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1 **Neural Signatures of Data-Driven Psychopathology Dimensions at the Transition**
2 **to Adolescence**

3
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34 **Shortened title:** Neural Basis of Youth Psychopathology

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40 **Abstract**

41 **Background:** One of the challenges in human neuroscience is to uncover associations
42 between brain organization and psychopathology in order to better understand the
43 biological underpinnings of mental disorders. Here we aimed to characterize the neural
44 correlates of psychopathology dimensions obtained using two conceptually different
45 data-driven approaches.

46 **Methods:** Dimensions of psychopathology that were either maximally dissociable or
47 correlated were respectively extracted by independent component analysis (ICA) and
48 exploratory factor analysis (EFA) applied to the Childhood Behavior Checklist (CBCL)
49 items from 9–10-year-olds (n=9983; 47.8% female, 50.8% white) participating in the
50 Adolescent Brain Cognitive Development study. The patterns of brain morphometry,
51 white-matter integrity and resting-state connectivity associated with each dimension
52 were identified using kernel-based regularized least squares and compared between
53 dimensions using Spearman's correlation coefficient.

54 **Results:** ICA identified three psychopathology dimensions, representing opposition-
55 disinhibition, cognitive dyscontrol, and negative affect, with distinct brain correlates.
56 Opposition-disinhibition was negatively associated with cortical surface area, cognitive
57 dyscontrol was negatively associated with anatomical and functional dysconnectivity
58 while negative affect did not show discernable associations with any neuroimaging
59 measure. EFA identified three dimensions representing broad externalizing,
60 neurodevelopmental, and broad Internalizing problems with partially overlapping brain
61 correlates. All EFA-derived dimensions were negatively associated with cortical surface

62 area, whereas measures of functional and structural connectivity were associated only
63 with the neurodevelopmental dimension.

64 **Conclusions** This study highlights the importance of cortical surface area and global
65 connectivity for psychopathology in pre-adolescents and provides evidence for
66 dissociable psychopathology dimensions with distinct brain correlates.

67 **Key words:** Adolescence, Development, Neuroimaging, Psychopathology, Population
68 Neuroscience

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70

71 **Introduction**

72 One of the challenges in human neuroscience is to uncover associations between brain
73 organization and psychopathology in order to better understand the biological
74 underpinnings of mental disorders. As individuals typically present with a range of
75 behavioral or self-reported problems, statistical modeling can be used to extract latent
76 dimensions of psychopathology.¹ The assumptions of these statistical models vary
77 which could be consequential for uncovering biologically meaningful phenomenon. A
78 widely used approach involves the application of factor analytic models to identify
79 dimensions (termed factors) allows for uncovering correlated constructs². The
80 dimensions specified by the Hierarchical Taxonomy of Psychopathology (HiTOP) model
81 is a key example^{3, 4}. Conversely, application of independent component analysis (ICA)
82 decomposes the variance of individual ratings to yield maximally dissociable dimensions
83 (termed components)^{5, 6, 7-10}. In this context, ICA can uncover statistically independent
84 psychopathology constructs while still allowing for individual symptoms to be shared
85 across dimensions. These dimensions can then be leveraged to identify potentially
86 distinct biological mechanisms underlying psychopathology. As an example,
87 independent dimensions of psychopathology in youth participating in the Philadelphia
88 Neurodevelopmental Cohort have been associated with distinct patterns of white matter
89 connectivity⁸.

90 Late childhood and adolescence is a period of particular interest in the contest of brain-
91 psychopathology associations because it coincides with major brain maturational
92 changes¹¹⁻¹⁴ and with the epidemiological peak for incident mental disorders^{15, 16}.
93 Accordingly, we focus on brain-psychopathology associations in a population sample of

94 9–10-year-olds participating in the multisite USA study of Adolescent Brain Cognitive
95 Development (ABCD)^{17, 18}. The ABCD study has a longitudinal design aiming to capture
96 changes in brain, behavior and cognition as participants traverse through adolescence.
97 Here we use baseline data to determine brain-psychopathology associations at the
98 point of transition to adolescence. Participants' psychopathology was rated using the
99 items of the Child Behavior Checklist (CBCL)¹⁹ to which we applied both factor and
100 independent components analyses with the aim of discovering brain features associated
101 with the dimensions identified by the two different models. The working hypothesis was
102 that decomposition of psychopathology into independent components, as opposed to
103 factors, would offer more mechanistic insights by identifying brain properties relating to
104 morphometry and connectivity that are differentially associated with psychopathology.

