



Stressful Life Events, ADHD Symptoms, and Brain Structure in Early Adolescence

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Abstract

Despite a growing understanding that early adversity in childhood broadly affects risk for psychopathology, the contribution of stressful life events to the development of symptoms of attention-deficit/hyperactivity disorder (ADHD) is not clear. In the present study, we examined the association between number of stressful life events experienced and ADHD symptoms, assessed using the Attention Problems subscale of the Child Behavior Checklist, in a sample of 214 children (43% male) ages 9.11–13.98 years ($M = 11.38$, $SD = 1.05$). In addition, we examined whether the timing of the events (i.e., onset through age 5 years or after age 6 years) was associated with ADHD symptoms. Finally, we examined variation in brain structure to determine whether stressful life events were associated with volume in brain regions that were found to vary as a function of symptoms of ADHD. We found a small to moderate association between number of stressful life events and ADHD symptoms. Although the strength of the associations between number of events and ADHD symptoms did not differ as a function of the age of occurrence of stressful experiences, different brain regions were implicated in the association between stressors and ADHD symptoms in the two age periods during which stressful life events occurred. These findings support the hypothesis that early adversity is associated with ADHD symptoms, and provide insight into possible brain-based mediators of this association.

Keywords Early life stress · ADHD · Attention problems · Neural correlates

Introduction

Attention deficit hyperactivity disorder (ADHD) is characterized by developmentally atypical levels of inattention, hyperactivity, and impulsivity (American Psychiatric Association 2013). The prevalence of ADHD is estimated to be 5% worldwide (Polanczyk et al. 2007); importantly, however, taxonomic analyses indicate that a dimensional, rather than

a dichotomous, approach best represents the latent structure of ADHD (Marcus and Barry 2011), suggesting that a far greater proportion of the population is affected by symptoms of ADHD. Much of the research examining ADHD has focused on its negative impact on individuals' functioning (Lee et al. 2008, 2011; Owens et al. 2009). Findings from this work have motivated interventions aimed at reducing specific symptoms and consequences of ADHD. It is possible, however, that the effectiveness of these treatments would be increased by elucidating etiological routes to symptoms of ADHD. Studies of the etiology of ADHD typically focus on genetic risk (e.g., Kustanovich et al. 2004; Nyman et al. 2007); in fact, behavioral genetic studies yield heritability estimates for ADHD of around 75% (Faraone et al. 2005). Importantly, however, behavioral genetics research also indicates that there are significant environmental contributions to ADHD symptoms; indeed, researchers have identified a number of risk factors for ADHD, including maternal smoking, low birth weight, nutritional factors, and parental psychopathology (Biederman et al. 2002; Braun et al. 2006; Linnert et al. 2003; Nikolas and Burt 2010; Thapar et al. 2003). Such findings challenge positions that ADHD has only a genetic etiological pathway, and suggest

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that there are opportunities to identify individuals at risk for ADHD due to exposure to specific environmental factors.

In this context, children with ADHD have been found to experience greater stress and adversity in early life than have their peers without ADHD (see Humphreys and Zeanah 2015); in fact, both abuse and neglect are associated with increased levels of ADHD symptoms. A recent study of a representative sample of adults found that the odds ratio of meeting criteria for ADHD following childhood physical and sexual abuse was 1.5 and 2.5, respectively (Fuller-Thomson and Lewis 2015). It is possible that the association between childhood maltreatment and adulthood ADHD is mediated by deviations in neurodevelopment. Both stress and ADHD have been associated with reduced volumes in the prefrontal cortex (PFC) and basal ganglia, as well as with reductions in cortical thickness across the prefrontal, parietal, and temporal cortices (McLaughlin et al. 2014). In addition, the timing of adversity may be relevant in this context. Because brain regions develop on different time scales, the effects of stress on brain development likely differ as a function of the age at which the stress was experienced (e.g., sensitive periods) (Andersen et al. 2008; Pechtel et al. 2014; Teicher 2008).

The present study was designed to examine the association between stressful life events and symptoms of ADHD in a community sample of early adolescents. We prioritized dimensional assessments of ADHD symptomatology, which capture variation within clinical and subclinical presentations of the disorder. Consistent with a cumulative risk approach (Evans et al. 2013), we examined the impact of stressful life events considered collectively (i.e., a count of the number of unique stressful events reported over the child's entire life); in addition, we also examined the effects of stress as a function of the age of stress onset, in order to test the possibility of a sensitive period in early childhood for the association between stress and symptoms of ADHD. We hypothesized a positive association between stressful life events and higher levels of ADHD symptoms; we also hypothesized that the number of experiences of stress earlier in life (i.e., through age 5 years) would be associated more strongly with ADHD symptoms than the number of stressful experiences occurring after age 6 years.

