

1 **The role of preterm birth and postnatal stress in neonatal structural**  
2 **brain development**

3  
4 Femke Lammertink<sup>1\*</sup>, Manon J.N.L. Benders<sup>1\*</sup>, Erno J. Hermans<sup>2</sup>, Maria L. Tataranno<sup>1</sup>, Jeroen  
5 Dudink<sup>1</sup>, Christiaan H. Vinkers<sup>3,4</sup>, Martijn P. van den Heuvel<sup>5,6</sup>  
6

7 *<sup>1</sup>Department of Neonatology, University Medical Center Utrecht, Utrecht University, Utrecht,*  
8 *The Netherlands*

9 *<sup>2</sup>Donders Institute for Brain, Cognition, and Behaviour, Radboud University Medical Center,*  
10 *Nijmegen, The Netherlands*

11 *<sup>3</sup>Department of Anatomy & Neurosciences, Amsterdam UMC, Vrije Universiteit Amsterdam,*  
12 *Amsterdam Neuroscience, Amsterdam, The Netherlands*

13 *<sup>4</sup>Department of Psychiatry, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam*  
14 *Neuroscience, Amsterdam, The Netherlands*

15 *<sup>5</sup>Connectome Laboratory, Amsterdam Neuroscience, Department of Complex Trait Genetics,*  
16 *Center for Neurogenomics and Cognitive Research, Vrije Universiteit Amsterdam, Amsterdam,*  
17 *Netherlands*

18 *<sup>6</sup>Department of Child Psychiatry, Amsterdam UMC, Amsterdam Neuroscience, Amsterdam,*  
19 *Netherlands*

20

21 **Corresponding Author:** Femke Lammertink, [femke.lammertink@gmail.com](mailto:femke.lammertink@gmail.com)

22 **Number of Pages:** 44

23 **Number of Figures:** 6

24 **Number of Tables:** 4

25 **Number of Words for Abstract:** 242

26 **Number of Words for Introduction:** 537

27 **Number of Words for Discussion:** 1458

28 **Competing Financial Interests:** The authors declare that the research was conducted in the  
29 absence of any commercial or financial relationships that could be construed as a potential  
30 conflict of interest.

31  
32 **Acknowledgements:** Femke Lammertink was supported by a grant from the Wilhelmina  
33 Children's Hospital (D-17-010007). Martijn P. van den Heuvel was supported by a VIDI (452-16-  
34 015) grant from the Netherlands Organization for Scientific Research (NWO), and a European  
35 Research Council grant (ERC-2015-CoG 101001062). Erno J. Hermans was supported by a  
36 European Research Council grant (ERC-2015-CoG 682591). The content is the sole  
37 responsibility of the authors and does not necessarily represent the official views of the funding  
38 agencies. The authors declare that the research was conducted in the absence of any commercial  
39 or financial relationships that could be construed as a potential conflict of interest.

40 **Abstract**

41 Preterm birth disrupts the emerging foundations of the brain's architecture, and the continuum of  
42 early-life stress-provoked alterations reaches from a healthy adaptation with resilience to severe  
43 vulnerability and maladjustment with psychopathology. The current study examined how  
44 structural brain development is affected by a stressful extra-uterine environment and whether  
45 changes in topological architecture at term-equivalent age could explain the increased  
46 vulnerability for behavioral symptoms during early childhood. Longitudinal changes in structural  
47 brain connectivity were quantified using diffusion-weighted imaging (DWI) and tractography in  
48 preterm born infants (gestational age <28 weeks), imaged at 30 and/or 40 weeks of gestation  
49 ( $N=145$ , 43.5% female). A global index of postnatal stress was based on invasive procedures  
50 during hospitalization (e.g., heel lance). Infants were classified as vulnerable and resilient based  
51 on having more or less internalizing symptoms at 2-5 years of age ( $n=71$ ). Findings were  
52 replicated in an independent validation sample ( $N=123$ , 39.8% female,  $n=91$  with follow-up).  
53 Higher stress levels impaired structural connectivity growth in the amygdala, insula,  
54 hippocampus, and posterior cingulate cortex. The hippocampus, amygdala, and subthalamic  
55 nucleus showed lower global connectivity in vulnerable relative to resilient individuals. The  
56 distinct characteristics of the resilient brain allowed for a good predictive accuracy of group  
57 membership using local network measures (80%,  $p<10^{-5}$ ,  $\kappa=0.61$ ). These findings emphasize the  
58 detrimental impact of postnatal stress and, more importantly, the relative plasticity of the preterm  
59 brain. Resilience following postnatal stress appertains to a potential compensatory or innate  
60 ability to propagate global information flow.

61 **Significance Statement**

62 The underdeveloped preterm brain is exposed to various external stimuli following birth.  
63 Although the importance of early adversity has been widely recognized, the essential  
64 understanding of the effects of early chronic stress on neonatal brain networks as well as the  
65 remarkable degree of resilience is not well understood. We aim to provide an increased  
66 understanding of the impact of postnatal stress on brain development between 30 and 40 weeks of  
67 gestation and describe the topological architecture of a resilient brain. We observed global  
68 alteration in neonatal brain networks following postnatal stress and identified key contributive  
69 regions conferring resilience to the development of future internalizing symptoms.

70 **Introduction**

71 During critical periods of brain development, the extra-uterine environment impacts the  
72 maturation of the structural brain and behavioral functions. Preterm birth has long-lasting adverse  
73 effects on brain development and increases the risk for psychiatric symptoms later in life  
74 (Eikenes et al., 2011; Fischi-Gómez et al., 2015; Loe et al., 2013; Spittle et al., 2009). The  
75 development of the preterm brain is contingent on several (clinical) factors, and emerging data  
76 suggest that postnatal stressors such as the number of invasive procedures also play a role (Chau  
77 et al., 2019; Doesburg et al., 2013; Ranger et al., 2015; Ranger & Grunau, 2013). A paucity of  
78 longitudinal studies has explored the complex interaction between postnatal stress, brain  
79 development, and behavioral functions following preterm birth. We thus examined the impact of  
80 extra-uterine postnatal stress on brain development and how alterations in brain network  
81 architecture influences vulnerability for behavioral symptoms during early childhood (2-5 years).

82  
83 Early-life adversities may alter trajectories of brain maturation during a critical period of  
84 development. Cross-sectional studies investigating the effects of preterm birth on brain structure  
85 and function have shown lower white matter integrity in association tracts (forceps minor,  
86 forceps major, inferior frontal-occipital fasciculus/inferior longitudinal fasciculus, superior  
87 longitudinal fasciculus, and uncinate fasciculus); and projection fibers (e.g., thalamic radiation,  
88 corticospinal tract; Duerden et al., 2018; Menegaux et al., 2017; Vollmer et al., 2017; Zwicker et  
89 al., 2013). Preterm birth is further related to an upregulation of functional connectivity between  
90 stress-related and stress-vulnerable regions, such as the temporal cortex, thalamus, anterior  
91 cingulate gyrus, hippocampus, and amygdala (De Asis-Cruz et al., 2020; Johns et al., 2019;  
92 Papini et al., 2016). More recently, advances in graph theory enabled researchers to reveal  
93 meaningful information about the topological architecture of the neonatal brain. Studies showed,

94 for instance, that the fundamental community structural properties (i.e., groups of densely  
95 connected regions reflecting subsystems or "building blocks" of a network) of a preterm born  
96 infant seem to be similar to typically developing fetuses and neonates (Song et al., 2017; Turk et  
97 al., 2019); initial connectomic studies also highlight a more segregated and less integrated  
98 network organization in preterm-born infants (Ball, Boardman, et al., 2013; Ball, Srinivasan, et  
99 al., 2013; Groppo et al., 2014; Sa de Almeida et al., 2021) and children (de Kieviet et al., 2021;  
100 Fisci-Gomez et al., 2016), indicating differences in connectomic composition. These neonatal  
101 alterations in brain connectivity architecture may play a significant role in developing future  
102 psychopathology (Gilchrist et al., 2021; Kaufmann et al., 2017; Van Essen & Barch, 2015).  
103 Indeed, altered brain connectivity is implicated in a wide range of major psychiatric conditions,  
104 from ADHD and anxiety to Major Depressive Disorder (Suo et al., 2017; Tozzi et al., 2021;  
105 Wang et al., 2021).

106  
107 In this study, we examined the influence of stress on the development of premature brain  
108 connectivity and, second, whether alterations in macroscale network architecture at term-  
109 equivalent age may be predictive of vulnerability for anxiety-related symptoms during early  
110 childhood (2-5 years of age). We examined diffusion imaging and tractography from preterm  
111 infants, combined with data on postnatal stress related to their hospitalization. We aim to identify  
112 specific differences in resilient and vulnerable infants that may enable resilient individuals to  
113 maintain relative mental wellbeing during early childhood.

## 114 **Materials and Methods**

### 115 **Subjects**

116 Infants were included when they were scanned between 28-32 and/or 39-42 post-menstrual age.  
117 Data collection was part of standard clinical care, with permission obtained to use this data for  
118 clinical research from the medical ethical review committee of the University Medical Center  
119 Utrecht (METC Utrecht). Preterm infants with chromosomal and/or congenital anomalies were  
120 excluded. Details and demographics of the main and validation datasets are outlined in Table 1.

121

#### 122 *Main dataset*

123 Data of  $N=145$  preterm infants born infants clinically diagnosed as 'extremely preterm' with a  
124 gestational age  $<28$  weeks were included in our study, admitted to the Neonatal Intensive Care  
125 Unit (NICU) between 2013 and 2019 at the Wilhelmina Children's Hospital Utrecht, The  
126 Netherlands. Infants were scanned using a 45 directions diffusion protocol.

127

#### 128 *Validation dataset*

129 A replication sample containing  $N=123$  preterm infants born infants with a gestational age  $<28$   
130 weeks was included to assess the robustness of our results. Infants were admitted to the NICU  
131 between 2008 and 2013 and were scanned using a 32 directions diffusion protocol.

132

### 133 **Magnetic Resonance Imaging**

134 MRI data included the examination of 3T structural anatomical T2-weighted imaging and  
135 diffusion-tensor imaging (main dataset: dMRI,  $n=45$  directions; validation dataset,  $n=32$   
136 directions) (3T Achieva MR scanner). Images were obtained as part of a 35-minute scanning

137 session.

138

139 T2 data were acquired using a Turbo Spin Echo (TSE) sequence, using parameters: TR=6112ms,

140 TE=120ms, voxel resolution in millimeters  $0.53 \times 0.64 \times 2$  for 30 weeks and TR=4851ms,

141 TE=150ms, voxel resolution in millimeters  $0.78 \times 0.89 \times 1.2$  for 40 weeks. dMRI data were

142 acquired at 2 mm isotropic resolution and SENSE factor of 2 in 2 shells; 45 non-collinear

143 directions for the main dataset, with a b-value of  $800 \text{ s/mm}^2$  and one non-diffusion weighted

144 image (b=0) with TR 6500 ms and TE 80 ms; and 32 non-collinear directions for the validation

145 dataset, with a b-value of  $800 \text{ s/mm}^2$  and one non-diffusion weighted image (b=0) with TR 5685

146 ms and TE 70 ms.

