Cortical thinning in preschoolers with maladaptive guilt

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ABSTRACT
Maladaptive guilt is a central symptom of preschool-onset depression associated with severe psychopathology in adolescence and adulthood. Although studies have found that maladaptive guilt is associated with structural alterations in the anterior insula (AI) and dorsomedial prefrontal cortex (dmPFC) in middle childhood and adolescence, no study has examined structural neural correlates of maladaptive guilt in preschool, when this symptom first emerges. This study examined a pooled sample of 3-to 6-year-old children (N = 76; 40.8% female) from two studies, both of which used the same type of magnetic resonance imaging scanner and conducted diagnostic interviews for depression that included clinician ratings of whether children met criteria for maladaptive guilt. Preschoolers with maladaptive guilt displayed significantly thinner dmPFC than children without this symptom. Neither children's depressive severity nor their vegetative or other emotional symptoms of depression were associated with dmPFC thickness, suggesting that dmPFC thinning is specific to maladaptive guilt. Neither AI gray matter volume or thickness nor dmPFC gray matter volume differed between children with and without maladaptive guilt. This study is the first to identify a structural biomarker for a specific depressive symptom in preschool. Findings may inform neurobiological models of the development of depression and aid in detection of this symptom.

1. Introduction
Identifying neurobehavioral markers of major depressive disorder in preschool (PO-MDD), the earliest developmental stage in which depression has been validated (Luby et al., 2009), holds promise in aiding early identification and intervention. The few studies of neural markers in currently depressed preschoolers (i.e., 3-to 6-year-olds) have pinpointed alterations consistent with those found in depressed adolescents and adults, such as blunted response to rewards (Gaffrey et al., 2013). However, no study has examined atypical neural structure associated with specific depressive symptoms during preschool, which could inform the developmental neurobiology of depression. Maladaptive guilt—guilt that is excessive/inappropriate (American Psychiatric Association, 2013)—is one of the most robust symptoms of PO-MDD (Luby et al., 2009) and is associated with psychosis and suicidality in adolescence and adulthood (Fang et al., 2018; Ohayon and Schatzberg, 2002). Given the centrality of maladaptive guilt to preschool depression and its association with poor outcomes in older children, it is critical to understand the neurobiological correlates of experiencing this symptom early in life, when guilt is developing (Muris and Meesters, 2014). Thus, the purpose of this study was to examine the structural neural correlates of maladaptive guilt within the context of preschool depression.

Guilt is triggered by a transgression and involves an affective component—empathy—and a cognitive component—awareness of fault for a transgression (Zahn-Waxler and Kochanska, 1990). A large literature has documented that the ability to experience guilt arises in the second year of life (Kochanska et al., 2002; Zahn-Waxler and Kochanska, 1990). Throughout early childhood, guilt develops alongside cognitive skills such as self-awareness, theory of mind, and internalization of social rules (Hay and Cook, 2007). Whereas moderate guilt is adaptive as it often motivates reparative prosocial behaviors (Donohue and Tully, 2019), maladaptive guilt is affectively excessive, or inappropriate, in that it involves misattributions of fault for events (American Psychiatric Association, 2013). Maladaptive guilt can occur in depressed children as young as three (Luby et al., 2009) and is a highly specific symptom of PO-MDD in that it successfully differentiates preschoolers with MDD from those with anxiety or disruptive disorders (Luby et al., 2009).

Although numerous cortical regions are involved in experiencing and regulating emotions, two particular regions, the anterior insula (AI) and dorsomedial prefrontal cortex (dmPFC), have been consistently
associated with both depression, generally, and guilt, specifically (Belden et al., 2015; Bora et al., 2012; Gifuni et al., 2017; Lai and Wu, 2014; Stratmann et al., 2014; Whittle et al., 2016; Zhang et al., 2016). Studies including meta-analyses have implicated altered AI and dmPFC structure in the onset and recurrence of adult MDD. Studies have found reduced AI gray matter volume in adults with first-episode depression (Zhang et al., 2016), recurrent depression (Stratmann et al., 2014), and depression in remission (Takahashi et al., 2010) compared to healthy adults. Similarly, studies have found reduced dmPFC gray matter volume in adult patients experiencing a first MDD episode (Lai and Wu, 2014) and those with multiple MDD episodes (Bora et al., 2012). AI and dmPFC function and structure appear even more specifically associated with guilt. Two meta-analyses found that functional activation of the AI and dmPFC was associated with guilt in adults (Bastin et al., 2016; Gifuni et al., 2017). Two studies of altered neural structure associated with maladaptive guilt in children and adolescents have also implicated the AI and dmPFC. In Belden et al. (2015), children who experienced maladaptive guilt before age 6 displayed significantly reduced AI volumes in middle childhood, which then predicted depression recurrence. This study also established specificity of reduced AI volume to maladaptive guilt by demonstrating that AI volume was unrelated to vegetative depressive symptoms. Greater maladaptive guilt was also associated with thicker dmPFC during adolescence (Whittle et al., 2016), though this effect did not survive correction for multiple comparisons. No study has identified structural alterations concurrently associated with maladaptive guilt during preschool, when this symptom first emerges (Luby et al., 2009).

