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Hippocampal volume as an amplifier of the effect of social context on adolescent depression

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Abstract

Recent models have focused on how brain-based individual differences in social sensitivity shape affective development in adolescence, when rates of depression escalate. Given the importance of the hippocampus in binding contextual and affective elements of experience, as well as its putative role in depression, we examined hippocampal volume as a moderator of the effects of social context on depressive symptoms in a sample of 209 Mexican-origin adolescents. Adolescents with larger versus smaller hippocampal volumes showed heightened sensitivity in their depressive symptoms to a protective factor inside the home (sense of family connectedness) and a risk factor outside of it (community crime exposure). These interactive effects uniquely predicted depressive symptoms and were greater for the left side, suggesting two independent social-contextual contributions to depression that were moderated by left hippocampal volume. Results elucidate complex brain-environment interplay in adolescent depression, offering clues about for whom and how social context plays a role.

Keywords

adolescence; depression; hippocampus; brain structure; neuroimaging

Introduction

Ever since hippocampal volume reductions in major depressive disorder (MDD) were first documented in the 1990s (Sheline, Wang, Gado, Csernansky, & Vannier, 1996), perhaps no other brain region has received as much interest nor sparked as much controversy regarding its role in depression (Lorenzetti, Allen, Fornito, & Yücel, 2009; Videbech & Ravnkilde, 2004). MDD is characterized by sadness, irritability, and loss of interest or pleasure that is chronic or persistent enough to hinder everyday functioning. Involvement of the hippocampus in MDD makes sense for several reasons. First, the hippocampus plays a central role in binding contextual and affective elements of experience (Burgess, Maguire, &

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O'Keefe, 2002; Hassabis & Maguire, 2009), including in episodic memory formation and retrieval (Maguire, Mummery, & Büchel, 2000; Squire, 1992) and discriminating between threat and safety (Ji & Maren, 2007; Lau et al., 2011). Second, the hippocampus is strongly connected with brain regions that subserve motivation and emotion processing, such as the nucleus accumbens, amygdala, and medial prefrontal cortex (Fastenrath et al., 2014; Thierry, Gioanni, Dégénétais, & Glowinski, 2000). Third, the hippocampus is sensitive to stress and facilitates regulation of the hypothalamic-pituitary-adrenal (HPA) axis, leading to speculation that a smaller hippocampus contributes to or results from depressive episodes or both (Sapolsky, Krey, & McEwen, 2002). Regardless of the causal direction of the effect, although smaller volumes are generally observed in adults with MDD (Videbech & Ravnkilde, 2004), far less clear is whether hippocampal volume plays a role in depressive symptomatology in youths with or at-risk for MDD. Not only has the majority of the relevant research been conducted in adults, but the findings are more equivocal for youths.

Adolescence is a time of enormous biological and social change and the peak developmental period for the onset of MDD (Paus, Keshavan, & Giedd, 2008). Adolescent-onset depression is more severe than adult-onset depression (Zisook et al., 2007), is four times more likely to lead to a recurrent episode (Naicker, Galambos, Zeng, Senthilselvan, & Colman, 2013), is more common in females (Nolen-Hoeksema & Girgus, 1994), and is associated with a broad range of difficulties in adulthood that include other mental health issues, interpersonal problems, unemployment, and suicide (McLeod, Horwood, & Fergusson, 2016; Weissman et al, 1999). About 67% of adolescents with subthreshold depression go on to develop MDD by their early 30s (Klein, Shankman, Lewinsohn, & Seeley, 2009), making subclinical symptoms in adolescence important to track. Because the brain undergoes an impactful set of changes during adolescence that alters mood regulation and boosts sensitivity to the social environment (Casey, Jones, & Hare, 2008; Crone & Dahl, 2012; Nelson & Guyer, 2011), investigating the brain bases of depression in adolescence may help clarify the conditions under which MDD is likely to emerge. Still, with regard to the hippocampus, no volumetric differences (MacMillan et al., 2003; Rosso et al., 2005; Yap et al., 2008), smaller volumes (Koolschijn, van IJzendoorn, Bakermans-Kranenburg, & Crone, 2013), larger volumes (MacMaster & Kusumakar, 2004), and even smaller and larger volumes depending on side (Little et al., 2014) or sex (Price et al., 2013) have been found in youths with or at-risk of MDD. This leaves open the question of whether hippocampal volume is related to adolescent vulnerability to depression.

Efforts to understand the brain-based mechanisms underlying susceptibility to depression in adolescence have increasingly focused on how the brain and social experiences interact to shape risk for depression. This approach aligns with recent frameworks on *adolescent neurobiological susceptibility to social context* (Schriber & Guyer, 2016), whereby properties of the adolescent brain (e.g., structure, function) index individual differences in social sensitivity that moderate the effects of experience, good or bad, on developmental outcomes. Indeed, the *neurobiological susceptibility* models (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2011) that ground this framework inherently involve some kind of biological moderation (Boyce, 2016). Through interaction of the environment with stable biological factors that are innate or conferred by early experience (e.g., allelic variation in certain genes; differences in physiological responsiveness to stress),

more “orchid-like” individuals are posited to be more permeable in their life outcomes to the influence of environmental exposures, whether helpful or harmful, whereas more “dandelion-like” individuals are relatively unaffected either way. Thus, cortisol reactivity in children, for example, moderated the link between exposure to family stress and prosocial development such that children defined by higher, as compared to lower, cortisol reactivity showed less prosocial behavior after exposure to more family stress yet more prosocial behavior after exposure to less (Obradović et al., 2010). Although differential susceptibility to non-social stressors has been noted (e.g., microbial products, Guerra & Martinez, 2008), the vast majority of relevant research concerns social factors, critical to survival and thriving for any social species.

At the psychological level, moderation is expected because individuals’ underlying biological systems are thought to differentially monitor the social environment to match its demands, including through more rapid learning in susceptible individuals of the “skills, schemas, attitudes, and values communicated by their environment” (Simons & Lei, 2013, p. 61). Such differential social sensitivity may be especially consequential in adolescence, when changes in the brain result in cognitive and affective enhancements in learning from the social environment both in and outside the home (Davey, Yucel, & Allen, 2008; Nelson, Jarcho, & Guyer, 2016). The drawback is that social stressors, at their worst when both social-evaluative and uncontrollable (Dickerson & Kemeny, 2004), contribute greatly to depressive symptoms in adolescence (Davey et al., 2008; Nelson et al., 2016; Rudolph & Hammen, 1999; Shih et al., 2010). Thus, adolescents as a whole may become more sensitive to the social risk and protective factors that shape depression in adolescence (e.g., affective dynamics at home; peer or romantic rejection vs. acceptance; community disorder), but stable individual differences in the hippocampus and other regions that promote social processing may render some adolescents – especially neurobiologically susceptible adolescents – more or less prone to depression. These “orchid-like” adolescents would be expected to fare the best and worst across all adolescents, depending on the supportiveness of their social contexts.