147

148 Infants were immobilized by wrapping them into a vacuum cushion. MiniMuffs (Natus Europe,

149 München, Germany) and earmuffs (EM's kids Everton Park, Australia) were used to reduce noise

150 and the infant's propensity to move during image acquisition. Before scanning, preterm born

151 infants scanned at 30 weeks were either sedated with 30 mg/kg oral chloral hydrate or not sedated

152 at all, whereas infants scanned at 40 weeks were all sedated with 50 to 60 mg/kg oral chloral

153 hydrate. Scanning was halted if the infant woke up, and attempts were made to re-settle the infant

154 without taking them out of the patient immobilization system. A neonatologist or physician

155 assistant was present at all times during the examination.

156

## 157 **Data processing**

### 158 *Structural images*

159 Volumetric tissue segmentation of grey and white matter, and labeling of subcortical and cortical

160 areas, was performed on the T2 image (voxel resolution in millimeters  $0.53 \times 0.64 \times 2$  for 30



161 weeks and  $0.78 \times 0.89 \times 1.2$  for 40 weeks) using the structural pipeline from the developmental  
162 human connectome project (dHCP; <http://www.developingconnectome.org/>). The dHCP pipeline  
163 utilizes an "Expectation-Maximization" scheme that combines structure priors and an intensity  
164 model of the images (Makropoulos et al., 2018). A total of 47 (sub-)cortical grey matter labels  
165 were automatically generated during segmentation (see Figure 1).

166

### 167 *DWI tractography*

168 Diffusion-weighted images were corrected for eddy current distortions, motion-induced signal  
169 drop-out, and head motion using a non-parametric approach using FSL (FSL EDDY) (Andersson  
170 & Stamatios, 2016). The b0 image (voxel-size  $2 \times 2 \times 2$  for the main dataset, voxel-size  
171  $1.41 \times 1.41 \times 2.00$  for validation dataset,  $b = 0$  s/mm<sup>2</sup>) was registered to the T<sub>2</sub>-weighted image for  
172 anatomical alignment of the DWI images using FLIRT with a boundary-based-registration (BBR)  
173 cost function (Greve & Fischl, 2009). The linear transformation matrix was combined with a non-  
174 linear warp registration using FSL FNIRT (Andersson et al., 2007) to map the diffusion space to  
175 an age-matched template. A single tensor model was used to estimate the main diffusion direction  
176 in each voxel (Basser et al., 1994) based on the 45 diffusion-weighted images ( $b = 800$  s/mm<sup>2</sup>; 32  
177 directions for the validation dataset). An FA and MD whole-brain map was created based on the  
178 fitted tensors. White matter pathways were reconstructed using FACT (fiber assignment by  
179 continuous tracking [Mori & Van Zijl, 2002]). Tractography involved starting eight streamline  
180 seeds in each white matter voxel, with fiber tracking, continued along the main diffusion  
181 direction of each voxel until a streamline showed high curvature ( $>65^\circ$ ), exited the brain mask,  
182 and/or when a streamline entered a voxel with low FA ( $<0.05$ ). The mean FA value of a  
183 streamline was computed as the weighted average FA value, including all voxels that a streamline  
184 passed. Individual brain networks consisting of 47 grey matter regions and their interconnecting

185 pathways were created by combining the subcortical and cortical segmentation map with all  
186 reconstructed white matter tractography streamlines, mapping for all combinations of regions  
187 their interconnecting streamlines, with the weight of each region-to-region connection taken as  
188 the non-zero mean FA of the selected streamlines. Connections with a low connectivity strength  
189 (lowest 5%) were taken as potential false-positive reconstructions and set to 0. A group-based  
190 threshold was applied, retaining connections present in at least 50% of the participants, balancing  
191 the number of false-positive and false-negative structural connections (de Reus & van den  
192 Heuvel, 2013). Results were validated using different levels of group-based consensus thresholds  
193 (50-90%, steps of 5%).

194  
195 Three summary measures were used to detect outliers among connectivity matrices, namely the  
196 presence of odd connections, the absence of common connections, and the average fractional  
197 anisotropy. We calculated the interquartile range (IQR) for each group separately by subtracting  
198 the 25th percentile from the 75th percentile (i.e.,  $IQR = Q3 - Q1$ ). Participants with a score below  
199  $Q1 - 2 \times IQR$  or above  $Q3 + 2 \times IQR$  for any of the three measures were considered outliers. This  
200 quantification led to the removal of 7 outliers at 30 weeks of gestation and 19 outliers at 40  
201 weeks of gestation.

202  
203 **Behavioral measures**  
204 *Postnatal stress*  
205 Data on invasive and stressful procedures were automatically extracted from the digital medical  
206 system. A global index of NICU-related stress was computed using a Principal Component  
207 Analysis on six parameters: skin-breaking procedures (i.e., heel lance, arterial and venous

208 punctures, peripheral venous line insertion), total days of invasive mechanical ventilation, and  
209 suctioning of the nose and mouth. Each row (i.e., subject) was weighted on the total days of  
210 NICU admission. The extracted component explained 72.5% of the variance, with factor loading  
211 ranging from 0.74 to 0.91. This approach avoids the confounding effects of multicollinearity and  
212 continuously measures global NICU-related stress in further analyses.

213

#### 214 *Residualized approach to postnatal stress*

215 All participants were invited for standard clinical follow-up at 2.5 and/or 5.75 years of age. Both  
216 the main and validation dataset had follow-up data, resulting in a total of 162 infants with both an  
217 MRI a term-equivalent age and data on behavioral symptoms (see Table 2 for an overview).  
218 During the clinical follow-up, parents reported on the level of internalizing symptoms of their  
219 child, such as depression and anxiety, using the Child Behaviour Checklist (CBCL; Achenbach &  
220 Rescorla, 2001). The CBCL is a parent-report questionnaire used to assess the frequency of  
221 dysfunctional behavior exhibited by the child in the past six months. Caregivers rate their  
222 children's behavior by answering questions about their child on a 3-point scale (0-2), zero being  
223 "not true" one being "somewhat or sometimes true", and two being "very true or often true". If  
224 children did not have a behavioral symptom assessment at 5.75 years of age, we used the 2.5  
225 years assessment (moderate correlation between the two-time points;  $r= 0.45, p < 0.001$ , see  
226 Figure 2-A). The follow-up also included other assessments not part of the current study, such as  
227 motor development and intelligence.

228

229 Resilience was quantified as a metric of mental health by indexing the internalizing symptoms  
230 subscale of the CBCL, taking into account the degree of NICU-related stressor exposure using  
231 simple linear regression. We observed a significant positive association between postnatal stress

232 and early childhood internalizing symptoms ( $t(11,151) = 4.08, p < 0.001$ ). The fitted regression  
233 line (see Figure 2-B) reflected the normative level, with participants positioned above the linear  
234 line (i.e., positive residual) expressing an over-reactivity of behavioral symptoms to stressor  
235 exposure in the neonatal period and data points below the linear line (i.e., negative residual)  
236 representing individuals with under-reactivity to stressor exposure (Amstadter et al., 2014; Van  
237 Harmelen et al., 2017).

238  
239 Preterm-born individuals were classified accordingly: the resilient group showed fewer  
240 behavioral symptoms than expected, and a vulnerable group showed more behavioral symptoms  
241 problems than expected.

242  
243 **Statistical analysis**  
244 Analyses (connectome development and group-differences, see below) were corrected for  
245 confounding factors, including gender, birthweight (z-scores), mean FA, gestational age, age at  
246 scan, degree of brain injury (i.e., intraventricular hemorrhage), neonatal surgeries, administration  
247 of pre-and postnatal corticosteroids (i.e., accelerates lung maturation), and days of morphine.

248  
249 *Stress and connectome development*  
250 Longitudinal changes in whole-brain structural connectivity between 30 and 40 weeks of  
251 gestation were examined using a time $\times$ postnatal stress interaction model using network-based  
252 statistic (NBS), a permutation-based method specifically designed to statistically assess network  
253 differences (Zalesky et al., 2010). We created a NBS linear-mixed model adjusting for gender,  
254 gestational age, age at scan, degree of brain injury (i.e., intraventricular hemorrhage), surgeries,

255 administration of pre-and postnatal corticosteroids (i.e., accelerates lung maturation), and  
256 administration of morphine in days, which was applied to all non-zero  $N_i \times N_j$  connections of the  
257 individual networks (lower triangle; consensus-based threshold). The  $N \times N$  matrix of F-statistics  
258 and matching  $p$ -values associated with the interaction effect was thresholded at a  $p$ -value of  $p <$   
259 0.05. NBS defines the largest connected component, and the size of the largest component is  
260 tested against a null-model of permuting subject labels 10000 times. The subsequent null  
261 distribution was used to calculate a  $p$ -value for the largest identified component. We used the  
262 main sample and validated the findings in a separate, independent population (see Table 1).

263

#### 264 *Group-differences between resilient and vulnerable individuals*

265 Differences in network organization between resilient and vulnerable individuals were assessed  
266 by examining global and local network metrics from the individual structural matrices at term-  
267 equivalent age (R packages *igraph*, *braingraph*; R Core Team, 2021). A GLM was specified to  
268 test for significant group-difference in network metrics and is compared to permuted data (on  
269 graph- or vertex-level), building a null-distribution. Graph-level analyses were permuted 10000  
270 times and vertex-level measures were permuted 5000 times. To correct for multiple comparison  
271 the contrast was thresholded on  $p < 0.001$ .

272 Local graph parameters, including clustering coefficient, nodal efficiency, eigenvector centrality,  
273 and communicability, were calculated to capture the influence of a region on the network. Global  
274 measures included clustering coefficient, modularity, strength, and global efficiency. *Clustering*  
275 *coefficient* describes the tendency of regions to cluster together in triangles and is computed by  
276 the ratio between the number of connections between region  $i$  and its neighbor regions and the  
277 total number of possible connections with neighbors. A higher clustering coefficient is considered

278 to be a measure of local network segregation (Rubinov & Sporns, 2010). The global measure is  
279 computed by taking the mean clustering coefficient of all individual regions in the network.  
280 *Nodal efficiency* describes for every region in the network the length of the shortest paths  
281 between a given region  $i$  and all other regions  $j$ , and measures the average lengths of all shortest  
282 paths identified for region  $i$  (Achard & Bullmore, 2007). Higher nodal efficiency is indicative of  
283 a higher capability of information integration, and these regions can also be categorized as a hub.  
284 The global measure is computed by taking the mean of nodal efficiency of all individual regions  
285 in the network. *Betweenness centrality* describes the influence of a region in the communication  
286 between pairs of regions and is measured by the frequency with which a region falls between  
287 pairs of other regions on their shortest interconnecting path (Rubinov & Sporns, 2010). This  
288 measure reflects the potential influence of a region to control information flow between non-  
289 directly connected regions. *Communicability* describes how well a region communicates with  
290 every other region in the network and is computed by the weighted sum of all paths and walks  
291 between region  $i$  and  $j$  (Estrada & Hatano, 2008). High communicability indicates that there are  
292 multiple and strong alternative paths connecting the region with other regions. *Modularity*  
293 describes the degree to which a network can be organized into modules of densely interconnected  
294 regions but sparsely connected between modules and is computed by the difference between the  
295 number of edges that lie within a community and a random network of the same degree sequence  
296 (Rubinov & Sporns, 2010). High modularity reflects a highly segregated network. *Strength*  
297 describes the total sum of the weights of all individual nodal connections in the network.  
298 Together, these provide a good understanding of the connectivity and influence of a particular  
299 region on the network.

