Structural Brain Correlates of Childhood Inhibited Temperament: An ENIGMA-Anxiety Mega-analysis

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Mega-analysis
ENIGMA-Anxiety mega-analysis of cIT

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Supplemental Material

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Study Synopsis

Introduction Summary

Temperament involves stable behavioral and emotional tendencies that differ between individuals, which can be first observed in infancy or early childhood and relate to behavior in many contexts and over many years. One of the most rigorously characterized temperament classifications relates to individuals’ tendency to avoid the unfamiliar and to withdraw from unfamiliar people, objects, and unexpected events. This temperament is referred to as ‘behavioral inhibition’ or ‘inhibited temperament’ (IT). IT is a moderately heritable trait that can be measured in multiple species. In humans, levels of IT can be quantified from the first year of life through direct behavioral observations or reports by caregivers or teachers. Similar approaches, as well as self-report questionnaires on current and/or retrospective levels of IT, can be used later in life.

Variations in IT are present on a continuous scale within the population, and research suggests that around 20% of young children are characterized by high IT, which is in general stable over time. Considerable data suggest that this high childhood IT (cIT) has adverse long-term consequences: infants with cIT often become more reserved adults, and, on average, such infants exhibit poorer outcomes than non-inhibited infants with respect to social relationships and internalizing psychopathology. More specifically, almost half of all children with elevated and stable cIT will develop social anxiety disorder (SAD) later in life, compared with only 12% of non-inhibited children. Thus, cIT predicts risk for later psychopathology, especially SAD.

Several neuroimaging studies have examined neurobiological correlates of cIT. Such research is important, since brain characteristics—including brain structure, function, and
connectivity—may mediate the cIT-related risk for poor outcomes\textsuperscript{10}. Previous studies have linked cIT to the structure and function of brain networks involved in emotion perception, experience, and regulation\textsuperscript{1}. These brain networks involve the dorsal (caudal) and ventral (rostral) anterior cingulate cortex (ACC), insula, amygdala, dorsolateral and medial prefrontal cortex (PFC), orbitofrontal cortex (OFC) and striatum (cf.\textsuperscript{1,10}), all of which have also been implicated in familial risk for SAD\textsuperscript{11}. In addition, translational work on anxious temperament has indicated involvement of the hippocampus\textsuperscript{3,12}. Despite this progress, the few available studies on the neural structural correlates of cIT are often restricted to specific regions of interest, while cortical surface area and cortical thickness have only been examined in one study, with an exploratory approach\textsuperscript{13}. Furthermore, most findings with respect to brain structure are unique to a specific sample, and cross-study comparisons are limited by relatively small sample sizes and failure to consider potential modifying variables such as age and biological sex.

In this ENIGMA-Anxiety project\textsuperscript{14}, we aim to extend previous work by examining brain structure associated with cIT in a large dataset, assembling data acquired at 12 research centers worldwide (17 samples, $N = 4,681$; Table 1). Compared to the individual studies, this new study is better powered due to the larger number of research participants available for analysis. Moreover, by combining data through a mega-analytic approach, the present study facilitates the differentiation of consistent, generalizable findings from false-positives that could emerge from smaller-sampled studies. Such work has the potential to establish reproducible anatomical correlates, and could inform the development of mechanistic studies and intervention research with clinical relevance\textsuperscript{15}.

We expect to corroborate findings in brain circuits found previously (involved in processing fear, reward and emotion regulation)\textsuperscript{1,10}, with small-to-medium effect sizes. We hypothesize
that structural alterations in brain regions involved in these processes, in particular gray matter volumes of multiple subcortical structures (amygdala, hippocampus, striatum including caudate and putamen), and characteristics of several frontal and temporal cortical areas, (OFC, ACC, insula superior temporal gyrus, transverse gyrus, fusiform gyrus) are neural substrates of cIT.

Method Summary

This ENIGMA-Anxiety working group project will include individual participant data assembled from studies where participants underwent MRI-scanning (T1-weighted anatomical MRI-scans) between 6 and 25 years of age. Regardless of age at scan, all participants will be phenotyped for cIT (defined as age ≤ 12 years). These temperament assessments could be behavioral observations in childhood, parental reports, or self-report questionnaires on current or retrospective temperament. We will perform a mega-analysis with a whole-brain approach (regional and vertex-wise; familywise error rate (FWER)-corrected) and investigate the relation between cIT (continuous) and three distinct neuroanatomical metrics (determined using FreeSurfer-software), namely volumes of subcortical structures, cortical thickness and cortical surface area. Additionally, analyses will be performed in three subsets, based on the method and thus age at which cIT was determined: 1st (early-life) behavioral observations, 2nd parental/teacher reports during childhood, and 3rd self-report measures acquired during late childhood/adolescence. A fourth sensitivity analysis will exclude samples with retrospective measures of cIT.