Evidence from human and animal studies suggests that volume of the hippocampus, in particular, may be a marker of susceptibility to social context, especially in adolescence. In contrast to the focus on smaller volumes in depression, this evidence points to a larger hippocampus as a susceptibility factor. Larger, not smaller, hippocampal volumes may confer greater sensitivity to the environment by (1) supporting more complex social interactions, consistent with the social brain hypothesis (Dunbar, 2009), (2) increasing hippocampus-dependent cognitive function whereby events and contexts become better consolidated and more finely represented regardless of valence (Østby, Tamnes, Fjell, & Walhovd, 2012; Redondo et al., 2014), and (3) instigating greater social stress-induced cortisol release within the HPA axis (Pruessner et al., 2005), itself an established susceptibility marker from the neuroendocrine system (Ellis et al., 2011). Consistent with these possibilities, one study found that girls (but not boys) with larger hippocampal volumes at baseline showed greater sensitivity to the protective effects of lower maternal aggression and harmful effects of higher maternal aggression on change in depressive symptoms across early to mid-adolescence (Whittle et al., 2011). Likewise, a rodent study found that late adolescent/young adult male mice with larger left, but not right, hippocampal

volumes at baseline later manifested greater social withdrawal and avoidance tendencies after exposure to social defeat as compared with mice with smaller left hippocampal volumes and control mice (Tse et al., 2014). The possibility of laterality is notable, given that the left, more so than right, hippocampus has been associated with autobiographical memory in humans (Burgess et al., 2002; Spreng, Mar, & Kim, 2008).

In light of the above theory and evidence, we tested hypotheses about the interplay of social-contextual exposures and hippocampal volume on depressive symptoms in adolescence, in adolescence, when the hippocampus is still developing and individual variation in its volume may be relatively stable (Dennison et al., 2013; Gogtay et al., 2006; Lenroot & Giedd, 2006). Our aims were five-fold. First, because emergent work on hippocampal moderation has focused on the effects of negative social environments, we tested hippocampal volume as a moderator of the effects of positive as well as negative social environments, as specified by neurobiological susceptibility models (Ellis et al., 2011; Schriber & Guyer, 2016). We thus examined hippocampal sensitivity to a protective factor inside the home – the experience of family connectedness – on adolescent depressive symptoms. Second, considering social context from a socioecological perspective (Bronfenbrenner, 1986), we moved beyond the home to examine the impact of a risk factor based in the school and neighborhood community – exposure to threat via crime. Investigating both contexts allowed us to test for the unique contributions of each in their interactions with hippocampal volume. Third, given evidence of functional distinctions between left and right hippocampus (Burgess et al., 2002) and laterality effects in the association between their volume and MDD (Bremner et al., 2000; Little et al., 2014; MacMaster & Kusumakar, 2004), we tested for differences between left and right hippocampus in their moderation of social-contextual effects. Fourth, to better understand the well-established gender differences in depressive outcomes (Nolen-Hoeksema & Girgus, 1994), we examined whether sex moderated any of the above associations. Finally, to gain specificity in our effects, we replicated analyses by assessing a different predictor (income-to-needs ratio, not a specifically “social” contextual stressor) as well as other outcomes (anxiety and externalizing symptoms).

We pursued these aims by studying a large sample of Mexican-origin adolescents who are participating with their families in a longitudinal study of risk and resilience for psychopathology. We focused on Mexican-origin adolescents for several reasons. First, this group is especially vulnerable to MDD, showing higher rates of depression as compared to peers from other ethnic/racial groups (Crockett et al., 2007). Second, despite the heightened risk, this group is understudied, including in research examining biology-environment interplay in psychopathology. Third, our sample is well-suited for testing the social-contextual effects of interest due to deep-seated emphasis in Mexican culture on family (Sabogal, Marín, Otero-Sabogal, Marín, & Perez-Stable, 1987) and greater likelihood of encountering crime due to the concentration of poverty and other social disadvantages in this group (South, Crowder, & Chavez, 2005). Finally, limiting our investigation to Mexican-origin adolescents provided an inherent control for the effects of race and ethnicity within our sample. Based on previous research, we expected that being female (Nolen-Hoeksema & Girgus, 1994) and experiencing less family connectedness (Campos, Ullman, Aguilera, & Dunkel Schetter, 2014; Hardway & Fuligni, 2006; Stein, Gonzalez, Cupito, Kiang, & Supple, 2015) and more community crime (Curry, Latkin, & Davey-Rothwell, 2008;

Cutrona, Wallace, & Wesner, 2006; Latkin & Curry, 2003) would predict adolescent depressive symptom severity. However, we were most interested in whether the effects of these social-contextual exposures were moderated by hippocampal volume, in accordance with the tenets of neurobiological susceptibility to social context.

Materials and Methods

Sample

Two-hundred twenty-nine adolescents (49.3% female; *M* age at MRI scan = 17.16 years, *SD* = .41, range = 16.24–17.98) were recruited from the California Families Project (CFP), a 10-year, prospective, longitudinal study of 674 Mexican-origin youths and their families. Families had originally been recruited based on having a child in grade 5 (age 10) who was randomly selected from school rosters of the 2006–2007 and 2007–2008 academic years. To ensure variability in depressive symptoms for the current study, recruitment oversampled youths with elevated levels. We used counts of adolescents' self-reported symptoms in grade 9 (age 14) on the Computerized Diagnostic Interview Schedule for Children-IV (C-DISC) (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) and indicators of elevated severity from the Anhedonic Depression and General Distress subscales of the Mood and Anxiety Symptom Questionnaire (MASQ; Watson et al., 1995). Specifically, we sought to recruit adolescents who scored above the median for the overall sample on one or more of these measures. The C-DISC is a highly structured diagnostic instrument that assesses 34 common psychiatric diagnoses (e.g., conduct disorder) by determining the presence or absence of symptoms according to diagnostic criteria specified by the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; DSM-IV-TR; American Psychiatric Association, 2000). The MASQ is a widely used measure of depression and anxiety with separate subscales for General Distress, Anhedonic Depression, and Anxious Arousal. These depression measures were again administered when the social contexts were measured. A third measure of depression was used as the outcome (see Measures below).

The proportions of adolescents from the recruited as compared to remaining sample who scored above the median on the recruitment measures were as follows: MASQ General Distress, 50.2% vs. 44.5% (median = 1.30); MASQ Anhedonic Depression, 48.3% vs. 48.2% (median = 1.67); and C-DISC MDD symptom counts, 46.5% vs. 42.3% (median = 3). Recruited as compared to remaining adolescents significantly differed on MASQ General Distress scores ($M = 1.50$, $SD = .54$, vs. $M = 1.40$, $SD = .45$, $t = 2.33$, $p < .05$) but not MASQ Anhedonic Depression scores ($M = 1.70$, $SD = .76$, vs. $M = 1.67$, $SD = .76$, $t = .39$, *ns*) or C-DISC MDD symptom counts ($M = 4.16$, $SD = 4.19$, vs. $M = 4.03$, $SD = 4.24$, $t = .36$, ns). According to the C-DISC, 22 participants met criteria for MDD at recruitment, and 15 met criteria for conduct disorder; criteria for no other disorders were met. Ten adolescents were ineligible for scanning (e.g., had contraindicated dental ware, a history of epilepsy, discomfort with the scanner), and two had neuroimaging data that were unavailable due to scanner malfunction, resulting in 217 youths who provided neuroimaging data. Of these, eight were omitted from analyses, as six had neuroimaging data showing artifact (e.g., motion, ghosting), and two were missing 20% or more of depression data. This resulted in a sample of 209 youths reported in final analyses. All parents provided informed consent, and

youths, assent, and participants were compensated for their participation in this study, which was approved by the Institutional Review Board (IRB).