300

301 *Multiclass prediction classification*

302 Random-forest regression with conditional inference trees (RFR-CIF) was used to assess how  
303 well node-wise centrality measures could predict the correct classification of the resilient (stress-  
304 underreactive) and vulnerable (stress- overreactive) individuals. The predictive multiclass model  
305 consisted of a centrality measure (i.e., betweenness centrality) of 47 grey-matter nodes. Analyses  
306 were repeated using the other node-wise centrality measures (see Table 4). The predictors were  
307 used to build and validate a predictive multiclass model that best fit the combined (main and  
308 validation) dataset using 10-fold cross-validation and was tested using a hold-out dataset (65%  
309 build and validation [ $n = 105$ ], 35% testing [ $n = 57$ ]). The model was fitted on the combined main  
310 and validation dataset to increase reliability in estimating probabilities. Slight differences in  
311 features due to technical variability in acquisition protocol were removed while preserving  
312 biological variability using ComBat prior to model fitting (Fortin et al., 2017, 2018; Johnson et  
313 al., 2007).

314

## 315 **Results**

316 The sample consisted of a main ( $N=145$ ,  $M_{age}=26.53$ ,  $M_{sd}=0.97$ , 43.5% female) and validation  
317 ( $N=123$ ,  $M_{age}=26.54$ ,  $M_{sd}=1.00$ , 39.8% female) dataset of preterm born individuals. Both the main  
318 ( $n=71$ ) and validation ( $n=91$ ) dataset have follow-up data on parent-reported internalizing  
319 symptoms. Key demographics of the two samples are presented in Table 1.

320

### 321 **The effects of postnatal stress on the development of whole-brain structural connectivity**

322 We performed network-based statistics (NBS; see Methods for details) to identify sub-networks  
323 of edge-wise effects that showed significant alterations in growth depending on the degree of  
324 postnatal stress exposure. NBS analysis revealed one significant cluster of connections, involving  
325 48 connections, with slower growth in connectivity strength from 30 to 40 weeks of gestation for

326 individuals exposed to higher stress ( $p = 0.003$ , consensus-based threshold, see Figure 1A and  
327 2A). The cluster spanned both hemispheres, involving 20 brain regions such as the amygdala,  
328 thalamus, caudate nucleus, and cortical regions such as the insula, fusiform, parahippocampal  
329 gyrus, anterior/posterior cingulate cortex, parietal lobe, and frontal lobe. Figure 3 provides a  
330 matrix of the vertices and edges involved. The sub-network reduced in size but remained  
331 significant across prevalence thresholds (Figure 4E). Also, postnatal stress significantly affected  
332 white-matter connectivity at term-equivalent age, with higher stress resulting in lower structural  
333 connectivity in a sub-network of 49 connections (Figure 4C,  $p = 0.014$ ).

334  
335 The NBS findings were replicated in an independent sample, providing robust evidence for the  
336 effects of postnatal stress on the growth of white-matter connectivity. We masked the  
337 connectivity matrix such that only connections were retained if they were part of the sub-network  
338 identified in the main sample. Then, we calculated a non-zero mean of connectivity strength and  
339 tested the effects of postnatal stress on changes in connectivity strength between 30 and 40 weeks  
340 of gestation. We observed a significant stress $\times$ time interaction such that higher levels of postnatal  
341 stress were associated with slower growth in connectivity strength (Estimate=-0.007(0.003),  $F(1,$   
342  $37) = 4.79$ ,  $p = 0.035$ , 95% CI [-0.014, -0.001], see Figure 4B). Also, higher stress was associated  
343 with significantly lower levels of white-matter connectivity at term-equivalent age ( $t(13,96) = -$   
344  $2.44$ ,  $p = 0.016$ , see Figure 4D).

345  
346 **Network architecture at term-equivalent age reveal differences between resilient and**  
347 **vulnerable individuals**

348 Based on the normative levels of stress-reactivity (based on the relationship between postnatal



349 NICU-related stress and long-term behavioral symptoms, see "*Resilience to postnatal stress*"  
350 Methods), 41 and 42 neonates were classified as stress under-reactive (now being referred to as  
351 resilient), and 30 and 49 infants were classified as stress over-reactive (now being referred to as  
352 vulnerable). There were no group differences in birth weight, age at birth, age at scan,  
353 corticosteroids, days of morphine administration, and mean FA (see Table 2). There was,  
354 however, a slight difference in gender in the main dataset (included as a covariate). The reported  
355 findings below were thresholded on 75% prevalence, i.e., connections were included if they were  
356 reported in at least 75% of the participants. The results reported below are based on structural  
357 connectivity at term-equivalent age.

358

#### 359 *Global measures*

360 Analyses revealed no significant group effects in measures of global network architecture.

361

#### 362 *Local measures*

363 We observed significant group effects on local network measures. Group differences were  
364 region-specific such that both reduced and increased centrality were observed in vulnerable  
365 relative to resilient individuals (see Table 3).

366

367 We first examined the contribution of regions in local network organization as measured by  
368 'nodal clustering'. Vulnerable infants, relative to resilient, showed a lower clustering of several  
369 cortical brain regions overall, including the posterior cingulate cortex ( $t(69) = -5.48, p < 0.001$ ),  
370 parahippocampal gyrus ( $t(69) = -5.25, p < 0.001$ ), frontal lobe ( $t(69) = -6.29, p = p < 0.001$ ), and  
371 parietal lobe ( $t(69) = -6.61, p = p < 0.001$ ). In contrast, higher clustering was observed in the  
372 hippocampus ( $t(69) = 7.19, p = p < 0.001$ ), amygdala ( $t(69) = 4.8, p = p < 0.001$ ), and medial

373 anterior temporal lobe ( $t(69) = 6.3, p = p < 0.001$ ). It is important to note that only differences in  
374 the posterior cingulate cortex and parietal lobe were successfully replicated in the validation  
375 sample. Statistical details of group differences found in the main and validation dataset can be  
376 found in Table 3.

377  
378 We assessed the contribution of regions in global communication across the brain through  
379 'betweenness centrality'. On average, vulnerable infants showed a lower centrality of the  
380 hippocampus ( $t(69) = -9.5, p = p < 0.001$ ) and the anterior fusiform ( $t(69) = -7.45, p = p < 0.001$ ),  
381 whereas a higher centrality was observed in the brain stem ( $t(69) = 3.76, p = p < 0.001$ ), posterior  
382 cingulate cortex ( $t(69) = 5.72, p = p < 0.001$ ), and parietal lobe ( $t(69) = 6.11, p = p < 0.001$ , see  
383 Table 3). These results suggest differential susceptibility in connections central to global brain  
384 communication.

385  
386 We further examined global network integration through 'communicability', a metric that  
387 considers all possible communication paths between regions in the network. Vulnerable  
388 individuals showed, on average, lower communicability of the hippocampus ( $t(69) = -16.03, p <$   
389  $0.001$ ), amygdala ( $t(69) = -3.74, p < 0.001$ ), and subthalamic nucleus ( $t(69) = -11.44, p < 0.001$ ,  
390 see Figure 5 and Table 3). A higher global integration was observed in the posterior  
391 parahippocampal gyrus ( $t(69) = 9.65, p < 0.001$ ), posterior fusiform ( $t(69) = 9.65, p < 0.001$ ), and  
392 parietal lobe ( $t(69) = 3.73, p < 0.001$ ).

393  
394 Resilient and vulnerable infants did not differ on measures of nodal efficiency.

395

396 **Multiclass predictive classification**

397 Random Forest regression with conditional inference trees was used to investigate potential  
398 predictive power from local network metrics. Local network measures (i.e., communicability) of  
399 the 47 (sub-)cortical grey matter regions were able to correctly classify vulnerable and resilient  
400 individuals with an accuracy of 80.4% ( $p < 10^{-5}$ ,  $\kappa = 0.606$ , AUC = 0.914). The combined sample  
401 (i.e., main and validation) correctly identified the groups with better than 80% balanced accuracy  
402 (see Table 4). Importantly, similar results were obtained with the other centrality measures. For  
403 model classification and calibration, see Figure 6.

404 **Discussion**

405 Preterm-born infants have a life-long increased risk for stress-related psychopathology  
406 characterized by anxiety and socio-emotional problems (Arpi & Ferrari, 2013; Upadhyaya et al.,  
407 2021). The current study showed that higher stress exposure during NICU admission is  
408 associated with slower growth in regions such as the amygdala, hippocampus, insula, and  
409 posterior cingulate cortex. Despite these global alterations in development, resilient infants at  
410 term-equivalent age can propagate information through regions central for bottom-up emotion  
411 regulation. We observed an excellent predictive accuracy of group membership using local  
412 network measures at term-equivalent age shortly following exposure. The extra-uterine,  
413 postnatal, stressful environment contributes to significant alterations in brain development, but  
414 only a proportion of infants show a higher susceptibility for future behavioral problems. A  
415 developmental approach is needed to understand longitudinal brain growth following postnatal  
416 stress and the neurobiological mechanisms that might confer resilience or vulnerability later in  
417 life.

418  
419 Our findings underscore the impact of postnatal stress on the growth of structural brain  
420 connections in corticolimbic pathways across both hemispheres, including critical regions  
421 involved in (bottom-up) emotion regulation and processing such as the amygdala, insula,  
422 hippocampus, parahippocampal gyrus, and posterior cingulate cortex. These findings align with  
423 evidence from other neuroimaging studies showing a delayed development in white matter  
424 pathways following preterm birth relative to term-controls (Bouyssi-Kobar et al., 2018; Dodson  
425 et al., 2017; Duerden et al., 2018). We now show evidence that in addition to the effects of  
426 prematurity, stressful early exposure significantly contributed to a more pronounced impact on  
427 delayed development in a sub-network of connections. Interestingly, our findings indicate that

428 resilient individuals can compensate for global alterations in white-matter pathways or  
429 reconfigure the brain's large-scale architecture by selecting resources facilitating information  
430 flow throughout the network.  
431  
432 Measures of integration estimate the efficiency of communication among all nodes in a network,  
433 enabling the integration and distribution of neural information between spatially distant brain  
434 regions (Rubinov & Sporns, 2010). Vulnerable individuals showed lower global integration of  
435 the hippocampus, a region that is a crucial regulator of the hypothalamic-pituitary-adrenal axis  
436 activation and plays a critical role in the storage and retrieval of emotional memories (Chan et al.,  
437 2014; Duval et al., 2015). Prior studies on (early-life) trauma indicated that the hippocampus is  
438 particularly vulnerable to chronic pain and stress, with lower volumes and a hypoconnectivity  
439 following early-life trauma (Andersen et al., 2008; Shin & Liberzon, 2009). We observed a  
440 similar pattern for the amygdala and subthalamic nucleus. The amygdala is part of the (medial)  
441 temporal lobe and densely connected with the prefrontal cortex, and has extensive anatomical  
442 connections with the paraventricular thalamus and hippocampus. This region plays a critical role  
443 in perception, regulation, and plasticity of emotion (Davis & Whalen, 2000; Yang et al., 2017). A  
444 less interconnected amygdala in vulnerable infants might seem contradictory, as it does not agree  
445 with studies showing evidence of lower amygdala connectivity in resilient trauma-exposed adults  
446 (Roeckner et al., 2021). However, a less interconnected amygdala might also be evidence of a  
447 decreased inhibitory control of more segregated, cortical, regions including the ventromedial  
448 prefrontal cortex (vmPFC) (Andrewes & Jenkins, 2019; Johnstone et al., 2007; Rogers et al.,  
449 2017). The lower centrality of the frontal lobe in vulnerable infants substantiates this  
450 interpretation. Hence, the increased integration of the hippocampus and amygdala might be a key  
451 system in a healthy adaptation with resilience following early disturbances of preterm birth.

