bracket That Were Classified as Having Adult Brain by the Machine-Learning Classifier

eResults. Structural Equation Model

A structural equation model was specified such that all outcomes of interest (cognition and psychopathology) were regressed on all independent variables of interest (trauma, SES, etc.). Additionally, brain parameters acted as mediators (both IVs and DVs) whereby they were regressed on the IVs of interest and also had direct effects on all DVs. All brain parameters were allowed to inter-correlate freely. Some relationships that do not make intuitive sense (e.g. Sex -> Age) were constrained. The model was estimated using the Bayesian estimator in Mplus, where the number of Markov chains was set to 1.

Fit of the model was acceptable (Posterior Predictive P-value > 0.05), and Table SX shows the results.

anisotropy; CBF = cerebral blood flow; vol = volume; REHO = regional homogeneity; ALFF = amplitude of low-frequency fluctuations; $GMD = gray$ matter density.

eTable 10. Correlation Matrix Among the Dependent Measures

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 $_{0.0}$ -0.5 $\frac{1}{2}$ -1.0

eFigure 2. **The Relation of Trauma Category to Cognitive Performance on the 4 Efficiency Domains**

Values are shown for groups with trauma by race and SES status (Benign SES=B_SES; Low SES=L_SES) in z-scores compared to the group with benign SES and no trauma

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