In addition, we used tensor based morphometry (TBM) to examine variation in brain structure. This approach allows for the potential to identify structural brain change in response to stress that is associated with ADHD symptoms. TBM has been applied extensively to a number of populations and contexts, including Alzheimer's Disease (Davatzikos 1996; Hua et al. 2008), development (Hua et al. 2009; Thompson et al. 2000), HIV/AIDS (Chiang et al. 2007), autism spectrum disorders (Hua et al. 2013), and traumatic brain injury (Dennis et al. 2017; Kim et al. 2008). The whole-brain approach of TBM permits a data-driven analysis that can yield a more complete picture of the structural changes associated with ADHD and early life stress, compared to focusing a priori on specific

structures. Voxel-based morphometry (VBM) is a similar approach in being data driven, but TBM offers several advantages over VBM (i.e., improved reliability and power) (Thompson et al. 2000) and inaccuracies in registration can be mistakenly identified as group differences in volume using a VBM approach (Bookstein 2001). We conducted analyses to determine whether variations in brain structure associated with ADHD symptoms overlap with brain regions that vary as a function of stressful life events. Given the large number of brain regions that have been linked separately to stressful life events and to ADHD, we did not generate hypotheses regarding specific brain regions of interest that would be related to both stressful life events and ADHD symptoms.

Methods

Participants/Procedure

This study was approved by the Stanford University Institutional Review Board. Participants were 214 children (43% male) ages 9.11–13.98 years ($M = 11.38$, $SD = 1.05$) who completed questionnaires and brain imaging as part of a longitudinal study of the psychobiological effects of early life stress across childhood and into adolescence. Children provided responses about their racial/ethnic identification in an interview. Of the 214 participants, 47% identified as White, 13% Biracial, 12% Asian, 10% Hispanic/Latino, 8% African American, and 8% Other. Participants were recruited from local communities around Stanford University through a variety of sources, including flyers, online advertisements (e.g., Craigslist), and emails to parent listservs in the area. In an initial phone interview, research staff provided information about the study protocol to families and screened participants for inclusion/exclusion criteria. Because the study involved a magnetic resonance imaging (MRI) session, criteria for exclusion from the study included factors that would preclude an MRI scan (e.g., metal implants, braces), as well as a history of major neurological or medical illness, severe learning disabilities that would make it difficult to comprehend the study procedures, proficiency in English, and, for females, the onset of menses. Inclusion criteria were that children be between ages 9–13 years; boys were matched to girls in self-reported pubertal stage (Morris and Udry 1980). Eligible families were invited to visit the lab at Stanford University to sign consent and assent forms as well as to complete interviews and questionnaires about the child and family. All participants were compensated for their time.

Measures

Early Life Stress Children were interviewed about their lifetime exposure to 30 types of stressful events using a modified version of the Traumatic Events Screening Inventory for Children

(TESI-C; Ribbe 1996). A trained member of the research staff transcribed a description of each stressor, removing details that would reveal the child's subjective perception of severity, and delivered to a panel comprised of three raters. Raters were advanced graduate students or postdoctoral fellows with experience in clinical interviewing, psychopathology, and child development, were trained by the lead author (KLH), and rated the objective severity of each type of stressor endorsed using a modified version of the UCLA Life Stress Interview coding system (Rudolph et al. 2000; Rudolph and Hammen 1999). Each coder provided an independent severity rating on a scale of 1–5, increasing in half-point increments (1 = *low impact*; 5 = *severe impact*), and there were high levels of agreement (ICC = 0.99). In cases of disagreement, consensus was reached via discussion. Further, in order to reduce rating drift, a record of stressful events with consensus ratings was kept in order to anchor subsequent ratings. Only stressors rated by the panel as being a 1.5 or higher were included in the total count (see supplemental Table 1 for a list of event types and rates of endorsement, although severity ratings often differ for events in each type based on supporting details). In addition to the count of total stressful events experienced, for events in which an age of onset was provided we examined whether the onset occurred through age 5 years (i.e., birth to 5.99 years) or age 6 years through the current assessment date. Given the positive skew of the count data, we applied a square root transformation to the data in analyses of the counts of stressful events.

Child Behavior Checklist (CBCL; Achenbach 1991) Parents completed the CBCL, a widely-used assessment of child psychopathology that was normed on a large sample of children and adolescents (Achenbach 1991). Response options ranged from 0 (*not true*) to 2 (*very true or often true*). For the purpose of the present study, the total score from the Attention Problems subscale was used as a measure of ADHD symptoms. The Attention Problems narrow-band scale items do not perfectly map onto the DSM-5 symptoms of ADHD (American Psychiatric Association 2013), although both sets include items assessing difficulty concentrating, trouble sitting still, and impulsivity. Further, the Attention Problems subscale has been found to be a useful discriminator (i.e., using receiver-operating characteristic analysis) of those with and without ADHD (Chen et al. 1994). In addition, in order to provide clinical context to the sample, we identified individuals with T-scores at or above 65, which corresponds to the 95th percentile in symptoms. Three participants' parents did not complete the CBCL.

