**SUPPLEMENTAL DATA**

**Early-Life Adversity Predicts Markers of Aging-Related Neuroinflammation, Neurodegeneration, and Cognitive Impairment in Women**

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**Cambridge Neuropsychological Automated Test Battery (CANTAB) Tasks**

Cognitive function was assessed using tasks from the prodromal Alzheimer’s disease and mild cognitive impairment test battery. The 3 tasks below were used for analyses **(**information taken and summarized from <https://cambridgecognition.com>1.

Spatial Working Memory (SWM)Task: Find yellow tokens hidden in colored boxes by selecting and eliminating options. The number of boxes increases up to 12, with colors and positions changing each trial.
Measure (SWMS; -ve sense): Strategy score at the 12-box stage, indicating how often a participant starts their search from the same box. Lower scores indicate better strategy use.

Rapid Visual Information Processing (RVP)Task: Identify target sequences of digits (e.g., 2-4-6) appearing at 100 digits per minute in a central white box. Respond by pressing a button when the target sequence appears.
Measure (RVPA; +ve sense): Sensitivity to detecting target sequences, reflecting accuracy in identifying the correct sequences.

Pattern Recognition Memory (PRM)Task: View a series of visual patterns, then choose between previously seen and new patterns in a recognition phase presented in reverse order.
Measure (PRMPCI; +ve sense): Percentage of correctly identified patterns in the immediate forced-choice condition.

**Adverse Childhood Experience (ACE) Descriptive Data**

Early-life stress was assessed using the German version of the Comprehensive Trauma Interview (CTI)2 and events were counted using items corresponding to the Centers for Disease Control definition of Adverse Childhood Experiences (ACE)3 in the CTI. Frequences (SF1), score distributions (SF2), and co-occurrence (SF3) are shown below.

**Figure SF1. Adverse Childhood Experience (ACE) Frequencies**



*Note*. Operational definitions of adverse childhood experiences (ACE). The prevalence is given as the number of women who experienced a specific ACE (N) prior to the onset of menarche and as a percentage of the total number of participants.

**Figure SF2. Adverse Childhood Experience (ACE) Score Distribution**



*Note*. Histogram showing the frequency distribution of participant adverse childhood experience (ACE) scores (calculated for each participant as the sum of the number of experienced stressors before menarche.

**Figure SF3. Adverse Childhood Experience (ACE) Co-occurrence**



*Note*. Venn diagram showing overlap between the three sub-types of adverse childhood experience (ACE). Results are given as the number of women who had experienced each sub-type(s) of ACE prior to menarche.

**Statistical Analysis**

Linear models, with an interaction term between age and adverse childhood experience (ACE) score, were implemented to assess heteroscedasticity and normality (ST1). Generalized additive models (GAMs) were implemented for all DVs to investigate the non-linear interaction effects between ACE score and age in the prediction of outcomes (Model 1). Goodness of fit for Model 1 was tested in comparison to Model 2 which capturs the interaction effect stratified by the levels of age for all DVs. Model fit was assessed using a combination of Akaike Information Criteria, Bayes Information Criteria, residual deviance, and residual degrees of freedom (ST2). Depression severity, state and trait anxiety, posttraumatic stress disorder severity, and SES were integrated as linear covariates into the main model. Bivariate Pearson correlations were conducted between these covariates, age, and ACE scores (ST3). The model performance was compared with and without covariates (ST4).

**Table ST1. Linear Model Tests**

|  |  |  |
| --- | --- | --- |
|   | **Goldfeld-Quandt test (p value)** | **Shapiro-Wilk test (p value)** |
| sGFAP  | 0.063 | < 0.001 |
| sNfL  | 0.013 | < 0.001 |
| sp-tau181 | 0.680 | 0.008 |
| TBV | < 0.001 | < 0.001 |
| tGMV | 0.233 | 0.1353 |
| sGMV | < 0.001 | < 0.001 |
| Left amygdala volume | < 0.001 | 0.001 |
| Right amygdala volume | < 0.001 | < 0.001 |
| tWMV | 0.3823 | 0.008 |
| Lateral ventricular volume | 0.036 | < 0.001 |
| Third ventricular volume | < 0.001 | < 0.001 |
| Fourth ventricular volume | 0.824 | < 0.001 |
| SWMS | 0.016 | < 0.001 |
| RVPA | 0.332 | < 0.001 |
| PRMPCI | 0.189 | < 0.001 |

*Note.*DV = dependent variable; sGFAP = serum glial fibrillary acidic protein; sNfL = serum neurofilament light chain; sp-tau181 = serum phosphorylated-tau181; TBV = total brain volume; tGMV = total grey matter volume; sGMV = subcortical grey matter volume; tWMV = total white matter volume; SWMS = spatial working memory strategy; RVPA = rapid visual information processing score; PRMPCI = pattern recognition memory percent correct instant.