452  
453 Previous studies in children and adults with depression and anhedonia consistently reported a  
454 lower capacity for integration (Cullen et al., 2014; Yang et al., 2017). The subthalamic nucleus  
455 interconnects with the amygdala and hippocampus and receives convergent cortical and pallidal  
456 projections (Accolla et al., 2016) and plays a role in threat appraisal (Serranová et al., 2011).  
457 Although the subthalamic nucleus received attention concerning Parkinson's disease, the  
458 increased social and affective alterations following deep-brain stimulation have been implicated  
459 in the emergence of enhanced affective processing and decreased depressive symptoms  
460 (Schneider et al., 2003; Smeding et al., 2006). Higher integration of these regions might be  
461 beneficial in retaining mental wellbeing following preterm birth.

462  
463 Preterm-born infants (Bouyssi-Kobar et al., 2019; Sa de Almeida et al., 2021) and children (de  
464 Kieviet et al., 2021; Young et al., 2018) show alterations in information flow. A balance between  
465 integration and segregation is essential for efficient communication through local processing and  
466 global communication. A lower integration between regions important for fear memory and  
467 emotion-processing in vulnerable infants renders their networks more susceptible. It puts them at  
468 increased risk for behavioral problems by making it harder to effectively compensate for second-  
469 hit abnormalities that might occur within a network or region.

470  
471 The dysconnectivity of neuroanatomical networks has been implicated in the emergence of  
472 several neurological and psychiatric disorders, including anxiety and depression (Akiki et al.,  
473 2018; Sang et al., 2018; Yu et al., 2013). The relative preservation of global integration of regions  
474 implicated in emotion processing and regulation may support impaired white matter pathways  
475 more effectively after preterm birth. These results might indicate that resilient individuals can

476 increase and diminish information flow of specific regions, enabling them to compensate for  
477 global alterations following preterm birth. Interestingly, however, it remains elusive whether a  
478 higher centrality of the hippocampus could be interpreted as a compensatory adaptation following  
479 preterm birth, enabling preterm-born individuals to "bounce back" or if it could be considered a  
480 preexisting protective factor. Resilience studies following childhood trauma indicated that an  
481 increased hippocampal connectivity aids emotion regulation and enables one to successfully cope  
482 with trauma (Richter et al., 2019; van Rooij et al., 2021). Similarly, resilient individuals exhibit  
483 lower insula activity, facilitating an appropriate adjustment of emotional resources (Haase et al.,  
484 2016; Waugh et al., 2008). Although the current study contributes to the literature of resilience  
485 following preterm birth, future studies investigating the (neuroprotective) mechanisms by which  
486 global integration is increased in resilient infants are warranted.

487  
488 While a direct inverse relationship between resilience and vulnerability does not exist,  
489 vulnerability studies seem to present the best available approximation for the concept of  
490 resilience in preterm-born individuals. In line with studies on trauma exposure, preterm-born  
491 individuals with more problem behavior seem to show reduced hippocampal connectivity and  
492 lower volumes (Aanes et al., 2015; Rogers et al., 2018) and a lower interconnected amygdala  
493 (Rogers et al., 2017). Further, preliminary interventional studies focusing on neuroprotection,  
494 reducing the impact of postnatal stress following preterm birth (e.g., music and massage therapy)  
495 showed significantly improved white matter maturation of the uncinate fasciculus (Sa de Almeida  
496 et al., 2020). Hence, these results implicate that increasing information flow of the amygdala and  
497 hippocampus may lead to symptom attenuation and is consistent with our observation that  
498 vulnerable and resilient individuals differ in a small number of regions or pathways that may  
499 facilitate compensation.

500

501 The differences in neural representations between resilience and vulnerable infants enable the  
502 accurate classification of group membership. The current study shows that at term-equivalent  
503 age, the connectome shows distinguishable features in topological architecture. Demonstrating  
504 these patterns highlights that resilience and vulnerability occur in the context of unique  
505 neurobiological differentiability and may be considered a valuable biomarker for predicting  
506 behavioral symptoms in early childhood.

507

508 Several methodological issues should be taken into consideration when interpreting our findings.  
509 Although our unique dataset enables us to investigate individual differences in longitudinal  
510 white-matter development, we could only model linear change. Studies involving three or more  
511 time points (Remer et al., 2017) can fit several slopes, including quadratic, logarithmic, and  
512 cubic, facilitating a more nuanced understanding of how postnatal stress affects brain  
513 development. For instance, a quadratic growth pattern would mean that the effects of postnatal  
514 stress emerge during a specific developmental period and then declines or disappear during a  
515 particular period and then reappears later. Despite this methodological limitation, our results  
516 nevertheless provide convincing evidence that between 30 and 40 weeks of gestation, postnatal  
517 stress significantly reduces linear growth in a sub-network of connections. Another limitation is  
518 that the resilient infants might have been healthier than the vulnerable infants. Although the  
519 residualisation approach controls for the degree of postnatal stress exposure, resilient infants  
520 could still have experienced fewer complications and clinical procedures compared to vulnerable  
521 infants. Notably, infants did not differ on a large set of clinical parameters (see Table 2). In other  
522 words, resilient preterm-born infants did not endure fewer clinical procedures, and it is unlikely  
523 that they were healthier than vulnerable infants.



524

525 Our longitudinal findings suggest that postnatal stress leads to sparser brain connectivity after  
526 preterm birth. Importantly, alterations in specific brain areas impacting bottom-up emotion  
527 regulation render preterm infants resilient to internalizing symptoms later in life. These findings  
528 emphasize the detrimental impact of postnatal stress and the relative plasticity of the preterm  
529 brain. The current results suggest that resilience appertains to a potential compensatory or innate  
530 ability to propagate global information flow, informing future intervention studies on fostering  
531 specific nodal changes.

## 532 **References**

- 533 Aanes, S., Bjuland, K. J., Skranes, J., & Løhaugen, G. C. C. (2015). Memory function and  
534 hippocampal volumes in preterm born very-low-birth-weight (VLBW) young adults.  
535 *NeuroImage*, *105*, 76–83. <https://doi.org/10.1016/j.neuroimage.2014.10.023>
- 536 Achenbach, T., & Rescorla, L. (2001). *Manual for the ASEBA School-Age Forms & Profiles*.
- 537 Akazawa, K., Chang, L., Yamakawa, R., Hayama, S., Buchthal, S., Alicata, D., Andres, T.,  
538 Castillo, D., Oishi, K., Skranes, J., Ernst, T., & Oishi, K. (2016). Probabilistic maps of the  
539 white matter tracts with known associated functions on the neonatal brain atlas: Application  
540 to evaluate longitudinal developmental trajectories in term-born and preterm-born infants.  
541 *NeuroImage*, *128*, 167–179. <https://doi.org/10.1016/j.neuroimage.2015.12.026>
- 542 Akiki, T. J., Averill, C. L., Wrocklage, K. M., Scott, J. C., Averill, L. A., Schweinsburg, B.,  
543 Alexander-Bloch, A., Martini, B., Southwick, S. M., Krystal, J. H., & Abdallah, C. G.  
544 (2018). Default mode network abnormalities in posttraumatic stress disorder: A novel  
545 network-restricted topology approach. *NeuroImage*, *176*, 489–498.  
546 <https://doi.org/10.1016/j.neuroimage.2018.05.005>
- 547 Amstadter, A. B., Myers, J. M., & Kendler, K. S. (2014). Psychiatric resilience: Longitudinal  
548 twin study. *British Journal of Psychiatry*, *205*(4), 275–280.  
549 <https://doi.org/10.1192/bjp.bp.113.130906>
- 550 Andersson, J. L. R., Jenkinson, M., & Smith, S. (2007). *Non-linear registration aka spatial*  
551 *normalisation* (Technical). Oxford: FMRIB Centre.
- 552 Andersson, J. L. R., & Stamatiou, S. N. (2016). An integrated approach to correction for off-  
553 resonance effects and subject movement in diffusion MR imaging. *NeuroImage*, *125*, 1063–  
554 1078. <https://doi.org/10.1016/j.neuroimage.2015.10.019>
- 555 Ball, G., Aljabar, P., Zebari, S., Tusor, N., Arichi, T., Merchant, N., Robinson, E. C., Ogundipe,  
556 E., Rueckert, D., Edwards, A. D., & Counsell, S. J. (2014). Rich-club organization of the  
557 newborn human brain. *Proceedings of the National Academy of Sciences of the United*  
558 *States of America*, *111*(20), 7456–7461. <https://doi.org/10.1073/pnas.1324118111>
- 559 Ball, G., Boardman, J. P., Aljabar, P., Pandit, A., Arichi, T., Merchant, N., Rueckert, D.,  
560 Edwards, A. D., & Counsell, S. J. (2013). The influence of preterm birth on the developing  
561 thalamocortical connectome. *Cortex*, *49*(6), 1711–1721.  
562 <https://doi.org/10.1016/j.cortex.2012.07.006>
- 563 Ball, G., Boardman, J. P., Rueckert, D., Aljabar, P., Arichi, T., Merchant, N., Gousias, I. S.,  
564 Edwards, A. D., & Counsell, S. J. (2012). The effect of preterm birth on thalamic and  
565 cortical development. *Cerebral Cortex*, *22*(5), 1016–1024.  
566 <https://doi.org/10.1093/cercor/bhr176>
- 567 Ball, G., Srinivasan, L., Aljabar, P., Counsell, S. J., Durighel, G., Hajnal, J. V., Rutherford, M.  
568 A., & Edwards, A. D. (2013). Development of cortical microstructure in the preterm human  
569 brain. *Proceedings of the National Academy of Sciences of the United States of America*,  
570 *110*(23), 9541–9546. <https://doi.org/10.1073/pnas.1301652110>

