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Hippocampal volume and depression among young children

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ABSTRACT

Clinical depression can occur in young children as early as age three. This very early onset variant of depression shows the same clinical features with developmental adjustments as depression that onsets later in life. One robust neural feature of adult depression is reduced hippocampal volume. We measured hippocampal volume in a sample of 35 children aged 4–7 who were either in a clinical trial for preschool onset depression or were recruited from the community. We used T1 MPRAGE acquisitions on a Siemen's Scanner, with Freesurfer 5.3 used to segment the hippocampus. Depression was measured using the K-SADS early childhood (K-SADS-EC) to create a dimensional depression severity score and the Child Behavior Checklist (CBCL) Depression T-Score. Multilevel models indicated that greater depression severity as measured by either the CBCL Depression Score or the K-SADS-EC was associated with lower hippocampal volume, even controlling for total gray matter, maternal depression, income-to-needs ratio, and stressful life events. These data indicate evidence for reduced hippocampal volume among children with PO-MDD who were more severely depressed. Findings are consistent with the idea that hippocampal volume reductions are an early occurring associated neural marker of MDD, particularly for more severe depression.

1. Introduction

Clinical depression has been validated to manifest as early as age 3 (Egger and Angold, 2006; Luby et al., 2009a, 2002, 2003; Luby et al., 2004), with prevalence rates similar to those found at school age (1–2%) (Egger and Angold, 2006; Gleason et al., 2011; Lavigne et al., 2009; Wichstrom et al., 2012). Importantly, young children with this preschool onset form of Major Depressive Disorder (PO-MDD) show many of the same clinical features as adults (Luby et al., 2009a, 2009b), including sad mood, excessive guilt, a reduction in the ability to experience pleasure (anhedonia), and disrupted sleep and eating. Further, PO-MDD shows homotypic continuity, such that young children with depression are at increased risk of depression at school age (Gaffrey et al., 2018b; Luby et al., 2009b).Importantly, there is also growing evidence that children with PO-MDD show many of the same disruptions in neural systems found in adolescents and adults with MDD (Belden et al., 2016; Gaffrey et al., 2017a). The goal of the current study is to test hypotheses about the continuity of PO-MDD with depression that onsets later in childhood or adulthood in terms of similar neural alterations, with a specific focus on hippocampal volume, a structural difference robustly associated with MDD in older children, adolescents and adults (McKinnon et al., 2009; Santos et al., 2018b; Schmaal et al., 2016; Wise et al., 2017; Zhao et al., 2014).

A growing body of literature examining very young children with depression (e.g., ages 3–7) has begun to show evidence of disruptions in brain structure and function similar to those seen in older individuals with depression (Belden et al., 2016; Gaffrey et al., 2018a; Whalen et al., submission). One neural difference robustly associated with major depression in adults is a reduction in hippocampal volume, as confirmed by numerous meta-analyses (McKinnon et al., 2009; Santos et al., 2018b; Schmaal et al., 2016; Wise et al., 2017; Zhao et al., 2014). However, there is debate as to the nature of the relationship between MDD and hippocampal volume. Some have argued that hippocampal volume reductions potentially occur prior to the onset of MDD and contribute to risk for depression. For example, it has been argued that early life adversity, poverty, and stress contribute to disruptions in hippocampal structure and function (Hanson et al., 2011; Johnson et al., 2016; Luby et al., 2013), that in turn contribute to dysregulated function of the hypothalamus-pituitary-adrenal (HPA) axis and disordered emotional regulation, which in turn contribute to risk for

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depression (Anacker et al., 2014; Frodl and O'Keane, 2013; Lajud and Torner, 2015; Pagliaccio and Barch, in press; van Bodegom et al., 2017). The hippocampus is important for regulating the response to stress via the inhibition of the hypothalamus-pituitary-adrenal (HPA) axis through the presence of glucocorticoid receptors that are part of a negative feedback loop (Frodl and O'Keane, 2013). This hypothesis that hippocampal impairments are part of the path to risk for depression is consistent with findings of reduced hippocampal volume even among first episode patients with depression (Cole et al., 2011), though not every study has found this (McKinnon et al., 2009; Schmaal et al., 2016). Further, this hypothesis is consistent with work that has found hippocampal volume reductions even among school age children and adolescents with depression (McKinnon et al., 2009; Rao et al., 2010), as well as among individuals at high risk for depression but whom have not yet experienced an episode of clinically diagnosable depression (Rao et al., 2010). This hypothesis would predict that we should see reductions in hippocampal volume even among young children with depression, though it may be that the magnitude of such reductions covary with the severity of clinical depression in children.

