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Socioeconomic Disparities Affect Children's Amygdala-Prefrontal Circuitry via Stress Hormone Response

Ting Tian, Christina B. Young, Yannan Zhu, Jiahua Xu, Ying He, Menglu Chen, Lei Hao, Min Jiang, Jiang Qiu, Xu Chen, and Shaozheng Qin

ABSTRACT

BACKGROUND: The socioeconomic status (SES) of a family can affect almost all aspects of a child's life, including health and current and future achievement. The potential adverse effects of low SES on children's emotional development are thought to result from proximal factors such as stress. The underlying neurobiological mechanisms, however, remain elusive.

METHODS: The effect of SES on children's integrative cortisol secretion and its modulations on emotion-related brain systems and connectivity were examined in children aged 6 to 12 years. In study 1, we investigated the relationship between SES and cortisol secretion in 239 children. In study 2, using resting-state and task-dependent functional magnetic resonance imaging in a subsample of 50 children, we investigated how SES affects children's amygdala-prefrontal functional organization through cortisol secretion.

RESULTS: Children from lower SES exhibited lower cortisol secretion, considering basal cortisol, nocturnal cortisol activity during sleep, and cortisol awakening response, which mediated higher amygdala nuclei intrinsic functional connectivity with the medial and dorsolateral prefrontal cortex (PFC). Critically, these children also exhibited higher task-evoked ventromedial PFC activity through higher intrinsic connectivity of the centromedial amygdala with the medial PFC. They also exhibited higher functional coupling of the centromedial amygdala with the dorsolateral PFC when processing negative emotions.

CONCLUSIONS: This study demonstrates that SES shapes children's amygdala-prefrontal circuitry through stress-sensitive cortisol secretion, with the most prominent effect in the centromedial amygdala's functional coordination with the ventromedial and dorsolateral PFC involved in processing negative emotions. Our findings provide important insight into the neurobiological etiology underlying how socioeconomic disparities shape children's emotional development.

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It is well established that socioeconomic status (SES) has an important contributory role in a wide array of achievement, cognitive, and health outcomes in children, with its effects continuing through adulthood (1,2). The far-reaching impact of low SES is thought to result from proximal factors such as stress (3), which affects neural networks critical for emotional development (4). Because the human brain undergoes rapid development during childhood, children are especially vulnerable to the effects of stress and SES disparities (5,6). However, our understanding of the neurodevelopmental mechanisms of how SES disparities affect children's emotional brain circuitry is still in its infancy.

Recent neurobiological models provide robust evidence that SES disparities affect the human brain through proximal factors such as stress and stress-sensitive hormone response (7,8). Children living in families of low SES, for instance, show an increased risk of psychopathology later in life, such as anxiety and depression (9,10), due in part to long-term stress exposure and abnormal stress hormone secretion from the hypothalamic-pituitary-adrenal (HPA) axis (11). Cortisol, the end product of the HPA axis, exhibits a diurnal rhythm over time with the following cardinal features in humans: a basal level before bedtime and nocturnal cortisol activity during sleep, both of which are relatively stable characteristics of HPA axis functioning (12), and the cortisol awakening response in the morning, which is a specific response to awakening and defined by a burst within 30 minutes after awakening (13). However, previous studies of SES-related disparities have focused on cortisol response in general (14,15) but have not taken these features into account. Thus, how SES disparities affect an integrative measure of cortisol secretion remains unclear.

One pivotal question regarding the neurobiology of SES-related disparities in mental health is how the cortisol response associated with SES affects children's brain networks underlying emotional development. The neuromodulatory

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effects of cortisol on emotion-related brain circuitry have been extensively studied in humans (16) and animal models (17) and have shown that both rapid and slow cortisol signaling pathways act on glucocorticoid and mineralocorticoid receptors in the amygdala and prefrontal cortex (PFC) (18). Among these emotional brain circuits, the most widely investigated pathway is the amygdala-medial PFC circuitry, which is critical in emotional processing (19–21). Indeed, studies focusing on early-life stress have demonstrated a negative association between childhood basal cortisol and amygdala-medial PFC intrinsic connectivity during adolescence (22). Another important emotional circuit is the amygdala-dorsolateral PFC pathway, which is crucial in voluntary emotion regulation (23,24), and there is evidence demonstrating that blunted cortisol response to stress is related to higher amygdala-dorsolateral PFC connectivity (25). However, how SES along with stress-sensitive cortisol response, especially an integrative measure that considers basal, overnight, and cortisol awakening response factors together, affects emotion-related brain circuitry during development is unknown.