Procedure

In grade 11 (T1), an average of 6.09 months (*SD* = 3.56) before hippocampal volumes and depressive outcomes were measured, adolescents reported on their social contexts (family connectedness, community crime) and experience of depressive symptoms concurrent with these social contexts (baseline depressive symptoms). Two participants had their MRI visit approximately one month before the social contexts and baseline symptoms were measured; results did not differ when excluding these participants from analyses. Subsequently, in grades 11 or 12 during a visit involving an MRI scan (T2), we measured hippocampal volumes and depressive symptoms concurrent to the scan (depressive symptoms as the outcome variable). In addition to the above key variables, income-to-needs ratio was assessed at T1, and anxiety and externalizing symptoms, at T1 and T2.

Measures

Depressive symptoms—At T1, the C-DISC major depression module and MASQ General Distress and Anhedonic Depression subscales were administered to adolescents, with z-scores of each averaged to provide a measure of *baseline depressive symptoms.* At T2, adolescents' responses on the Children's Depression Inventory-2 (CDI-2; Kovacs, 1984) provided the dependent variable for this study. The CDI-2 is a widely used measure of presence and severity of depressive symptoms in youths aged 7–17 years, including in Hispanic/Latino youths (Cowell, Gross, McNaughton, Ailey, & Fogg, 2005; Twenge & Nolen-Hoeksema, 2002; Vaughn-Coaxum, Mair, & Weisz, 2016). Cognitive, emotional, and behavioral symptoms of depression from the previous two weeks were reported on 28 items. Three response options (e.g., "I am sad once in a while," "I am sad many times," and "I am sad all the time") reflect different degrees of having experienced a symptom, with answers coded as 0 (*None to very little*), 1 (*Some*), or 2 (*A lot*). Item 9, which asks about suicidal ideation, was excluded due to requirements of the IRB. Items were summed to derive a measure of *depressive symptoms.* Scores were prorated for eight participants whose missing data was not in excess of six questionnaire items (i.e., approximately 20% of the data). Reliability in our sample was excellent (coefficient $\alpha = .86$). Using a cut-off score of 20 on the CDI-2 (Kovacs, 1984), 13 adolescents (10 females, 3 males) reported symptoms suggesting clinical levels of depression.

Anxiety symptoms—At T1, the C-DISC anxiety module was administered to adolescents, with z-scores of three symptom counts (General Anxiety, Social Anxiety, Panic Disorder) averaged to provide a measure of *baseline anxiety symptoms.* At T2, adolescents reported on anxiety symptoms using the Screen for Child Anxiety Related Emotional Disorders (SCARED; Birmaher et al. 1997). Consistent with diagnostic criteria specified in the DSM-IV, 41 items (e.g., "I am afraid I'll do something embarrassing") were rated on a 4-point Likert scale from 0 (*Never*) to 3 (*Always*) to assess frequency of experiencing anxiety symptoms. A measure of *anxiety symptoms* that corresponded with our baseline measure was created by averaging across mean scores on three subscales (General Anxiety, Social

Anxiety, Panic Disorder). Reliability in our sample across these items was excellent (coefficient α = .92).

Externalizing symptoms—At T1, the C-DISC disruptive behavior module was administered to adolescents, with z-scores of symptom counts (Conduct Disorder, Oppositional Defiant Disorder) averaged to provide a measure of *baseline externalizing symptoms.* At T2, adolescents reported on their externalizing symptoms using the Strengths and Difficulties Questionnaire (SDQ; Goodman, Meltzer, & Bailey, 1998). This 25-item scale measures five domains of psychological functioning with five items each (e.g., "I fight a lot") rated on a 3-point Likert scale from 0 (*Not true*) to 2 (*Certainly true*). Responses on the externalizing subscale were averaged to provide a measure of *externalizing symptoms.* Reliability in our sample was adequate (coefficient α = .63).

Family connectedness—At T1, adolescents reported on their feelings of connectedness, closeness, love, and support in their families on a measure of familism (Villarreal, Blozis, & Widaman, 2005), a widely upheld value in Hispanic culture emphasizing the centrality of the family. Five items (e.g., "You are proud of your family," "You cherish the time you spend with your family") were rated on a 4-point Likert scale ranging from 1 (*Strongly disagree*) to 4 (*Strongly agree*) and averaged. Reliability in our sample was excellent (coefficient α = .85).

Community crime—At T1, adolescents reported on their exposure to crime in their communities with two measures. The Neighborhood Criminal Events Scale (NCES; Aneshensel & Sucoff, 1996) was used to assess the frequency of criminal events in their neighborhood with ten items (e.g., "How often did violent crimes including stabbings, shootings, and violent assaults happen in your neighborhood in the past year?"). The Violence, Gangs, and Crime in Schools Scale, adapted from the NCES, was similarly used to assess the frequency of criminal events at school with ten items (e.g., "How often are there groups of kids hanging around who make you feel unsafe?"). Responses were made on a 4-point Likert scale ranging from 1 (*Almost never or never*) to 4 (*Almost always or always*). These measures were moderately correlated, $r = .54$, $p < .05$, so their items were averaged to derive an index of community crime exposure. Reliability in our sample was excellent for this combined scale (coefficient α = .90).

Income-to-needs ratio—At T1, to provide an index of family economic status, income-to-needs ratio was computed by dividing total annual family income as reported by mothers by the official poverty threshold in 2010 for the identified household size. A ratio of less (or more) than 1 signified the extent to which the family was under (or over) the poverty line.

Demographic characteristics—During the wave assessed for recruitment, in grade 5, measures of verbal and fluid cognitive abilities were derived based on performance on the Verbal Comprehension and Visual Matching subtests of the Woodcock-Johnson III Test of Cognitive Abilities (WJ III; Woodcock, McGrew, & Mather, 2001). This measure was examined in relation to depressive and other psychiatric symptoms for potential inclusion as a covariate.

Hippocampal volume

Magnetic resonance imaging data acquisition: Neuroimaging data were collected at T2 using a Siemens 3T Tim Trio scanner with a 32-channel head coil. Extensive instructions to remain still were given to adolescents to decrease head motion, which was also limited with foam padding and surgical tape placed below the chin to the head coil. Whole-brain high-resolution structural images were acquired using a T1-weighted magnetization-prepared rapid-acquisition gradient echo (MPRAGE) scan collected in the sagittal plane (TR = 2500 ms; TE = 4.33 ms; slices = 208; flip angle = 7°; field of view (FOV) = 243 mm; image matrix = 243 * 243 mm; voxel size = 0.9 * 0.9 * 0.9 mm; slice thickness = .95 mm; duration of scan = 5 min 9 sec). These high-resolution structural images were used to quantify hippocampal volume.