- 571 Batalle, D., Hughes, E. J., Zhang, H., Tournier, J. D., Tusor, N., Aljabar, P., Wali, L., Alexander,  
572 D. C., Hajnal, J. V., Nosarti, C., Edwards, A. D., & Counsell, S. J. (2017). Early  
573 development of structural networks and the impact of prematurity on brain connectivity.  
574 *NeuroImage*, *149*, 379–392. <https://doi.org/10.1016/j.neuroimage.2017.01.065>
- 575 Bouyssi-Kobar, M., Brossard-Racine, M., Jacobs, M., Murnick, J., Chang, T., & Limperopoulos,  
576 C. (2018). Regional microstructural organization of the cerebral cortex is affected by  
577 preterm birth. *NeuroImage: Clinical*, *18*, 871–880.  
578 <https://doi.org/10.1016/j.nicl.2018.03.020>
- 579 Bouyssi-Kobar, M., De Asis-Cruz, J., Murnick, J., Chang, T., & Limperopoulos, C. (2019).  
580 Altered Functional Brain Network Integration, Segregation, and Modularity in Infants Born  
581 Very Preterm at Term-Equivalent Age. *Journal of Pediatrics*, *213*, 13–21.e1.  
582 <https://doi.org/10.1016/j.jpeds.2019.06.030>
- 583 Broyd, S. J., Demanuele, C., Debener, S., Helps, S. K., James, C. J., & Sonuga-Barke, E. J. S.  
584 (2009). Default-mode brain dysfunction in mental disorders: A systematic review.  
585 *Neuroscience and Biobehavioral Reviews*, *33*(3), 279–296.  
586 <https://doi.org/10.1016/j.neubiorev.2008.09.002>
- 587 Brummelte, S., Grunau, R. E., Chau, V., Poskitt, K. J., Brant, R., Vinall, J., Gover, A., Synnes, A.  
588 R., & Miller, S. P. (2012). Procedural pain and brain development in premature newborns.  
589 *Annals of Neurology*, *71*(3), 385–396. <https://doi.org/10.1002/ana.22267>
- 590 Buff, C., Brinkmann, L., Neumeister, P., Feldker, K., Heitmann, C., Gathmann, B., Andor, T., &  
591 Straube, T. (2016). Specifically altered brain responses to threat in generalized anxiety  
592 disorder relative to social anxiety disorder and panic disorder. *NeuroImage: Clinical*, *12*,  
593 698–706. <https://doi.org/10.1016/j.nicl.2016.09.023>
- 594 Chan, E., Baumann, O., Bellgrove, M. A., & Mattingley, J. B. (2014). Negative emotional  
595 experiences during navigation enhance parahippocampal activity during recall of place  
596 information. *Journal of Cognitive Neuroscience*, *26*(1), 154–164.  
597 [https://doi.org/10.1162/jocn\\_a\\_00468](https://doi.org/10.1162/jocn_a_00468)
- 598 Chen, H. J., Qi, R., Ke, J., Qiu, J., Xu, Q., Zhang, Z., Zhong, Y., Lu, G. M., & Chen, F. (2020).  
599 Altered dynamic parahippocampus functional connectivity in patients with post-traumatic  
600 stress disorder. *World Journal of Biological Psychiatry*, 1–10.  
601 <https://doi.org/10.1080/15622975.2020.1785006>
- 602 De Asis-Cruz, J., Krishnamurthy, D., Zhao, L., Kapse, K., Vezina, G., Andescavage, N.,  
603 Quistorff, J., Lopez, C., & Limperopoulos, C. (2020). Association of Prenatal Maternal  
604 Anxiety With Fetal Regional Brain Connectivity. *JAMA Network Open*, *3*(12), e2022349.  
605 <https://doi.org/10.1001/jamanetworkopen.2020.22349>
- 606 de Kieviet, J. F., Lustenhouwer, R., Königs, M., van Elburg, R. M., Pouwels, P. J. W., &  
607 Oosterlaan, J. (2021). Altered structural connectome and motor problems of very preterm  
608 born children at school-age. *Early Human Development*, *152*, 105274.  
609 <https://doi.org/10.1016/j.earlhumdev.2020.105274>

- 610 Degnan, A. J., Wisnowski, J. L., Choi, S., Ceschin, R., Bhushan, C., Leahy, R. M., Corby, P.,  
611 Schmithorst, V. J., & Panigrahy, A. (2015). Altered Structural and Functional Connectivity  
612 in Late Preterm Preadolescence: An Anatomic Seed-Based Study of Resting State Networks  
613 Related to the Posteromedial and Lateral Parietal Cortex. *PLOS ONE*, *10*(6), e0130686.  
614 <https://doi.org/10.1371/journal.pone.0130686>
- 615 Disselhoff, V., Jakab, A., Schnider, B., Latal, B., Wehrle, F. M., & Hagmann, C. F. (2020).  
616 Inhibition is associated with whole-brain structural brain connectivity on network level in  
617 school-aged children born very preterm and at term; Inhibition abilities and structural brain  
618 connectivity in prematurity. *NeuroImage*, *218*.  
619 <https://doi.org/10.1016/j.neuroimage.2020.116937>
- 620 Dodson, C. K., Travis, K. E., Ben-Shachar, M., & Feldman, H. M. (2017). White matter  
621 microstructure of 6-year old children born preterm and full term. *NeuroImage: Clinical*, *16*,  
622 268–275. <https://doi.org/10.1016/j.nicl.2017.08.005>
- 623 Eikenes, L., Løhaugen, G. C., Brubakk, A. M., Skranes, J., & Håberg, A. K. (2011). Young  
624 adults born preterm with very low birth weight demonstrate widespread white matter  
625 alterations on brain DTI. *NeuroImage*, *54*(3), 1774–1785.  
626 <https://doi.org/10.1016/j.neuroimage.2010.10.037>
- 627 Fischi-Gomez, E., Muñoz-Moreno, E., Vasung, L., Griffa, A., Borradori-Tolsa, C., Monnier, M.,  
628 Lazeyras, F., Thiran, J. P., & Hüppi, P. S. (2016). Brain network characterization of high-  
629 risk preterm-born school-age children. *NeuroImage: Clinical*, *11*, 195–209.  
630 <https://doi.org/10.1016/j.nicl.2016.02.001>
- 631 Gogolla, N. (2017). The insular cortex. In *Current Biology* (Vol. 27, Issue 12, pp. R580–R586).  
632 Cell Press. <https://doi.org/10.1016/j.cub.2017.05.010>
- 633 Greve, D. N., & Fischl, B. (2009). Accurate and robust brain image alignment using boundary-  
634 based registration. *NeuroImage*, *48*(1), 63–72.  
635 <https://doi.org/10.1016/j.neuroimage.2009.06.060>
- 636 Groppo, M., Ricci, D., Bassi, L., Merchant, N., Doria, V., Arichi, T., Allsop, J. M., Ramenghi, L.,  
637 Fox, M. J., Cowan, F. M., Counsell, S. J., & Edwards, A. D. (2014). Development of the  
638 optic radiations and visual function after premature birth. *Cortex*, *56*, 30–37.  
639 <https://doi.org/10.1016/j.cortex.2012.02.008>
- 640 Haase, L., Stewart, J. L., Youssef, B., May, A. C., Isakovic, S., Simmons, A. N., Johnson, D. C.,  
641 Potterat, E. G., & Paulus, M. P. (2016). When the brain does not adequately feel the body:  
642 Links between low resilience and interoception. *Biological Psychology*, *113*, 37–45.  
643 <https://doi.org/10.1016/j.biopsycho.2015.11.004>
- 644 Johns, C. B., Lacadie, C., Vohr, B., Ment, L. R., & Scheinost, D. (2019). Amygdala functional  
645 connectivity is associated with social impairments in preterm born young adults.  
646 *NeuroImage: Clinical*, *21*, 101626. <https://doi.org/10.1016/j.nicl.2018.101626>
- 647 Karolis, V. R., Froudust-Walsh, S., Brittain, P. J., Kroll, J., Ball, G., Edwards, A. D., Dell'Acqua,  
648 F., Williams, S. C., Murray, R. M., & Nosarti, C. (2016). Reinforcement of the Brain's Rich-

- 649 Club Architecture Following Early Neurodevelopmental Disruption Caused by Very  
650 Preterm Birth. *Cerebral Cortex*, 26(3), 1322–1335. <https://doi.org/10.1093/cercor/bhv305>
- 651 Kilpatrick, L., & Cahill, L. (2003). Amygdala modulation of parahippocampal and frontal regions  
652 during emotionally influenced memory storage. *NeuroImage*, 20(4), 2091–2099.  
653 <https://doi.org/10.1016/j.neuroimage.2003.08.006>
- 654 Lautarescu, A., Pecheva, D., Nosarti, C., Nihouarn, J., Zhang, H., Victor, S., Craig, M., Edwards,  
655 A. D., & Counsell, S. J. (2020). Maternal Prenatal Stress Is Associated With Altered  
656 Uncinate Fasciculus Microstructure in Premature Neonates. *Biological Psychiatry*, 87(6),  
657 559–569. <https://doi.org/10.1016/j.biopsych.2019.08.010>
- 658 Leech, R., & Sharp, D. J. (2014). The role of the posterior cingulate cortex in cognition and  
659 disease. In *Brain* (Vol. 137, Issue 1, pp. 12–32). Oxford University Press.  
660 <https://doi.org/10.1093/brain/awt162>
- 661 Loe, I. M., Lee, E. S., & Feldman, H. M. (2013). Attention and internalizing behaviors in relation  
662 to white matter in children born preterm. *Journal of Developmental and Behavioral*  
663 *Pediatrics*, 34(3), 156–164. <https://doi.org/10.1097/DBP.0b013e3182842122>
- 664 Marusak, H. A., Etkin, A., & Thomason, M. E. (2015). Disrupted insula-based neural circuit  
665 organization and conflict interference in trauma-exposed youth. *NeuroImage: Clinical*, 8,  
666 516–525. <https://doi.org/10.1016/j.nicl.2015.04.007>
- 667 Menegaux, A., Meng, C., Neitzel, J., Bäuml, J. G., Müller, H. J., Bartmann, P., Wolke, D.,  
668 Wohlschläger, A. M., Finke, K., & Sorg, C. (2017). Impaired visual short-term memory  
669 capacity is distinctively associated with structural connectivity of the posterior thalamic  
670 radiation and the splenium of the corpus callosum in preterm-born adults. *NeuroImage*, 150,  
671 68–76. <https://doi.org/10.1016/j.neuroimage.2017.02.017>
- 672 Menon, V. (2011). Large-scale brain networks and psychopathology: A unifying triple network  
673 model. *Trends in Cognitive Sciences*, 15(10), 483–506.  
674 <https://doi.org/10.1016/j.tics.2011.08.003>
- 675 Mullen, K. M., Vohr, B. R., Katz, K. H., Schneider, K. C., Lacadie, C., Hampson, M., Makuch,  
676 R. W., Reiss, A. L., Constable, R. T., & Ment, L. R. (2011). Preterm birth results in  
677 alterations in neural connectivity at age 16 years. *NeuroImage*, 54(4), 2563–2570.  
678 <https://doi.org/10.1016/j.neuroimage.2010.11.019>
- 679 Papini, C., White, T. P., Montagna, A., Brittain, P. J., Froudast-Walsh, S., Kroll, J., Karolis, V.,  
680 Simonelli, A., Williams, S. C., Murray, R. M., & Nosarti, C. (2016). Altered resting-state  
681 functional connectivity in emotion-processing brain regions in adults who were born very  
682 preterm. *Psychological Medicine*, 46(14), 3025–3039.  
683 <https://doi.org/10.1017/S0033291716001604>
- 684 R Core Team (2021). R: A language and environment for statistical computing. R Foundation for  
685 Statistical Computing, Vienna, Austria. <https://www.R-project.org/>.
- 686 Remer, J., Croteau-Chonka, E., Dean, D. C., D'Arpino, S., Dirks, H., Whiley, D., & Deoni, S. C.  
687 L. (2017). Quantifying cortical development in typically developing toddlers and young