MRI Data Acquisition

MRI scans were acquired at the Center for Cognitive and Neurobiological Imaging at Stanford University using a 3 T

Discovery MR750 (GE Medical Systems, Milwaukee, WI, USA) equipped with a 32-channel head coil (Nova Medical, Wilmington, MA, USA). Whole-brain T1-weighted images (T1w) were collected using the following spoiled gradient echo pulse sequence: 186 sagittal slices; TR (repetition time)/TE (echo time)/TI (inversion time) = 6.24/2.34/450 ms; flip angle = 12°; voxel size = 0.9 mm × 0.9 mm × 0.9 mm; scan duration = 315 s. Data were quality checked at multiple stages, including after brain masking, and after both linear and non-linear registration. No participants were excluded for excessive motion, and no participants failed registration steps.

Tensor-Based Morphometry

Each participant's T1-weighted anatomical data were N3-corrected using c3d (<http://www.itksnap.org>) to correct for intensity in homogeneities. Volumes were automatically skull-stripped using FreeSurfer (<https://surfer.nmr.mgh.harvard.edu>) and these masks were manually edited by trained neuroanatomical experts (LS and AC; see acknowledgements). We linearly registered each participant to the Montréal Neurological Institute (MNI) template using FSL FLIRT (<http://fsl.fmrib.ox.ac.uk>). Thirty participants, selected to be representative of the population, were used to make the minimal deformation template (MDT). The MDT is the template that deviates least from the anatomy of the participants with respect to a mathematically defined metric of difference; in some circumstances, using a MDT can improve statistical power (Leporé et al. 2007). The MDT serves as an unbiased registration target for nonlinear registrations.

Next, each participant's masked, non-uniformity-corrected, template-aligned T1-weighted image was non-linearly aligned to the MDT, using Advances Normalization Tools Symmetric Normalization (SyN; Avants et al. 2008). SyN registration utilized a multi-level approach, i.e., the "moving" and fixed T1 images were successively less smoothed at each level, with a full resolution registration occurring at the final level. We used 150, 80, 50, and 10 iterations at each level, with a Gaussian kernel smoothing sigma set to 3, 2, 1, and 0 respectively (7.05, 4.7, 2.35, and 0 voxels full width at half maximum). Image similarity was measured using the ANTs implementation of mutual information (Avants et al. 2011). Image intensities were winsorized, excluding top and bottom 1% of voxels, and histogram matching was used. This resulted in jacobian determinant images, where the values indicate the direction and magnitude of the deformation in registering an individual's T1 to the MDT. Both TBM and behavioral measures were available for 173 participants.

Data Analysis

To examine the association between stressful life events and ADHD symptoms, we used linear regression analysis

covarying for age, sex, pubertal stage, and race (White vs. other). Stress exposure was characterized in three ways: (1) total number of stressful events reported; (2) total number of stressful events reported through age 5 years; (3) total number of stressful events reported at age 6 years and older (Table 1).

We first conducted a linear regression testing for associations between regional brain structure and ADHD symptoms. The jacobian determinant images resulting from TBM were examined voxel-wise with ADHD symptoms from the CBCL. We included age, sex, pubertal stage, race/ethnicity, and intracranial volume (ICV) as covariates (see Table 2 and Fig. 1 for areas of interest found in these analysis). We conducted similar models examining regional associations with the three stress variables described above. The results from the model that included ADHD symptoms were corrected for multiple comparisons across the whole brain using searchlight false discovery rate correction (Langers et al. 2007). To examine areas of the brain in which ADHD symptoms and number of stressful life events overlapped in their effects, we used the results from the ADHD symptoms model as a mask to view the stress results. These were run as follows:

$$X \sim A + \beta_{\text{Variable}} \text{Variable} + \beta_{\text{age}} \text{Age} + \beta_{\text{sex}} \text{Sex} \\ + \beta_{\text{Pubertalstage}} \text{Pubertalstage} + \beta_{\text{Race}} \text{Race} + \beta_{\text{ICV}} \text{ICV} + \varepsilon$$

where X is the jacobian determinant value at a given position, A is the constant jacobian determinant term, “variable” is either ADHD symptoms or the count of stressful events, the β s are the covariate regression coefficients, and ε is an error term. Within the ADHD symptoms mask, we ran multiple comparison correction in the three stress models so that we were only correcting for multiple comparisons within regions that showed a significant association with ADHD symptoms.

This approach yielded clusters that were significantly related to both ADHD symptoms and number of stressful life events. We then extracted the jacobian determinant values for each subject within these clusters to use in mediator analyses. These resulting regions of interest summaries express whether a given participant had more or less volume in a given area relative to the study-specific template, as well as the magnitude of the difference from the template.

Results

Using a T-score cutoff of 65 or higher on the Attention Problems narrow-band subscale, we found that 15% of the sample met the threshold for clinical concern in ADHD symptoms. Bivariate correlations and descriptive statistics are presented in Table 1. Without considering potential covariates, there were moderate positive associations between number of stressful events throughout the child’s life and ADHD symptoms. Further, when the number of events was considered based on timing of the onset of each event, both the number of events that occurred through age 5 years and the number of events that occurred at age 6 years or later were significantly positively associated with ADHD symptoms. Importantly, however, the number of events occurring in these two time periods were positively intercorrelated, indicating that early and later childhood stressors should be considered jointly in order to determine their unique contributions to ADHD symptoms.