Identifying neural correlates of maladaptive guilt in preschool has implications for informing the developmental neurobiology of guilt and depression. Thus, this study aimed to examine structural differences in the AI and dmPFC between preschoolers with and without maladaptive guilt. Although our focus was on the influence of guilt on AI gray matter volume and dmPFC thickness following the only two prior studies on this topic, we examined thicknesses and gray matter volumes of both regions to comprehensively examine associations between guilt and brain structure. Gray matter volume displays a non-linear trajectory with an increase peaking around age 10 to 11 followed by a decline in adolescence (Giedd et al., 1999). Thus, preschool is a period in which increasing gray matter volume is normative. Although studies increasingly indicate that the cortex begins to thin as early as age 3 (Walhovd et al., 2016), greater depression has been associated with thinner cortex in the preschool period (Ducharme et al., 2014) and early-onset psychopathology has been associated with accelerated cortical thinning (e.g., depression; Luby et al., 2016). Thus, we hypothesized that maladaptive guilt would be associated with reduced gray matter volumes and thinner AI and dmPFC. Following Belden et al. (2015), we also examined whether AI and dmFC volumes and thicknesses were related to vegetative and emotional depressive symptoms to assess specificity of the finding to guilt.

2. Methods and materials

2.1. Participants

This study examined two samples of preschoolers that each had diagnostic interviews that included assessments of guilt and were scanned on the same type of MR scanner running the same software version. The Study 1 sample was composed of 3-to 6-year-old children who participated in a single-blind randomized control trial (RCT) of Parent-Child Interaction Therapy Emotion Development (PCIT-ED) between 2014 and 2017. Children were recruited from the metropolitan St. Louis community using the Preschool Feelings Checklist (PFC; Luby et al., 2004) to identify children at high-risk for depression (≥3 items endorsed). High-risk children who met criteria for MDD based on a diagnostic interview were invited to enroll. Further details about study design and recruitment are reported elsewhere (Luby et al., 2018). Exclusionary criteria are reported in Section 2.1, Supplement. The trial was registered with clinicaltrials.gov (NCT02076425).

The Study 2 sample was composed of 4-to 6-year-old children with and without MDD and conducted between 2010 and 2013. Children were again recruited from the St. Louis community (Gaffrey et al., 2013). High-risk children were recruited in the identical manner as in Study 1, except that low-risk children (≤1 PFC items endorsed) were also invited to enroll. For both studies, the institutional review board at Washington University School of Medicine approved all procedures and materials, and written informed consent and verbal assent were obtained from caregivers and children, respectively.

In both studies, a MR scan and a diagnostic interview that included a guilt assessment were collected at three possible timepoints, hereafter referred to as Time 1, Time 2, and Time 3. There were approximately 6 months between each timepoint. Many young children had serious emotional and behavioral disturbances and were unable to successfully complete a MRI at one or more timepoints. For more detailed information about the number and timing of scans at each timepoint included, see Section 2.2, Supplement. The final sample included 123 scans from 76 child participants (Baseline M_age = 5.67 (SD = 1.00) years; 59.2% male). Children who met criteria for maladaptive guilt (see Measures) contributed 30 scans and children without this symptom contributed 93. Children with usable scan data were significantly more likely to be Caucasian and have a higher family income than children with unusable scan data; there were no clinical differences (Table S1).