Localization of brain structures and functions impacted by SES has been the primary focus of studies examining the neural correlates of SES (3). Multiple lines of research have demonstrated smaller gray matter volume in the amygdala (26,27) and prefrontal regions (28,29), as well as hyperconnectivity of the amygdala with dorsolateral PFC (30) in those from low SES backgrounds. These studies provide useful information about specific brain systems linked to SES, but offer limited insight into how SES-related proximal factors, such as cortisol, mediate the relationship between SES and alterations in the brain. Moreover, the amygdala encompasses several major nuclei including the centromedial amygdala (CMA) and basolateral amygdala (BLA), which have distinct connections with other target regions. The CMA serves as the main output station of the whole amygdala and is essential for regulating emotional expression, whereas the BLA receives sensory input through projections to widespread neocortical areas (31) and is responsible for detecting emotional content of stimulus inputs (32). To our knowledge, no studies to date have investigated whether SES impacts the functional organization of these amygdala nuclei with different prefrontal systems.

Based on theoretical models of SES and stress-sensitive cortisol, we hypothesize that lower family SES would modulate higher CMA and BLA functional connectivity with the medial and dorsolateral PFC through reduced cortisol secretion in young children. To test this hypothesis, we conducted two studies that combine SES, integrative cortisol secretion, and brain activation and connectivity using functional magnetic resonance imaging (fMRI) in children aged 6 to 12 years. In study 1, we investigated the relationship between SES and cortisol secretion in 239 children. In study 2, we conducted two fMRI experiments in a subsample of 50 children to investigate how SES-related integrative cortisol secretion affects the functional organization of children's CMA/BLA-prefrontal circuitry. The two fMRI experiments provided complementary information about functional organization of emotion-related brain circuitry during resting state and an active emotion task. Mediation analysis was implemented to determine whether family SES modulates intrinsic and task-evoked amygdala-prefrontal functional organization through cortisol secretion during childhood.

METHODS AND MATERIALS

Participants

A total of 239 typically developing school-aged children (6–12 years, 108 girls and 131 boys) participated in study 1. SES and cortisol data were a reanalysis of our previous study (11) but also included new participants and new measures (Supplement). A subset of 50 children (24 girls and 26 boys; Table S1) completed both resting-state and task-dependent fMRI scans for study 2. All children denied history of neurological/psychiatric disorders and had not received any medical treatment in the previous 6 months. All children provided assent, and parents/legal guardians provided written informed consent before participation. All protocols were approved by the local institutional review board under the standards of the Declaration of Helsinki.

SES Assessment

Family SES was quantified using a well-established self-report family background questionnaire (33) that assessed education and monthly income of each parent or legal guardian, with 10- and 6-point scales, respectively. For each parent, income and education scores were first transformed into separate z scores and then averaged across both parents to form a composite SES score (11).

Salivary Cortisol Analysis

Children's salivary cortisol samples were collected at five time points: prebedtime basal cortisol level before sleep (S0) and immediately (S1), 15 minutes (S2), 30 minutes (S3), and 60 minutes (S4) after awakening the next morning. Children were asked to provide sleep and awakening times and the exact time of collection of each salivary cortisol sample. An integrative measure considering basal cortisol levels, overnight secretion, and cortisol awakening response was computed with the following formula:

$$AUC_{integrative} = \frac{sleep\ duration\ (S0+S1)}{2} + \frac{0.25\ (S1+S2)}{2} + \frac{0.25\ (S2+S3)}{2} + \frac{0.5\ (S3+S4)}{2} - S0\ (sleep\ duration + 0.25 + 0.25 + 0.5)$$

This measure integrates three major characteristics of HPA axis activity, including bedtime basal cortisol, sleep-related cortisol secretion, and accelerating cortisol activity after awakening, to reflect the effect of SES as a multidimensional environmental factor on cortisol secretion. Further rationale and justification on a proximal estimate of sleep-related cortisol secretion are provided in Figure S1. Cortisol values were $\log_{10}$-transformed to ensure a normal distribution, and outliers were excluded. We used 2-day cortisol measures, when available, to obtain a more stable metric of HPA axis activity; otherwise, 1-day measures were used.

Task Procedure

Participants were instructed to relax, remain still with eyes open, stay awake, and not think about anything in particular during the 6-minute resting scan. In the emotion-matching task, we utilized a widely used negative emotion paradigm (34–36) that involves matching the emotion of a target face (see Supplement). Participants viewed a trio of negative facial expressions in the emotion or control condition and were asked to indicate which of the stimulus in the bottom row displayed the same category as the target stimulus in the top row. The task consisted of 5 emotion and 5 control blocks with 6 trials (5 s) each. Emotion-related brain responses were assessed using the contrast of negative emotion versus control condition to ensure amygdala reactivity.