105 **Sample**

106 The ABCD baseline sample comprises 11,875 individuals aged 9-10 years enrolled at
107 22 sites (<https://abcdstudy.org/>) (Supplemental Methods, Section 1). The analyses
108 presented here used data from 9983 unrelated participants with an average age of 9.9
109 years (47.8% female, 50.8% white). The ABCD study was approved by the institutional
110 review board of the University of California, San Diego.

111 **Measures**

112 *Psychopathology*: Parents rated their children's behavior over the preceding 6-months
113 based on the 119 items of the CBCL (Supplement Methods, Section 2.1, Table S1).

114 *Child characteristics*: We used a wide range of measures pertaining to cognition,
115 academic functioning psychological traits, and mental health service utilization

116 (Supplement Methods, Section 2.2, Table S2) for the external validation of the
117 psychopathology dimensions.

118 *Neuroimaging measures:* ABCD participants underwent structural magnetic resonance
119 imaging (sMRI), diffusion MRI (dMRI) and resting-state functional MRI (rs-fMRI) using
120 standardized acquisition and analyses protocols (Supplement Methods, Section 3). We
121 downloaded preprocessed data from the ABCD repository to analyze features of
122 morphometry (cortical thickness, surface area and subcortical volume), white matter
123 integrity (fractional anisotropy, mean, radial and axial diffusivity) and cortical resting-
124 state networks (RSN) (detailed description of the neuroimaging variables in Tables S3-
125 S5).

126 **Statistical Analysis**

127 *Extraction of psychopathology dimensions:* All dimensions of psychopathology were
128 extracted from the CBCL items using either independent component analysis (ICA) or
129 exploratory factor analyses (EFA). The EFA-derived factors were derived by Michelini et
130 al for a prior study on the ABCD dataset²⁰. Both ICA and EFA are exploratory methods
131 that can represent data hierarchically. The difference between the two methods is that
132 ICA assumes statistical independence of the extracted dimensions, whereas EFA if
133 used with an oblique rotation allows for a correlated factor structure.

134 ICA was implemented using the Big Omics Data computational pipeline
135 (<https://github.com/LabBandSB/BIODICA>)^{5, 21} Models with 2 to 10 components were
136 generated and the optimal solution was chosen based on stability through 100 random
137 runs. Stability across sites was established using a leave-one-site-out approach (details
138 provided in Supplemental Methods, Section 5). The derived psychopathology

139 dimensions were further characterized by examining their Neurobehavioral and
140 Functional Profile. The EFA dimensions were provided by Michelini and colleagues²⁰
141 based on their analyses of the ABCD dataset (Supplemental Methods, Section 5).
142 Briefly, in the EFA, the hierarchical structure of psychopathology was explored by
143 applying principal component analysis to the matrix of polychoric correlation between
144 CBCL items and using an oblique rotation (geomin) to extract factor solutions with an
145 increasing number of factors. The maximum number of factors were determined using
146 parallel analysis while ensuring factor interpretability.

147 *Neuroimaging Correlates of Psychopathology Dimensions:* We used a series of kernel-
148 based regularized least squares (KRLS) analyses^{22, 23} to quantify the associations
149 between each ICA- and EFA-derived psychopathology dimension and the neuroimaging
150 variables. We chose KRLS because it does not make assumptions about the shape of
151 the associations (i.e., linear or nonlinear) and is easily interpretable. KRLS yields
152 average effect estimates of the independent variables, analogous to the beta
153 coefficients of linear regression models. KRLS models were conducted separately for
154 each modality (i.e., sMRI, dMRI, and rs-fMRI). For the sMRI and dMRI models, both
155 global (i.e., mean cortical thickness, total surface area and total intracranial volume,
156 average fractional anisotropy and diffusivity) and regional measures were used as
157 predictors; in the rs-fMRI models, measures of between- and within-network
158 connectivity were used as predictors. All models were adjusted for sex, age, and race,
159 handedness, scanner, weight, height, pubertal stage while motion was also included in
160 models considering rs-fMRI and dMRI variables. The analyses were not adjusted for
161 total intracranial volume (TIV), because we consider TIV as a marker of global

162 neurodevelopment. However, by adjusting for demographic and anthropometric
163 variables, we controlled for the portion of TIV that is determined by non-
164 neurodevelopmental factors.

165 To establish that the results of all KRLS models were independent of sample
166 composition all analyses were repeated 100 times, each time by randomly resampling
167 50% of the total dataset. Subsequently, the t-value vectors (regardless of significance)
168 obtained from the KRLS models for each psychopathology dimension were compared
169 using Spearman's correlation coefficient. The stability of the associations was judged
170 based on the number of times they were statistically significant at $P_{\text{False Discovery Rate}}$
171 $(\text{FDR}) \leq 0.05$. The direction of association was informed by the original model with the full
172 dataset.