Regression Analyses

We formally tested the association between the number of stressful events throughout the child’s life and ADHD

Table 1 Bivariate pearson correlations and descriptive statistics for study variables

	Age	Sex	Pubertal stage	Race	Events, whole life	Events, through age 5 years	Events, age 6 years and older	ADHD symptoms
Age	1							
Sex (Male=1)	0.35***	1						
Pubertal Stage	0.31***	−0.13	1					
Race (White=1)	0.10	0.06	0.05	1				
Number of stressful events, whole life	−0.07	−0.01	0.03	−0.10	1			
Number of stressful events, through age 5 years	−0.20**	−0.04	0.01	−.18**	0.72***	1		
Number of stressful events, age 6 years and older	0.03	0.01	0.04	−0.02	0.90***	0.36***	1	
ADHD symptoms	−0.13	0.11	−0.09	−0.12	0.30***	0.29***	0.23**	1
Mean (SD) or %	11.38 (1.05)	43%	2.03 (0.74)	47%	4.60 (3.43)	1.31 (1.73)	3.29 (2.44)	3.05 (3.19)
Range	9.11–13.98	0–1	1.0–4.5	0–1	0–17	0–11	0–16	0–14

Square root transformations were applied to the number of stressful events for the correlation matrix, and raw values are presented for Mean (SD) and range

Table 2 Brain regions associated with ADHD symptoms

Voxels	Max	X	Y	Z	Side	Structure	Tissue
Greater volume with more ADHD symptoms							
1228	1.9%	27	-39	19	R	Splenium/posterior corona radiata	WM
489	1.6%	14	-46	21	R	Cingulum	WM
365	1.7%	-41	-48	-45	L	Cerebellum	GM
269	1.7%	-43	-47	-4	L	Middle temporal gyrus	WM
238	2.0%	-50	-45	-6	L	Inferior temporal gyrus	GM
188	2.3%	53	-15	6	R	Transverse temporal gyrus	GM/WM
184	4.2%	30	-27	67	R	Postcentral gyrus	GM
181	2.4%	-42	-36	-17	L	Fusiform gyrus	GM
162	2.0%	-1	-67	-12	L	Cerebellum	GM
151	2.1%	8	-81	-20	R	Lingual gyrus	GM
150	1.7%	-29	9	-10	L	Insula	GM/WM
137	1.8%	-44	-23	8	L	Transverse temporal gyrus	GM/WM
128	2.4%	-26	51	1	L	Middle frontal gyrus	GM
104	2.0%	50	-10	29	R	Postcentral gyrus	GM/WM
Smaller volume with more ADHD symptoms							
515	-2.4%	-36	-71	13	L	Lateral occipital gyrus	GM
377	-1.8%	38	-73	40	R	Angular gyrus	GM
340	-1.9%	15	-76	21	R	Cuneus	WM
124	-2.1%	-55	1	-6	L	Superior temporal gyrus	GM/WM
89	-2.2%	-8	0	50	L	Cingulate gyrus	GM
88	-2.6%	4	39	-29	R	Straight gyrus	GM
72	-1.7%	39	-74	22	R	Lateral occipital gyrus	GM/WM
71	-1.5%	43	-16	-23	R	Inferior temporal gyrus	GM

For each cluster we list the number of voxels, max regression coefficient (expressed as % difference in volume with 1 point difference in ADHD symptoms), coordinates in MNI space, hemisphere, structure, and tissue type ADHD = attention-deficit/hyperactivity disorder. GM = gray matter. WM = white matter

symptoms using hierarchical linear regression after covarying for age, sex, and pubertal stage. Lifetime stressful events explained significant variance in ADHD symptoms ($\beta = 0.29$, $t(204) = 4.36$, $p < 0.001$, $\Delta R^2 = 0.08$) after controlling for covariates.

We repeated this analysis using the number of stressful events occurring through age 5 years. Number of stressful events in early life explained significant variance in ADHD

symptoms ($\beta = 0.26$, $t(204) = 3.77$, $p < 0.001$, $\Delta R^2 = 0.06$) after controlling for covariates. Further, when the number of stressful events from age 6 years and older was included as an additional step, the model was significantly improved ($\beta = 0.17$, $t(203) = 2.43$, $p = 0.016$, $\Delta R^2 = 0.03$), indicating that events in both early life and later childhood are important in predicting ADHD symptoms in early adolescence (the effect of event through age 5 years remained statistically significant