Image processing: Image preprocessing, subcortical segmentation, and cortical parcellation were performed with the FreeSurfer image analysis suite version 5.3.0 (http://surfer.nmr.mgh.harvard.edu). This automated processing pipeline has been detailed elsewhere (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999). In brief, FreeSurfer assigns a neuroanatomical label to every voxel in a brain volume using probabilistic information that constrains the permissible locations of brain structures relative to one another based on the likelihood of (1) a tissue class occurring at a specific atlas location, (2) image intensity given that tissue class, and (3) the local spatial configuration of labels for that tissue class (Walhovd et al., 2005). Automated segmentation has been found to be statistically indistinguishable from manual labeling (Fischl et al., 2002), with high correlations between segmentation and manual labeling observed for the hippocampus, including in depressed samples (Morey et al., 2009). We used measures of hippocampal volume (Fischl et al., 2002) and total intracranial volume (Buckner et al., 2004) in our analyses. Volumetric segmentation of the hippocampus for each participant was visually inspected for inaccuracies by two raters (R.A.S., Z.A.) blind to participant identity and level of depressive symptoms; three volumes were discarded due to poor segmentation coming from low-quality MR images. Volumes were extracted from the left and right hippocampus, respectively, and divided by total intracranial volume (ICV) to produce a measure of left and right hippocampal volume corrected for whole-brain size (Walhovd et al., 2005).

Data analysis

Statistical analyses were performed using IBM SPSS Statistics version 23.0 (SPSS Inc., Chicago, IL). Initial analyses indicated that age, cognitive abilities, and income-to-needs ratio were not associated with adolescent depressive symptoms. Thus, in our primary analysis, these variables were not included as covariates, which consisted of sex and baseline depressive symptoms. We controlled for baseline depressive symptom because we wanted to test whether the social-contextual variables prospectively predicted change in depressive symptoms. After initial levels of depressive symptoms are controlled for, residual variance in later depressive symptoms reflects increases (or decreases) in depressive symptoms. For example, a positive relation between a T1 social context and residualized T2 depressive symptoms would suggest that the social context predicted subsequent increases in symptom severity. Furthermore, unique relations between a T1 social context and T2 depressive symptoms would rule out the possibility that their cross-lagged effect was due merely to

concurrent association of these variables at T1 plus stability of these variables over time. Ultimately, the temporal precedence and robustness of our social-contextual predictors were important to establish if the effect of social context was proposed to be causal and moderated by hippocampal volume, which was measured at T2.

In our primary analysis, a hierarchical linear regression model was conducted that tested left and right hippocampal volumes as moderators of the effect of social context on depressive symptoms. Depressive symptoms concurrent with the scan were the dependent variable. In Step 1, the main effects of sex (0 = Male, 1 = Female), depressive symptoms concurrent with social context (Baseline Depressive Symptoms), social context (Family Connectedness, Community Crime), and hippocampal volume (Hippocampal Volume [Left, Right]) were entered. In Step 2, to test our main hypothesis that hippocampal volume moderated the effects of social context on depressive symptoms, we added the four 2-way interactions of each social context with hippocampal volume (Family Connectedness × Hippocampal Volume [Left, Right], Community Crime × Hippocampal Volume [Left, Right]). In Step 3, to determine whether sex moderated any of the above relations, all 2- and 3-way interactions with sex were entered. Interaction terms were computed after centering all continuous variables, and significant interactions were probed using simple slopes analysis. We deemed any simple slope found to be significant at the $p < .05$ level as important for understanding the moderating effects. To obtain standardized regression coefficients to report in tables, we ran regression models using z scores of all continuous independent variables, including interaction terms, given that β coefficients of interaction terms obtained with unstandardized regression coefficients are inaccurate (Friedrich, 1982).

Finally, to gain specificity in our effects, we replicated the foregoing analyses in three separate models evaluating different predictors or outcomes. For one, income-to-needs ratio, a broad contextual factor that is not as immediately social as family connectedness and community crime exposure, was tested as a predictor of depressive symptoms, including in its interaction with hippocampal volume and sex. Then, in two additional models, anxiety, not depressive, symptoms were treated as the outcome variable (controlling for baseline anxiety symptoms), as were externalizing, not depressive, symptoms (controlling for baseline externalizing symptoms). In the last two models, family connectedness, community crime, sex, hippocampal volume, and their interactions again served as predictors.

Results

Table 1 shows means and standard deviations of demographic, social-contextual, and volumetric measures, as well as when measures were collected. Table 2 shows bivariate correlations among these variables. Girls reported significantly higher levels of fluid IQ, as well as depressive, anxiety, and baseline externalizing symptoms. There were no sex differences in hippocampal volume adjusted for ICV. Aside from sex, no demographic variables were associated with depressive symptoms; thus, they were not included as covariates. Of note, hippocampal volume was not significantly related to either social context, reinforcing its suitability as a potential moderator (Boyce, 2016; Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001). In addition, hippocampal volume was not significantly related to either T1 or T2 depressive or other symptoms.

For our key analysis, the hierarchical linear regression model of depressive symptoms as predicted by sex, baseline depressive symptoms, social context, hippocampal volume, and their interactions was significant (R^2 = .40, F(18, 190) = 8.56, p < .001, f^2 = .67) (Table 3). Step 1 showed main effects of Sex (being female), Baseline Depressive Symptoms (more elevated symptoms), and Family Connectedness (lower connectedness), on depressive symptoms, all $ps \leq .05$; the main effect of Community Crime (higher crime) was marginally significant, p = .06. At Step 2, we tested our key hypothesis that hippocampal volume would moderate the effects of both social contexts on depressive symptoms. The expected 2-way interactions between Family Connectedness × Hippocampal Volume and Community Crime × Hippocampal Volume were significant for left (ps < .05) but not right (ps > .09) hippocampus. Finally, Step 3 indicated that sex did not moderate the main effects of Family Connectedness or Community Crime (ps > .40) nor their interactions with Hippocampal Volume (e.g., Family Connectedness × Left Hippocampal Volume × Sex, p > .10).

Because results from the regression model suggested that left, but not right, hippocampal volume was a significant moderator of the effects of social context on depressive symptoms, we directly tested for differences between left and right hippocampus in their moderating roles, thus assessing laterality effects. Following Cohen, Cohen, West, & Aiken (2013), we applied the following equation to statistics from the previous model:

$$t_{df} = \frac{b_1 - b_2}{\sqrt{s.e._{b_1}^2 + s.e._{b_2}^2 - 2cov(b_1, b_2)}}$$

wherein b_1, b_2 are the regression coefficients of the interaction terms involving left vs. right hippocampal volume, $s.e._{b_1}^2$, $s.e._{b_2}^2$ are the squared standard errors of these regression coefficients, $cov(b_1, b_2)$ is the covariance between the regression coefficients, and df is the sample size minus the number of predictors at the relevant step minus 1. Thus, according to this equation, $b_1 - b_2$ is the difference between the moderating effects of left vs. right hippocampal volume, follows a t distribution, and is tested for being significantly greater than zero. We found that left, as compared to right, hippocampal volume was a significantly or nearly significantly greater moderator of the effect of both social contexts on depressive symptoms, that is, of family connectedness, $t(198) = -1.96$, p = .05, and community crime exposure, $t(198) = 2.51$, p = .01.