173

174 **Results**

175 **Psychopathology Dimensions**

176 Amongst the plausible the ICA solutions, the three-component solution was maximally
177 stable (stability=0.90, leave-one-site-out stability of 0.85-0.92) and minimally correlated
178 (Spearman's ρ =-0.03 to 0, Figure 1b) (Figure 1; Supplemental Results, Section1;
179 Figures S1-S3). Based on the items with the highest loadings, these three dimensions
180 represented opposition-disinhibition, cognitive dyscontrol and negative affect (Table
181 S7). In the opposition-disinhibition dimension, CBCL items relating to rule breaking,
182 impulsivity, and hostility-aggression had the highest loadings. In the cognitive dyscontrol
183 dimension, high-loading CBCL items related to inattention, poor concentration, and
184 restlessness, and in the negative affect dimension, high-loading CBLC items reflected
185 fears, sadness, worries and social discomfort. The opposition-disinhibition dimension
186 was mainly associated with poorer general cognitive ability, whereas cognitive
187 dyscontrol was associated with lower performance across cognitive domains; both
188 opposition-disinhibition and cognitive dyscontrol were associated with poorer academic
189 function (Supplement Results, Section 2; Tables S8-S9; Figure S4) but the opposite
190 was the case for the negative affect dimension.

191 To allow direct comparison with the three-component ICA solution, the EFA-dimensions
192 considered were the 3-factor solution consisting of broad externalizing dimension, the
193 neurodevelopmental problems dimension, and broad internalizing dimension which
194 showed marked correlation (Spearman's ρ =0.53 to 0.65). The highest loading CBCL
195 items on the broad externalizing, the neurodevelopmental, and broad internalizing
196 dimensions were similar to the opposition-disinhibition, cognitive dyscontrol, and

197 negative affect dimensions respectively (Tables S8-S9). A comparison of the most fine-
198 grained solutions for both ICA and EFA (consisting of five dimensions each) is provided
199 in the supplemental material (Figures S20-S29).

200 The broad externalizing and neurodevelopment dimensions were associated with lower
201 cognitive tasks performance and academic function while the broad internalizing
202 dimension was positively associated with behavioral inhibition and lack of perseverance
203 (further details in Tables S8-S9).

204

205 ***Neuroimaging Correlates of Dimensional Psychopathology***

206 **Brain Morphometry:** With respect to the ICA-derived dimensions, opposition-
207 disinhibition was the only dimension associated with brain morphometry involving
208 negative associations with global and regional cortical surface area and regional
209 subcortical volumes and a positive association with cortical thickness in frontotemporal
210 regions (Figure 3, Table S10, Figures S5-S6 and S8). By contrast, all three EFA-
211 derived dimensions were significantly associated with the reduced surface area; the
212 broad externalizing dimension was additionally associated with the frontotemporal
213 thickness (Figure 3, Figures S5, S7 and S9). The similarity of the regional morphometric
214 profiles between ICA-derived dimensions was low (Spearman's $\rho = -0.10$ to 0.23)
215 (Figure S11) while it was very high for the EFA-derived dimensions (Spearman's $\rho = 0.87$
216 to 0.91).

217

218 **White Matter Integrity:** the ICA-derived dimension of cognitive dyscontrol as well as
219 the EFA-derived neurodevelopmental dimension were both associated with mean radial

220 diffusivity and with multiple regional measures (Figure 4, Table S11, Figures S12-S15).
221 Except for negative affect and broad externalizing, all other ICA- and EFA-derived
222 dimensions showed localized associations with dMRI measures in the superior
223 corticostriate and corticospinal tracts (Figures S12-S14). The pair-wise similarity in
224 regional white matter integrity profiles was moderate for ICA-derived dimensions (Figure
225 S16) (Spearman's $\rho=0.44$ to 0.59) and high for EFA-derived dimensions (Spearman's
226 $\rho=0.71$ - 0.89).

227

228 **RSN-Connectivity:** Significant associations between resting-state connectivity and
229 psychopathology were noted only for the ICA-cognitive dyscontrol and the EFA-
230 developmental dimensions. Cognitive dyscontrol mainly showed (a) positive
231 associations with the inter-network connectivity of the cingulo-opercular/default mode
232 networks, the frontoparietal/sensorimotor-hand networks, and the default mode/dorsal
233 attention networks; and (b) negative associations with the intra-network connectivity of
234 the sensorimotor-hand, the default mode, and the cingulo-opercular networks (Figures
235 S17-18). Similar associations were observed between the neurodevelopmental
236 dimension and resting state functional connectivity measures (Figure S18). The
237 similarity between functional connectivity profiles was low between the ICA- dimensions
238 (Figure S19, Spearman's $\rho =-0.32$ to 0.02) and moderate for the EFA- dimensions
239 (Spearman's $\rho=0.38$ to 0.64).