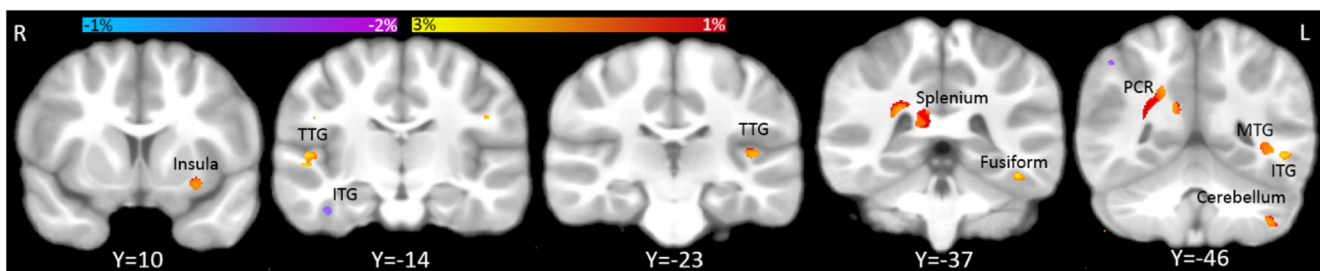


Fig. 1 Associations between attention-deficit/hyperactivity disorder symptoms and regional brain volume. Blue-purple areas indicate negative associations between regional brain volume and ADHD symptoms. Red-yellow areas indicate positive associations between regional brain volume and ADHD symptoms. TTG = transverse temporal

gyrus. ITG = inferior temporal gyrus. PCR = posterior corona radiata. MTG = middle temporal gyrus. Left in image is right in brain, Y coordinates of slices are shown (Montréal Neurological Institute [MNI] space)

in this larger model ($\beta=0.20$, $t(203)=2.74$, $p=0.007$, $\Delta R^2=0.03$). A test of dependent correlations (Lee and Preacher 2013) indicated that, contrary to expectations regarding support for a sensitive period for the effects of stress, the number of stressful events experienced through age 5 years and at age 6 years and older did not differ significantly in their association with ADHD symptoms in early adolescence ($z=0.22$, $p=0.822$).

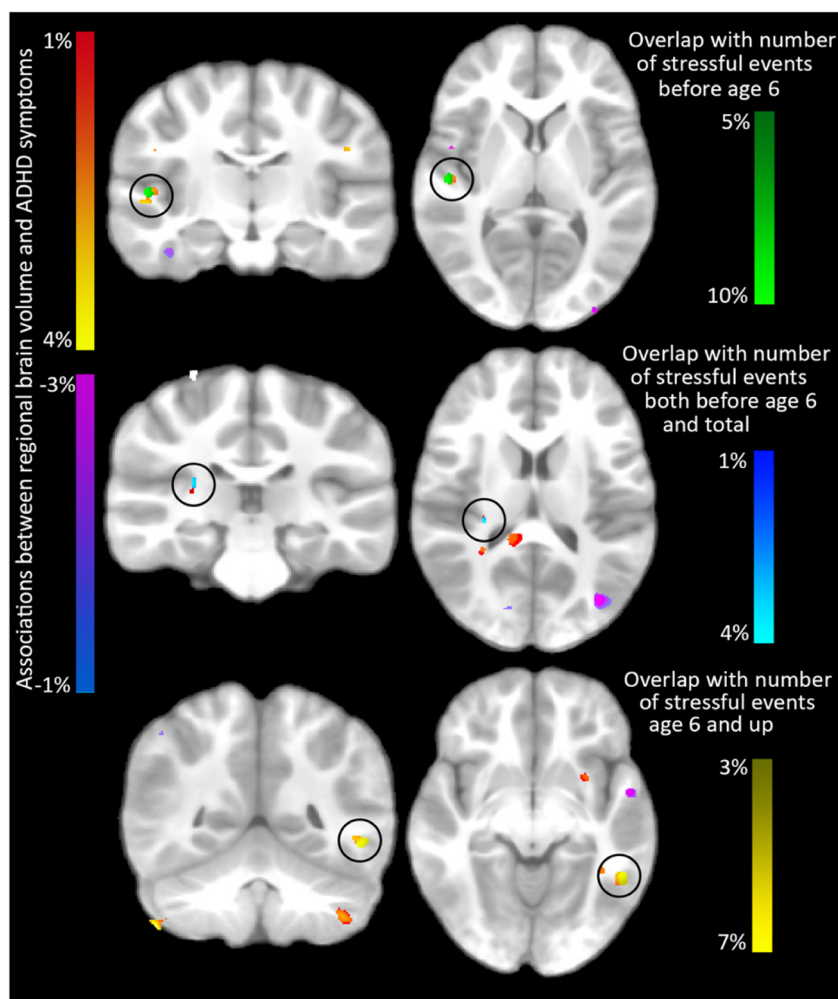
TBM Overlap

We conducted voxel-wise linear regressions, testing for associations between regional brain volume and the variables of interest, including ADHD symptoms and number of stressful events (a) in the child's entire life; (b) through age 5 years; and (c) at age 6 years and older (see Fig. 2). In this regression, we included covariates of age, sex, pubertal stage, race (because of race-related differences in stress exposure in early life), and ICV.