**Table ST2. Fit Indices of Model 1 and Model 2**

|  |  |  |
| --- | --- | --- |
|  | **Model 1** | **Model 2** |
| DV | AIC | BIC | Residual deviance | Residual df | AIC | BIC | Residual deviance | Residual df |
| sGFAP  | 185.86 | 208.02 | 27.33 | 162.19 | 187.97 | 204.84 | 28.23 | 164.18 |
| sNfL  | 187.87 | 211.35 | 27.52 | 163.73 | 184.00 | 202.06 | 27.46 | 165.78 |
| sp-tau181 | 263.71 | 279.94 | 44.18 | 165.74 | 261.96 | 276.36 | 44.03 | 166.15 |
| TBV | -309.96 | -299.22 | 1.541 | 167 | -311.79 | -309.96 | 1.543 | 168 |
| tGMV | -653.47 | -642.9 | 0.207 | 167 | -655.47 | -653.47 | 0.21 | 168 |
| sGMV | -1275.5 | -1264.1 | 0.005 | 167 | -1276.7 | -1275.5 | 0.005 | 168 |
| tWMV | -814.97 | -804.4 | 0.08 | 167 | -816.97 | -814.97 | 0.08 | 168 |
| Lateral ventricular volume | -1236.2 | -1221.6 | 0.006 | 160.27 | -1238.2 | -1236.2 | 0.007 | 166.3 |
| Third ventricular volume | -2441.8 | -2417.7 | 6.122e-6 | 163.56 | -2437.2 | -2431.8 | 6.013e-6 | 165.3 |
| Fourth ventricular volume | -2227.2 | -2216.2 | 2.0831e-5 | 167 | -2228.8 | -2227.2 | 2.088e-5 | 168 |
| SWMS  | 815.34 | 834.75 | 1073.0 | 166.37 | 813.04 | 825.63 | 1085.8 | 169 |
| RVPA | -524.07 | -507.82 | 0.461 | 168.77 | -525.60 | -512.98 | 0.464 | 170 |
| PRMPCI | 1392.02 | 1411.34 | 25186 | 171.48 | 1389.66 | 1392.02 | 25444 | 174 |

*Note.* Model 1: Main model with both non-linear predictors; Model 2: model with non-linear (ACE score) + linear specification (age); DV = dependent variable; AIC = Akaike information criterion; BIC = Bayesian information criterion; df = degrees of freedom; ACE = Adverse Childhood Experience; sGFAP = serum glial fibrillary acidic protein; sNfL = serum neurofilament light chain; sp-tau181 = serum phosphorylated-tau181; TBV = total brain volume; tGMV = total grey matter volume; sGMV = subcortical grey matter volume; tWMV = total white matter volume; SWMS = spatial working memory strategy; RVPA = rapid visual information processing score; PRMPCI = pattern recognition memory percent correct instant.

**Table ST3. Correlation Table Between Age, ACE scores, and Covariates (psychopathology & SES)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Age** | **ACE score** | **BDI-II score** | **STAI-trait score** | **STAI-state score** | **DSM-IV PTSD****score** |
| ACE score | 0.077 |  |  |  |  |  |
| BDI-II score | 0.058 | 0.512\*\* |  |  |  |  |
| STAI-trait score | -0.028 | 0.471\*\* | 0.871\*\* |  |  |  |
| STAI-state score | -0.005 | 0.490\*\* | 0.788\*\* | 0.828\*\* |  |  |
| DSM-IV PTSD score | 0.129 | 0.498\*\* | 0.692\*\* | 0.603\*\* | 0.561\*\* |  |
| SES | -0.207\*\* | -0.295\*\* | -0.267\*\* | -0.151\* | -0.172\* | -0.267\*\* |

*Note.* Pearson r; ACE = Adverse Childhood Experience; BDI-II = Beck’s Depression Inventory; STAI = State-Trait-Anxiety Inventory; DSM-IV PTSD = Diagnostic and Statistical Manual of Mental Disorders Posttraumatic Stress Disorder; SES = current socioeconomic status; \*\* p < 0.01.