However, it has also been argued that hippocampal volume deficits emerge as a function of experience with depression, potentially reflecting a type of neuro-toxicity associated with a cumulative history of stress and adversity, disrupted emotion regulation, stress reactivity and excessive HPA mediated glucocorticoid release (Sheline, 1996, 2011). This latter hypothesis is consistent with evidence that hippocampal volume reductions are even more apparent among individuals with longer illness duration or more than one episode of MDD (Cheng et al., 2010; McKinnon et al., 2009; Sheline et al., 1999, 1996). This hypotheses would suggest that we might not see reductions in hippocampal volume among children with depression, as reductions might only emerge after children have experienced a longer duration of depression or repeated episodes. In prior work with a different sample of children with depression followed through school age and adolescence, evidence was found for reductions in hippocampal volume at school age/preadolescence (8–12 years old) among children who had experienced early signs and symptoms of depression during the pre-school period (Suzuki et al., 2013). However, to our knowledge, no one has examined whether reductions in hippocampal volume are related to depression in very young children, when they first experience depression.

The hypothesis that hippocampal deficits contribute to risk for depression would suggest that we should see a relationships between depression and hippocampal volume even in very young children with depression. However, the hypothesis that the experience of depression contributes to hippocampal deficits suggests that we might not see such a relationship in young children with PO-MDD. Thus, the goal of the current study was to examine whether depression severity would be related to hippocampal volume even among preschoolers. To do so, we used structural MRI data acquired from a unique sample of 4–7 years old children who were participating in a randomized clinical trial of a novel treatment for PO-MDD called Parent-Child Interaction Therapy-Emotion Development (PCIT-ED) (Luby et al., 2018) as well as young children recruited from the community. Given the evidence reviewed above that children with preschool onset depression show many of the same neural differences seen in older children, adolescents, and adults with depression, we hypothesized that we would see reductions in hippocampal volume associated with depression in very young children. Further, we hypothesized that these relationships would be present even when controlling for whole brain volume, which would suggest evidence of specificity. We also examined whether hippocampal volume deficits associated with depression remained when controlling for early stress/adversity factors such as life events or poverty. As noted above, one hypothesis about the role of hippocampal volume reduction in depression is that it reflects experiences with early stress and adversity that disruption hippocampal contributions to stress reactivity and emotion regulation, putting children at risk for depression. If so, then it is possible that life-events and poverty will be more strongly related to hippocampal volume than depression, and will account for any relationship between hippocampal volume and depression.

2. Method

2.1. Participants

Children (aged 3.0–6.11) were either participants in a single-blind randomized control trial (RCT) of PCIT-ED compared to a waitlist (WL) control or they were community children. Analyses of the primary depression outcome measures are reported elsewhere (Luby et al., 2018). Further details about recruitment are provided in the *Supplemental Materials*. Inclusion criteria for the RCT were: (1) meeting early onset major depressive disorder (MDD) symptom criteria on the K-SADS-early childhood (see below), with the validated syndrome requiring 4 instead of 5 symptoms of MDD or MDD-NOS (2 children); (2) no autism spectrum disorder; (3) no serious neurological syndrome or chronic medical disorder; (4) no significant developmental delay; and (5) no antidepressant medication or ongoing psychotherapy (see *Supplemental Materials for* Consort Diagram from Parent RCT study). Inclusion criteria for the community children were a score of <3 on the Preschool Feelings Checklist, and below a 65 on the depression subscale of the Child Behavior Checklist, with the same exclusions as above. All study materials and procedures were approved by the WUSM institutional review board, and written informed consent was obtained from all caregivers, with verbal assent obtained from children. The parent trial was registered with clinicaltrials.gov (NCT02076425).

The MRI component was added 12 months after initiation of the trial and the parents of 101 of the 132 children in the RCT after MRI initiation approached agreed to participate. The original goal of the MRI component was to measure neural responses to reward pre- and post-treatment, with good quality structural MRI needed to process these functional data. However, too few of these very ill children were able to successfully complete the MRI either or both pre- and post-treatment. Of the 101 children in the RCT who agreed to participate in the MRI component, 4 were not able to be scheduled, 16 refused to try the mock scan, 14 were not asked to participate in the mock scan because their behavior during other parts of the visit suggested it would not be successful, 26 had difficulty holding still during the mock scan and we did not have them proceed to the real scan, and 2 refused to do the real scan after completing the mock scan. Of the 39 children who were able to complete at least one MRI session, 23 provided at least one usable structural MRI (see below for quality control), with 10 children in the RCT providing a usable structural MRI both pre- and post-treatment. As shown in Table S1, of the children in the PCIT who attempted the MRI, those who did not provide a usable MRI were significantly more likely to have lower income-to-needs. Given how seriously ill these children were, it is not surprising that the scanning success rates were lower than seen in studies of typically developing children (Walton et al., 2018).