Regions of Interest Definition

CMA and BLA regions of interest were created using cytoarchitectonically defined probabilistic maps of the amygdala (37). Maximum probability maps were used to create nonoverlapping amygdala subregions using the Anatomy Toolbox (38). Voxels were assigned to the region that had the greatest probability, and each voxel was assigned exclusively to one region only (39), resulting in four nonoverlapping masks: left BLA, left CMA, right BLA, and right CMA.

Image Data Acquisition and Preprocessing

Whole-brain functional images were acquired from a Siemens 3T scanner (TIM Trio, Erlangen, Germany) using a 12-channel head coil and a T2*-sensitive echo-planar imaging sequence with the following parameters: 33 axial slices, 4-mm slice thickness, 0.6-mm gap, 2000-ms repetition time, 30-ms echo time, 90° flip angle, voxel size 3 × 3 × 4 mm^3, field of view 200 × 200 mm^2. Functional images were preprocessed using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). The first five volumes of resting and first four volumes of emotional task were discarded for signal stabilization. The remaining images were corrected for slice acquisition timing, realigned for head motion correction, spatially normalized into the Montreal Neurological Institute space, resampled into 2-mm isotropic voxels, and smoothed by convolving a 6-mm isotropic three-dimensional Gaussian kernel.

Functional Connectivity and Activation Analysis

Resting-state data were analyzed using seed-based intrinsic functional connectivity analysis for the left and right CMA and BLA seeds separately. Task-evoked brain activation and functional connectivity for the left CMA and BLA were estimated using the general linear model and the generalized psychophysiological interaction method (40). Extensive analyses with 6- and Friston-24 motion parameters were conducted to account for confounds by micro-motion/physiological artifacts. Detailed procedures are provided in the Supplement. Individual-level intrinsic connectivity maps, task-evoked psychophysiological interaction, and activation contrast images were submitted into a second-level multiple regression analysis, with cortisol secretion as the covariate of interest, and age and sex as nuisance variables. Significant clusters were determined at a height threshold of $p < .001$ and an extent threshold $p < .05$ corrected using 3dClustSim (41). Parameter estimates were extracted from significant clusters.

Mediation Analysis

The mediation models and statistical tests were examined using PROCESS in SPSS version 21 (IBM Corp., Armonk, NY) (42), which is based on regression analysis. The significance of the indirect or mediated effect was assessed using 5000 bias-corrected bootstrapping (43). The indirect effect was considered significant if the 95% confidence interval (CI) did not include zero (see Supplement).

RESULTS

Lower SES Links to Lower Children's Cortisol Secretion

To assess general HPA axis functioning, we computed the area under the curve of the increase through five time points relative to basal cortisol level (Figure 1A) in study 1. This integrative measure is a composite indicator of overnight cortisol secretion and the accelerating activity of the HPA axis while awakening. Pearson correlation analysis revealed that lower SES was associated with lower cortisol secretion ($r = .18$, $p = .01$), even after controlling for age and sex ($r = .17$, $p = .02$) (Figure 1B). Analyses based on 1-day cortisol data yielded almost identical results (Figure S2 and

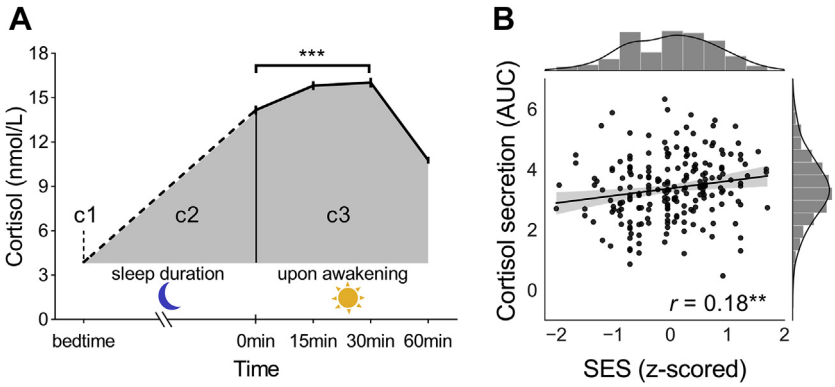

Figure 1. Children from lower socioeconomic status (SES) backgrounds showed lower cortisol secretion. **(A)** Dynamic cortisol levels were assessed with five sampling time points spanning bedtime to 60 minutes after awakening the next morning (N = 239), as illustrated by our previous study (11). The gray area is an integrative measure of nocturnal cortisol during sleep (c2) and accelerating cortisol activity after awakening (c3) relative to a bedtime basal cortisol level (c1). **(B)** SES was positively correlated with children's cortisol secretion, even when regressing out age and sex (r = .17, p = .02). The gray histograms on the top and right side show the frequency distribution of SES and cortisol secretion, respectively. Error bar, SEM; ***$p < .001$; **$p = .01$.