**Table ST4. Estimates and p Values for Main Model with and without Covariates**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **DV** | **Covariate** | **Coefficient estimate (Model 1)** | **p value****(Model 1)** | **Coefficient estimate (Model 3)** | **p value****(Model 3)** |
| sGFAP | Interaction | 4.346 | 0.012 | 4.11 | 0.021 |
| BDI-II |  |  | 0.004 | 0.528 |
| STAI-trait |  |  | < 0.001 | 0.361 |
| STAI-state |  |  | -0.005 | 0.923 |
| PTSD |  |  | < 0.001 | 0.988 |
| SES |  |  | < 0.001 | 0.987 |
| sNfL | Interaction | 4.674 | < 0.001 | 4.566 | < 0.001 |
| BDI-II |  |  | -0.017 | 0.039 |
| STAI-trait |  |  | 0.010 | 0.796 |
| STAI-state |  |  | < 0.001 | 0.054 |
| PTSD |  |  | 0.010 | 0.281 |
| SES |  |  | 0.051 | 0.095 |
| sp-tau181 | Interaction | 3.089 | 0.948 | 3 | 0.945 |
| BDI-II |  |  | -0.022 | 0.017 |
| STAI-trait |  |  | 0.007 | 0.426 |
| STAI-state |  |  | 0.005 | 0.260 |
| PTSD |  |  | 0.022 | 0.072 |
| SES |  |  | 0.009 | 0.824 |
| TBV | Interaction | 3 | 0.006 | 3 | 0.007 |
| BDI-II |  |  | 0.002 | 0.190 |
| STAI-trait |  |  | < 0.001 | 0.754 |
| STAI-state |  |  | < 0.001 | 0.433 |
| PTSD |  |  | -0.044 | 0.060 |
| SES |  |  | -0.006 | 0.396 |
| tGMV | Interaction | 3 | 0.001 | 3 | < 0.001 |
| BDI-II |  |  | < 0.001 | 0.834 |
| STAI-trait |  |  | < 0.001 | 0.606 |
| STAI-state |  |  | < 0.001 | 0.482 |
| PTSD |  |  | < -0.001 | 0.422 |
| SES |  |  | < 0.004 | 0.171 |
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|  |  |  |  |  |  |
| **DV** | **Covariate** | **Coefficient estimate (Model 1)** | **p value****(Model 1)** | **Coefficient estimate (Model 3)** | **p value****(Model 3)** |
| tWMV | Interaction | 3.002 | 0.117 | 3.001 | 0.157 |
| BDI-II |  |  | < 0.001 | 0.073 |
| STAI-trait |  |  | < -0.001 | 0.437 |
| STAI-state |  |  | < -0.001 | 0.886 |
| PTSD |  |  | < -0.001 | 0.325 |
| SES |  |  | < 0.001 | 0.429 |
| sGMV | Interaction | 3.001 | 0.049 | 3 | 0.030 |
| BDI-II |  |  | < -0.001 | 0.646 |
| STAI-trait |  |  | < 0.001 | 0.723 |
| STAI-state |  |  | < 0.001 | 0.387 |
| PTSD |  |  | < -0.001 | 0.496 |
| SES |  |  | < -0.001 | 0.173 |
| Lateral ventricular volume | Interaction | 6.164 | 0.129 | 5.706 | 0.183 |
| BDI-II |  |  | < -0.001 | 0.294 |
| STAI-trait |  |  | < 0.001 | 0.756 |
| STAI-state |  |  | < -0.001 | 0.556 |
| PTSD |  |  | < 0.001 | 0.467 |
|  | SES |  |  | < -0.001 | 0.616 |
| Third ventricular volume | Interaction | 4.367 | 0.001 | 3.519 | 0.002 |
| BDI-II |  |  | < 0.001 | 0.786 |
| STAI-trait |  |  | < -0.001 | 0.597 |
| STAI-state |  |  | < -0.001 | 0.794 |
| PTSD |  |  | < 0.001 | 0.462 |
| SES |  |  | < 0.001 | 0.262 |
| Fourth ventricular volume | Interaction | 3.002 | 0.257 | 3.003 | 0.193 |
| BDI-II |  |  | < 0.001 | 0.738 |
| STAI-trait |  |  | < 0.001 | 0.479 |
| STAI-state |  |  | < -0.001 | 0.042 |
| PTSD |  |  | < -0.001 | 0.366 |
| SES |  |  | < -0.001 | 0.076 |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
| **DV** | **Covariate** | **Coefficient estimate (Model 1)** | **p value****(Model 1)** | **Coefficient estimate (Model 3)** | **p value****(Model 3)** |
| SWMS | Interaction | 3.706 | 0.003 | 3.69 | 0.008 |
| BDI-II |  |  | 0.011 | 0.984 |
| STAI-trait |  |  | 0.01 | 0.778 |
| STAI-state |  |  | 0.004 | 0.746 |
| PTSD |  |  | -0.043 | 0.441 |
| SES |  |  | -0.241 | 0.203 |
| RVPA | Interaction | 3.079 | 0.024 | 3 | 0.102 |
| BDI-II |  |  | <0.001 | 0.720 |
| STAI-trait |  |  | <0.001 | 0.591 |
| STAI-state |  |  | <0.001 | 0.255 |
| PTSD |  |  | -0.002 | 0.199 |
| SES |  |  | 0.014 | <0.001 |
| PRMPCI | Interaction | 3.644 | 0.005 | 3.623 | 0.052 |
| BDI-II |  |  | -0.131 | 0.944 |
| STAI-trait |  |  | 0.021 | 0.915 |
| STAI-state |  |  | 0.088 | 0.906 |
| PTSD |  |  | 0.059 | 0.693 |
| SES |  |  | 2.730 | 0.002 |

