



PAPER

What are the links between maternal social status, hippocampal function, and HPA axis function in children?

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Abstract

The association of parental social status with multiple health and achievement indicators in adulthood has driven researchers to attempt to identify mechanisms by which social experience in childhood could shift developmental trajectories. Some accounts for observed linkages between parental social status in childhood and health have hypothesized that early stress exposure could result in chronic disruptions in hypothalamic-pituitary-adrenal (HPA) axis activation, and that this activation could lead to long-term changes. A robust literature in adult animals has demonstrated that chronic HPA axis activation leads to changes in hippocampal structure and function. In the current study, consistent with studies in animals, we observe an association between both maternal self-rated social status and hippocampal activation in children and between maternal self-rated social status and salivary cortisol in children.

Introduction

There is a strong association between parental social standing and indicators of child health and achievement across a number of variables, indicating that family social standing in childhood impacts child well-being (Benjet, Borges & Medina-Mora, 2010; Hackman & Farah, 2009; Melchior, Moffitt, Milne, Poulton & Caspi, 2007; Poulton, Caspi, Milne, Thomson, Taylor, Sears & Moffitt, 2002; Raizada & Kishiyama, 2010). Social standing can be measured via objective measures of socioeconomic status (SES), such as individual's income, educational attainment, and job status. Subjective social standing (SSS) measures social standing by directly asking participants for their perception of their standing relative to their community or country (e.g. compared to others in the United States). Both SES and SSS,

measured in adulthood or adolescence, are reliably associated with health outcomes (Adler, Epel, Castellazzo & Ickovics, 2000; Adler, Boyce, Chesney, Cohen, Folkman & Kahn, 1994). In some cases SSS predicts variance in particular mental health outcomes after controlling for objective measures of SES (Franzini & Fernandez-Esquer, 2006; Goodman, Huang, Schafer-Kalkhoff & Adler, 2007), indicating that SSS may account for the experience of low social standing over and above objective SES (but see also, Macleod, Davey Smith, Metcalfe & Hart, 2005).

In childhood, family social standing can be estimated by measuring SES or SSS in parents. Low parental social standing is associated with a higher incidence of risky health behaviors and lower academic performance in children (Marmot, Smith, Stansfeld, Patel, North, Head, White, Brunner & Feeney, 1991; Cohen, Doyle, Turner,

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Alper & Skoner, 2004; Miller & Chen, 2007; Melchior *et al.*, 2007; Pollitt, Rose & Kaufman, 2005; Ben-Shlomo & Kuh, 2002).

The association of parental social status with multiple health and achievement indicators in children has inspired the search for mechanisms by which social experience in childhood could shift developmental trajectories resulting in differences in health and well-being. Some accounts for observed linkages between childhood social status and health have focused on structural or material exposures, such as nutrition and health care. However, these variables do not explain the broad association of parental social status with health, health behaviors, and achievement, nor do they account for the graded relation between social status and health outcomes that exist even in the context of adequate health care and nutrition (Adler *et al.*, 1994).

Low family social status is associated with increased exposure to childhood adversity, including exposure to violence in the neighborhood and at home, disorganization in school environments, environmental toxins, crowding, and noise (Evans, 2006; Evans & Kantrowitz, 2002; Evans & Kim, 2010). Exposure to adversity in childhood or adulthood is linked to activation of the stress response. The stress response is a physiological response to situations in which the individual experiences challenges to his/her well-being that are larger than his/her resources for coping. The stress response includes activation of the hypothalamic-pituitary-adrenal (HPA) axis. Elevated HPA axis activity results in increased levels of circulating cortisol and provides one biological index of stress.

Several studies have examined activity of the HPA axis in humans by measuring circulating free cortisol in saliva. Cortisol measured in this way has been previously linked with levels of free cortisol in the blood (Laudat, Cerdas, Fournier, Guiban, Guilhaume & Luton, 1988). Salivary cortisol can be collected at 'baseline', after a participant arrives at a laboratory, and/or after a stress task designed to elevate HPA axis activity is administered to the participant. Cortisol typically follows a diurnal rhythm where it is greatest in the morning and declines across the course of the day. Because of this pattern, cortisol should be collected at approximately the same time of day across participants. Several studies have linked levels of salivary cortisol with social status in childhood. While some of these studies have identified negative associations between salivary cortisol and social status (Lupien, King, Meaney & McEwen, 2000), these associations are quite variable, and there are several instances where diurnal cortisol rhythms are found to be flatter or blunted in children from poor families (Fuller-Rowell, Doan & Eccles, 2012), cortisol reactivity is found