Subsequently, the interaction of each social context with left hippocampal volume was probed using simple slopes analysis. The significant interaction between Family Connectedness × Left Hippocampal Volume was interpreted by analyzing the simple regression lines for adolescents grouped by hippocampal volume. For adolescents with high (+1 SD), average (mean), and low (−1 SD) hippocampal volumes, equations were used to plot values of depressive symptoms at high (+1 SD), average (mean), and low (−1 SD) levels of family connectedness (Figure 1). Slopes of the regression lines were significantly different from zero for adolescents with average ($\beta = -.29$, $t = -4.90$, p < .001) and larger-than-average ($\beta = -.47$, $t = -5.12$, p < .001) left hippocampal volumes. Conversely, adolescents with smaller-than-average left hippocampal volumes showed no association between family connectedness and levels of depression ($\beta = -.11$, $t = -1.30$, p = .19). These

results suggested that, with regard to their depressive symptoms, adolescents with larger left hippocampal volumes were more sensitive to the protective effects of higher family connectedness and adverse effects of lower family connectedness, but that adolescents with smaller hippocampal volumes were relatively unaffected by level of family connectedness, whether for better or for worse (Figure 1).

Likewise, the significant interaction between Community Crime × Left Hippocampal Volume was interpreted by analyzing the simple regression lines for adolescents grouped by hippocampal volume (Figure 1). Slopes of the regression lines were significantly different from zero for adolescents with average ($\beta = .20$, $t = 2.63$, $p < .01$) and larger-than-average ($\beta = .40$, $t = 3.58$, $p < .001$) left hippocampal volumes. Conversely, adolescents with smaller-than-average left hippocampal volumes showed no association between community crime and levels of depression ($\beta = -.01$, $t = -.09$, $p = .92$). These results suggested that, with regard to their depressive outcomes, adolescents with larger left hippocampus volumes were more sensitive to the negative effects of community crime, whereas adolescents with lower hippocampal volumes were relatively unaffected by this facet of their social environment (Figure 1).

Finally, we replicated the foregoing analyses, assessing different predictors or outcomes. First, we tested income-to-needs ratio as a predictor of depressive symptoms. The model ($R^2 = .29$, $F(12, 186) = 7.72$, $p < .001$) showed a main effect of baseline depressive symptoms ($\beta = .52$, $t = 8.33$, $p < .001$) at Step 1 and no significant model improvements or 2- or 3-way interactions with hippocampal volume at Steps 2 and 3. Second, we tested our original model's prediction of anxiety symptoms, controlling for baseline anxiety symptoms (see Table S1 in the Supplemental Material available online). The model ($R^2 = .31$, $F(18, 190) = 6.21$, $p < .001$) showed main effects of sex and baseline anxiety symptoms at Step 1 and no significant model improvements at Steps 2 and 3 (even if a significant Community Crime × Right Hippocampal Volume interaction at Step 3 suggested that, for males, there was similar hippocampal moderation of the effect of community crime on anxiety symptoms as that seen for depressive symptoms). Third, we tested the model's prediction of externalizing symptoms, controlling for fluid IQ (based on bivariate correlations) and baseline externalizing symptoms (see Table S2 in the Supplemental Material available online). The model ($R^2 = .14$, $F(19, 187) = 2.74$, $p < .001$) showed main effects of fluid IQ, baseline externalizing symptoms, and family connectedness at Step 1 and no significant model improvements at Steps 2 and 3 (even if a significant Family Connectedness × Left Hippocampal Volume interaction at Step 2 showed similar hippocampal moderation of the effect of family connectedness on externalizing symptoms as that seen for depressive symptoms).

Post hoc analyses

Alternative hypotheses to the moderation model that drove our research question were plausible. Thus, we tested these hypotheses to help us gain temporal and, to some extent, causal specificity in interpreting our findings.

Hippocampal volume as a mediator—Although hippocampal volume might have mediated, rather than moderated, the effects of social context on depressive symptoms, bivariate correlations (Table 2) suggested that social-contextual exposures did not significantly predict hippocampal volumes, nor did hippocampal volumes significantly predict depressive outcomes. Thus, conditions for considering mediation were not met.

Hippocampal volume as a state marker—Although hippocampal volume might have reflected concurrent levels of depressive symptoms, bivariate correlations (Table 2) suggested that hippocampal volumes were not significantly related to depressive outcomes assessed concurrently.

Hippocampal volume as a scar—Although hippocampal volume may have reflected previous levels of depressive symptoms, bivariate correlations (Table 2) indicated that hippocampal volumes were not significantly related to previous depressive symptoms assessed six months prior.

Ruling out the above possibilities, our results support the hypothesis that hippocampal volume may serve as a "vulnerability" marker that reflects greater susceptibility to the effects of social context, whether positive or negative.

Discussion

In this investigation, we found evidence that hippocampal volume interacted with two important experiential social contexts for youths – their sense of family connectedness and exposure to crime in the community – to predict depressive symptom severity in late adolescence. Specifically, adolescents with larger left hippocampal volumes showed more sensitivity to the protective effect of family connectedness and harmful effect of community crime on change over time in their depressive symptoms. Indeed, by accounting for baseline depressive symptoms concurrent with social contexts, that is, six months prior to assessment of hippocampal volume and depressive outcomes, we were able to show a prospective effect of each social context that was moderated by hippocampal volume. With one social context centered in the home, and the other, in the community, our study captured a substantial range of the adolescent social milieu whose effects were magnified by volume of the left hippocampus. Moreover, results suggested that these social contexts provided independent pathways to depression that were modulated by hippocampal volume, and more so by left than right hippocampal volume. Despite the robust sex differences consistently found in depression, including in this study, none of these associations were moderated by sex. Finally, our models were not significant when assessing a less precisely "social" contextual predictor (income-to-needs ratio) or other outcomes (anxiety, externalizing).

Conceptually, alternative hypotheses to our moderation model were plausible. We ruled out these alternatives in post-hoc analyses. For example, because hippocampal volume may fluctuate with social-contextual exposures (Luby et al., 2012; Whittle et al., 2013) and with onset and remission of depression (Phillips, Batten, Tremblay, Aldosary, & Blier, 2015), hippocampal volume may have mediated the effects of social context on depressive symptoms. However, conditions for considering mediation were not met. Likewise, we

found no support for hippocampal volume as a "state" marker of depressive symptoms or as a "scar" (e.g., Chan et al., 2016) that reflected previous history of depressive symptom severity. Rather, our findings suggest that hippocampal volume may be viewed as a "vulnerability" marker that reflects susceptibility to social context.