In addition, 60 community children were also invited to complete MRI sessions at baseline, with the original goal of comparing them to the children in the RCT. The parents of 48 of the 60 children agreed to participate. Of these 48 children, 4 refused to try the mock scan, 9 were not asked to participant in the mock scan because of their behavior during other parts of the visit, 22 had difficulty holding still during the mock scan and thus we did not have them proceed to the real scan. Of the 13 eligible children who attempted the MRI sessions, 12 provided a usable structural MRI (see below for quality control). Of note, our success rate of achieving usable structural MRI from awake community children who participated in the MR session (92%) was quite high and comparable to other studies (Walton et al., 2018). However, given that few studies report how they selected children to participate or what percentage of children failed any motion prescreening prior to scanning, we are unable to compare our rates to other studies. There were

no significant demographic differences between those community children who did or did not provide a usable MRI (Table S1, available online).

2.2. Measures

2.2.1. Child psychopathology

The children in the RCT, but not the community children, received the K-SADS-early childhood (EC), a semi-structured clinical interview for DSM-5 disorders adapted for use in children aged 3.0–6.11. The K-SADS-EC was used to assess for the presence and severity of MDD and other Axis I comorbidities at baseline and post treatment or WL. This measure has good test re-test reliability and construct validity and generates both categorical and dimensional measures of DSM-5 Axis I disorders (Gaffrey et al., 2017b; Gaffrey and Luby, 2012). All K-SADS-EC interviews were conducted by master's level clinicians, videotaped, reviewed for reliability, and calibrated for accuracy. Satisfactory inter-rater reliability was established prior to onset of the study and kappas during the study were maintained on a monthly basis with overall kappas of $\mathbf{K} = 0.74$ for MDD; all diagnoses achieved $\mathbf{K} = 0.88$ during the study period. The MDD severity score was the number of core MDD symptoms endorsed on the K-SADS-EC.

2.2.2. Child behavior checklist

The parents of all children were administered the Child Behavior Checklist (CBCL), which is a 123-item scale (Achenbach, 2009) that provides an age and gender normed subscale score for depression as part of the DSM scoring ("Depressive Problems"), as well as for other forms of psychopathology.

2.2.3. Income-to-needs ratio

An income-to-needs ratio was calculated as the total family income at each scan divided by the federal poverty level based on family size for the year of data collection.

2.2.4. Life-events

The Life Events Checklist was administered to parents of PO-MDD and community children. It was based on the Social Readjustment Scale (Holmes and Rahe, 1967), but modified to be age-appropriate. Events assessed were 25 stressful (e.g., new school, parental divorce, death of a pet) and 8 traumatic life events (e.g., death of a family member, parental arrest). The number of different stressful and traumatic events occurring at any point in the child's life up until the time of each scan was determined and used for analysis.

2.2.5. Maternal depression

Because of the age of the children, all of the measures of child psychopathology are based on parent report, primarily maternal report. As such, there is a concern that mother's own level of depression may be influencing their report of child depression. Thus, we also controlled for maternal report of depression on the Beck Depression Inventory II (BDI-II) (Beck and Steere, 1987).

2.3. MRI scanning

Children completed a "mock" scan on a day that they come in for a behavioral assessment, prior to the real MR imaging Children practiced within an MRI simulator (i.e., "mock scanner") equipped with MoTrak and SimFx software (PST, Inc.). This involves attaching a small sensor to the child's head using comfortable straps that determines the position of the head in space relative to the transmitter. This information is logged by the program in real-time Children watched a video that stopped when the child's head moved outside of a pre-specified window. They did this for ~six minutes, starting with a 1-minute trial with only the movie playing where verbal instructions were given on how to keep their body still. Once the child understood how to keep their entire body still, they were instructed to stay still while they watched the movie and heard the scanner sounds. During this time, the goal was for them to stay within the parameters for 3 consecutive minutes. If the child moved outside of the parameters, a wiggle break was offered to the child if needed, and then the timer for 3 consecutive minutes was restarted. If the child moved outside of the parameters more than 3 times before hitting the 3-minute mark, the mock scan was terminated and we did not follow up for the MRI study. Children were allowed to pick out candy if they were able to "make like a popsicle and freeze" during the mock scan process.