to be lower (Sturge-Apple, Davies, Cicchetti & Manning, 2012) or where baseline cortisol is *positively* associated with poverty (Fernald, Burke & Gunnar, 2008). Further, it is not uncommon to observe blunted cortisol responses and flatter rhythms not just in association with social status, but also in children exposed to known adversities such as institutionalization (Gunnar & Vazquez, 2001), natural disaster (Vigil, Geary, Granger & Flinn, 2010), and removal from the family of origin into foster care (Bruce, Fisher, Pears & Levine, 2009). Thus, while these findings constitute evidence that stress exposure serves as one pathway by which family social status in childhood influences health, there is less clear evidence regarding the direction of the effect of social status on cortisol. There have been several formal presentations of the hypothesis that HPA axis function is dysregulated following adversity exposure, which is likely the best description of the association between salivary cortisol and adversity experiences in childhood (McEwen & Gianaros, 2010; Shonkoff, Boyce & McEwen, 2009; Obradovic, in press).

In contrast to work in humans, where random assignment to rearing environment is quite difficult, studies in animals have examined the impact of randomization to chronic stress exposure on activation to the HPA axis with relative ease. In rodents, chronic activation of the HPA axis has known impacts on neural structures. Studies in adult rats have demonstrated that exposure to chronic stress results in reductions in dendritic spines in the CA3 region of the hippocampus (McEwen, 2007). In the context of stress exposure, the hippocampus provides a negative feedback mechanism, which modifies the HPA axis response (as reviewed in Kim & Yoon, 1998). The role of the hippocampus in dampening the stress response may be one reason it is impacted by chronic HPA axis activation. When immature rodents are exposed to stress early in life, they exhibit dysregulated HPA function as adults and decreased hippocampal volume in adulthood (Liu, Diorio, Tannenbaum, Caldji, Francis, Freedman, Sharma, Pearson, Plotsky & Meaney, 1997; see Sanchez, Liu, et al., 1997; for review, see Sanchez, Ladd, & Plotsky, 2001). Similarly, in studies of human adults, stress-related psychopathology, such as post-traumatic stress disorder (PTSD), correlate with decreased hippocampal volume (Campbell, Marriott, Nahmias & MacQueen, 2004; Geuze, Vermetten & Bremner, 2004; Kitayama, Vaccarino, Kutner, Weiss & Bremner, 2005; Sheline, Gado & Kraemer, 2003; Smith, 2005) and altered activity (Bremner, 2006). In healthy middle-aged adults, self-reported stress over a 12-year period was associated with decreases in hippocampal grey matter volume acquired at year 13 (Gianaros, Jennings, Sheu, Greer,

Kuller & Matthews, 2007). In addition, adults who were exposed to abuse during childhood have decreased hippocampal volume (Bremner, Randall, Vermetten, Staib, Bronen, Mazure, Capelli, McCarthy, Innis & Charney, 1997).

When these same outcomes are observed in children, the association between hippocampal volume and stress exposure is more equivocal. For example, children exposed to abuse during childhood do not differ in hippocampal volume from their non-abused peers (De Bellis, Hall, Boring, Frustaci & Moritz, 2001; Woon & Hedges, 2008). One explanation for this discrepancy is that the developmental timing of assessment matters, that is, the structural impact of stress on hippocampal volume does not occur until adulthood. It is likely that this impact would be preceded by other neural changes in childhood, such as volume and structure differences in the amygdala (Tottenham & Sheridan, 2009). Another potential explanation is that, in humans, measurement of volumetric data using structural magnetic resonance imaging (MRI) is variable and prone to error. More sensitive measurements, such as examining the function of the hippocampus using functional MRI (fMRI), may permit the detection of stress-related differences. In the current study we examine hippocampal function using fMRI (see Supplementary Information for hippocampal volume results).