For total number of stressful events across the child's life, only one cluster – the posterior internal capsule – was identified using the analyses described above. This region of interest

overlapped in TBM analyses of ADHD symptoms and of the total number of stressful life events. Greater volume in this region was marginally associated with greater ADHD symptoms ($\beta=0.14$, $t(178)=1.86$, $p=0.064$, $\Delta R^2=0.02$) and significantly associated with a greater number of lifetime stressful life events ($\beta=0.26$, $t(178)=3.58$, $p<0.001$, $\Delta R^2=0.07$), controlling for the effects of age, sex, pubertal stage, race, and ICV. Using the same approach, two areas overlapped in the association with ADHD symptoms and number of stressful events through age 5 years: again, the posterior internal capsule, as well as the transverse temporal gyrus (TTG). Greater volume in these two regions was significantly associated with greater ADHD symptoms ($\beta=0.15$, $t(178)=1.99$, $p=0.048$, $\Delta R^2=0.02$ and $\beta=0.20$, $t(178)=2.75$, $p=0.007$, $\Delta R^2=0.04$, respectively). Further, greater volume in both the posterior internal capsule ($\beta=0.25$, $t(178)=3.51$, $p<0.001$, $\Delta R^2=0.06$) and the TTG ($\beta=0.23$, $t(178)=3.24$, $p<0.001$, $\Delta R^2=0.05$) was associated with experiencing a higher number of stressful life events through age 5 years. Only one brain region was identified in the overlap in brain morphometry for ADHD symptoms and the number of stressful events experienced at

Fig. 2 Overlap between regional brain associations with attention-deficit/hyperactivity disorder symptoms and stressful life events. Red-yellow and blue-purple areas are those positively and negatively associated with ADHD symptoms. Green indicates regions where regional brain volume was associated with both ADHD symptoms and the number of stressful events through age 5 years (i.e., before age 6 years). Yellow indicates regions where regional brain volume was associated with both ADHD symptoms and the number of stressful events after age 6. Blue indicates regions where regional brain volume was associated with ADHD symptoms, number of stressful events through age 5 years (i.e., before age 6 years), and total number of stressful events. Percents listed indicate the degree of brain volume difference with one point difference in ADHD symptoms or number of stressful events. *Note.* ADHD = attention-deficit/hyperactivity disorder



age 6 years and older: the inferior temporal gyrus (ITG). Greater volume in the ITG was significantly associated with both greater ADHD symptoms ($\beta=0.24$, $t(178)=3.31$, $p=0.001$, $\Delta R^2=0.06$) and number of stressful life events in later childhood ($\beta=0.23$, $t(178)=3.13$, $p=0.002$, $\Delta R^2=0.05$), controlling for the effects of age, sex, pubertal stage, race, and ICV.

Discussion

In a sample of 214 children, we found that the number of stressful life events that children experienced was associated with ADHD symptoms. Specifically, we observed that greater stressful events, both in early and later childhood, was associated with higher levels of ADHD symptoms. Furthermore, we found that variation in the posterior internal capsule, TTG, and ITG were shared based on experiences of stressful life events and symptoms of ADHD, indicating a potential structural brain change in response to stress that is associated with greater ADHD symptom presentation. Contrary to expectations, the number of stressful events experienced earlier in life was no more strongly associated with ADHD symptoms than were the number of stressful events experienced in later childhood.

Despite the high heritability estimates provided by twin studies regarding genetic influences on ADHD symptoms, there is a growing appreciation of environmental contributions to this form of psychopathology. For stressful experiences in particular, previous research has linked significant stress exposure to an increased risk of ADHD and related symptoms (Humphreys et al. 2015; Pechtel and Pizzagalli 2011; Stevens et al. 2008; Wozniak et al. 1999). “Natural experiments” of children reared in orphanages and later placed in families at different ages provide the opportunity to examine the timing of stressors and their removal on child functioning. Although Stevens and colleagues suggested a sensitive period as early as two years of age for institutionalized children who later develop ADHD (Stevens et al. 2008), the Bucharest Early Intervention Project found no effects of age of placement on ADHD symptoms (Humphreys et al. 2015; Zeanah et al. 2009); however, quality of foster care was associated with reduced ADHD symptoms in girls in this sample (Tibu et al. 2014). The present study, using a community sample, also does not provide support for a sensitive period for the effects of stress, but instead indicates that greater exposure to stressful events in both early and later childhood is associated with higher levels of symptoms of ADHD in early adolescence, even after controlling for the influence of the other developmental period.