Table S2). These results indicate that children from lower SES backgrounds show lower cortisol secretion.

SES-Related Cortisol Secretion Affects Chidren's CMA/BLA-Prefrontal Intrinsic Connectivity

In study 2, we investigated how children's cortisol secretion related to SES disparities modulates intrinsic functional connectivity of the CMA and BLA (Figure 2A). Whole-brain multiple regression analyses were conducted for CMA and BLA intrinsic connectivity targets separately, with children's cortisol secretion as the covariate of interest while controlling for age and sex. These analyses revealed significant clusters in the medial and dorsolateral PFC without further multiple comparison adjustments for the four amygdala seeds tested. Left CMA intrinsic connectivity with medial and dorsolateral PFC (Figure 2B, C and Table S3) was negatively correlated with cortisol secretion ($r = -.49$, $p < .001$; $r = -.47$, $p = .001$, respectively). Left BLA intrinsic connectivity with medial and dorsolateral PFC was also negatively correlated with cortisol secretion ($r = -.43$, $p = .002$; $r = -.48$, $p = .001$, respectively). A median split was used to categorize children into lower and higher groups for visualization only. Equivalent analyses with 1-day cortisol data only yielded identical results for left CMA/BLA-prefrontal connectivity (Figure S3).

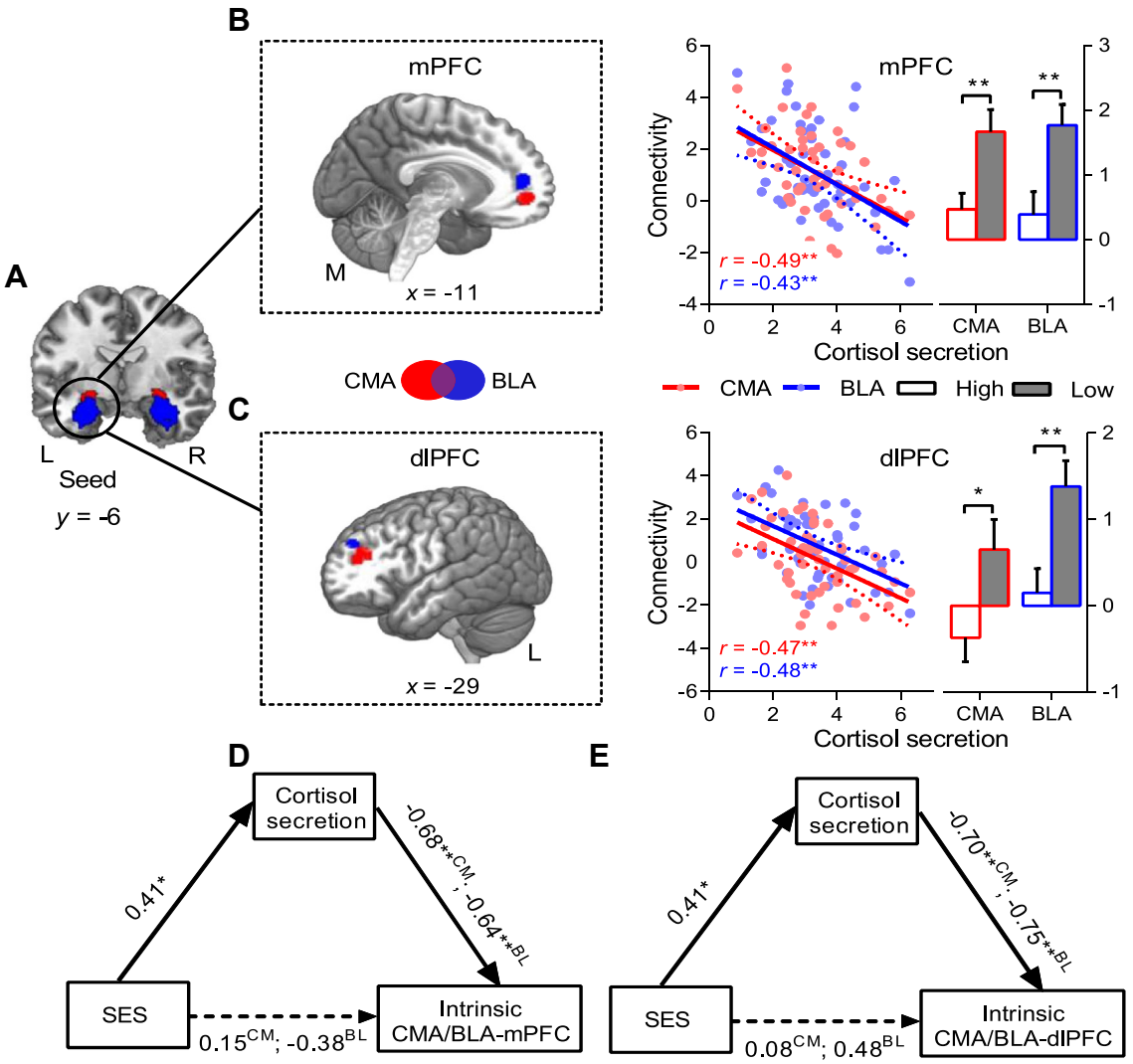

Figure 2. Children with lower cortisol secretion showed higher intrinsic connectivity of both centromedial amygdala (CMA) and basolateral amygdala (BLA) with the medial prefrontal cortex (mPFC) and dorsolateral PFC (dlPFC) in study 2. **(A)** A representative coronal slice shows the CMA and BLA. The left CMA (red) and BLA (blue) inside the circled