240

241

242

243 **Discussion**

244 We leveraged the ABCD dataset with the expressed intention of delineating how
245 different conceptualizations of psychopathology may influence associations with
246 measures of brain organization. The most significant differences between ICA- and
247 EFA- derived dimensions were noted for brain morphometry, where all EFA-dimensions
248 were associated negatively with global and regional measures of cortical surface area
249 while this was the case only for the opposition-disinhibition ICA- dimension. Cognitive
250 dyscontrol and developmental problems showed similar associations with measures of
251 white matter integrity and functional connectivity. Negative affect and internalizing
252 dimensions had minimal associations with neuroimaging measures.

253

254 There are three general observations arising from this study which appear to reflect
255 general principles in brain-psychopathology associations. First, across dimensions,
256 robust associations between psychopathology and measures of brain organization were
257 generally spatially diffuse. Prior multivariate studies have also reported that associations
258 between brain organization and behavior are typically global rather than regionally
259 specific²⁴⁻²⁶. Second, although some brain properties showed more robust associations
260 with specific dimensions, the overall profiles of their brain correlates showed moderate
261 correlations; this was the case even for the ICA-derived dimensions that were
262 statistically dissociable. Similar findings have been reported in a population sample of
263 older individuals with respect to the genetic correlates of ICA-derived behavioral traits⁷.
264 These findings align with the “multiple realizability” brain-behavior framework, where
265 distinct clinical phenomena can arise as a result of neurobiological processes with

266 considerable overlap²⁷. Third, the presence of psychopathology was associated with
267 cortical dysmaturation. Typical maturational changes involve cortical thinning and
268 cortical surface area expansion^{13, 28}. Psychopathology (and primarily opposition-
269 disinhibition and broad externalizing problems) was associated with aberrant cortical
270 maturation indexed by negative associations between psychopathology with cortical
271 surface area and positive associations with cortical thickness in frontal association
272 regions involved in top-down inhibitory control. Additionally, cognitive dyscontrol was
273 associated with lower anatomical and functional connectivity. These findings add to the
274 current debate as to the nature of brain maturation for externalizing/conduct problems²⁹
275 and cognitive difficulties^{30, 31}.

276

277 Arguably the most surprising finding was that the ICA-derived negative affect and EFA-
278 derived internalizing dimensions had minimal associations with any imaging measures.
279 Two prior studies on the ABCD sample reached the same conclusion with regards to
280 the association between broad internalizing and RSN connectivity as well as between
281 suicidal ideas and structural and functional brain measures^{32, 33}. Even amongst youths
282 with established internalizing disorders, a significant proportion had been reported to
283 have preserved brain structure and cognitive functioning with despite high levels of
284 internalizing psychopathology³⁴. These observations are open to several interpretations.
285 Negative affect in youth may not be associated with significant brain abnormalities as
286 indicated by its positive association with cognition. It could be argued that
287 negative/internalizing problems reflect meta-cognitive alternations involving negative
288 evaluations occurring in the context of largely intact brain organization. Alternatively, it is

289 possible that brain properties associated with negative affect and internalizing problems
290 are below macro-level resolution or that detectable macro-level changes may become
291 apparent either at different stages of development or when they are chronic. The
292 longitudinal design of the ABCD study will enable testing these hypotheses.

293

294 It is important to note several methodological issues. First, the ICA implementation was
295 methodologically rigorous and included steps to optimize its stability and external
296 validity of the dimensions identified. Second, the kernel-based approach ensures that
297 complex association can be detected as these can be missed when linear models only
298 are employed. Third, to address the computational costs of the analysis, the current
299 study used atlas-based measures of brain structure and function which may involve loss
300 of information compared to more fine-grained approach such as voxel-wise analysis.
301 Fourth, no assumptions of causality can be made on the basis of cross-sectional data,
302 but the study sets the foundation for future hypothesis testing in the longitudinal ABCD
303 dataset.

304

305 In sum, detailed characterization of psychopathology undertaken in the largest available
306 sample of preadolescents highlights cortical surface area and connectivity as the brain
307 phenotypes with the most robust associations with psychopathology dimensions
308 regardless of how they were defined.