Significance Summary

This initiative is the first mega-analysis of brain structure associated with the temperamental risk for developing internalizing psychopathology. This provides the possibility of detecting
novel cIT-related brain alterations and clarifying inconsistent findings of prior work\textsuperscript{10}. Mega-analyses combine existing datasets to increase the overall sample size. This is particularly valuable for data acquired in vulnerable participants which are often difficult to recruit. Such studies exemplify next-generation science: previous studies within the ENIGMA-Consortium have resulted in important insights in the neurobiology of psychiatric conditions\textsuperscript{17}. These discoveries reflect the advantages of large-scale data-analyses for testing the reproducibility and robustness of neuroimaging findings\textsuperscript{17}. We expect the current project to provide similar insights, increasing our understanding of the development of psychopathology in youth at risk. In addition, by pre-registering the study in advance of performing the analyses, we hope to contribute to a reduction of the potential publication bias in the field, and to advance a more complete scientific record on this topic (cf.\textsuperscript{18}).
<table>
<thead>
<tr>
<th>Sample (location)</th>
<th>Type of sample</th>
<th>n (n female) with MRI and cIT data</th>
<th>Design*</th>
<th>Age MRI-scan (range; mean ± SD)</th>
<th>Age cIT (range; mean ± SD)</th>
<th>Measure of cIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brains study (Pennsylvania State University, USA)</td>
<td>Oversampled for high/low cIT data</td>
<td>130 (72)</td>
<td>C</td>
<td>9.2 - 13.2 y (10.8 ± 1.0)</td>
<td>9.2 - 13.2 y (10.8 ± 1.0)</td>
<td>BIQ – parent rated</td>
</tr>
<tr>
<td>Brazilian High Risk Cohort (National Institute of Developmental Psychiatry (INPD), Brazil)</td>
<td>Community sample and a high-risk sample of children with increased familial risk for mental disorders</td>
<td>678 (290)</td>
<td>C</td>
<td>5.8 - 13.0 y (9.7 ± 1.6)</td>
<td>5.8 - 13.0 y (9.7 ± 1.6)</td>
<td>EATQ-R - shyness scale</td>
</tr>
<tr>
<td>Cohort 3 / 4 (University of Maryland, College park Maryland, USA)</td>
<td>Community sample: prospective longitudinal study on infants thought likely to display behavioral inhibition later in infancy and early childhood</td>
<td>95 (51)</td>
<td>L</td>
<td>13.3 - 21.1 y (18.0 ± 1.9)</td>
<td>Around 24 months (no data at individual level)</td>
<td>Standard laboratory observations: composite score of stranger, robot, tunnel episodes</td>
</tr>
<tr>
<td>Generation R - sample with behavioral observations (Erasmus University Medical Center, Rotterdam, the Netherlands)</td>
<td>Longitudinal community sample</td>
<td>584 (297)</td>
<td>L</td>
<td>8.7 - 12.0 y (10.2 ± 0.6)</td>
<td>34.7 - 44.2 months (37.4 ± 1.4)</td>
<td>Standard laboratory observations: stranger approach and jumping spider episode from the Lab-TAB</td>
</tr>
<tr>
<td>Generation R - sample with questionnaire data (Erasmus University Medical Center, Rotterdam, the Netherlands)</td>
<td>Longitudinal community sample</td>
<td>1,982 (1,030)</td>
<td>L</td>
<td>8.6 - 12.0 y (10.0 ± 0.5)</td>
<td>4.5 - 11.8 months (6.7 ± 1.1)</td>
<td>Infant behavior questionnaire – revised (IBQ-r) – fear subscale</td>
</tr>
<tr>
<td>Maryland-PAX (University of Maryland, Maryland, USA)</td>
<td>30-month longitudinal study on a sample of first-year university students enriched for internalizing risk</td>
<td>220 (109)</td>
<td>C</td>
<td>18 - 19 y (18.3 ± 0.4)</td>
<td>Retrospective: remembered inhibited behaviors in childhood</td>
<td>RBI</td>
</tr>
<tr>
<td>Maryland-TAX (University of Maryland, Maryland, USA)</td>
<td>Cross-sectional community sample</td>
<td>53 (28)</td>
<td>C</td>
<td>13 - 17 y (15.0 ± 1.2)</td>
<td>Retrospective: remembered inhibited behaviors in childhood</td>
<td>RSRI – child rated</td>
</tr>
<tr>
<td>Nijmegen Longitudinal Study (Radboud University, Nijmegen, the Netherlands)</td>
<td>Longitudinal community sample</td>
<td>71 (31)</td>
<td>L</td>
<td>17 y</td>
<td>1.20 - 1.28 y (1.24 ± 0.02)</td>