2.2. Measures

2.2.1. Depression symptoms and severity

Children’s depression symptoms and severity were determined at each timepoint using the Kiddie Schedule for Affective Disorders and Schizophrenia—Early Childhood (K-SADS-EC; Gaffrey and Luby, 2012) in Study 1 and the Preschool Age Psychiatric Assessment (PAPA; Egger et al., 2003) in Study 2. The K-SADS-EC and PAPA are diagnostic interviews for DSM disorders adapted for use in children aged 3.0–6.11 years that demonstrate good test re-test reliability and construct validity. Both interviews were conducted by the same research group. One study that assessed a group of preschoolers with both the K-SADS and the PAPA found that diagnoses were consistent between interviews (Birmaher et al., 2009). Diagnostic interviews were conducted by trained raters, and were videotaped, reviewed for rater drift, and calibrated for accuracy. Satisfactory inter-rater reliability for MDD was established (K-SADS-EC K = 0.74; PAPA K = 1.00).

In the K-SADS-EC and PAPA, a rater judged, based on parent-report, whether the child met criteria for each MDD symptom over the previous month based on the identical DSM criteria. Following previous studies (Belden et al., 2015), maladaptive guilt was assessed through the guilt item in the K-SADS-EC/PAPA. A rater asked multiple questions to assess children’s experience of guilt; parents provided examples and raters probed for additional information until they had sufficient information to determine whether the child met criteria for clinically significant maladaptive guilt as defined by the DSM (1) or did not meet criteria (0). Children met criteria if they had guilt that occurred 2–3 days per week or was partially unmodifiable (i.e., subthreshold) or that occurred nearly every day of the week or was unmodifiable (i.e., threshold). Thus, this study examined dichotomous groups of children with and without this symptom. Children were included in the guilt group if they met criteria at any timepoint; fluctuation in meeting criteria to not meeting between timepoints was very rare (i.e., only occurred for 4 children). We also examined vegetative and emotional depressive symptoms, which also yielded dichotomous scores. Children met criteria for having a vegetative symptom (1) if they met criteria for any of the following: reduced appetite, weight loss, increased need for sleep, and excessive fatigue (Belden et al., 2015). Children met criteria for having an emotional symptom (1) if they endorsed any of the following: anhedonia, irritability, and suicidal ideation (ideation, plan, or attempt).
Depression severity was assessed through a count of the number of core MDD symptoms endorsed (possible range: 0–9).

2.3. Neuroimaging

2.3.1. Image acquisition

Participants completed a neuroimaging battery including high-resolution structural scans collected using one of two 3.0 Tesla TIM TRIO Siemens whole body scanners and a 12-channel head coil that used the same software version and identical scan acquisition parameters. T1-weighted structural images were acquired in the sagittal plane using an MPRAGE 3D sequence (TR = 2400 ms, TE = 3.16 ms, flip angle = 8°, slab = 160 mm, 160 slices, matrix size = 256 × 224, voxel size = 1 × 1 × 1 mm). All participants from Study 1 were scanned on the same scanner, and all participants from Study 2 on the other scanner. Previous studies have shown good reliability across scanner manufacturers and field strengths, particularly when identical scanner platforms, field strengths, and software versions are used; reliability also improves when using longitudinal pipelines (for review, see: Mills and Tamnes, 2014). Indeed, our own unpublished work has shown that estimates of cortical volume are no more different within an individual across two different scanners of the same vendor and software version than across two sessions on the exact same scanner. There were no significant interactions between guilt group (i.e., children with and without maladaptive guilt) and scanner on any ROI, suggesting that scanner did not affect results (Tables S4–S11).

2.3.2. Image processing and analysis

AI and dmPFC volumes and thicknesses were generated using the FreeSurfer longitudinal pipeline v5.3 [http://surfer.nmr.mgh.harvard.edu] with visual inspection of the white and pial surfaces for errors followed by exclusion by an experienced rater blinded to children’s clinical characteristics (Reuter et al., 2010). Processing steps including skull stripping, atlas registration, spherical surface registration, and parcellation were initialized with common information from an unbiased within-subject template. Each scan was visually inspected and given a quality rating between 1 and 3, with 1 being the worst (significant motion artifact, such as ripples and major blurring); scan quality ratings below 1.75 were considered unusable. Manual edits were not made since this can introduce non-reproducible error. Given evidence that motion can be correlated with variation in structural estimates, we examined associations between scan quality ratings and 1) each ROI and 2) total gray matter volume in the full sample. We found correlations of 0.40 for insula volume, 0.35 for insula thickness, 0.40 for dmPFC volume, 0.36 for dmPFC thickness, and 0.45 for total gray matter volume, which were each significant (p < .001). However, when we examined the same associations in the subsample of usable data (scan quality ≥ 1.75), no correlation was significant.