The lack of main effects for hippocampal volume on depression symptoms is consistent with the conflicting evidence regarding hippocampal volume and its role in clinical, subclinical, or risk for MDD in adolescence. As a moderator, hippocampal volume should not be expected to have a straightforward relation with depression but rather to confer vulnerability to depression or protection against it depending on social context, especially in susceptible adolescents with larger volumes. For these adolescents, experience in different social environments appears to have a greater beta weight for adolescents' mental health, as evidenced in their depressive symptoms (or lack thereof). Conversely, according to our findings, adolescents with smaller volumes might be considered relatively impervious to the effects of social context on depressive symptoms. This was not because adolescents with smaller volumes were at floor or ceiling in their depressive symptoms, as indicated by the lack of main effects of hippocampal volume on depressive symptoms. Due to the observation of moderation, these findings give general support to neurobiological susceptibility models (Ellis et al., 2011) and particular support to a recent iteration of this framework that focuses on neurobiological susceptibility in adolescence as reflected in properties of the brain (Schriber & Guyer, 2016). Indeed, the earlier foundational models (Ellis et al., 2011) generally propose that susceptible individuals are more susceptible due to genetic, temperamental, and other biological reasons. Here, we reveal a possible marker of susceptibility as indexed by a brain-based measure.

Involvement of the hippocampus in depression from a susceptibility perspective is unsurprising given the role of the hippocampus in stress, learning, memory, and more specific cognitive processes such as rumination (Mandell et al., 2014). Yet, although a smaller hippocampus has been implicated in MDD, our research finds a role for a larger hippocampus. Consistent with the link between a larger hippocampus and established susceptibility factors from other systems (Barrós-Loscertales et al., 2006; Pruessner et al., 2005), a larger hippocampus may indicate a greater capacity to bind contextual elements across space and time (Ashtari et al., 2011; Clayton & Krebs, 1994; Ergorul & Eichenbaum, 2004; but see Van Petten, 2004). Even for basic abilities like spatial navigation, species that require complex spatial maps have larger hippocampi than comparable species that do not (Clayton & Krebs, 1994). Similar data have been generated for London taxi-cab drivers, who must learn and act upon the intricate roadway system of the city (Maguire et al., 2000). In the context of our study, such findings may suggest that larger volumes reflect greater experience-based function in susceptible adolescents, who theoretically process their social contexts more deeply over long periods of time. These effects may be prospective. Tse et al. (2014) found that mice characterized as susceptible to social defeat based on their manifestation of social avoidance and withdrawal behaviors were those who had larger left hippocampal volumes at baseline; hippocampal volumes post-stressor were not related to social behavior. Likewise, Whittle et al. (2011) found that adolescent girls who showed greater sensitivity in their depressive symptoms to low and high maternal aggressiveness were those who started with larger hippocampal volumes a year prior.

It is important for the current findings to be considered from a developmental perspective. It is possible, for example, that larger hippocampal volumes index susceptibility to social context in adolescence but not in childhood or adulthood. Indeed, because the hippocampus is still developing across adolescence into adulthood (Dennison et al., 2013; Gogtay et al., 2006), when smaller hippocampal volumes in MDD are more commonly observed (McKinnon, Yucel, Nazarov, & MacQueen, 2009; Videbech & Ravnkilde, 2004), it may be that, in adulthood, hippocampal volume reflects a delayed scarring effect of social stress and depression through increased atrophy and diminished neurogenesis in the hippocampus (Chan et al., 2016). Interestingly, in the rodent study mentioned above (Tse et al., 2014), although baseline left hippocampal volumes were larger in late adolescent/young adult mice that were defined as more susceptible to social defeat based on subsequent behavior, the left hippocampal volumes of control and resilient mice showed increases pre- to post-stressor, whereas those of susceptible mice *decreased* or stayed the same. Thus, the normal trajectory of hippocampal growth appeared to be disrupted or blunted in susceptible mice once they were acutely and chronically stressed, a finding consistent with the neurotoxicity account of hippocampal volume decrease in depression (Sapolsky et al., 2002).

Another possibility regarding hippocampal volume and the pathophysiology of depression in adolescence is that there are multiple pathways to depression involving hippocampal volume. One may be characterized by a larger hippocampus that confers greater social-contextual sensitivity, as observed in our study. Another pathway may be defined by smaller hippocampal volumes and familial risk for depression. For example, adolescent girls at heightened risk for developing depression due to maternal history of recurrent depression showed smaller hippocampal volumes than girls with no such history (Chen, Hamilton, & Gotlib, 2010). Adding consideration of social context, a more recent study suggested that genetic vulnerability to adolescent depression, as conferred by allelic variation in the serotonin transporter gene, was mediated by smaller bilateral hippocampal volumes and expressed only in conditions of high parental aggression and/or low positive parenting (Little et al., 2015). Thus, there may be multiple paths to depression that involve interplay between hippocampal volume and the environment, with one weighted more by direct genetic risk for depression and another by greater sensitivity to positive and negative environments and the learning they engender (e.g., that one is safe and valued vs. unprotected and unimportant, with implications for depression).

Our findings also contribute to a line of evidence that links depression and other stress-related psychopathology to abnormalities of the left hippocampus in particular. Smaller hippocampal volumes in adults with a history of childhood maltreatment have been localized to the left, especially in females (Vythilingam et al., 2002). In adolescents with a history of maltreatment, larger left, but not right, hippocampal volumes were found, as well as truncated growth in the same that was associated with experience of psychopathology (Whittle et al., 2013). Regarding depression, adult patients with remitted MDD as compared to non-depressed adults showed 19% smaller volumes of left hippocampus but no differences in right hippocampus (Bremner et al., 2000). Likewise, a study showing smaller hippocampal volumes in adolescents with vs. without MDD found the effect more strongly localized to the left (and a positive association between left hippocampal volume and illness duration in the depressed group) (MacMaster & Kusumakar, 2004). With regard to

susceptibility and consistent with left hemispheric specialization for language and narrative (O'Keefe & Nadel, 1978; Vigneau et al., 2006), involvement of the left hippocampus may promote integrating and reconstructing spatiotemporal contexts (Burgess et al., 2002; Iglói, Doeller, Berthoz, Rondi-Reig, & Burgess, 2010) and even identifying with social agents within them (Cheetham, Hanggi, & Jancke, 2014; Frisk & Milner, 1990). Lateralization of susceptibility could also relate to greater expression of corticosteroid receptors in the left hippocampus (Hou, Yang, & Yuan, 2013).