309

310 **Data Availability:** The ABCD dataset is available upon request to the National Data
311 Archive <https://nda.nih.gov/abcd>

312

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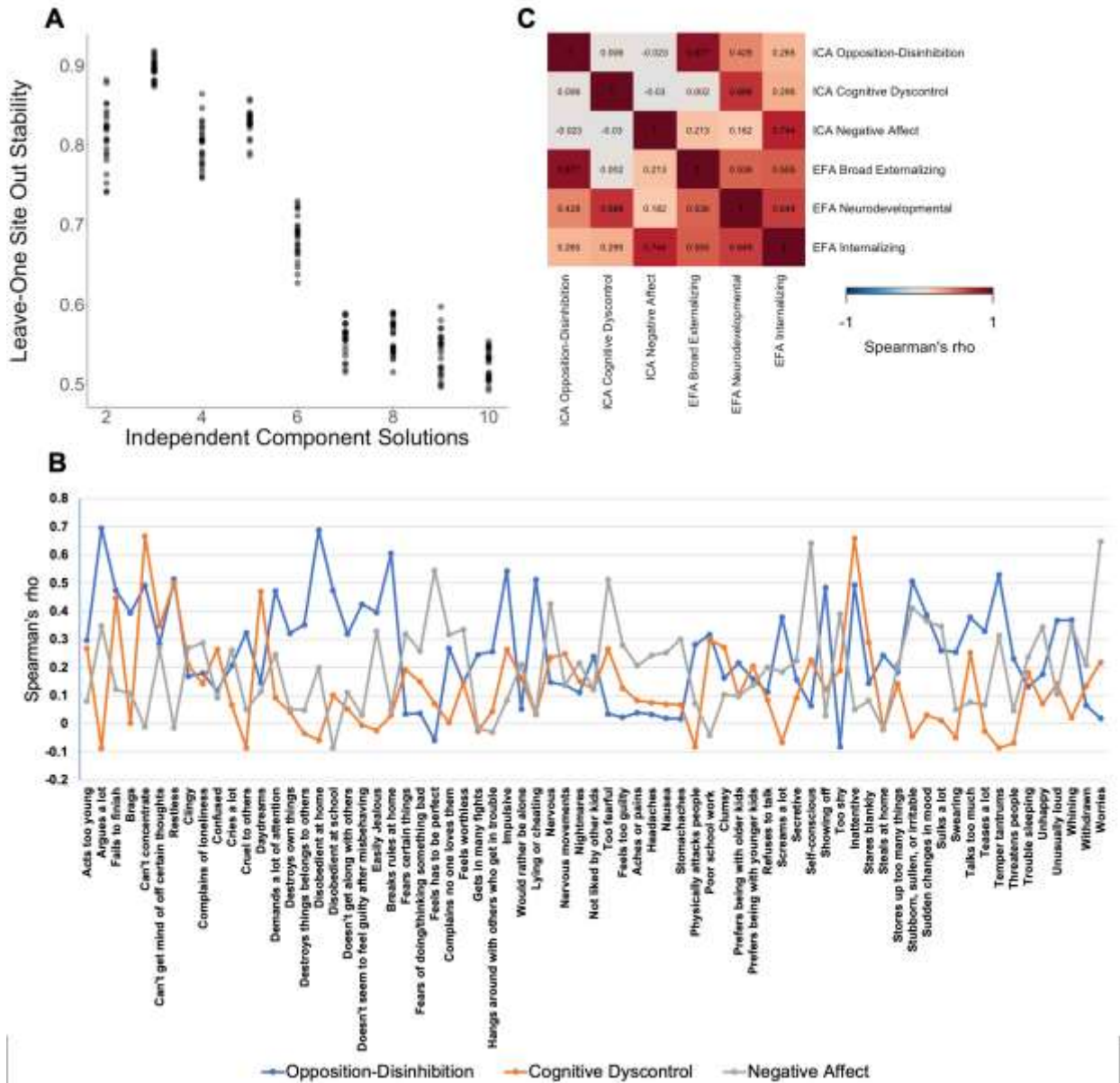
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438 **Figure 1. Data-driven structure of psychopathology in the ABCD dataset captured**