The hippocampus is integral to long-term memory formation (Gabrieli, 1993; Gabrieli, Cohen & Corkin, 1988), thus damage to the hippocampus via exposure to stress would be likely to disrupt both stress reactivity and memory formation. When the hippocampus is removed surgically, encoding of long-term memories is disrupted resulting in anterograde amnesia: new memories cannot be formed (Markowitsch & Pritzel, 1985; Brizzolara, et al., 2003; Temple & Richardson, 2004; Vargha-Khadem, Gadian, Watkins, Connelly, Van Paesschen & Mishkin, 1997). Within long-term memory, it is argued that the hippocampus is specifically important in relational memory, memory in which two items are 'bound' together in space or time, the result of hippocampally driven co-activation of representations in cortex (Eichenbaum, 1999). Evidence for the importance of hippocampal function in memory formation in childhood has been observed across several neuroimaging studies (Ofen, Kao, Sokol-Hessner, Kim, Whitfield-Gabrieli & Gabrieli, 2007; Chai, Ofen, Jacobs & Gabrieli, 2010; Ghetti, DeMaster, Yonelinas & Bunge, 2010; Paz-Alonso, Ghetti, Matlen, Anderson & Bunge, 2009).

As reviewed above, evidence has accumulated that social status is associated with an increased risk of exposure to stressful circumstances in childhood. In animals there is a large body of literature linking stress

exposure to hippocampal structure and function, leading to the proposition that a similar mechanism exists in humans. It is hypothesized that disruption of the HPA axis response underlies the social status gradient in health and achievement partially via neural impacts on the hippocampus. However, evidence in support of this mechanism is as yet equivocal. There appears to be a link between HPA axis regulation and social status in children, however evidence for both increased and decreased HPA axis activity has been observed. Additionally, a few studies have reported associations between social status in childhood and long-term memory function have been observed (Farah, Shera, Savage, Betancourt, Giannetta, Brodsky, Malmud & Hurt, 2006). However, no study to date has identified associations between hippocampal structure or function, social status in childhood, and HPA axis function. In the current study we assess the effect of social status on hippocampal function during a relational memory task in children ages 8–12 years. In this same sample we measure salivary cortisol, allowing measurement of this potential pathway by which social status comes to affect child health.

Methods

Participants

Forty right-handed child participants were included in this study (ages 8.3–11.8 years, mean (M) = 9.83; 19 female). All children completed a two-subscale version of the Weschler Abbreviated Scale of Intelligence (WASI, Range: 88–147, M = 113.5). Two participants were excluded from all analyses because they had an IQ lower than 80. Twenty-two children were able to participate in the fMRI portion of the study due to external constraints on fMRI scanning such as scheduling and funding. Of these 22, one was excluded due to IQ (above) and two were unable to participate due to claustrophobia. Thus, of the original 40 participants, 19 successfully participated in an fMRI session (ages 8.3–11.8 years, mean (M) = 9.82; 8 female).

Children included in the fMRI study did not differ from the total group (two-sample t -tests) in age ($t(36) = -.16$, $p = .87$), IQ ($t(36) = .60$, $p = .55$), income-to-needs ratio ($t(35) = .17$, $p = .86$), maternal education ($t(36) = -.14$, $p = .89$), or maternal SSS ($t(36) = -.45$, $p = .66$). Because salivary cortisol was an outcome measure and can be influenced by health and medication, all participants were given a health questionnaire to assess current health and medication use. Despite this precaution, one child had implausibly high salivary cortisol values. Four other participants did not have cortisol measurements

(experimenter error) during the TSST-C session. These five participants are excluded from all analyses using this cortisol value (final N for analyses with cortisol = 33).

All mothers completed the MacArthur SES questionnaire. This questionnaire allows parents to report their education (Range: 10–20 years, $M = 16.2$, $SD = 2.3$), combined family income, and SSS. One mother chose not to divulge her income, and income-to-needs is not reported for this participant. For each family, income-to-needs ratio (Range: .19 to 5.46 ($M = 2.9$; $SD = 1.5$)) was calculated by dividing the income of the participating family by the national poverty-level income for a family of the same size (using 2000 census data; <http://www.census.gov/>). Mother's subjective social standing (Range: 1–9, $M = 6.5$; $SD = 1.8$) was rated on a scale depicted as a ladder from 1 (lowest) to 10 (highest) compared to others in the United States. Age and gender are covariates in all subsequent analyses.

Each child's family received financial compensation (approximately \$20/hour) for their participation. Informed consent was obtained for all participating families and the Committee for Protection of Human Subjects at Children's Hospital Boston approved all experimental procedures.

Materials and methods

All subjects participated in two sessions. The first session lasted for 3 to 4 hours, during which the WASI IQ test and a Trier Social Stress Task for children (TSST-C) were administered. The TSST-C alone lasted approximately 1 hour. Within 1 to 4 weeks, approximately half of the participants returned to complete the fMRI study. During this session, which lasted 1 to 2 hours, children first participated in a 'mock' scan designed to familiarize them with the experience of being in an fMRI scanner, then participated in an fMRI study which lasted approximately 45 minutes.