Children then completed a neuroimaging battery including high-resolution structural, functional task, and resting state scans collected using a 3.0 Tesla TIM TRIO Siemens whole body scanner at Washington University in St. Louis and a 12-channel head coil. The high-resolution structural data were the focus of the current analysis. 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). During setup and the acquisition of structural images, children watched a video.

Hippocampal volumes were generated using the FreeSurfer pipeline v5.3 [http://surfer.nmr.mgh.harvard.edu] (Reuter et al., 2010) with visual inspection of the white and pial surfaces for errors by an experienced rater blinded to diagnostic category. Processing steps included skull stripping, atlas registration, spherical surface registration, and parcellation. Each scan was visually inspected and given a quality rating between 1 and 3, with 1 being the worst (significant motion artifact), and scan quality ratings below 1.75 were considered to be unusable. Given the evidence that motion can be associated with variation in structural estimates, we correlated scan quality rating with total gray volume and hippocampal volume in the full sample, and found correlations of 0.203 ($p = 0.0722$) for hippocampus and 0.548 ($p < 0.0001$) for total gray volume. However, when we computed the same correlations in the sample of usable data (≥ 1.75), we no longer saw any significant association between quality ratings with either whole brain volume or hippocampal volume. Volume of the left and right hippocampus in the subjects' 'native space' were obtained with FreeSurfer's "aseg.stats" report. Given the previous literature showing bilateral hippocampus reduction in depression (Santos et al., 2018a; Schmaal et al., 2016) as well as reductions in both left (Wise et al., 2017) and right hippocampus (Arnone et al., 2016), we summed the left and right hippocampus.

2.4. Data analysis

Multi-level models (MLM's) with a random intercept and unstructured covariance structure were conducted for all analyses. MLM's account for the fact that some children had more than one MR scan. We chose to use more than one observation per child when available to maximize power given the modest sample size, though essentially the same results were found in linear regressions when only one observation per child was used (see Supplemental Materials, available online). First, we examined the relationship between hippocampal volume and depression severity in PO-MDD and community children using a MLM that covaried for age and gender and the dimensional measures of depression as the independent variables predicting hippocampal volume. All children were administered the CBCL, so relationships between CBCL Depression T-score and hippocampal volume were assessed in PO-MDD and community children. However, the relationship between the K-SADS-EC MDD severity score and hippocampal volume was only examined in PO-MDD children. Then, to assess specificity, total gray matter volume was added to the model to determine whether these relationships remained. Two additional MLM's included maternal depression and, in a separate model, income-to-needs ratio and number of different life events as covariates.

Table 1
Demographic, clinical, and hippocampal volume characteristics in PO-MDD and community children with useable MRI data.

	PO-MDD (N = 23)	Community (N = 12)	χ^2	p
Male gender,% (N)	78.3 (18)	50.0 (6)	F.E.	0.1297
Hispanic ethnicity,% (N)	8.7 (2)	0.0 (0)	F.E.	0.5361
Race,% (N)			F.E.	1.0000
Caucasian	95.7 (22)	100.0 (0)		
African-American	0.0 (0)	0.0 (0)		
More than 1 Race	4.4 (1)	0.0 (0)		
			t	p
Age, mean (SD)	5.86 (0.92)	5.35 (0.82)	1.62	0.1138
Income-to-needs ratio, mean (SD)	3.12 (1.13)	3.16 (1.32)	−0.09	0.9294
Number of different life events, mean (SD)	9.26 (3.74)	7.82 (2.89)	1.12	0.2692
Maternal depression BDI-II score, mean (SD)	13.39 (10.78)	2.92 (3.65)	4.22	0.0002
Hippocampal volume (cm^3), mean (SD)	7.71 (0.90)	7.51 (0.54)	0.68	0.5021
K-SADS-EC MDD severity scores	4.87 (2.38)	NA	NA	NA
CBCL depression T-scores	65.96 (7.27)	52.64 (4.50)	5.56	<0.0001

F.E. = Fisher's Exact Test; *Age, income-to-needs ratio, and frequency of life events were taken from the time of the first useable scan.

3. Results

3.1. Demographic and clinical characteristics

The demographic and clinical characteristics of the children in the PCIT-ED RCT and the community children are shown in Table 1. There were a total of 35 children who provided 45 scan observations, though as noted above, the analyses described below provided essentially the same results when only one observation per child was used.