Investigation of the observed moderated effects will benefit from research that unpacks the underlying mechanisms. For example, the link between crime exposure and adolescent depression has been found to be mediated, in part, by increased feelings of hopelessness, unpredictability, uncontrollability, and lack of purpose in life (DuRant, Getts, Cadenhead, Jean, & Woods, 1995). Thus, it would be informative, particularly for treatment efforts, to determine if among adolescents living in crime-ridden communities, those with larger hippocampal volumes manifest these depressogenic social-cognitive schemas to a greater extent. With a focus on externalizing outcomes and a genetic index of social susceptibility, one study found that susceptible as compared to non-susceptible African Americans demonstrated more aggression and commitment to the street code (i.e., informal set of rules that govern behavior in urban contexts) when exposed to violent neighborhoods, but *less* aggression and commitment to the street code in more favorable environments (Simons et al., 2011). Indeed, the hippocampus may contribute to self-reflective and, often, social acts such as self-projection (Spreng et al., 2008) and rumination (Mandell et al., 2014), including via connectivity of the hippocampus within the default mode network (Greicius, Supekar, Menon, & Dougherty, 2009; Price & Drevets, 2009; Sambataro et al., 2014). Thus, through brain-based susceptibility factors, like the hippocampus, social contexts may not only get "under the skin" but "into the mind." For this reason, adolescents with larger left hippocampus who encounter supportive family environments may be more likely to see themselves as safe, valued, loved, and supported, all guarding against depression (Campos et al., 2014).

Our study was not without limitations. First, although the inclusion of males and females allowed us to test for gender interactions, the uneven distribution of gender across the continuum of depressive symptom severity may have limited our power to detect these interactions. Second, by focusing on global volume of the hippocampus, our study cannot speak to whether subregions of the hippocampus (e.g., anterior, posterior) were differentially responsible for moderating the effect of social context on adolescent depression. Notably, subregions of the hippocampus are functionally distinct (Fanselow & Dong, 2010) and have different time courses of development (Gogtay et al., 2006). Third, we assessed hippocampal volume at only one time point, treating individual differences in hippocampal volume as a susceptibility factor that was taken to be relatively stable. However, the hippocampus is a plastic structure that is shaped by earlier social contexts (Luby et al., 2012; Luby, Belden, Harms, Tillman, & Barch, 2016; Tupler & De Bellis, 2006; Whittle et al., 2013), and future work should use a longitudinal design to disentangle the temporal course of our observed effects. Finally, although the use of a Mexican-origin sample was a strength of our study (i.e., given the heightened risk for depression in this group and the direct relevance of our social-contextual predictors), it is unknown whether results would generalize to other racial/

ethnic groups. At the same time, behavioral work has suggested that even in the face of differential emphasis by culture, fundamental social contexts – such as perceiving strong family bonds — impact people quite similarly (Campos et al., 2014). There is no reason to suspect underlying differences in the biology, either.

Ultimately, the current research marks an important step toward better understanding the complex interactive role of biological and environmental factors in both risk and resilience to depressive symptoms in adolescence. Adolescence is a time of increased social sensitivity and, accordingly, a time of increased vulnerability to depression across all adolescents (Davey et al., 2008). However, some adolescents may be more neurobiologically sensitive than others to their social environments, for better and for worse (Schriber & Guyer, 2016). This was suggested by our current findings, in which adolescents with larger left hippocampal volumes showed more or less severe depressive symptoms than adolescents with smaller volumes, depending on the supportiveness and/or safety perceived in their social environments. As adolescents with more severe depressive symptoms are at greater risk of developing depressive disorders in adolescence and beyond, our results have important implications for prevention and intervention strategies aimed at depressive disorders in adolescence. As researchers continue to find ways to make the clinical application of neuroimaging findings more feasible, our results deepen understanding of risk for depression in adolescence, offering clues about for whom and how social context plays a role.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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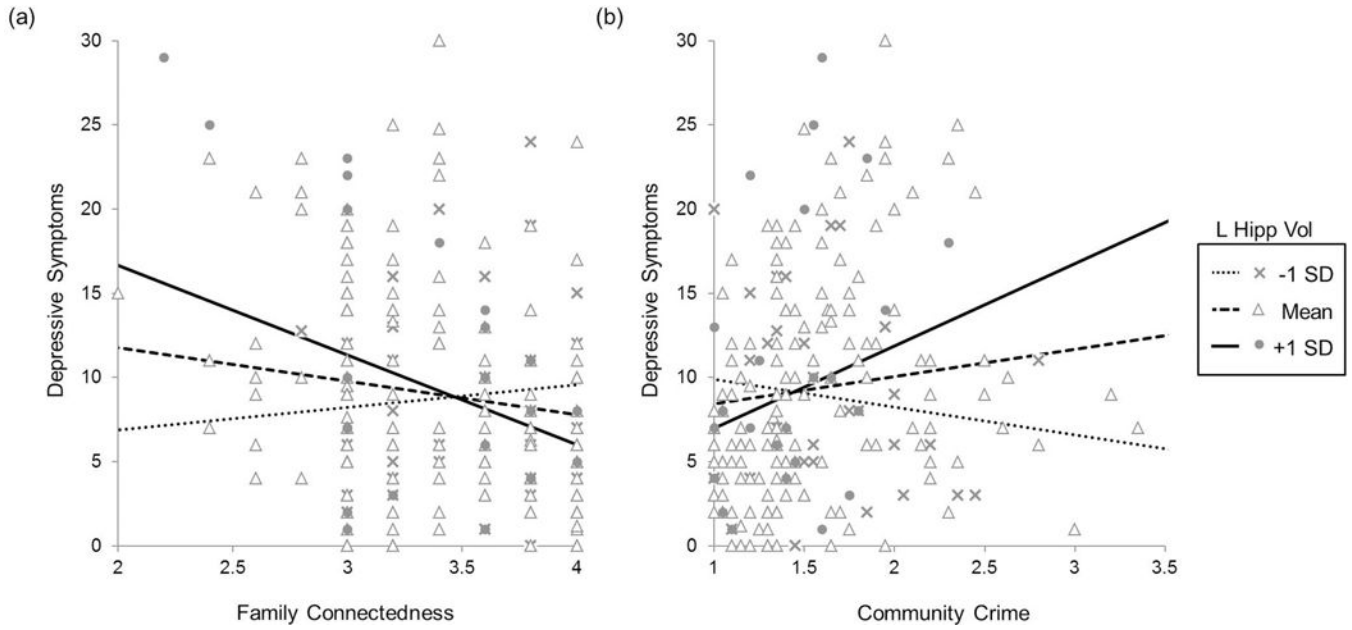

Figure 1.

Plots of simple slopes showing the interaction of adolescents' left hippocampal volumes with their (a) sense of family connectedness and (b) exposure to community crime, respectively, in the prediction of depressive symptoms, controlling for sex and baseline depressive symptoms. Plots of simple slopes when not including these covariates were similar to those above (e.g., slopes at same relative position, approximate angle, and placement along axes). For (a) and (b), slopes were significant for adolescents with average ("Mean") and larger-than-average ("+1 SD") left hippocampal volumes.