The early life environment has the potential to have a profound impact on the trajectory and development of a wide range of behaviors, which may be mediated by variation in

the cognitive and emotional circuits in the brain (Pechtel and Pizzagalli 2011). Severe social deprivation has been linked to decreased cortical thickness, which in turn is associated with greater inattention and impulsivity (McLaughlin et al. 2014). Such findings provide insight into the etiological pathways by which stress may get “under the skin” in a manner that contributes to symptoms of ADHD. Rather than using an automated segmentation approach (as used in McLaughlin et al. 2014), we used TBM to examine variation in brain volume without selecting *a priori* regions of interest. We found three brain regions in which volume varied as a function of both ADHD symptoms and number of stressful events experienced. For both the number of stressful events across the child’s entire life and specifically in early life, we identified the posterior internal capsule as a neural correlate of both stressful events and ADHD symptoms: we found greater volume of the internal capsule in individuals with a higher number of reported stressful events which, in turn, were associated with more symptoms of ADHD. The internal capsule is a fiber bundle in the central white matter (WM) that conveys fibers between lobes and from the cerebellar hemisphere to the peripheral nervous system. As with other WM structures, the internal capsule matures well into the third decade of life, with an age-at-peak of nearly 32 years (Kochunov et al. 2012). Studies using diffusion tensor imaging (DTI) have implicated the internal capsule in ADHD, finding altered white matter organization in children and adolescents with ADHD (Pavuluri et al. 2009; Qiu et al. 2011). Indeed, one study examining the interaction of ADHD and early life stress found that the internal capsule was implicated in both constructs (Park et al. 2016).

We also found a positive association between TTG volume and number of stressful events through age 5 years. The TTG, also known as Heschl’s gyrus, is involved in processing auditory stimuli (Howard et al. 2000). The superior temporal cortex, in which the TTG is sometimes included, is one of the last regions of the brain to mature (Gogtay et al. 2004). Interestingly, two studies have shown greater volume in the superior temporal gyrus in individuals who were exposed to early life stress (De Bellis et al. 2002; Tomoda et al. 2011). Finally, we found greater ITG volume in individuals who had reported experiencing a greater number of stressful events starting at age 6 years and older; in turn, variation in this region was associated with increased ADHD symptoms. The ITG is part of the ventral “what” pathway, involved in object recognition (Goodale and Milner 1992). One study using DTI and focusing on boys found greater connectivity in the ITG WM in the ADHD group than in healthy comparison youth (Silk et al. 2009). The temporal gray matter as a whole has a more protracted development than does that of other lobes, showing peak volume around age 17 (Giedd et al. 1999). For this reason, it may be sensitive to disruption over a longer developmental period than are other brain structures. One

research group showed delayed maturation in a large ADHD cohort: the ADHD group reached peak cortical thickness several years after the typically developing group in some parts of the brain, including large areas of the frontal cortex, along with posterior aspects of the superior, middle, and inferior temporal cortex (Shaw et al. 2006). Delayed age-at-peak can mean delayed entry into the cortical thinning phase of brain maturation, which could result in larger volume calculations among individuals with ADHD in a cross-sectional analysis.

Our results were unexpected; prior work reported smaller brain volumes in the overlap between ADHD and early life stress (McLaughlin et al. 2014), and generally, ADHD is associated with smaller brain volumes (Shaw et al. 2007). Our finds may differ due to several methodological reasons. First, studies have used many different techniques for measuring brain volume, including cortical thickness and gray matter focused techniques, or VBM (De Brito et al. 2013; Langevin et al. 2015; Lim et al. 2014; Norman et al. 2016; Qiu et al. 2011). TBM has better accuracy compared to VBM and allows for investigation of both gray and white matter volumes. Two studies that have used TBM to investigate the effects of early life stress found smaller prefrontal cortex volume, along with larger volume in a number of WM clusters (Hanson et al. 2010, 2012). Another possible reason for the discrepancy involves variations in atlases and nomenclature – the TTG is a small structure that is sometimes reported as part of the superior temporal gyrus.

Further, our non-clinical sample may have identified different groups of children than are typically used in studies examining the neural correlates of ADHD. Our measure of ADHD symptoms only included two items that assess hyperactivity/impulsivity; therefore, the findings may better map onto inattention symptoms than hyperactivity/impulsivity symptoms. This sample also likely differs from clinical samples in functional impairment and in levels of comorbidity. In addition, given the heterogeneity within ADHD (Fair et al. 2012; Wählstedt et al. 2009), it is likely that children with similar levels of symptoms have different neural correlates. While heritability estimates represent the average degree to which a disorder or set of symptoms is explained by genetic factors, across individuals the degree to which ADHD is accounted for by genes varies widely. It is likely that there are a number of neurobiological pathways that can be disrupted in individuals with higher ADHD symptoms, and it may be that the mechanisms through which early life stress increases vulnerability to ADHD represent only one of these pathways. Symptoms of ADHD may be secondary to posttraumatic stress disorder (PTSD) or other reactions to experiences of adversity; given the overlap between PTSD and ADHD (Adler et al. 2004; Daud and Rydelius 2009), it may be worthwhile to consider whether reactions to trauma are responsible for elevated symptoms of ADHD or if ADHD is elevated even after accounting for PTSD. Among those for

whom the environment is a stronger etiological factor, increases in brain volume in these areas may account for variation in symptoms, whereas a different pattern of brain volume findings may characterize those individuals whose environments did not significantly influence their ADHD symptom presentation.