Day 1 – TSST-C

All families participated in session 1 during the afternoon. Families were instructed to have their children not participate in rigorous exercise for at least 30 minutes prior to their visit. See Figure 1 for a timeline of the study. At the beginning of the TSST-C part of the session salivary cortisol was assayed (Baseline 2) which served as the baseline cortisol for the TSST-C. The TSST-C used in this experiment followed the experimental procedures outlined by Buske-Kirschbaum, Jobst, Wustmans, Kirschbaum, Rauh & Hellhammer, 1997. In this report, Buske-Kirschbaum and colleagues describe a social stress test similar to the TSST (Dickerson & Kemeny,

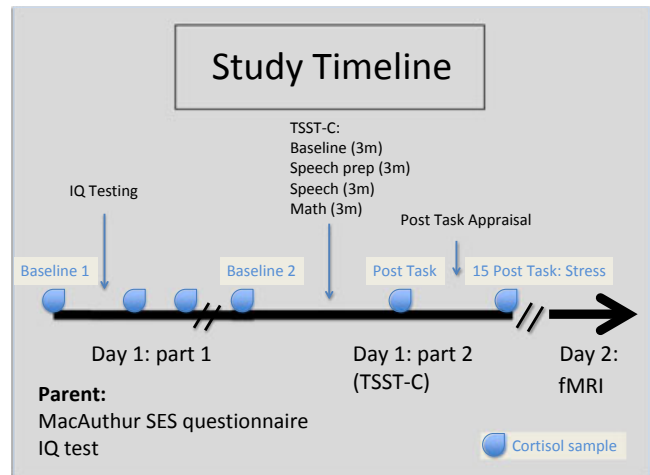


Figure 1 Study time line. During Day 1 participants came to a lab visit that lasted between 3 and 4 hours. Approximately 20 minutes after their arrival, the first salivary cortisol assay was collected (Baseline 1: EEG baseline). Next the child participated in part 1 of an EEG study (~45 minutes), and the IQ test (~20 minutes), after which a second salivary cortisol (20 minutes post- EEG administration) was measured. Finally, the child received a small toy (worth less than \$5.00 USD), and a third salivary cortisol was assayed (30 minutes after IQ administration). After this, the child walked or was driven to a second close-by location on the same campus with their family, where they participated in the trier social stress test for children (TSST-C). During the TSST-C, salivary cortisol was measured three more times; upon arrival at the new location (Baseline 2: TSST-C baseline), directly following the TSST-C (Post task), and 15–20 minutes after the end of the TSST-C (Post task: Stress).

2004) but designed to be used with children. The TSST-C is comprised of four periods: an initial baseline, a preparation for the speech, a speech, and backwards subtraction. Each period lasted 3 minutes in this study. At the end of the TSST-C the child was asked to rate how the speech and backwards math made them feel on a number of dimensions using a visual scale (post task questionnaire). Cortisol was assayed for a final time at the end of the study. Salivary cortisol was measured in all children using sterile salivettes. Please see Data S1 for a complete description of the TSST-C.

Day 2 – fMRI

During the fMRI portion of the study, children were taken to a 'mock scanner' where they became accustomed to the scanning environment. Children had practiced the task they were going to perform in the scanner at day 1, but they were reminded of the task

instructions prior to fMRI scanning, which lasted approximately 45 minutes. During this time, children completed the paired-associate learning task (PAL task).

Paired Associate Learning (PAL) task

During encoding, participants were shown pictures of faces alone (item), pictures of houses alone (item), and pictures of faces inside houses (pairs, see Figure 2). The recognition test was administered directly following the encoding period. Responses to correctly paired pictures (hit rate) and responses to incorrectly paired pictures (false alarms) were normalized and subtracted from one another to estimate sensitivity (d -prime) for each subject.

Data analysis

Analysis of association between SSS and task performance was performed using ordinary least squares (OLS) regression. Analysis of the effect of TSST-C on salivary cortisol was performed using paired t -tests. Statistical significance was set at $p < .05$.

fMRI data analysis

Please see Data S1 for a full description of fMRI acquisition and data preprocessing. FMRI data analysis

was performed using a general linear model (GLM) in SPM5. Covariates representing a boxcar convolution with the hemodynamic response was used to model blocks of pairs, items, and fixation. Additional covariates modeling motion parameters, outliers (from artifact detection), and run effects were also included. Contrasts between Pairs, Items, or Fixation were constructed by directly subtracting BOLD-related activity in one type of block from the other. These individual contrasts were then input into a group-level analysis, and another one-sample t -test was performed across subjects to identify significant activation for the contrasts between Pairs, Items, and Fixation. All reported clusters are significant at a cluster-level correction of $p < .001$ (20 voxel extent). Cluster-level correction was performed using *fmristat* (<http://www.math.mcgill.ca/keith/fmristat/>).