Table 1

Descriptive Statistics and Timing of Demographic, Behavioral, and Brain Volume Measures

Measure	Time Point	Grade	*M*	*SD*
Age (At Scan)	T2	11–12	17.17	.41
Verbal IQ	Recruitment	5	91.53	12.32
Fluid IQ	“	“	94.75	14.98
Income to Needs	T1	11	1.27	.82
Family Connectedness	“	“	3.35	.44
Community Crime	“	“	1.55	.45
Baseline Symptoms	“	“	–	–
Depressive (Composite)	“	“	.00	1.00
MDD Symptom Counts (C DISC)	“	“	1.46	.43
General Distress (MASQ)	“	“	3.03	.60
Anhedonic Depression (MASQ)	“	“	3.53	3.73
Anxiety (Composite)	“	“	.00	1.00
GAD (C DISC)	“	“	1.44	1.73
Social Anxiety (C DISC)	“	“	2.52	3.37
Panic Disorder (C DISC)	“	“	.27	.50
Externalizing (Composite)	“	“	.00	1.00
CD (C DISC)	“	“	1.23	1.65
ODD (C DISC)	“	“	1.79	2.21
Symptoms	T2	11–12	–	–
Depressive (CDI 2)	“	“	9.23	6.62
Anxiety (SCARED)	“	“	.47	.33
GAD	“	“	.57	.44
Social Anxiety	“	“	.72	.48
Panic Disorder	“	“	.27	.30
Externalizing (SDQ conduct)	“	“	1.38	.32
L Hipp, mm^3	“	“	4198.19	555.50
R Hipp, mm^3	“	“	4246.69	437.24
ICV, mm^3	“	“	1459735.95	167428.74
L Hipp/ICV, %	“	“	2.89×10^{-1}	$.37 \times 10^{-1}$
R Hipp/ICV, %	“	“	2.93×10^{-1}	$.29 \times 10^{-1}$

Note. $n = 209$. T1 = Time 1. T2 = Time 2. IQ = Intelligence Quotient. C-DISC = Computerized Diagnostic Interview Schedule for Children (Shaffer et al., 2000). MASQ = Mood and Anxiety Symptom Questionnaire (Watson et al., 1995). CDI-2 = Children’s Depression Inventory-2 (Kovacs, 1984). CD = Conduct disorder. ODD = Oppositional defiant disorder. SCARED = Screen for Child Anxiety Related Emotional Disorders (Birmaher et al., 1997). SDQ = Strengths and Difficulties Questionnaire (Goodman, Meltzer, & Bailey, 1998). L = Left. R = Right. Hipp = Hippocampus. mm^3 = Cubic Millimeters. ICV = Intracranial Volume. % = Percent of Intracranial Volume.

Table 2

Zero-Order Correlations Among Demographic, Behavioral, and Brain Volume Measures

Measure	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Sex	–														
2. Age	.00	–													
3. Verbal IQ	−.09	−.10	–												
4. Fluid IQ	.16*	−.13†	.17*	–											
5. Income-to-Needs	.04	−.02	.15*	.02	–										
6. Family Connectedness	.14†	.05	.09	.05	.05	–									
7. Community Crime	.04	−.06	.09	.02	−.22**	.16*	–								
8. T1 Depressive Symptoms	.26**	.01	−.07	−.12†	−.08	−.26**	.16*	–							
9. T2 Depressive Symptoms	.24**	−.11	−.08	−.05	.04	−.26**	.20**	.57**	–						
10. T1 Anxiety Symptoms	.39**	−.01	−.06	−.00	−.01	−.08	.04	.57**	.48**	–					
11. T2 Anxiety Symptoms	.32**	−.01	−.01	.04	.01	−.14*	.08	.48**	.62**	.52**	–				
12. T1 Externalizing Symptoms	.19**	−.02	−.03	−.02	−.08	−.09	.46**	.34**	.26**	.28**	.21**	–			
13. T2 Externalizing Symptoms	.03	−.06	−.10	−.15*	−.06	−.23**	.18**	.29**	.45**	.13†	.22**	.28**	–		
14. L Hipp/ICV, %	.11	−.01	.05	.01	.03	−.11	−.07	.03	.10	.06	.12†	−.03	.05	–	
15. R Hipp/ICV, %	.10	−.06	.00	−.06	−.05	−.13†	−.07	.03	.13†	.01	.13†	−.11	.10	.63**	–

Note. n = 209. L = Left. R = Right. Hipp = Hippocampus. ICV = Intracranial Volume. % = Percent of Intracranial Volume.

$^{\dagger}p < .10$;

$^{*}p < .05$;

$^{**}p < .01$.

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Table 3

Regression of Depressive Symptoms Predicted by Baseline Depressive Symptoms, Sex, Family Connectedness, Community Crime, and Left and Right Hippocampal Volumes

Regressions	**β**	***t***	***p***	***df*1**	***df*2**	**Δ*F***	**ΔR^2**	**Sig Δ*F***	**f^2**
Step 1:				6	202	19.86	.37	<.01	.59
Sex	.12	2.07	.04						.02
Baseline Depressive Symptoms	.48	7.86	<.01						.30
Family Connected	−.13	−2.17	.03						.02
Community Crime	.11	1.90	.06						.01
L Hipp	.00	.05	.96						.00
R Hipp	.09	1.30	.20						.01
Step 2:				10	198	5.62	.06	<.01	.69
Sex	.12	2.02	.04						.01
Baseline Depressive Symptoms	.49	8.24	<.01						.31
Family Connected	−.13	−2.19	.03						.02
Community Crime	.12	2.09	.04						.01
L Hipp	−.01	−.10	.92						.00
R Hipp	.10	1.40	.16						.01
Family Connected × L Hipp	−.22	−2.70	<.01						.05
Family Connected × R Hipp	.06	.80	.43						.00
Community Crime × L Hipp	.19	2.69	<.01						.04
Community Crime × R Hipp	−.12	−1.68	.09						.01
Step 3:				18	190	.55	.01	.82	.66
Sex	.12	2.04	.04						.02
Baseline Depressive Symptoms	.50	8.17	<.01						.33
Family Connected	−.12	−1.91	.06						.01
Community Crime	.12	2.13	.04						.01
L Hipp	−.01	−.11	.91						.00
R Hipp	.09	1.19	.24						.01
Family Connected × L Hipp	−.25	−2.91	<.01						.06
Family Connected × R Hipp	.10	1.15	.25						.01

Regressions	β	*t*	*p*	*df1*	*df2*	Δ*F*	ΔR^2	Sig Δ*F*	f^2
Community Crime × L Hipp	.21	2.56	.01						.04
Community Crime × R Hipp	−.12	−1.40	.16						.01
Family Connected × Sex	−.02	−.26	.80						.00
Community Crime × Sex	.05	.85	.40						.00
L Hipp × Sex	.04	.58	.56						.00
R Hipp × Sex	.02	.21	.84						.00
Family Connected × L Hipp × Sex	.13	1.50	.14						.02
Family Connected × R Hipp × Sex	−.12	−1.41	.16						.01
Community Crime × L Hipp × Sex	.04	.54	.59						.00
Community Crime × R Hipp × Sex	.00	−.04	.97						.00

Note. *n* = 209. Family Connected = Family Connectedness. L = Left. R = Right. Hipp = Hippocampus.