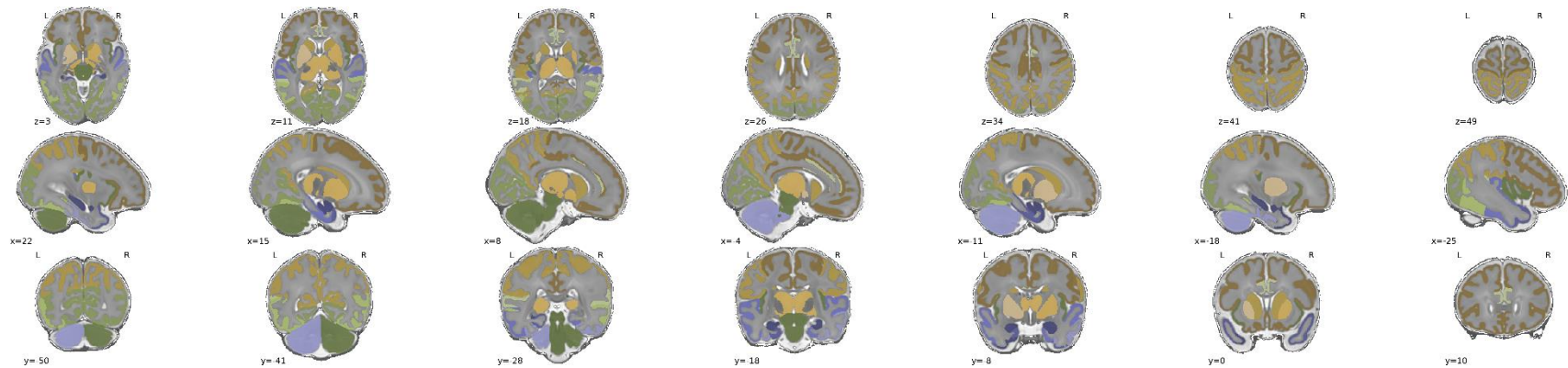


- 688 children, 1–6 years of age. *NeuroImage*, 153, 246–261.  
689 <https://doi.org/10.1016/j.neuroimage.2017.04.010>
- 690 Richter, A., Krämer, B., Diekhof, E. K., & Gruber, O. (2019). Resilience to adversity is  
691 associated with increased activity and connectivity in the VTA and hippocampus.  
692 *NeuroImage: Clinical*, 23, 101920. <https://doi.org/10.1016/j.nicl.2019.101920>
- 693 Rimol, L. M., Botellero, V. L., Bjuland, K. J., Løhaugen, G. C. C., Lydersen, S., Evensen, K. A.  
694 I., Brubakk, A. M., Eikenes, L., Indredavik, M. S., Martinussen, M., Yendiki, A., Håberg, A.  
695 K., & Skranes, J. (2019). Reduced white matter fractional anisotropy mediates cortical  
696 thickening in adults born preterm with very low birthweight. *NeuroImage*, 188, 217–227.  
697 <https://doi.org/10.1016/j.neuroimage.2018.11.050>
- 698 Rogers, C. E., Lean, R. E., Wheelock, M. D., & Smyser, C. D. (2018). Aberrant structural and  
699 functional connectivity and neurodevelopmental impairment in preterm children. In *Journal*  
700 *of Neurodevelopmental Disorders* (Vol. 10, Issue 1, pp. 1–13). BioMed Central Ltd.  
701 <https://doi.org/10.1186/s11689-018-9253-x>
- 702 Rogers, C. E., Sylvester, C. M., Mintz, C., Kenley, J. K., Shimony, J. S., Barch, D. M., &  
703 Smyser, C. D. (2017). Neonatal Amygdala Functional Connectivity at Rest in Healthy and  
704 Preterm Infants and Early Internalizing Symptoms. *Journal of the American Academy of*  
705 *Child and Adolescent Psychiatry*, 56(2), 157–166. <https://doi.org/10.1016/j.jaac.2016.11.005>
- 706 Sa de Almeida, J., Lordier, L., Zollinger, B., Kunz, N., Bastiani, M., Gui, L., Adam-Darque, A.,  
707 Borradori-Tolsa, C., Lazeyras, F., & Hüppi, P. S. (2020). Music enhances structural  
708 maturation of emotional processing neural pathways in very preterm infants. *NeuroImage*,  
709 207, 116391. <https://doi.org/10.1016/j.neuroimage.2019.116391>
- 710 Sa de Almeida, J., Meskaldji, D. E., Loukas, S., Lordier, L., Gui, L., Lazeyras, F., & Hüppi, P. S.  
711 (2021). Preterm birth leads to impaired rich-club organization and fronto-paralimbic/limbic  
712 structural connectivity in newborns. *NeuroImage*, 225, 117440.  
713 <https://doi.org/10.1016/j.neuroimage.2020.117440>
- 714 Sang, L., Chen, L., Wang, L., Zhang, J., Zhang, Y., Li, P., Li, C., & Qiu, M. (2018).  
715 Progressively disrupted brain functional connectivity network in subcortical ischemic  
716 vascular cognitive impairment patients. *Frontiers in Neurology*, 9(FEB), 94.  
717 <https://doi.org/10.3389/fneur.2018.00094>
- 718 Scheinost, D., Kwon, S. H., Shen, X., Lacadie, C., Schneider, K. C., Dai, F., Ment, L. R., &  
719 Constable, R. T. (2016). Preterm birth alters neonatal, functional rich club organization.  
720 *Brain Structure and Function*, 221(6), 3211–3222. <https://doi.org/10.1007/s00429-015-1096-6>
- 722 Scholtens, L. H., de Lange, S. C., and van den Heuvel, M. P. (2021). “Simple Brain Plot”.  
723 Zenodo. <https://doi.org/10.5281/zenodo.5346593>
- 724 Sølunes, A. E., Sripada, K., Yendiki, A., Bjuland, K. J., Østgård, H. F., Aanes, S., Grunewaldt, K.  
725 H., Løhaugen, G. C., Eikenes, L., Håberg, A. K., Rimol, L. M., & Skranes, J. (2016).  
726 Limited microstructural and connectivity deficits despite subcortical volume reductions in

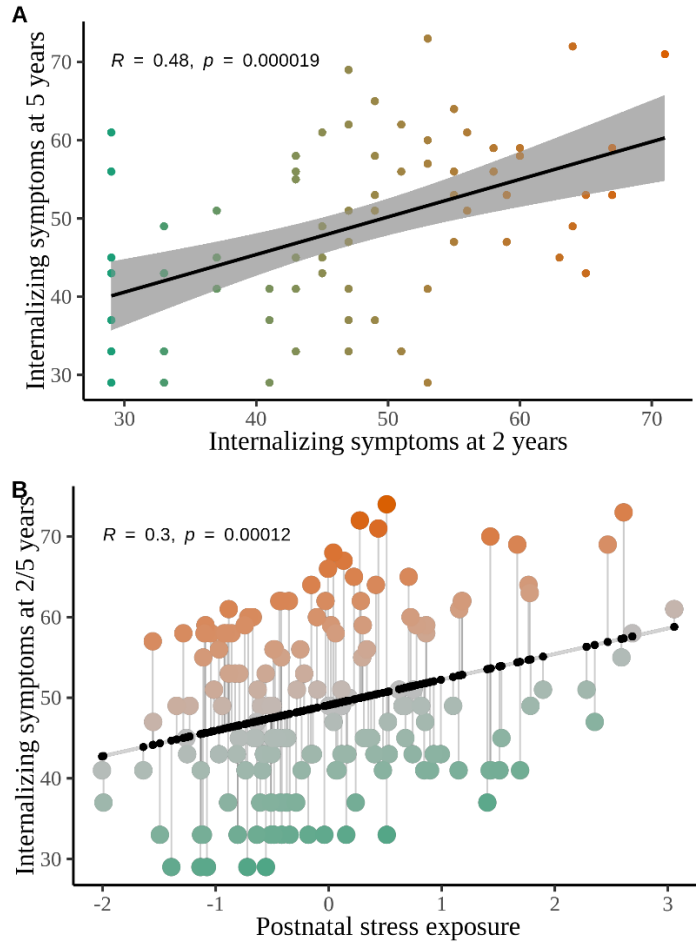
- 727 school-aged children born preterm with very low birth weight. *NeuroImage*, 130, 24–34.  
728 <https://doi.org/10.1016/j.neuroimage.2015.12.029>
- 729 Song, L., Mishra, V., Ouyang, M., Peng, Q., Slinger, M., Liu, S., & Huang, H. (2017). Human  
730 fetal brain Connectome: Structural network development from middle fetal stage to birth.  
731 *Frontiers in Neuroscience*, 11(OCT). <https://doi.org/10.3389/fnins.2017.00561>
- 732 Teicher, M. H., Anderson, C. M., Ohashi, K., & Polcari, A. (2014). Childhood maltreatment:  
733 Altered network centrality of cingulate, precuneus, temporal pole and insula. *Biological*  
734 *Psychiatry*, 76(4), 297–305. <https://doi.org/10.1016/j.biopsych.2013.09.016>
- 735 Turk, E., van den Heuvel, M. I., Benders, M. J., de Heus, R., Franx, A., Manning, J. H., Hect, J.  
736 L., Hernandez-Andrade, E., Hassan, S. S., Romero, R., Kahn, R. S., Thomason, M. E., &  
737 van den Heuvel, M. P. (2019). Functional Connectome of the Fetal Brain. *The Journal of*  
738 *Neuroscience : The Official Journal of the Society for Neuroscience*, 39(49), 9716–9724.  
739 <https://doi.org/10.1523/JNEUROSCI.2891-18.2019>
- 740 Van Harmelen, A. L., Kievit, R. A., Ioannidis, K., Neufeld, S., Jones, P. B., Bullmore, E., Dolan,  
741 R., Fonagy, P., & Goodyer, I. (2017). Adolescent friendships predict later resilient  
742 functioning across psychosocial domains in a healthy community cohort. *Psychological*  
743 *Medicine*, 47(13), 2312–2322. <https://doi.org/10.1017/S0033291717000836>
- 744 van Rooij, S. J. H., Ravi, M., Ely, T. D., Michopoulos, V., Winters, S. J., Shin, J., Marin, M. F.,  
745 Milad, M. R., Rothbaum, B. O., Ressler, K. J., Jovanovic, T., & Stevens, J. S. (2021).  
746 Hippocampal activation during contextual fear inhibition related to resilience in the early  
747 aftermath of trauma. *Behavioural Brain Research*, 408, 113282.  
748 <https://doi.org/10.1016/j.bbr.2021.113282>
- 749 Venkatraman, A., Edlow, B. L., & Immordino-Yang, M. H. (2017). The Brainstem in Emotion: A  
750 Review. *Frontiers in Neuroanatomy*, 11(March), 1–12.  
751 <https://doi.org/10.3389/fnana.2017.00015>
- 752 Vollmer, B., Lundequist, A., Mårtensson, G., Nagy, Z., Lagercrantz, H., Smedler, A. C., &  
753 Forsberg, H. (2017). Correlation between white matter microstructure and executive  
754 functions suggests early developmental influence on long fibre tracts in preterm born  
755 adolescents. *PLoS ONE*, 12(6). <https://doi.org/10.1371/journal.pone.0178893>
- 756 Waugh, C. E., Wager, T. D., Fredrickson, B. L., Noll, D. C., & Taylor, S. F. (2008). The neural  
757 correlates of trait resilience when anticipating and recovering from threat. *Social Cognitive*  
758 *and Affective Neuroscience*, 3(4), 322–332. <https://doi.org/10.1093/scan/nsn024>
- 759 Wig, G. S. (2017). Segregated Systems of Human Brain Networks. In *Trends in Cognitive*  
760 *Sciences* (Vol. 21, Issue 12, pp. 981–996). Elsevier Ltd.  
761 <https://doi.org/10.1016/j.tics.2017.09.006>
- 762 Young, J. M., Vandewouw, M. M., Morgan, B. R., Smith, M. Lou, Sled, J. G., & Taylor, M. J.  
763 (2018). Altered white matter development in children born very preterm. *Brain Structure*  
764 *and Function*, 223(5), 2129–2141. <https://doi.org/10.1007/s00429-018-1614-4>
- 765 Yu, Q., Sui, J., Kiehl, K. A., Pearlson, G., & Calhoun, V. D. (2013). State-related functional