A region of interest (ROI) analysis was conducted using the REX toolbox (<http://web.mit.edu/swg/software.htm>) to test a priori hypotheses about hippocampal activation (see Data S1 for ROI identification). The association between activation in these ROIs and variables of interest (salivary cortisol, family social status) was performed using OLS regression.

Results

TSST-C results

Children reported similar levels of subjective stress to the TSST-C regardless of social status (Figure 3). Associations between salivary cortisol and social status were assessed using multiple regression (Table 1a). Maternal education and income-to-needs ratio did not predict baseline cortisol before TSST-C or change in salivary cortisol across the TSST-C. However, maternal SSS was a significant predictor of baseline cortisol (before the TSST-C), controlling for gender and age. Salivary cortisol response to the TSST-C was assessed by examining change in salivary cortisol between *Baseline 2* (first cortisol sample from the TSST-C session) and *Post task: Stress* (final cortisol sample from the TSST-C session). *Baseline 2* cortisol was significantly higher than *Post task: Stress* cortisol (Figure 4), indicating an overall decrease in cortisol across the afternoon, following a diurnal rhythm. While this is inconsistent with studies in adults where salivary cortisol often increases across the time of the TSST, it is consistent with previous studies of children (Gunnar, Wewerka, Frenn, Long & Griggs, 2009; Stroud, Foster, Papandonatos, Handwerker, Granger, Kivlighan & Niaura, 2009) which demonstrate that relative to adolescents or adults, salivary cortisol is often less reactive to the TSST-C in children. Given the lack of

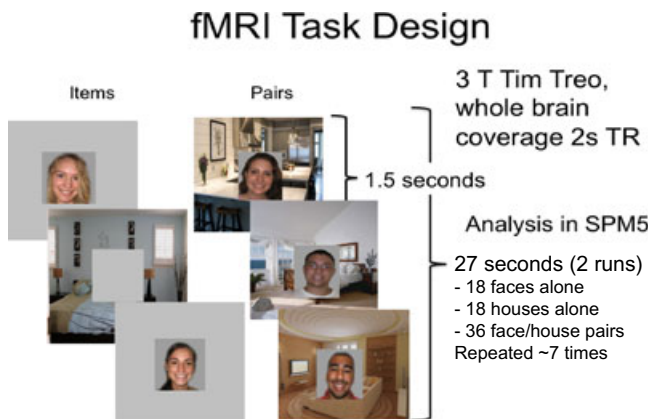


Figure 2 Depiction of behavioral task which children experienced in the scanner. During the encoding portion of the task, children saw blocks of 'items' (either faces or houses presented alone) or 'pairs' (randomly assigned face/house pairs). Children were told that the pairs were pictures of individuals living in their own house. In addition, they were instructed to 'Remember the houses, faces, and people living in their own house.' Each stimulus was presented 6–7 times for 1.5 seconds to the child during encoding. No face or house that was presented as an item was ever presented as part of a pair.

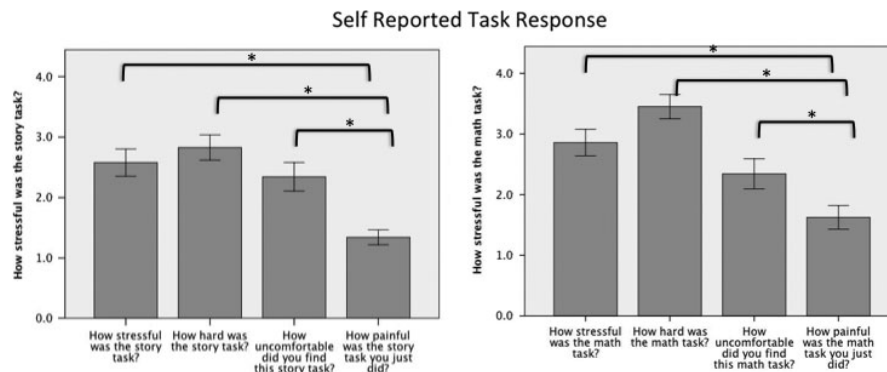


Figure 3 In the post task questionnaire, children were asked how much they found the speech and math portions of the TSST-C hard, stressful, uncomfortable, and painful. The first three adjectives were designed to assess level of discomfort in the task. The final adjective was a control adjective to observe if all negative affect was increased as a result of the task (because the task was not physically painful) Ratings were on a scale from 0 to 4, from 'not at all' to 'very'. As predicted, the task was experienced as difficult and stressful for the children but not as painful. * Indicates that the mean values for all other ratings are significantly different from 'painful' across the 38 participants (paired sample *t*-tests, $p < .05$).