<td>Standard laboratory observations at 15 months of age: stranger and robot episodes</td>
</tr>
<tr>
<td>Pittsburgh (University of Pittsburgh School of Medicine, USA)</td>
<td>High and low-risk (control) children/adolescents from ongoing family studies</td>
<td>15 (3)</td>
<td>L</td>
<td>19.2 - 24.8 y (21.5 ± 1.7)</td>
<td>4.1 - 6.4 y (5.1 ± 0.7)</td>
<td>Laboratory observations during peer play</td>
</tr>
<tr>
<td>Sample (location)</td>
<td>Type of sample</td>
<td>n (n female) with MRI and cIT data</td>
<td>Design*</td>
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<td>Measure of cIT</td>
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<tr>
<td>San Raffaele (Vita-Salute San Raffaele University and San Raffaele Scientific Institute, Milan, Italy)</td>
<td>Community sample</td>
<td>20 (8)</td>
<td>L</td>
<td>13 – 16 y (14.8 ± 1.1)</td>
<td>8 – 10 y (9.1 ± 0.7)</td>
<td>Empirical composite index</td>
</tr>
<tr>
<td>SDAN (NIMH, Bethesda, Maryland, USA)</td>
<td>Treatment seeking children and control group of healthy volunteers.</td>
<td>55 (26)</td>
<td>C</td>
<td>7.3 - 14.6 y (10.3 ± 1.7)</td>
<td>8.0 - 12.8 y (10.4 ± 1.5)</td>
<td>BIQ – child rated</td>
</tr>
<tr>
<td>Stony Brook Temperament Study (Stony Brook University, New York, USA)</td>
<td>Community sample; MRI subsample oversampled for youth with temperamental high negative emotionality, low positive emotionality, and high behavioral inhibition at age 3</td>
<td>74 (31)</td>
<td>L</td>
<td>9 - 12 y (10.2 ± 0.9)</td>
<td>2.9 - 4.0 y (3.4 ± 0.3)</td>
<td>Lab-TAB: 3 Kagan-like tasks around age 3</td>
</tr>
<tr>
<td>TOTS (University of Maryland, Maryland, USA)</td>
<td>Longitudinally followed sample of children selected at 4 months of age based on their behavior in the laboratory</td>
<td>96 (56)</td>
<td>L</td>
<td>9.1 - 19.5 y (11.4 ± 2.1)</td>
<td>1.9 - 2.7 y (2.1 ± 0.2)</td>
<td>Standard laboratory observations (composite score of stranger, robot, tunnel episodes)</td>
</tr>
<tr>
<td>Vanderbilt – children (Vanderbilt University Medical Center, Nashville, USA)</td>
<td>Study with extreme discordant phenotypes approach: inhibited and uninhibited children at the extreme ends</td>
<td>55 (33)</td>
<td>C</td>
<td>8 - 12 y (9.3 ± 1.1)</td>
<td>8 – 12 y (9.3 ± 1.1)</td>
<td>BIQ – child rated</td>
</tr>
<tr>
<td>Vanderbilt - young adults (Vanderbilt University Medical Center, Nashville, USA)</td>
<td>Study with extreme discordant phenotypes approach: inhibited and uninhibited young adults at the extreme ends</td>
<td>150 (83)</td>
<td>C</td>
<td>18 – 25 y (21.8 ± 2.0)</td>
<td>Retrospective: remembered inhibited behaviors in childhood</td>
<td></td>
</tr>
<tr>
<td>Western University (The Brain and Mind Institute, Western University, Ontario, Canada)</td>
<td>Children selected based on presence/absence maternal depression</td>
<td>87 (38)</td>
<td>L</td>
<td>9.2 - 12.4 y (11.1 ± 0.7)</td>
<td>3.0 - 4.0 y (3.4 ± 0.3)</td>
<td>Lab-TAB: risk room, stranger approach and jumping spider</td>
</tr>
<tr>
<td>Wisconsin Twin Project - RDoC twin study (University of Wisconsin–Madison, Madison, WI, USA)</td>
<td>Longitudinally followed samples of twins, recruited from statewide birth records for birth cohorts 1989 - 2004</td>
<td>316 (145)</td>
<td>L</td>
<td>15.1 – 23.9 y (17.5 ± 1.6)</td>
<td>6.5 – 9.0 y (7.5 ± 0.5)</td>
<td>Ratings on Approach and Shyness from a 3-hour home visit, and scores from videotaped reactions to the “Conversation with a Stranger” episode of Lab-TAB.</td>
</tr>
</tbody>
</table>

Total N | 4,681 (2,331) |
Note: BI = behavioral inhibition; BIQ = Behavioral Inhibition Questionnaire; CBQ = Child Behavior Questionnaire; cIT = childhood inhibited temperament; EATQ-R = Early Adolescent Temperament Questionnaire; Lab-TAB = Laboratory Temperament Assessment Battery; RMBI = Retrospective Measure of Behavioral Inhibition; RSRI = Retrospective Self-report of Inhibition.

a With respect to timepoint temperament assessment and MRI-scan, for data used in this study: cross-sectional (C) or longitudinal (L)
References


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The experience of the generalized anxiety disorder working group. *Hum Brain Mapp.*