area were used as seeds for connectivity analyses. **(B)** Significant clusters in the mPFC showed negative correlations between cortisol secretion and intrinsic left CMA/BLA-mPFC connectivity, as well as **(C)** between cortisol secretion and intrinsic left CMA/BLA-dlPFC connectivity when regressing out age and sex. **(D)** Separate mediation models demonstrated a mediatory role of cortisol secretion on the association between socioeconomic status (SES) and intrinsic left CMA/BLA-mPFC connectivity. **(E)** Separate mediation models demonstrated a mediatory role of cortisol secretion on the association of SES with intrinsic left CMA/BLA-dlPFC connectivity. $n = 50$ participants; error bar, SEM; $^{*}p \leq .05$, $^{**}p < .01$. BL, basolateral; CM, centromedial; High, high cortisol secretion group; L, left; Low, low cortisol secretion group; M, medial; R, right.

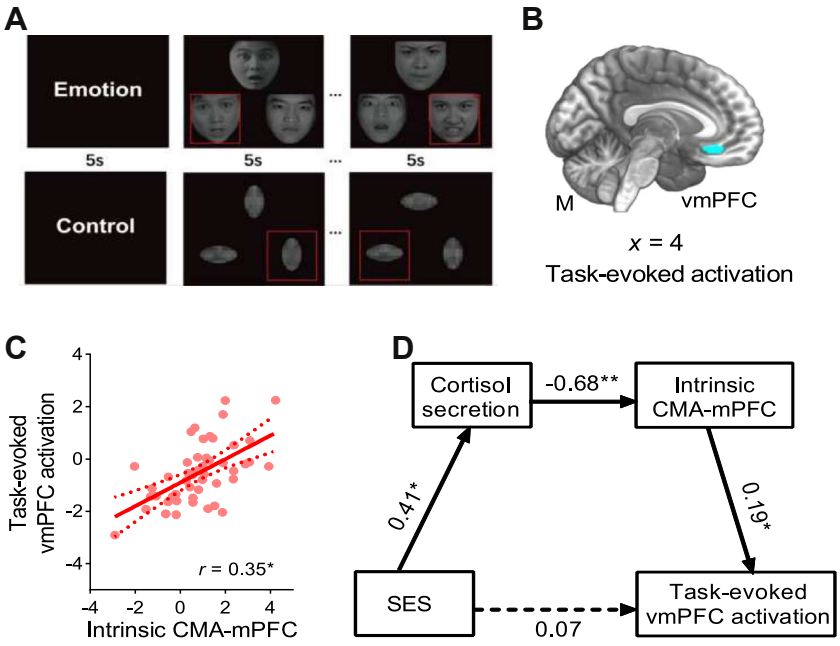

Figure 3. Lower socioeconomic status (SES) and cortisol secretion affect task-evoked ventromedial prefrontal cortex (vmPFC) activity through intrinsic centromedial amygdala (CMA)-medial PFC (mPFC) connectivity in children. **(A)** Task-evoked activity was assessed using an emotion-matching paradigm that involves selecting the face that matches the emotion of the target face in the top row. **(B)** vmPFC activation showed a significantly positive association with cortisol secretion during emotion vs. control conditions. **(C)** Intrinsic left CMA-mPFC connectivity positively correlated with task-evoked vmPFC activation. **(D)** SES affected task-evoked vmPFC activation through children's cortisol secretion and intrinsic left CMA-mPFC circuitry. n = 50 participants; error bar, SEM; $^{*}p \leq .05$, $^{**}p < .01$. M, medial.