elevation in cortisol response across the TSST-C, baseline cortisol was used for all subsequent analyses.

fMRI results

Children attended to the encoding portion of the fMRI task: they consistently pressed a button when they saw the alerting stimulus. In addition, they recalled the items encoded during fMRI scanning at a rate better than chance ($M d\text{-prime} = 1.64$, $SD = .53$). Behavioral performance on this task ($d\text{-prime}$) was not associated with parental SES as measured by income-to-needs ratio ($B = -.42$, $t = .29$, $p = .771$), maternal education ($B = -.07$, $t = 1.24$, $p = .23$), or SSS ($B = -.09$, $t = -1.31$, $p = .21$). This indicates that all participants found the task equally difficult and fMRI activation can be

compared across groups without confounding contributions from performance differences.

We report activation across all children for pairs > items; pairs > fixation, and items > fixation (Figure 5 and Table 3). In these comparisons children activated regions consistent with a paired associate learning task including areas in the medial temporal lobe (parahippocampal and hippocampal activation).

Hypothesis-driven associations between hippocampal activation to pairs and parental social status were tested (Table 2). SSS was associated with hippocampal activation; as SSS increased, hippocampal activation increased.

Mediation results

In this study we assess the possibility that stress is one pathway by which social status in childhood impacts hippocampal function. To assess stress as a mediator, three primary criteria must be met: First, there must be a significant association between predictors (family SES) and dependent measures (function of the hippocampus). In this analysis, this criterion was met: maternal report of SSS was significantly associated with hippocampal activation to pairs (controlling for age and gender). Second, there must be significant associations between potential mediators (baseline salivary cortisol) and dependent measures (function of the hippocampus). This criterion was not met: baseline salivary cortisol ($B = .009$, $SE = .03$, $\beta = -.08$, $t = -.33$, $p = .75$) was not significantly associated with hippocampal activation to pairs (controlling for age and gender). Third, there must be a significant association between potential mediators (salivary cortisol) and the predictor that is

Table 1 Results of three models using three measures of SES to predict baseline salivary cortisol, controlling for gender

	1a. Baseline Salivary Cortisol	
	β (SE)	beta (t-value)
Maternal SSS	.46 (.23)	.34 (2.00)*
Age	-.49 (.45)	-.18 (-1.09)
Gender	.35 (.81)	.07 (.426)
Income to needs	.21 (.31)	.12 (.681)
Age	-.54 (.48)	-.20 (-1.13)*
Gender	.26 (.87)	.06 (.305)
Maternal ed.	.32 (.20)	.29 (1.61)
Age	-.30 (.47)	-.11 (-.629)
Gender	-.22 (.82)	.05 (.269)

Abbreviations: SSS, subjective social status *Significant at the .05 level, two-sided test.