- 766 integration and functional segregation brain networks in schizophrenia. *Schizophrenia*  
767 *Research*, 150(2–3), 450–458. <https://doi.org/10.1016/j.schres.2013.09.016>
- 768 Zalesky, A., Fornito, A., & Bullmore, E. T. (2010). Network-based statistic: Identifying  
769 differences in brain networks. *NeuroImage*, 53(4), 1197–1207.  
770 <https://doi.org/10.1016/j.neuroimage.2010.06.041>
- 771 Zwicker, J. G., Grunau, R. E., Adams, E., Chau, V., Brant, R., Poskitt, K. J., Synnes, A., &  
772 Miller, S. P. (2013). Score for neonatal acute physiology-II and neonatal pain predict  
773 Corticospinal tract development in premature newborns. *Pediatric Neurology*, 48(2), 123-  
774 129.e1. <https://doi.org/10.1016/j.pediatrneurol.2012.10.016>
- 775

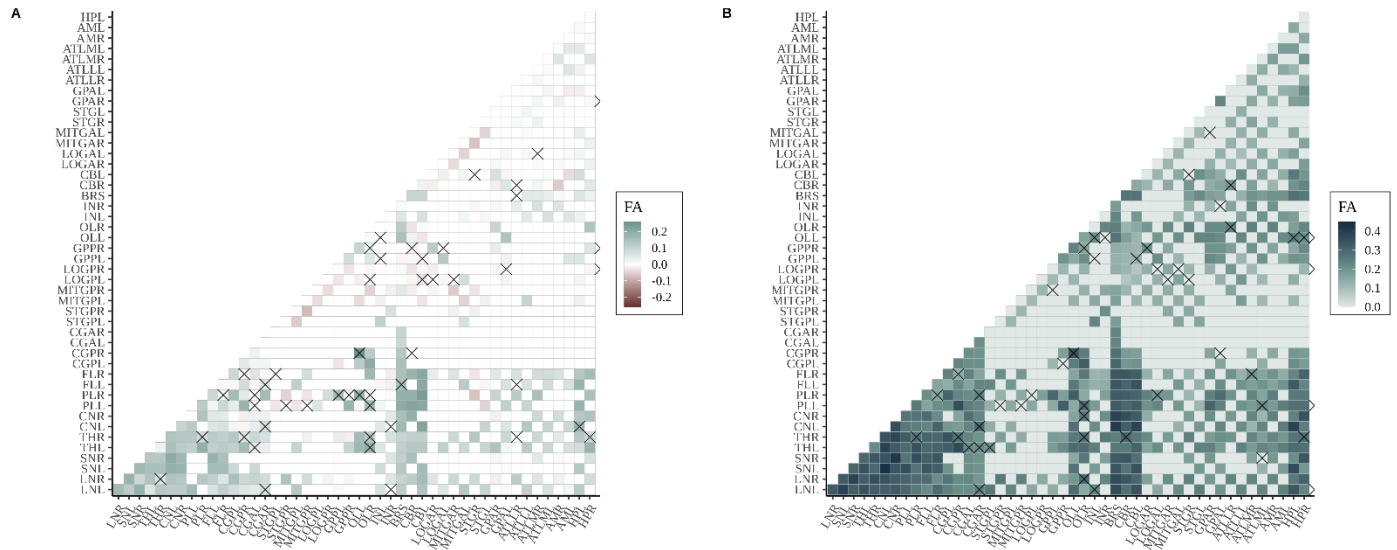




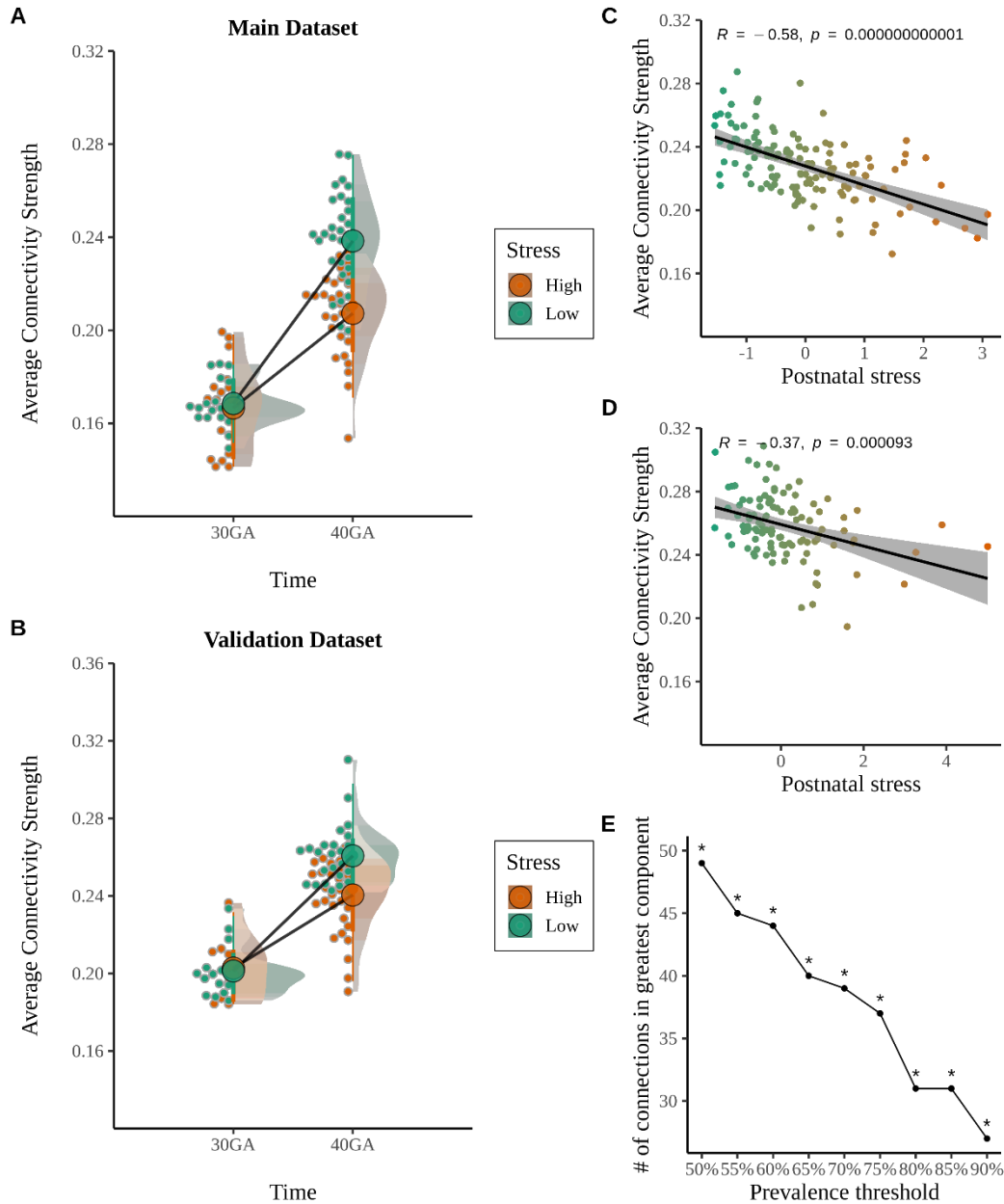
*Figure 1.* A total of 47 grey matter regions are segmented by the structural pipeline of the developmental Human Connectome Project (dHCP). HPL; hippocampus left, HPR; hippocampus right, AML; amygdala left, AMR; amygdala right, ATLML; anterior temporal lobe medial part left, ATLMR; anterior temporal lobe medial part right, ATLLL; anterior temporal lobe lateral part left; ATLLR; anterior temporal lobe lateral part right, GPAL; gyri parahippocampalis et ambiens anterior part left, GPAR; gyri parahippocampalis et ambiens anterior part right, STGL; superior temporal gyrus middle part left, STGR; superior temporal gyrus middle part right, MITGAL; medial and inferior temporal gyri anterior part left, MITGAR; medial and inferior temporal gyri anterior part right, LOGAL; lateral occipitotemporal gyrus/anterior fusiform left, LOGAR; lateral occipitotemporal gyrus/anterior fusiform right, CBL; cerebellum left, CBR; cerebellum right, BRS; brainstem, OLL; occipital lobe left, OLR; occipital lobe right, GPPL; gyri parahippocampalis et ambiens posterior part left; GPPR; gyri parahippocampalis et ambiens posterior right, LOGPL; lateral occipitotemporal gyrus/posterior fusiform part left, LOGPR; lateral occipitotemporal gyrus/posterior fusiform part right, MITGPL; medial and inferior temporal gyri posterior part left, MITGPR; medial and inferior temporal gyri posterior part right, STGPL; superior temporal gyrus posterior part left, STGPR; superior temporal gyrus posterior part right, CGAL; cingulate gyrus anterior part left, CGAR; cingulate gyrus anterior part right, FLL; frontal lobe left, FLR; frontal lobe right, PLL; parietal lobe left, PLR; parietal lobe right, CNL; caudate nucleus left, CNR; caudate nucleus right, THL; thalamus left, THR; thalamus right, SNL; subthalamic nucleus left, SNR; subthalamic nucleus right, LNL; lentiform nucleus left, LNR; lentiform nucleus right.



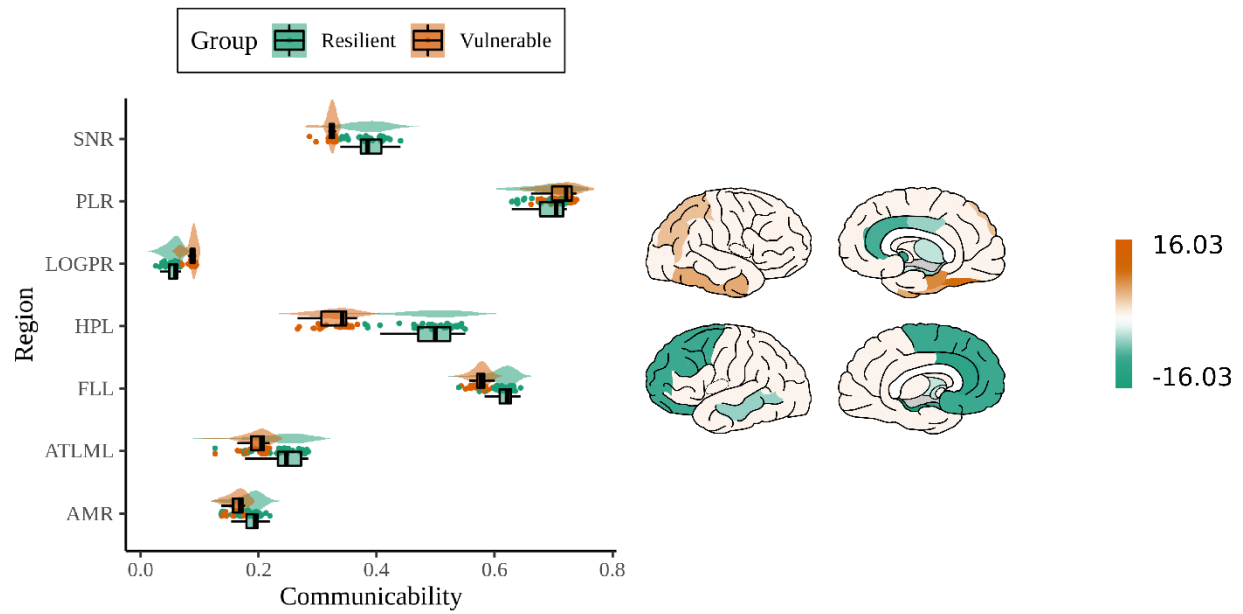
**Figure 2. A.** Significant and positive association between internalizing symptoms assessed at 2 and 5 years of age. **B.** Residualisation approach; orange observations are categorized as stress-overreactive (vulnerable), and green observations are characterized as stress-underreactive (resilient).