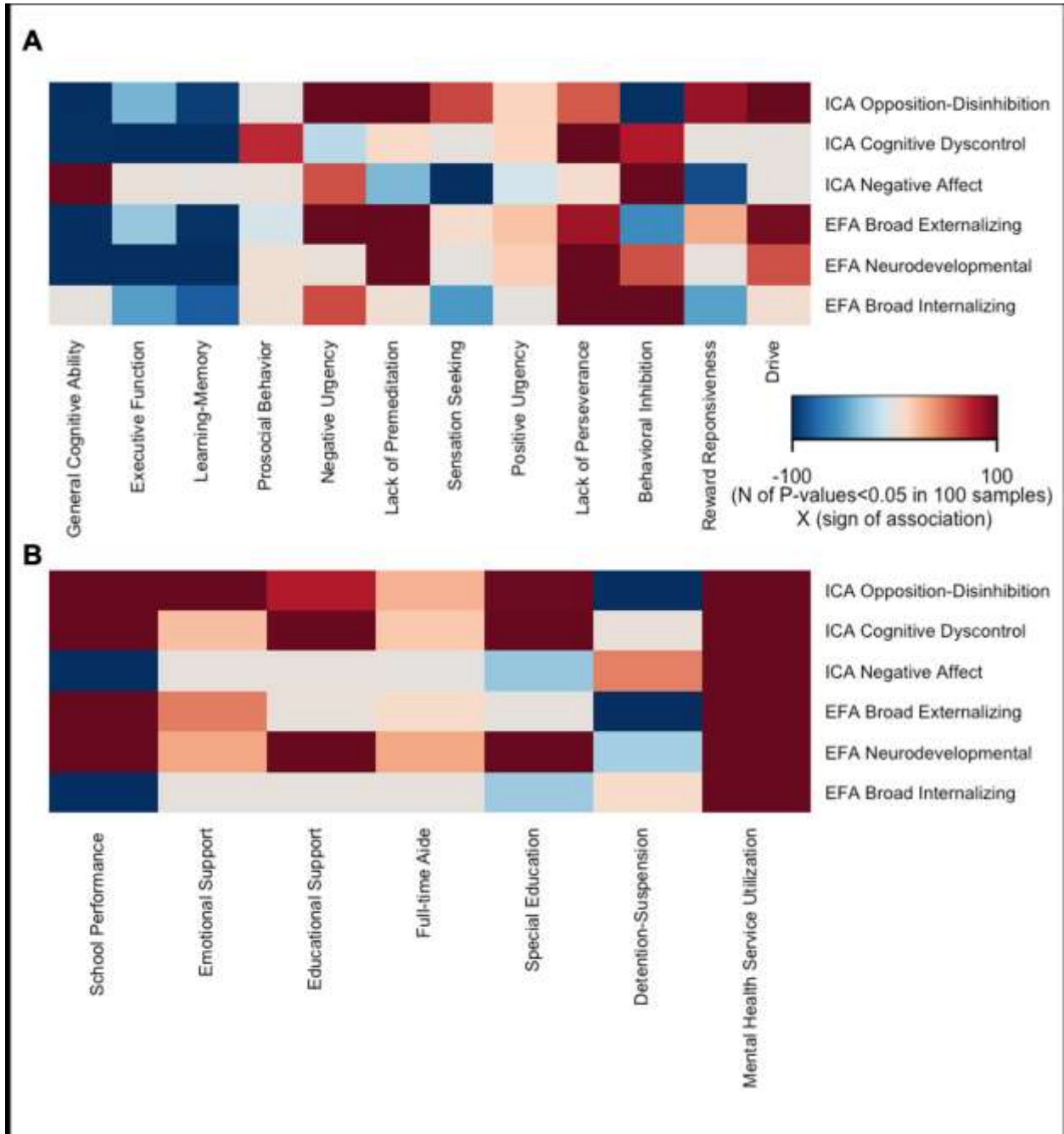
439 **independent component analysis (ICA). A.** Leave-one site stability for ICA solutions

440 from 2-10 components; **B.** Item loadings on each independent component for the three-