*Note.* Model 1: Main model with both non-linear predictors; Model 3: main model with both non-linear predictors and linear covariates; sGFAP = serum glial fibrillary acidic protein; sNfL= serum neurofilament light chain; sp-tau181 = serum phosphorylated tau 181; TBV = total brain volume; tGMV = total grey matter volume; sGMV = subcortical grey matter volume; tWMV = total white matter volume; SWMS = spatial working memory strategy; RVPA = rapid visual information processing score; PRMPCI = pattern recognition memory percent correct instant; BDI-II = Beck’s Depression Inventory; STAI = State-Trait-Anxiety Inventory, DSM-IV PTSD = Diagnostic and Statistical Manual of Mental Disorders Posttraumatic Stress Disorder; SES = current socioeconomic status; pvalues for Model 3 were not adjusted as this was an exploratory sensitivity analysis.

**Supplementary Analysis: Age at Menarche Onset**

M=12.98 years, SD=1.27

We examined the relationship between age at menarche onset and ACE score using Pearson correlation (r=-0.03; p=0.65). Further, we computed correlations between age at menarche onset and all dependent variables and all were non-significant (p>0.05).

**Table ST5: Correlation Table Between Outcomes and Age at Menarche Onset**

|  |  |
| --- | --- |
| **DV** | **Correlation between DV and age at menarche; r (p value)** |
| sGFAP | -0.06 (0.44) |
| sNfL | 0.10 (0.20) |
| sp-tau181 | 0.09 (0.23) |
| TBV | 0.10 (0.22) |
| tGMV | 0.06 (0.47) |
| sGMV | 0.03 (0.68) |
| tWMV | 0.15 (0.06) |
| Lateral ventricular volume | -0.14 (0.06) |
| Third ventricular volume | -0.12 (0.12) |
| Fourth ventricular volume | -0.03 (0.63) |
| SWMS | 0.02 (0.77) |
| RVPA | -0.14 (0.06) |
| PRMPCI | -0.01 (0.88) |

*Note*. Pearson r; DV = dependent variable; sGFAP = serum glial fibrillary acidic protein; sNfL= serum neurofilament light chain; sp-tau181 = serum phosphorylated tau 181; TBV = total brain volume; tGMV = total grey matter volume; sGMV = subcortical grey matter volume; tWMV = total white matter volume; SWMS = spatial working memory strategy; RVPA = rapid visual information processing score; PRMPCI = pattern recognition memory percent correct instant.

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