We then implemented mediation analyses to test whether SES affects children's emotion-related brain circuitry via cortisol secretion. These analyses showed that cortisol secretion mediated the association between SES and four left CMA/BLA-prefrontal pathways without multiple comparison adjustments. Specifically, these pathways were left CMA-medial PFC (indirect estimate = −0.28, $p < .05$, 95% CI = −0.609 to −0.042), left BLA-medial PFC (indirect estimate = −0.26, $p < .05$, 95% CI = −0.695 to −0.034) (Figure 2D and Table S4), left CMA-dorsolateral PFC (indirect estimate = −0.29, $p < .05$, 95% CI = −0.674 to −0.029), and left BLA-dorsolateral PFC (indirect estimate = −0.31, $p < .05$, 95% CI = −0.704 to −0.049) (Figure 2E and Table S5). Control analyses with six head motion parameters (Figure S4) and regressing out the time series of the other amygdala nuclei (Figure S5) revealed very similar results. We tested alternative models with amygdala-prefrontal connectivity as a mediator and observed weaker and less reliable mediation effects when performing model comparisons (Figure S6 and Table S6). These results indicate that children's cortisol secretion mediates the associations between SES and left CMA/BLA intrinsic connectivity with the medial and dorsolateral PFC.

SES-Related Cortisol Secretion Affects Children's Ventromedial PFC Response to Negative Emotion via CMA-Medial PFC Intrinsic Connectivity

We then investigated whether SES-related cortisol secretion modulates task-evoked brain response to negative emotion versus control conditions (Figure 3A), using whole-brain regression analyses with children's cortisol secretion as the covariate of interest while controlling for age and sex. This revealed that lower cortisol secretion was associated with greater task-evoked response in the ventromedial PFC (Figure 3B and Table S7). This cluster is located near the medial PFC cluster identified in the left CMA intrinsic connectivity analyses (Figure S7).

Given the close proximity of the medial PFC clusters identified in the task-evoked response and intrinsic left CMA connectivity analyses, we then examined the relationship between them. This analysis revealed significantly positive correlation between left CMA-medial PFC intrinsic connectivity and task-evoked ventromedial PFC response (r = .35, p = .01) (Figure 3C). This likely reflects activity flow over task-free intrinsic pathways in support of functional activation during task performance (44). To investigate whether SES and cortisol response affect task-evoked ventromedial PFC response through left CMA-medial PFC intrinsic connectivity, we conducted mediation analyses. This revealed a chain mediating pathway with lower SES initially linked to lower cortisol secretion, which then related to higher left CMA-medial PFC intrinsic connectivity (not for left BLA-medial PFC connectivity), which further led to higher task-evoked ventromedial PFC response to negative emotions (indirect estimate = −0.05, $p < .05$, 95% CI = −0.159 to −0.008) (Figure 3D and Table S8). Parallel analyses for 1-day cortisol data (Figure S8), six head motion parameters (Figure S9), and regressing out time series of the other amygdala nuclei (Figure S10) again revealed very similar results. We also tested other alternative models and found null effects (Figure S6). These results indicate that lower SES along with reduced cortisol secretion is indirectly related to higher task-evoked ventromedial PFC activity through the left CMA intrinsic connectivity with the medial PFC.

SES-Related Cortisol Secretion Affects Children's CMA Coupling With Dorsolateral PFC in Emotion Processing

We further investigated whether children's cortisol secretion mediates the relationship between SES and task-evoked

functional connectivity of left CMA and BLA with prefrontal systems. Whole-brain regression analyses were conducted for the left CMA- and BLA-seeded task-dependent connectivity maps under emotion versus control conditions with children's cortisol secretion as the covariate of interest while controlling for age and sex. This revealed that lower cortisol secretion was associated with greater left CMA task-dependent functional connectivity with the dorsolateral PFC (Figure 4A and Table S9) ($r = -.53$, $p < .001$) when processing negative emotions. Parallel analyses for task-dependent left BLA connectivity revealed no PFC regions that showed a relationship with cortisol secretion (Table S9).

We finally examined whether children's cortisol secretion mediated the relationship between SES and left CMA task-dependent connectivity with the dorsolateral PFC. Critically, this analysis revealed an indirect mediatory effect of children's cortisol secretion (indirect estimate = −0.12, $p < .05$, 95% CI = −0.316 to −0.017) (Figure 4B and Table S10). Several control analyses using 1-day cortisol data (Figure S11) and fMRI data with classic 6-motion parameter correction produced very similar results (Figure S12). We did not observe any other alternative models with the left CMA-dorsolateral PFC connectivity as a mediator (Figure S6). Taken together, these results indicate that lower SES is related to reduced cortisol secretion, which is associated with higher task-evoked left CMA-dorsolateral PFC functional coupling during negative emotion processing.