We should note a number of limitations of this study. First, we used a dimensional approach to assess symptoms of ADHD, and relied on a symptom scale that does not map isomorphically onto the symptoms of ADHD included in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association 2013). Future studies would benefit from assessing all symptoms of ADHD. Using dimensional measures has advantages in understanding the relations between social and biological variables and phenotypic differences among individuals who may not meet diagnostic thresholds. Nevertheless, conducting categorical assessments will be an important extension of this work; the use of precise criteria will help to provide structure and reliability among researchers (Helzer et al. 2006). Second, we used parent reports of ADHD. Although parent reports are considered reliable for ADHD symptomatology (Faraone et al. 1995), the use of multiple informants is important in determining symptom presentation across contexts. Third, we cannot determine the specificity of these symptoms to ADHD. Indeed, many disorders have in common difficulties in concentration (American Psychiatric Association 2013), including disorders found at higher rates in children who experienced early adversity (e.g., major depressive disorder, generalized anxiety disorder, and PTSD) (Green et al. 2010). Considerations of comorbidity, contributions of symptom dimensions of ADHD (i.e., inattention symptoms and hyperactivity/impulsivity symptom), as well as the inclusion in future research of related neuropsychological measures of executive function and cognitive ability (e.g., IQ), would increase our understanding of the breadth vs. specificity of these findings.

The fourth limitation of this study concerns our measurement of stressful life events. Specifically, we used a count of events rather than the severity of the ratings of the events; these metrics might capture slightly different types and severity of stressors (Zeanah and Sonuga-Barke 2016). Further, the events were generated via retrospective child reports. Such reports may be prone to errors of commission or omission and bias in reporting, as the nature of reporting on very early events typically relies on information obtained by the individual after the event occurred. Despite this concern, however, it is important to note that there is evidence supporting the validity of retrospective reports for serious adverse experiences in childhood (Brewin et al. 1993; Brown et al. 2007). Fifth, in our sample we matched boys and girls in their pubertal staging within a specified age range, rather than matching boys and girls on the basis of age, given that, on average, boys and girls make the transition through puberty at different ages. This

approach may have led us to exclude girls in precocious puberty and instead oversample girls who were relatively late maturing; it is not clear what effect that would have had on our findings. Boys and girls differ in trajectories of brain development (Lenroot et al. 2007), in the prevalence of ADHD (Scahill and Schwab-Stone 2000), and potentially in reactivity to stress (Pechtel and Pizzagalli 2011); therefore, in future studies it will be important to consider sex differences longitudinally across development in order to elucidate the nature of the interrelations among these constructs. Finally, although we cannot determine causality, stressful life events may be causal in affecting symptoms of ADHD. Nevertheless, given the uncontrolled nature of these associations, that ADHD may evoke differential responses from others (Harold et al. 2013), and that the increased risk-taking behavior found in individuals with ADHD may increase their exposure to stressful events (Garzon et al. 2008; Humphreys and Lee 2011), the directional nature of the association between stressful life events and ADHD is far from clear.

In conclusion, we provide evidence that ADHD symptoms in early adolescence vary as a function of cumulative stress exposure during the child's life. Specifically, both the number of stressful events experienced in early (i.e., through age 5 years) and later (age 6 years and older) childhood were associated with increased levels of ADHD symptoms. Importantly, stress during each time period explained unique variance in ADHD symptoms; moreover, they did not differ in the size of their effect, indicating that ADHD symptomatology is affected by the experience of events throughout childhood. It is noteworthy, however, that different brain areas were linked to events occurring during these two periods in relation to ADHD symptoms, suggesting that the impact of stressful events on the brain may differ as a function of stage of development in ways that may also help to explain increases in symptoms of ADHD.

These findings suggest several potential next steps in this program of research. Studies examining the etiology and course of ADHD should include careful assessments of the environment in early life, tracked longitudinally, in order to increase our understanding of the naturalistic course of the emergence of ADHD symptoms and the potential role of stress. This may mean attending not only to the timing of stressors, but also the type, severity, and duration of events in order to determine whether some experiences of stress are more strongly associated with ADHD symptoms than are other experiences. Finally, we encourage researchers to include ADHD symptoms as an outcome measure of interest in intervention programs, given the possibility that if ADHD symptoms are associated with stress, efforts to prevent these events (e.g., Nurse Family Partnership) or improve functioning after such events (e.g., trauma-focused cognitive behavioral therapy) could have beneficial effects on this domain of functioning as well.

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Compliance with Ethical Standards

Conflict of Interest The authors report no possible conflicts of interest

Ethical Approval This study was approved by the Stanford University 124 Institutional Review Board.

Informed Consent Eligible families were invited to 148 visit the lab at Stanford to sign consent and assent forms as well 149 as to complete interviews and questionnaires about the child 150 and family.

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