3.2. Relationship between CBCL depression and hippocampal volume

CBCL Depression T-scores were significantly associated with reduced hippocampal volume across all children (Table 2A and Fig. 1), even when controlling for total gray matter volume. In addition, CBCL Depression T-scores continued to be significantly associated with reduced hippocampal volume even when controlling for maternal depression and total gray matter volume (Table 2B), and maternal depression severity itself was not associated with hippocampal volume. CBCL Depression T-scores were still significantly associated with reduced hippocampal volume even when adding income-to-needs ratio and stressful life events to the model (Table 2C), and neither income-to-needs ratio or stressful life events were associated with hippocampal volume. CBCL Depression T-scores continued to be significantly associated with hippocampal volume in the PO-MDD children alone with even larger effect sizes, controlling for all of the same variables (Table S2, available online). Further, CBCL Depression T-scores continued to be associated with reduced hippocampal volume even when using only one observation per child (Table S3A/B), other than the analysis controlling for income-to-needs and life events (Table S3/C, available online), where it was trend level.

Table 2
Relationship between hippocampal volume and CBCL depression scale scores (N = 44* observations in 34 PO-MDD and community children).

	Estimate	SE	t	p
A: model controlling for total gray volume				
Intercept	7.7347	0.1158	66.81	<0.0001
Female gender	0.0595	0.2120	0.28	0.7808
Age in years	0.2352	0.1043	2.26	0.0304
Total gray volume	0.0077	0.0016	4.74	<0.0001
CBCL depression T-score	−0.0231	0.0101	−2.29	0.0280
B: *Model controlling for total gray volume and maternal depression*				
Intercept	7.7196	0.1121	68.88	<0.0001
Female gender	0.0823	0.2047	0.40	0.6908
Age in years	0.2299	0.1013	2.27	0.0296
Total gray volume	0.0081	0.0016	5.15	<0.0001
Maternal BDI-II total score	0.0143	0.0096	1.49	0.1462
CBCL depression T-score	−0.0276	0.0107	−2.59	0.0136
C: Model controlling for total gray volume, income-to-needs ratio, and life events				
Intercept	7.7446	0.1168	66.29	<0.0001
Female gender	0.0322	0.2184	0.15	0.8837
Age in years	0.2362	0.1080	2.19	0.0366
Total gray volume	0.0079	0.0017	4.74	<0.0001
Income-to-needs ratio	−0.0946	0.0810	−1.17	0.2519
Number of different life events	0.0028	0.0227	0.12	0.9018
CBCL depression T-score	−0.0226	0.0102	−2.21	0.0333

* Note, one child was missing a CBCL score.

3.3. Relationship between K-SADS-EC MDD severity score and hippocampal volume among PO-MDD children

K-SADS-EC MDD severity scores were significantly associated with reduced hippocampal volume in PO-MDD children in an MLM that covaried for age, gender, and total gray matter volume (3A and Fig. 2). Further, K-SADS-EC MDD severity scores continued to be significantly associated with reduced hippocampal volume even when controlling for maternal depression, and maternal depression severity itself was not associated with hippocampal volume (3B). K-SADS-EC MDD severity scores continued to be significantly associated with reduced hippocampal volume even when adding income-to-needs ratio and stressful life events to the model, and neither income-to-needs ratio or stressful life events was associated with hippocampal volume (3C). Lastly, K-SADS-EC MDD severity scores continued to be associated with reduced hippocampal volume in all analyses even when using only one observation per child (Table S4, available online).

4. Discussion

The goal of the current study was to examine whether hippocampal volume reductions would be associated with depression severity even very early in childhood. We found that greater depression severity was associated with reduced hippocampal volume, both in the combined group of children with PO-MDD and community children, and within just the PO-MDD children. These data are the first to show evidence of hippocampal volume reductions at first onset of depression in very young children with more severe depression, consistent with the hypotheses that hippocampal volume reductions are present very early in the course of depression, at least for more severe depression, maybe a risk factor for depression, and do not require a long history of depression to emerge. However, somewhat surprisingly, neither income-to-needs nor life events were associate with hippocampal volume deficits.