DISCUSSION

In two studies, we investigated whether stress hormone response mediated the indirect relationship between SES and children's amygdala-prefrontal circuitry. We found that children from lower SES backgrounds exhibited lower integrative cortisol secretion, which mediated higher left CMA/BLA intrinsic connectivity with medial and dorsolateral PFC. Critically, lower SES along with reduced cortisol secretion was associated with higher task-evoked ventromedial PFC engagement through the left CMA, but not left BLA intrinsic connectivity with the medial PFC. Children's cortisol secretion also mediated the indirect relationship between SES and task-dependent left CMA, but not left BLA, coupling with the dorsolateral PFC during negative emotion processing. Our findings suggest that stress hormone response acts as a neurobiological mediator for how socioeconomic backgrounds shape children's emotion-related brain circuitry that is critical for appraisal and regulation of emotions.

SES Affects Children's Cortisol Secretion

We utilized an integrative cortisol measure that takes basal cortisol, overnight cortisol during sleep, and the postawakening response into account. This measure reflects three key characteristics of HPA axis functioning: a relatively stable basal cortisol at bedtime (12,45), nocturnal cortisol secretion during sleep with an initial mild decline followed by a gradual increase likely from 2:00 to 7:00 AM (46,47), and accelerating cortisol activity after awakening reflecting psychophysiological processes pertaining to sleep-wake transition (13,48,49) and energetic/stress demands of the upcoming day (50,51). According to SES models, families of low SES often experience a scarcity of resources (1), which might cause higher levels of stress that are often repetitive or long term, such as routine stressors and negative parenting (52). Indeed, behavioral research has emphasized the importance of considering family SES as a multidimensional construct that involves exposure to routine stressors for individuals of low SES, which would most likely alter the integrity of HPA axis system as a whole, rather than only certain aspect(s) of its circadian rhythm. Thus, examinations of cortisol at isolated point(s) may be missing overall HPA axis activity, including during sleep. Low SES environments and exposure to chronic stress have been linked to dysregulation of the HPA axis with reduced cortisol secretion (53), likely because of prolonged activation of negative feedback to the HPA axis (54). Our previous study also demonstrated that children from lower SES backgrounds show reduced cortisol awakening response (11). By using an integrative measure of cortisol response, our results converge with the literature suggesting that children from lower SES backgrounds show lower cortisol secretion, which may suggest far-reaching effects of SES on the overall HPA axis functioning.

SES Along With Cortisol Secretion Shapes Children's Amygdala-Prefrontal Intrinsic Architecture

With neuroimaging data, we found that children's lower cortisol secretion mediated the indirect associations between lower SES and higher left CMA/BLA intrinsic connectivity with the medial and dorsolateral PFC during resting state. This suggests that SES background shapes amygdala-prefrontal intrinsic architecture through children's cortisol secretion. A similar pattern of amygdala hyperconnectivity with medial and dorsolateral prefrontal systems is seen in individuals exposed

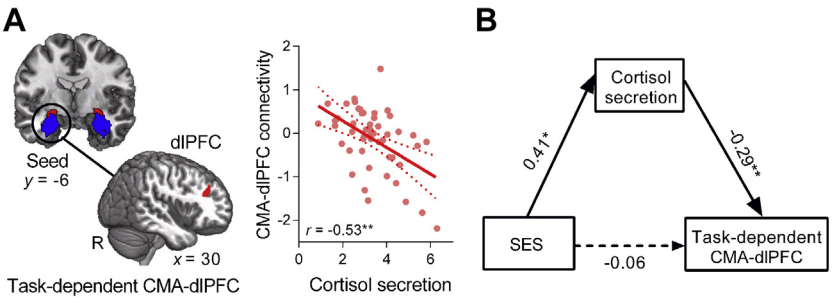

Figure 4. Socioeconomic status (SES) affects task-dependent centromedial amygdala (CMA)-dorsolateral prefrontal cortex (dlPFC) functional connectivity through children's cortisol secretion. **(A)** Lower cortisol secretion was associated with greater left CMA-dlPFC connectivity in negative emotion vs. control conditions. **(B)** A mediation model showed that SES affected task-evoked left CMA-dlPFC functional connectivity through children's cortisol secretion. $n = 50$ participants; Error bar, SEM; $^{*}p = .05$, $^{**}p < .01$. R, right.

to early-life stress, those with pathological anxiety (55,56), and healthy children with high anxiety (37).