2.3.3. Selection of ROIs

An ROI approach was used for hypothesis testing. ROIs were generated based on the Destrieux (Destrieux et al., 2010) and Desikan (Desikan et al., 2006) atlases as implemented in FreeSurfer. Following Belden et al. (2015), AI gray matter volumes and thicknesses were taken from the “S_circular_insula_ant + G_insular_short” parcellations of the Destrieux atlas. Following Whittle et al. (2016), dmPFC thicknesses and gray matter volumes were taken from the superior frontal gyrus region as delineated by the Desikan atlas (Whittle et al., 2016). As we did not have a priori laterality hypotheses, we summed the left and right for each ROI. Follow-up analyses examined all ROIs using both atlases; results were consistent across atlases (see Supplemental Tables 4–11).

2.4. Data analysis

Multi-level models (MLM) were conducted in SAS, version 9.4 (SAS Institute, Inc.) to account for the fact that some children (n = 35) had more than one MR scan. We used more than one scan per child when possible to maximize power given our modest sample size; however, results did not differ when only one observation per participant was used. The MLMs included a random intercept with all other variables fixed effects; time was coded as age at scan. An unstructured covariance matrix was used as it was the best fit for the data according to the Bayesian Information Criterion (BIC). For further model details, see Section 2.3, Supplement.

We first examined whether children with maladaptive guilt differed from children without maladaptive guilt in AI and dmPFC volumes (cm3) and thicknesses (mm). Covariates included age, sex, family income, psychotropic medication history (yes/no), study (i.e., scanner), and, for analyses examining ROI volumes, total gray matter volume. If there were significant results, we then examined if they held if we included children’s depression severity as an additional covariate. This allowed us to examine whether any differences in ROI volumes/thicknesses were specific to maladaptive guilt or were simply related to depression, generally. If any results remained significant after adding depression severity as a covariate, we then tested whether there were also significant group differences in the ROI between children (1) with and without vegetative symptoms and (2) with and without emotional symptoms. This allowed us to further determine whether any differences in volumes/thicknesses were specific to maladaptive guilt or were also related to other depressive symptoms. To account for multiple comparisons, p-values of planned analyses were FDR corrected.

3. Results

3.1. Preliminary analyses

Table S3 displays demographic and clinical differences between studies; Study 1 children were more likely to have maladaptive guilt and had greater Time 1 depressive severity than Study 2 children, which was expected given that Study 1 was a treatment-seeking sample. All further results presented below reflect the combined study sample. Table S2 displays correlations among study variables. Girls had significantly lower AI and dmPFC volumes than boys; these associations were not significant when controlling for total gray matter volume. Older age was significantly associated with thinner AI and dmPFC but unassociated with AI and dmPFC volumes. Lower income was associated with greater depression severity and lower AI and dmPFC volumes. Compared to children without a history of psychotropic medication use, children with a medication history had greater depressive severity and were more likely to have maladaptive guilt. Table 1 displays demographic and clinical differences between children with and without maladaptive guilt. Children with maladaptive guilt had greater depression severity than children without this symptom.

3.2. Tests of study hypotheses

3.2.1. Relationship between maladaptive guilt and AI structure

As displayed in Tables S4–5, AI volume did not significantly differ between guilt groups (Estimate = −0.04, SE = 0.13, t = −0.32, p = .75, FDR p = .75). Although children with guilt displayed thinner AI than children without guilt (r = −0.19, p = .04), this association was not significant in the MLM that accounted for covariates (Tables S6–7; Estimate = −0.06, SE = 0.07, t = −0.90, p = .37).

3.2.2. Relationship between maladaptive guilt and dmPFC structure

As displayed in Tables S8–9, children’s dmPFC volume did not significantly differ between guilt groups (Estimate = 0.20, SE = 0.58, t = 0.35, p = .73). As displayed in Tables S10–11 and Fig. 1, meeting criteria for maladaptive guilt significantly predicted thinner dmPFC (Estimate = −0.08, SE = 0.03, t = −2.44, p = .02, FDR p = .03). This result continued to be significant when children’s depression severity was included in the analyses.