Our findings of reduced hippocampal volume associated with greater depression severity held even when we controlled for total gray matter volume, suggesting some level of specificity in this association. Further, we found that this relationship to depression severity held even

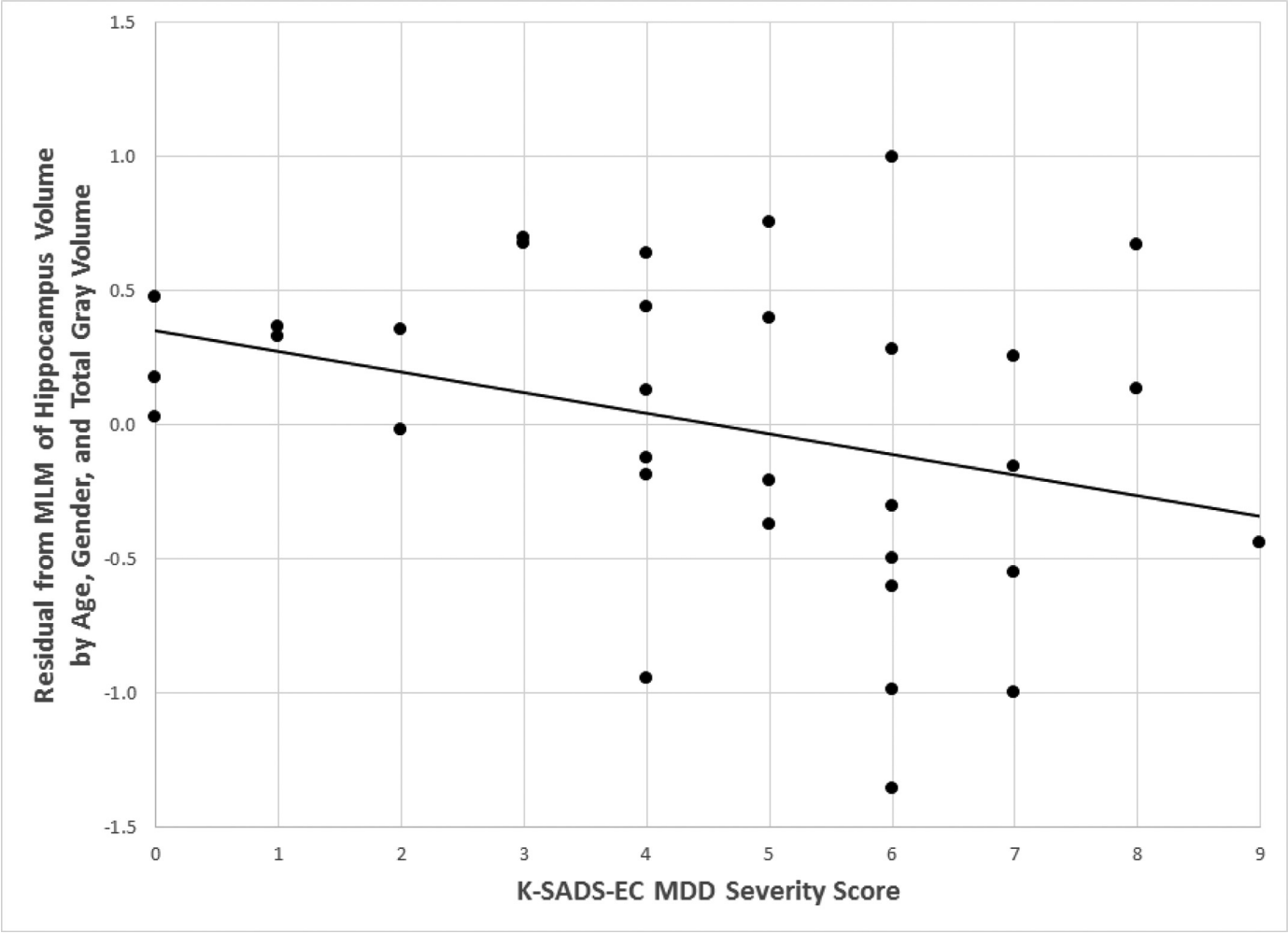

Fig. 1. Scatterplot illustrating the relationship between CBCL depression T-scores and hippocampal volume in all children. Points represent the residuals from a multi-level model of hippocampal volume by age, gender and total gray matter volume.

Table 3
Relationship between hippocampal volume and K-SADS-EC MDD severity scores (N = 33 observations in 23 PO-MDD children).