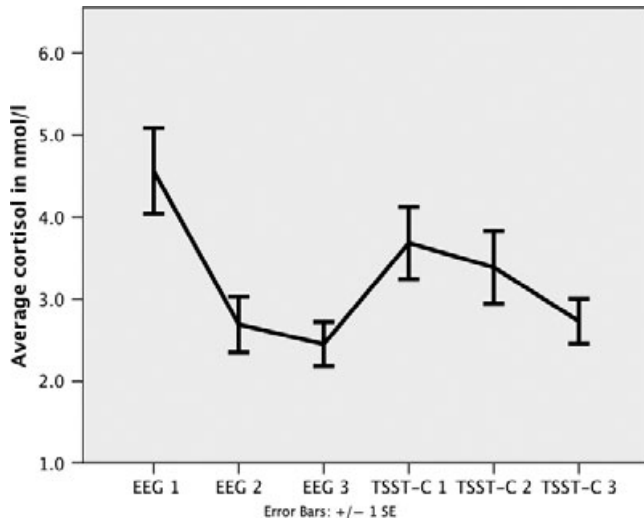


Figure 4 Cortisol in nmol/l across the course of Day 1 of the study. Across the two-hour EEG session (Baseline 1 – Final EEG Cortisol) salivary cortisol decreased significantly, as would be expected by the diurnal rhythm ($t(32) = 2.20$, $p = .04$), and indicated that the EEG/WASI administration did not activate the HPA axis in these children. Thus, the TSST-C session can be considered independently. Across the 1 hour TSST-C session (Baseline 2 – Post Task: Stress), salivary cortisol decreased significantly, again following the diurnal rhythm (paired sample t -test; $t(33) = 2.7$, $p = .03$).

being assessed (maternal SSS). In this analysis baseline salivary cortisol was significantly associated with maternal SSS, however overall only 2 of three basic criteria for mediation were met in this data set.

Discussion

In this study we observed an association between hippocampal activation in the context of a PAL task and maternal SSS but not income-to-needs ratio or maternal education. In addition, we observed an association between maternal SSS and baseline salivary cortisol, such that as social status increased, so did salivary cortisol at baseline, replicating some previous studies (Fernald *et al.*, 2008). These findings are consistent with the common hypothesis that HPA axis dysregulation is the mediator by which social status in childhood comes to affect health and well-being in adulthood (Shonkoff *et al.*, 2009; McEwen & Gianaros, 2010).

However, in this study we also test a critical piece of this puzzle: the direct association between salivary cortisol (at baseline or reactivity) and hippocampal function. We observed that salivary cortisol was unrelated to hippocampal function and therefore in this

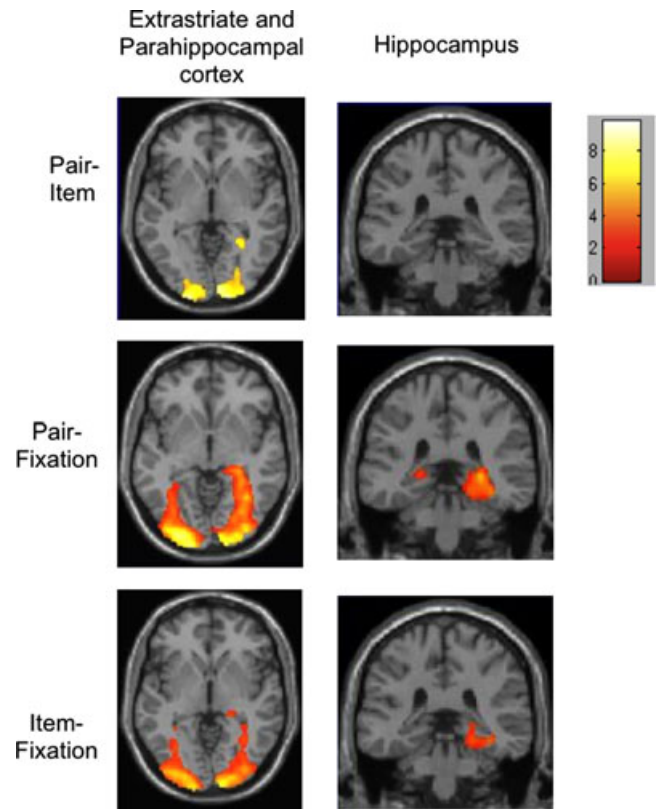


Figure 5 Activation maps are rendered on a standard T1-weighted brain. Maps are thresholded at $p < .001$; cluster threshold > 20 voxels. T-value scale is presented at the top right.

Table 2 Results of three models using three measures of SES to predict hippocampal function, controlling for gender and age

	Hippocampal Activation -Pairs	
	β (SE)	beta (t-value)
Maternal SSS	.08 (.04)	.48 (2.27)*
Age	-.04 (.06)	-.14 (-.653)
Gender	-.19 (.13)	-.30 (-1.45)
Income to needs	.03 (.06)	.11 (.450)
Age	-.05 (.07)	-.17 (-.681)
Gender	-.23 (.16)	-.35 (-1.43)
Maternal ed.	.000 (.04)	-.003 (-.010)
Age	-.05 (.08)	-.18 (-.670)
Gender	-.20 (.15)	-.33 (-1.33)

Abbreviations: SSS, subjective social status *Significant at the .05 level, two-sided test.

study, salivary cortisol did not mediate the association between maternal SSS and child hippocampal activation. The finding that the simple association between salivary cortisol and hippocampal function was not significant