As displayed in Table S12 and Fig. 2, dmPFC thicknesses were associated with greater depression severity and lower AI but not with maladaptive guilt (Estimate = −0.04, SE = 0.08, t = −0.50, p = .61, FDR p = .61). This result continued to be significant when children’s depression severity was included in the analyses.
4. Discussion

Given that maladaptive guilt is a highly specific symptom of PO-MDD associated with severe affective psychopathology later in life, this study aimed to elucidate concurrent relations between maladaptive guilt and structural brain development during preschool. We found that preschoolers who met criteria for maladaptive guilt displayed significantly thinner dmPFC compared to children without this symptom. Neither AI volume or thickness nor dmPFC volume differed between children with and without maladaptive guilt. To our knowledge, this study is the first to identify a structural biomarker concurrently associated with a specific depressive symptom in the preschool period.

Preschool-onset maladaptive guilt emerged as a unique symptom in the prediction of dmPFC thickness. Whereas the study by Whittle et al. (2016) found an association between maladaptive guilt and thicker dmPFC in adolescents, we found that preschoolers with maladaptive guilt displayed thinner dmPFC than peers without this symptom. This seeming discrepancy is consistent with evidence that whereas greater depression is associated with thinner cortex (e.g., in the vmPFC) in preschool, it is associated with thicker cortex beginning around age 12, when cortical thinning is developmentally normative (Ducharme et al., 2014). Neither children’s depression severity nor vegetative or other emotional symptoms of depression were related to dmPFC thickness, suggesting that dmPFC thinning is associated with maladaptive guilt, specifically, rather than depression, generally, or other depressive symptoms. Experiencing excessive and/or inappropriate guilt this early in life may impact the development of the dmPFC, which may subsequently place children at risk for recurrent depression, given evidence of altered dmPFC structure in adults with chronic depression (Bora et al., 2012). On the other hand, dmPFC thinning may have predated the onset of maladaptive guilt, and thus may be a predisposing brain marker of this symptom. Longitudinal studies beginning in toddlerhood are needed to elucidate the timing of dmPFC thinning in relation to maladaptive guilt onset. The volume of the dmPFC did not differ between children with and without maladaptive guilt; it may be that guilt is specifically related to cortical thinning, consistent with evidence of accelerated cortical thinning in children with early-onset psychopathology (Luby et al., 2016).

The dmPFC is associated with both theory of mind and perspective-taking skills (Schurz et al., 2014). These higher-order cognitive capacities contribute to the experience of guilt and develop across preschool (Dadds et al., 2008; Sabbagh et al., 2006). Investigating how these capacities influence the association between maladaptive guilt and dmPFC thinning may aid our mechanistic understanding of this relationship. For example, meta-analyses indicate that the dmPFC is recruited during tasks that elicit cognitive empathy, or the understanding of another’s emotions (Fan et al., 2011). Guilt involves both feeling empathy and cognitively understanding that one is personally

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**Table 1**

Characteristics between children with and without maladaptive guilt.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 76)</th>
<th>Guilt* (n = 21)</th>
<th>No Guilt (n = 55)</th>
<th>χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, % (N)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic ethnicity*, % (N)</td>
<td>9.5 (2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race, % (n)</td>
<td></td>
<td></td>
<td></td>
<td>F.E.</td>
<td>0.8924</td>
</tr>
<tr>
<td>Caucasian</td>
<td>85.7 (60)</td>
<td></td>
<td>90.0 (18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>8.6 (6)</td>
<td></td>
<td>5.0 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hawaiian/Pacific Islander</td>
<td>1.4 (1)</td>
<td></td>
<td>0.0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiracial</td>
<td>4.3 (3)</td>
<td></td>
<td>5.0 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychotropic medication use, % (N)</td>
<td>5.3 (4)</td>
<td>14.3 (3)</td>
<td>1.8 (1)</td>
<td>F.E.</td>
<td>0.0617</td>
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<tr>
<td>Baseline income, % (N)</td>
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<td></td>
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<td>0.3640</td>
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<td>&lt;$20,000</td>
<td>13.2 (10)</td>
<td></td>
<td>4.8 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$20,001 - $40,000</td>
<td>10.5 (8)</td>
<td></td>
<td>4.8 (1)</td>
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<tr>
<td>$40,001 - $60,000</td>
<td>67.1 (51)</td>
<td></td>
<td>76.2 (16)</td>
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<tr>
<td>$60,000+</td>
<td>5.37 (5)</td>
<td></td>
<td>63.6 (35)</td>
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<td>Study, % (N)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Study 1</td>
<td>27.6 (21)</td>
<td></td>
<td>71.4 (15)</td>
<td>27.84</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Study 2</td>
<td>72.4 (55)</td>
<td></td>
<td>28.6 (6)</td>
<td></td>
<td></td>
</tr>
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<td>Number of scans, % (N)</td>
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<td></td>
<td>F.E.</td>
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<td>1</td>
<td>53.9 (41)</td>
<td></td>
<td>61.9 (13)</td>
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<td>30.3 (23)</td>
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<td>33.3 (7)</td>
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<td>15.8 (12)</td>
<td></td>
<td>4.8 (1)</td>
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<tr>
<td>Baseline age, M (SD)</td>
<td>5.67 (1.00)</td>
<td>5.92 (0.83)</td>
<td>5.57 (1.05)</td>
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<tr>
<td>Baseline depression severity, M (SD)</td>
<td>2.66 (2.39)</td>
<td>4.81 (2.16)</td>
<td>1.84 (1.92)</td>
<td>5.83</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Includes children who met criteria for guilt at any timepoint; F.E. = Fisher’s Exact Test; a Collected in Study 1 only.