	Estimate	SE	t	p
A: Model controlling for total gray volume				
Intercept	7.6450	0.1250	61.17	< 0.0001
Female gender	0.5370	0.2746	1.96	0.0648
Age in years	0.2050	0.1209	1.70	0.1054
Total gray volume	0.0098	0.0017	5.64	< 0.0001
K-SADS-EC MDD severity score	−0.0966	0.0414	−2.34	0.0276
B: Model controlling for total gray volume and maternal depression				
Intercept	7.6447	0.1268	60.28	< 0.0001
Female gender	0.5270	0.2821	1.87	0.0776
Age in years	0.2022	0.1233	1.64	0.1173
Total gray volume	0.0099	0.0018	5.56	< 0.0001
Maternal BDI-II total score	0.0028	0.0106	0.27	0.7911
K-SADS-EC MDD severity score	−0.0969	0.0422	−2.30	0.0302
C: *Model controlling for total gray volume, income-to-needs ratio, and life events*				
Intercept	7.6613	0.1289	59.45	< 0.0001
Female gender	0.4850	0.2865	1.69	0.1077
Age in years	0.2143	0.1244	1.72	0.1021
Total gray volume	0.0102	0.0019	5.35	< 0.0001
Income-to-needs ratio	−0.0853	0.1051	−0.81	0.4265
Number of different life events	−0.0096	0.0267	−0.36	0.7214
K-SADS-EC MDD severity score	−0.1081	0.0454	−2.38	0.0249

if we controlled for maternal depression, income-to-needs, and stressful life-events. These findings are generally consistent with findings of reduced hippocampal volume even among very young first episode patients with depression, (Cole et al., 2011) though this is not seen in every study, (McKinnon et al., 2009; Schmaal et al., 2016) as well as with prior work showing reduced hippocampal volume among school age children and adolescents with depression. (McKinnon et al., 2009; Merz et al., 2018; Rao et al., 2010)

It is somewhat surprising though that we did not find a relationship between hippocampal volume and either stressful life events or income-to-needs in the primary analyses in our sample. Numerous previous studies, including our work in older children, have found a relationship between early adversity/poverty and hippocampal volume. (Dahmen et al., 2018; Hanson et al., 2011; Johnson et al., 2016; Luby et al., 2013) It has been argued that this disruption in hippocampal volume contributes to deficits in stress reactivity and emotion regulation, which in turn contributes to risk for depression. (Anacker et al., 2014; Frodl and O'Keane, 2013; Lajud and Torner, 2015; Pagliaccio and Barch, in press; van Bodegom et al., 2017) However, a recent meta-analysis in adults did not find evidence for a relationship between early adversity and hippocampal volume, (Frodl et al., 2017) though the literature on poverty and reduced hippocampal volume has been relatively robust. (Pagliaccio and Barch, in press) One possible explanation for the lack of relationship with income-to-needs in our sample was that this was a relatively high SES sample, with the mean income to needs approximately three times the poverty line. Further, the children who were