Table 3 All significant fMRI activations during encoding for pairs> items, pairs> fixation, and items> fixation. Significance set at $p < .001$ cluster level corrected with a cluster size of at least 20

Comparison	Region	x	y	z	t-value
Pair>Items	Extra-striate cortex [R]	18	-104	0	6.08
	Extra-striate cortex [L]	-18	-104	2	6.58
	Parahippocampal Gyrus [R]	28	-50	-2	4.62
	Precuneus [R]	20	-58	18	3.98
	Hippocampus [L]	-22	-34	2	4.52
Pair>Fixation	Extra-striate cortex [R]	24	-94	-8	8.2
	Extra-striate cortex [L]	-20	-100	-8	13.04
	Parahippocampal Gyrus [R]	32	-44	-12	10.96
	Parahippocampal Gyrus[L]	-36	-48	-16	6.93
	Hippocampus [R]	28	-32	-2	7.69
Item>Fixation	Extra-striate cortex [R]	16	98	-2	7.2
	Extra-striate cortex [L]	-16	-96	-10	8.99
	Parahippocampal Gyrus [R]	36	-38	-16	5.7
	Parahippocampal Gyrus[L]	-32	-50	-12	6.11
	Fusiform Gyrus [R]	30	-56	-14	7.52
	Fusiform Gyrus [L]	-36	-70	-14	12.16

constitutes a null result. While the sample size used in this study is typical for an fMRI study, it was quite small, and this lack of an effect may be due to a lack of power.

In rodents, quality of maternal care is causally linked to the function and structure of the hippocampus in adulthood (Francis, Champagne, Liu & Meaney, 1999), including links to long-term memory performance (Liu, Diorio, Day, Francis & Meaney, 2000). Thus, multiple researchers have proposed that a similar pathway functions in humans and that this is the primary pathway by which social status comes to affect health (Shonkoff *et al.*, 2009).

In favor of the idea that stress is the mediator by which social status comes to affect health is the consistent evidence that children from low social status families have increased exposure to environmental stressors (Evans & Kantrowitz, 2002; Evans & Kim, 2010). In addition, there is evidence that HPA axis function is associated with SES in childhood (Dowd, Simanek & Aiello, 2009). However, this association is notoriously ambiguous. Baseline salivary cortisol is sometimes observed to be increased in children exposed to adversity during childhood, consistent with animal studies. However, other associations are also observed: curvilinear, blunted diurnal rhythms, and decreased baseline cortisol (for review see Obradovic, *in press*). Here we observe a positive association between maternal SSS and child baseline cortisol.

To date there has been debatable evidence that children exposed to stressors differ in hippocampal

structure or function in the manner suggested by rodent work. For example, children exposed to abuse do not differ from non-exposed peers in hippocampal volume (De Bellis *et al.*, 2001). However, in some studies family social status *is* associated with child performance on long-term memory tasks (Farah *et al.*, 2006) and hippocampal volume, although both negative (Hanson, Chandra, Wolfe & Pollak, 2011) and positive (Rao, Betancourt, Giannetta, Brodsky, Korczykowski, Avants, Gee, Wang, Hurt, Detre & Farah, 2010) associations with family social status have been observed. In at least one study, the direction of these associations depended on the measure of social status used (Noble, Houston, Kan & Sowell, 2012). In the current study, in line with these findings, we observe that hippocampal activation during a long-term memory task is associated with maternal SSS. To maximize comparability between our investigation of the hippocampus and social status, and that of other researchers (including animal studies), we also examined hippocampal volume in this sample. We report these results in full in the Data S1; in summary, we do not observe an association between maternal SSS and hippocampal volume in this sample ($r(17) = .039$, $p = .88$). Finally, salivary cortisol is unrelated to hippocampal function in this sample.

The findings from the current study constitute evidence, albeit incomplete, in support of a stress pathway by which exposure to low social status environments in childhood come to affect neural function. In keeping with previous investigations, this study shows that social status and stress are linked in childhood, as are social status and neural function. However our results differ from animal studies; it may be that, in humans, with long and complex socio-emotional developmental trajectories, the link between increased stress exposure and impaired hippocampal function will prove to be more complex. To better understand the interactions that are likely to arise from this complexity, larger sample sizes, diversity of measurement, and designs that include randomization will be required. The current study highlights one way in which stress exposure may impact human development, and how this impact may be related to the health effects of exposure to low social status environments, and points in the direction for future research into this phenomenon.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Supplementary material.