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severity was added to the model (Estimate = −0.08, SE = 0.03, t = −2.43, p = .02, FDR p = .03). The effect size of the between-group difference was medium in magnitude, d = 0.56. Interestingly, children’s depression severity was not significantly related to dmPFC thickness in this model. Children’s dmPFC thickness did not differ significantly depending on whether they met criteria for vegetative or emotional symptoms (Tables S10–11).
responsible for a wrongdoing, and thinner dmPFC during preschool may be specifically related to experiencing the cognitive component of maladaptive guilt. Indeed, preschoolers have been found to be particularly vulnerable to misattributing personal responsibility for events (Leitenberg et al., 1986). Future studies that measure the affective and cognitive components of maladaptive guilt separately would elucidate whether the two components are related to alterations in distinct cortical regions.

When controlling for covariates, there was no difference in AI structure between children with and without maladaptive guilt. The previous study reporting an effect of preschool-onset maladaptive guilt on AI volume measured AI volume during middle childhood (Belden et al., 2015). As such, AI volume loss and/or thinning may be a consequence rather than a cause of early-onset maladaptive guilt. Moreover, as our sample was smaller than that of Belden et al., there may be an effect of guilt on AI volume loss that we did not have the power to detect. Similarly, it is possible that the effect of guilt on AI volume is less robust than the effect of guilt on dmPFC thickness. Longitudinal studies that begin in early childhood and include repeated measures of AI volume and thickness are needed to systematically investigate the impact of maladaptive guilt on the developing AI.

Several limitations should be noted. First, this study was cross-sectional and therefore cannot conclude that maladaptive guilt causes alterations in dmPFC structure. We examined a combined sample, and Study 1 children displayed more severe depression than Study 2 children, although we controlled for children's depressive severity. The sample also included a relatively small number (n = 21) of participants with maladaptive guilt. As is common in imaging studies with young children, many scans were unusable, which could have introduced sampling bias. The two studies also used different scanners of the same type, although all analyses controlled for study/scanner and there were no significant interactions between guilt and scanner predicting any ROI, and different diagnostic interviews, though both used the identical DSM criteria. Finally, maladaptive guilt was measured using only a single parent-report item. This limitation is common to virtually all studies of maladaptive guilt in preschoolers, as there are no dimensional measures of maladaptive guilt validated for this age. However, whereas questionnaires lack clinical cut-offs, and thus sensitivity to determine clinical significance, clinical interviews clearly indicate whether or not children met criteria for this symptom. Nonetheless, including behaviorally coded indications of guilt during laboratory paradigms may be an important addition to future studies. Future work should also examine the role of parental guilt socialization in associations between altered dmPFC structure and maladaptive guilt (Zahn-Waxler and Kochanska, 1990).

This study provides novel evidence suggesting that an association between maladaptive guilt and thinner dmPFC is present as early as the preschool period. Our findings demonstrate a brain-behavior relationship that may contribute to knowledge about the developmental neurobiology of depression very early in life. Using biomarkers to identify children at-risk for this symptom may inform early detection and intervention efforts during a developmental period of relatively high neuroplasticity in which guilt is still developing.

Contributors

MRD conceptualized and drafted the manuscript. RT conducted statistical analyses. JL, DB and MG obtained funding, acquired data, critically revised the manuscript and provided supervision.

Declaration of Competing Interest

The authors report no conflicts.

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Supplementary materials


References