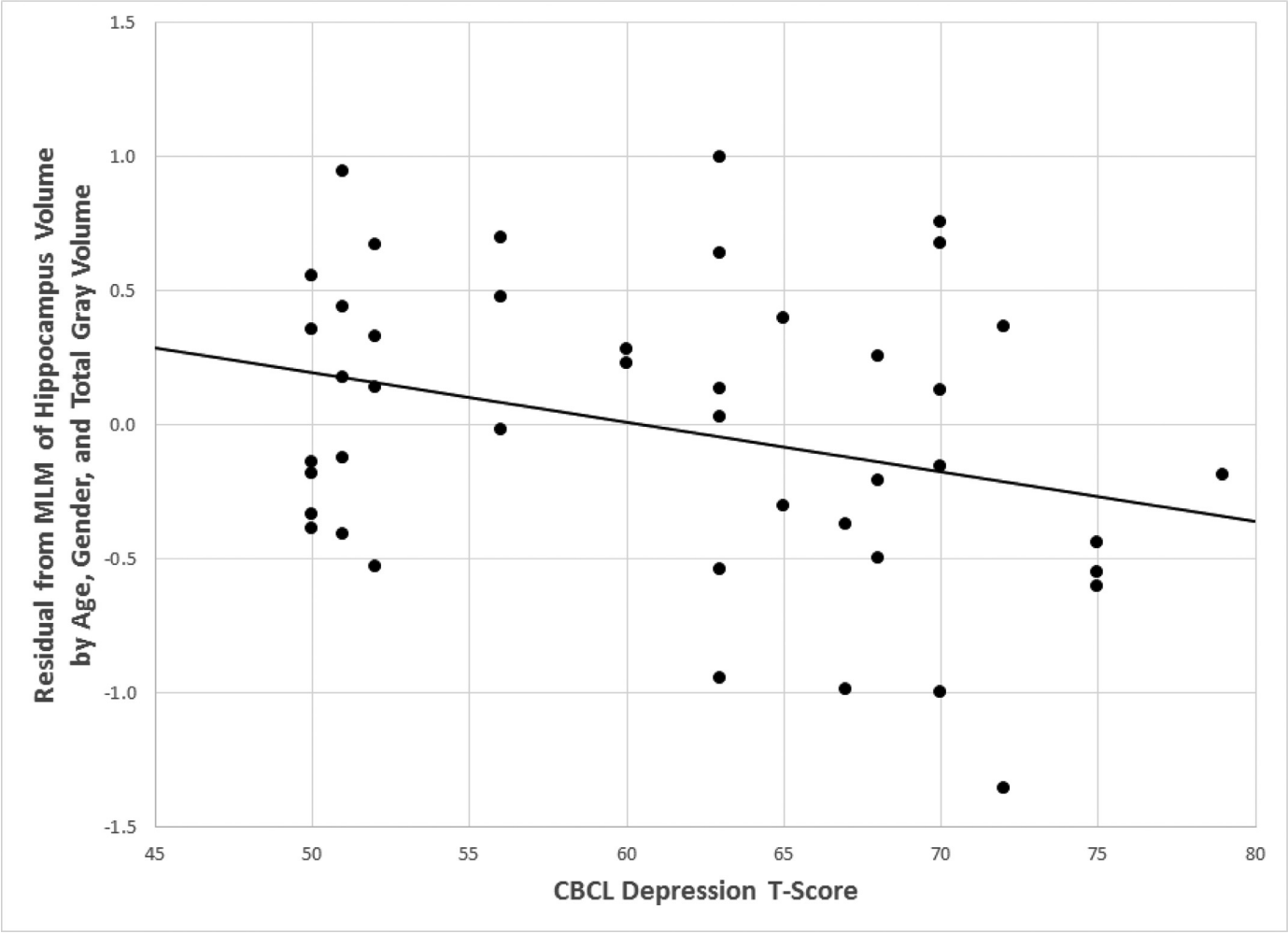

Fig. 2. Scatterplot illustrating the relationship between K-SADS-EC MDD severity scores and hippocampal volume in PO-MDD children. Points represent the residuals from a multi-level model of hippocampal volume by age, gender and total gray matter volume.

able to provide usable MRIs had higher income-to-needs than the children who could not. In regards to life events, there was also no association. Similar to poverty levels, this sample did not have large numbers of life events and thus we may have been limited in our power to detect relationships to poverty and early life events. Further, it is possible that a relationship with hippocampal volume and stress or income-to-needs will emerge slightly later in development as children accumulate greater exposure, though we saw evidence for such a relationship in 8–12 years old children in our prior work. (Luby et al., 2013)

There are several limitations to the current analyses. First, the sample sizes are small. However, the scatterplots suggest that the hippocampal volume reduction is less apparent in children with less severe depression, even if they met criteria for PO-MDD. Second, some of the children completed scans twice and both scans were included in the multi-level models to enhance power. However, the same results were found if only a single scan per child were used. Third, there were a number of children who could not provide usable MRIs, and they were more likely to have lower income-to-needs. Thus, these results may not be fully representative of the population of children with PO-MDD. Fourth, these data came from a treatment study and some of the scans occurred pre-treatment and some occurred post-treatment, though the vast majority of the data in the analyses presented in Tables S3 and S4 were baseline pre-treatment. Although there is some evidence that electroconvulsive therapy may be associated with hippocampal volume increases in patients with major depression, (Wilkinson et al., 2017) there is little evidence as to whether psychotherapeutic approaches to treatment of depression are associated with changes in hippocampal volume. Further, treatment effects would have been likely to make it more difficult to find the predicted results. Nonetheless, treatment effects will be an important question for future studies in larger samples either in children or older populations.

In sum, our results provide further evidence for a relationship between hippocampal volume and depression severity even among very young children. These findings are consistent with the idea that hippocampal volume reductions occur early in the course of depression, and do not require repeated episodes to emerge, though they were more apparent in children with more severe depression. Somewhat surprisingly, we did not also see a relationship of early stressful life events or poverty to hippocampal volume in this sample, potentially because this was a relatively high SES sample compared to previous studies. Taken together, these results provide further evidence for the similarity of PO-MDD to clinical depression that first emerges later in childhood, adolescent or adulthood.

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Supplementary materials

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