441 IC solution; **C.** Correlation between the three-IC solution and corresponding EFA-

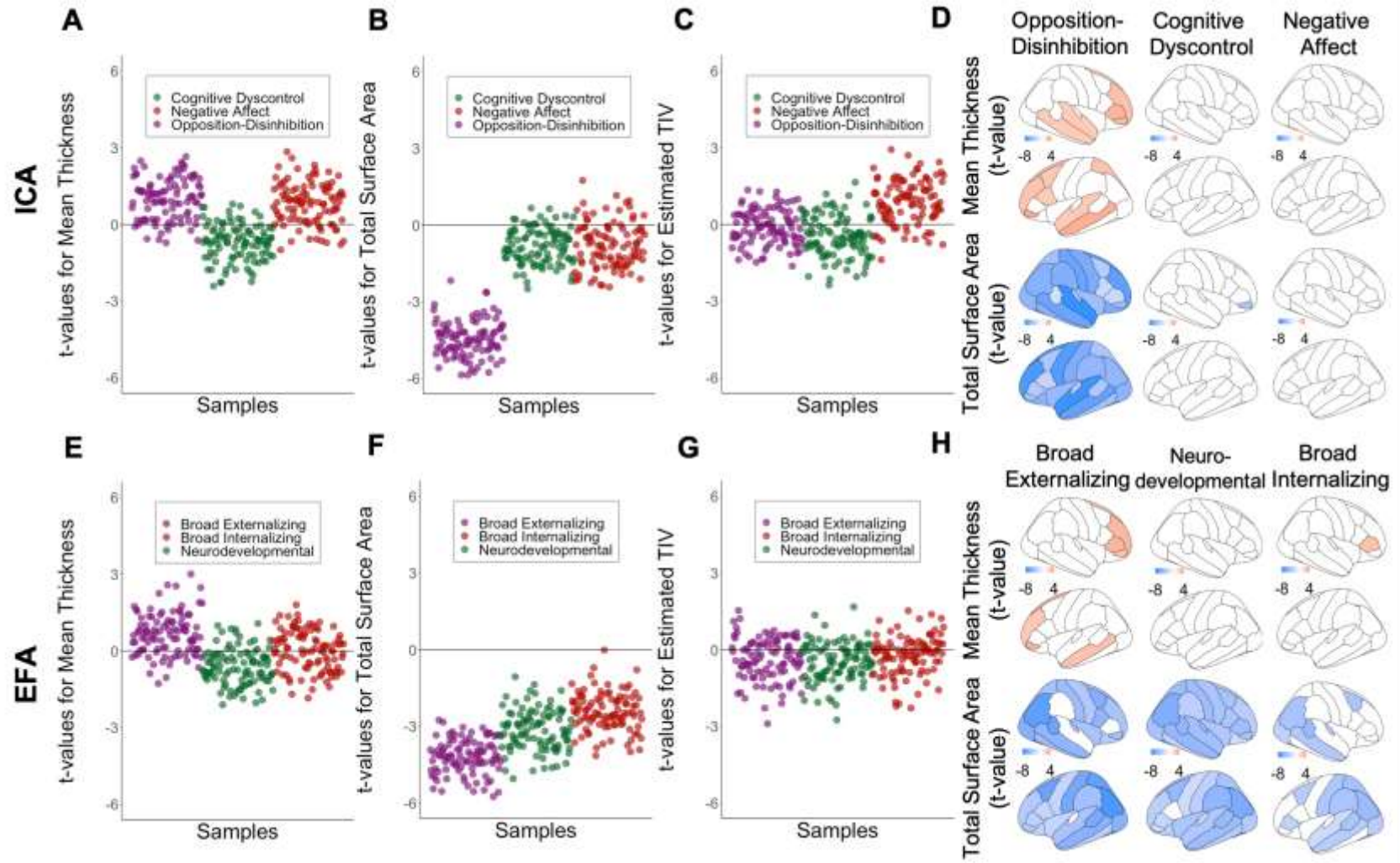
442 derived factors.

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 445 **Figure 2. Validity of the Psychopathology Dimensions.** Each cell represents number
 446 of FDR-corrected P-values < 0.05 in 100 reruns of the Kernel regularized least squares
 447 (KRLS) analysis on 50% randomly resampled data multiplied by the sign of the
 448 association. All analyses were adjusted for sex, race, age, and site; **A.** Association of
 449 psychopathology dimensions with cognitive and behavioral measures; for each