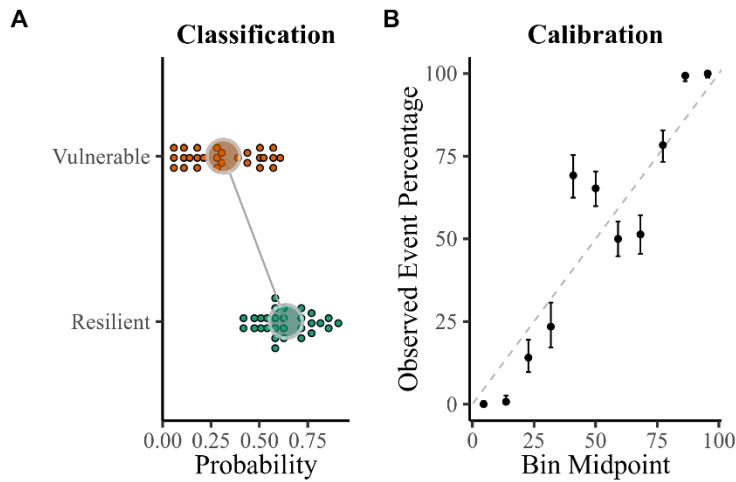
**Figure 3.** Matrix of largest significant subnetwork (NBS threshold of 50%) identified in the main dataset. Edges with a cross are part of the subnetwork showing a significant time $\times$ stress effect (matrix shows the delta in mean connectivity between 30 and 40 weeks of gestation) (**A**) or a significant main effect of stress (**B**) at term-equivalent age. An overview of abbreviations can be found in Figure 1. FA = fractional anisotropy.



**Figure 4.** **A.** Schematic representation of the longitudinal time×stress effects, orange representing high stress (highest 25%) and green representing low stress (lowest 25%). **B.** Replication of time×stress effects in an independent sample (32 directions diffusion protocol). **C.** Negative effect of postnatal stress on structural connectivity at term-equivalent age (included 49 connections; 45 directions diffusion protocol). **D.** Replication of stress effects in an independent sample (32 directions diffusion protocol). **E.** Robustness of NBS findings across a range of prevalence thresholds (50%:  $p < 0.05$ ; prevalence threshold of 60%:  $p < 0.05$ , prevalence threshold of 70%:  $p < 0.05$ , two-sided permutation testing, 10,000 permutations).



*Figure 5.* Distribution of group differences in communicability values between vulnerable and resilient infants (left) and regions colored according to T-value (right; vulnerable < resilient [green], Scholtens, L. H, de Lange, S. C., & van den Heuvel, 2021).



**Figure 6.** **A.** Shows the difference between the mean of predicted probabilities of the vulnerable and resilient group. **B.** Shows the true frequency of the positive label against its predicted probability, the x-axis represents the average predicted probability in each bin and the y-axis is the proportion of sample whose class is the vulnerable class (*fraction of positives*).

**Table 1.** *Sample demographic and neonatal clinical details of participants (N = 268)*

<b>Demographics</b>	<b>Main Protocol A (N = 145)</b>	<b>Validation Protocol B (N = 123)</b>
Age at birth, mean $\pm$ SD, weeks	26.53 $\pm$ 1.01	26.54 $\pm$ 1.00
Age at scan, mean $\pm$ SD, weeks	31.00 $\pm$ 0.84 41.27 $\pm$ 0.68	30.71 $\pm$ 0.84 41.33 $\pm$ 1.01
30 week MRI, n	76	55
40 weeks MRI, n	128	110
serial MRI, n	59	42
Gender, female/male, n	63/82	49/74
Birthweight z-score <sup>a</sup> , mean $\pm$ SD, grams	-0.61 $\pm$ 1.41	-0.52 $\pm$ 1.44
Postnatal stress <sup>b</sup> , median [range]	-0.69 (-3.26-5.14)	-1.26(-1.59-4.80)
Days of morphine, mean $\pm$ SD	3.72 $\pm$ 7.11	3.17 $\pm$ 5.18
Prenatal corticosteroids [yes/no]	128/17	115/8
Postnatal corticosteroids [yes/no]	39/106	40/83
Intraventricular hemorrhaging [yes/no]	44/101	37/85
Necrotizing enterocolitis, n	21	10
Retinopathy of prematurity, n	53	40

*nb. Protocol A refers to 45 diffusion directions, Protocol B refers to 32 diffusion directions.*

**Table 2.** Sample demographic and neonatal clinical details of resilient and vulnerable infants

Demographics	Main dataset			Validation dataset		
	Resilient (N = 41)	Vulnerable (N = 30)	<i>p</i> -value	Resilient (N = 42)	Vulnerable (N = 49)	<i>p</i> -value
Age at birth, mean ± SD, weeks	26.63±1.00	26.54±0.92	ns	26.47±1.00	25.57±0.92	ns
Age at scan, mean ± SD, weeks	41.17±0.78	41.22±0.46	ns	41.14±0.48	41.46±1.36	ns
Gender, female/male, n	12/29	16/14	< 0.05	16/26	14/35	ns
Birthweight z-score <sup>a</sup> , mean ± SD, grams	-0.44±1.35	-0.82±1.47	ns	-0.61±1.31	-0.68±1.66	ns
Fractional anisotropy, mean ± SD	0.22±0.04	0.22±0.04	ns	0.27±0.04	0.27±0.03	ns
Postnatal stress, median [range]	-0.43 [-2.84,2.62]	-0.73 [-2.56, 3.24]	ns	-1.29 [-3.53, 1.42]	-1.48 [-2.93, 1.53]	ns
Days of morphine, mean ± SD	2.68±4.36	2.29±2.25	ns	2.95±3.99	3.20±5.79	ns
Prenatal corticosteroids [yes/no]	36/5	26/4	ns	39/3	47/2	ns
Postnatal corticosteroids [yes/no]	12/29	9/21	ns	15/27	17/32	ns
Intraventricular hemorrhaging (yes/no)	15/26	9/21	ns	12/30	11/38	ns
Necrotizing enterocolitis [yes/no]	5/36	5/25	ns	1/41	4/45	ns
Retinopathy of prematurity [yes/no]	15/26	13/17	ns	17/25	13/36	ns



---

Internalizing symptoms T-score, median [range]	43 [33-55]	58 [49-73]	< 0.001	41 [29-51]	58 [47-74]	< 0.001
---	------------	------------	---------	------------	------------	---------

---

<sup>a</sup> Dutch Perinatal registry reference data (Perined)

Statistical significance was assessed with either a T-test (for continuous data) or a Kruskal-Wallis test (for ordinal data).

**Table 3.** Group-difference on nodal centrality measures for contrast vulnerable > resilient.

	Main		Validation	
	T-value	95% CI	T-value	95% CI
<b>Communicabili</b>				
HPL	-16.03	[-0.102, -0.066]	-9.6	[-0.035, -0.017]
HPR	-5.56	[-0.047, -0.011]		
AML	-9.25	[-0.038, -0.017]		
AMR	-3.74	[-0.016, -0.001]	-7.01	[-0.024, -0.008]
ATLML	-5.73	[-0.039, -0.01]	-3.31	[-0.028, -0.0001]
MITGAR	5.13	[0.005, 0.027]		
LOGAR	9.1	[0.011, 0.025]		
CBL	4.84	[0.003, 0.021]		
BRS	-9.49	[-0.027, -0.012]		
GPPR	7.35	[0.018, 0.051]		
LOGPR	9.65	[0.009, 0.02]	7.96	[0.003, 0.007]
CGAR	-8.96	[-0.066, -0.029]		
CGAL	-11.33	[-0.08, -0.043]		
CGPR	-5.7	[-0.028, -0.007]		
FLL	-9.63	[-0.029, -0.014]		
PLR	3.73	[0.001, 0.025]	5.52	[0.005, 0.022]
THR	-4.18	[-0.023, -0.002]		
SNR	-11.44	[-0.041, -0.022]	-5.17	[-0.032, -0.006]
LNL	-4.06	[-0.023, -0.002]		
<b>Betweenness</b>				
HPL	-9.5	[-5.781, -2.689]	-8.06	[-2.153, -0.87]
AML	-6.79	[-0.747, -0.242]		
AMR	-5.04	[-0.512, -0.094]		
ATLML	-4.68	[-1.118, -0.166]		
ATLMR	-7.18	[-2.358, -0.821]		
GPAL	5.22	[0.594, 2.953]		
LOGAL	-7.45	[-0.555, -0.202]	-8.72	[-0.591, -0.258]
CBL	4.58	[0.751, 5.444]		
BRS	3.76	[0.161, 3.963]	6.32	[2.499, 8.388]
GPPR	7.3	[0.982, 2.764]		
CGAL	-7.19	[-0.232, -0.081]		
CGPR	4.65	[0.076, 0.523]		
CGPL	5.72	[0.191, 0.78]	4.99	[0.135, 0.725]
PLR	6.11	[3.175, 11.527]	8.97	[4.038, 9.021]
PLL	4.84	[1.868, 11.306]		
CNR	6.25	[1.05, 3.673]		
CNL	5.96	[1.056, 3.998]		
SNL	9.42	[0.145, 0.314]		
<b>Clustering</b>				
HPL	7.19	[0.014, 0.04]		
AML	4.8	[0.007, 0.044]		

ATLMR	6.3	[0.009, 0.032]		
GPAL	-4.29	[-0.027, -0.003]		
STGL	-4.94	[-0.035, -0.006]		
LOGAL	5.21	[0.006, 0.028]		
CBL	-3.68	[-0.021, -0.001]		
GPPR	-5.25	[-0.047, -0.01]		
CGPR	-8.03	[-0.049, -0.019]		
CGPL	-5.48	[-0.045, -0.01]	-5.12	[-0.033-0.007]
FLR	-6.29	[-0.026, -0.007]		
FLL	-5.2	[-0.021, -0.004]		
PLR	-7.45	[-0.019, -0.007]	-6.61	[-0.019-0.006]
PLL	-8.49	[-0.023, -0.01]		
CNR	-5.14	[-0.035, -0.007]		
CNL	-8.46	[-0.034, -0.014]		
SNL	-7.34	[-0.026, -0.009]		
<b>Nodal efficiency</b>				
ATLLL	3,9	[0.001, 0.001]		
HPL	-7,04	[-0.02, 0.02]		
ATLML	-4,27	[-0.009, 0.009]		
CGAL	-5,92	[-0.021, 0.021]		

**Table 4.** Multiclass classification using 10-fold cross-validation

	Vulnerable versus Resilient	Overall
<b>Communicability</b>		
Sensitivity	0.778	Accuracy: 0.804
Specificity	0.828	95% CI: [0.676, 0.898]
Balanced accuracy	0.803	K=0.606
<b>Betweenness centrality</b>		
Sensitivity	0.704	Accuracy: 0.768
Specificity	0.828	95% CI: [0.636, 0.87]
Balanced accuracy	0.766	K =0.533
<b>Nodal efficiency</b>		
Sensitivity	0.630	Accuracy: 0.746
Specificity	0.862	95% CI: [0.616-0.856]
Balanced accuracy	0.75	K =0.495
<b>Clustering coefficient</b>		
Sensitivity	0.741	Accuracy: 0.77
Specificity	0.793	95% CI: [0.636-0.87]
Balanced accuracy	0.767	K =0.534