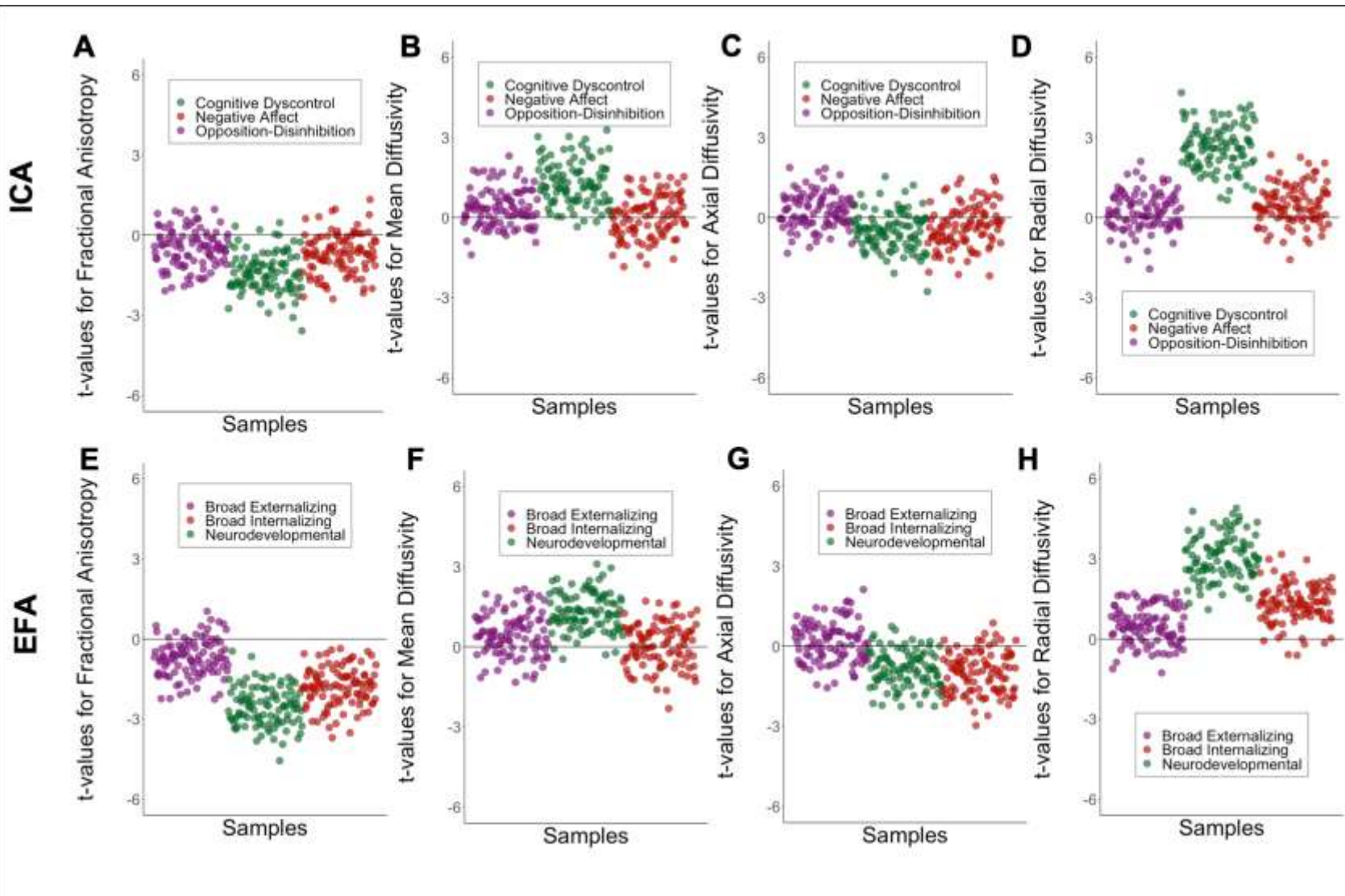
450 psychopathology dimension, all measures are modeled together to characterize their
451 independent contribution to psychopathology; **B.** Association of psychopathology
452 dimensions with academic outcomes and service utilization; for each outcome, all three
453 dimensions (ICA-derived or EFA-derived) are entered into the model together to
454 quantify their independent contribution to the outcome.



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457 **Figure 3. Association between global measures of brain morphometry and the most stable ICA solution, and**
458 **corresponding EFA factors using kernel regularized least squares (KRLS);** Values represent t-value for the
459 association between morphometric brain measures and dimensions of psychopathology. For global measures, values
460 represent t-values in 100 randomly resampled dataset of 50% original sample size. For regional measures values
461 represent t-value from the model on the whole dataset; All analyses were adjusted for sex, age, and race, handedness,
462 scanner, weight, height, pubertal stage; **A, B, C** Association between brain morphometric measures and ICA-derived
463 opposition-disinhibition, cognitive dyscontrol, and negative affect dimensions. **D, E, F.** Association between brain
464 morphometric measures and EFA-derived broad externalizing, neurodevelopmental, and broad internalizing factors.



466 **Figure 4. Association between global measures of white matter integrity and the most stable ICA solution, and**
467 **three corresponding EFA factors using kernel regularized least squares (KRLS).** Values represent t-value for the
468 association between the measures of white matter integrity and psychopathology dimensions in 100 randomly resampled
469 dataset of 50% original sample size; All analyses were adjusted for sex, age, and race, handedness, scanner, weight,
470 height, pubertal stage, and head motion; **A,B,C,D.** Association between measures of white matter integrity and ICA-
471 derived opposition-disinhibition, cognitive dyscontrol, and negative affect dimensions. **E, F, G, H.** Association between
472 measures of white matter integrity and EFA-derived broad externalizing, neurodevelopmental, and broad internalizing
473 factors
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