Neurobiological research has recognized both rapid nongenomic (20) and slow genomic (57) actions of glucocorticoids (cortisol in humans) on neural excitability and endocrinal control, which allow for one to adapt to changing environmental situations. For example, an optimal level of accelerating cortisol secretion upon awakening in the morning is essential to prepare the body with sufficient energy supply for metabolic consumptions and upcoming challenges (13). Through slow genomic actions that regulate HPA axis activity, cortisol binding to corresponding receptors in the amygdala and PFC can normalize neuronal activity so that it is in an optimal state that maintains homeostatic functions (18). In this context, insufficient cortisol secretion in children from lower SES backgrounds may lead to suboptimal inhibition of spontaneous neural activity in these regions, as indicated by higher amygdala-prefrontal intrinsic connectivity. Although we observed similar effects of SES-related cortisol secretion on both CMA- and BLA-prefrontal intrinsic connectivity, these amygdala nuclei may play distinct roles in negative emotion processing, given their unique projections to specific PFC regions.

SES Along With Cortisol Secretion Affects Children's Ventromedial PFC Emotion Processing via CMA-Medial PFC Intrinsic Connectivity

In conjunction with greater CMA/BLA-prefrontal intrinsic connectivity, we found that lower cortisol secretion was associated with higher task-evoked activity in the ventromedial PFC. This suggests that insufficient cortisol secretion may lead to higher ventromedial PFC engagement when processing negative emotions owing to suboptimal energy supply for neuromodulation in the ventromedial PFC (58,59). Moreover, phasic activation of the locus coeruleus-norepinephrine (LC-NE) system and autonomic reactions to negative stimuli are known to play a critical role in modulating prefrontal activity (60). We speculate that the slow effects of insufficient cortisol secretion may work in concert with phasic LC-NE activation to mediate greater task-evoked ventromedial PFC activity in children from lower SES backgrounds.

Critically, the indirect association between children's lower cortisol secretion and higher task-evoked activity in the ventromedial PFC was mediated by intrinsic connectivity of the medial PFC with the left CMA, but not the BLA. The brain's intrinsic pathways serve as the foundation for information transfer between distant regions to support cognitive and affective functions (44). The CMA is as an output station of the amygdala and is crucial for regulating emotional responses and arousal via its connections with the hypothalamus, brainstem, and sensorimotor system (61). Importantly, CMA projections to the hypothalamus in particular play a role in endocrinal control over HPA axis activity (62). Thus, our findings suggest that higher ventromedial PFC activity is attributed to physiological and neuroendocrine effects that act on CMA-medial PFC intrinsic pathways, likely reflecting suboptimal downregulation of autonomic reactions to negative stimuli in children from lower SES backgrounds with insufficient cortisol secretion.

SES Along With Cortisol Secretion Alters Children's CMA-Dorsolateral PFC Coupling During Emotion Processing

We found that children's lower cortisol secretion mediated the indirect association between SES and greater CMA-dorsolateral PFC coupling during negative emotion processing. This complements our results demonstrating greater left CMA-dorsolateral PFC intrinsic connectivity, suggesting that insufficient cortisol secretion in children from lower SES backgrounds affects not only CMA-dorsolateral PFC intrinsic architecture but also their functional coupling during negative emotion processing. Indeed, blunted cortisol levels along with CMA-dorsolateral PFC hypercoupling are linked to pathological anxiety and psychosis (63,64). Insufficient cortisol may result in suboptimal downregulation of emotional response via CMA-dorsolateral PFC coupling. Interestingly, we did not find reliable effects of BLA-prefrontal coupling during negative emotion processing, although the BLA contributes to emotional reactivity in response to fear and aversive stimuli in rodents (61).

It is worth noting that the LC-NE phasic activation may also play a role in mediating higher CMA-dorsolateral PFC coupling during negative emotion processing. The CMA, receiving inputs from noradrenergic cells (65), contributes to regulating the emotional expression and/or autonomic responses to negative stimuli, especially in those with fear, stress, or anxiety (63,66), through its projections to prefrontal systems, including the dorsolateral PFC. Thus, it is possible that emotion-induced noradrenergic activation may work in concert with insufficient cortisol availability to account for greater CMA-dorsolateral PFC coupling during negative emotion processing in children from lower SES backgrounds. Future studies addressing cortisol interplay with LC-NE activity are needed in humans. Together, findings from intrinsic and task-evoked fMRI data converge onto a neurobiological model by which lower SES and cortisol secretion affect children's amygdala-prefrontal intrinsic architecture and functional organization during negative emotion processing.

Limitations

First, our study utilized a proximal estimate of basal cortisol, sleep-associated cortisol activity and awakening cortisol response, and more precise approaches are needed. Second, CMA and BLA parcellation could lead to partial volume effects owing to limited resolution, which should be addressed by higher spatial-resolution neuroimaging techniques. Future studies are also required to decipher distinct contributions of CMA- and BLA-medial PFC pathways to mediating the associations of SES with cortisol secretion and task-evoked medial PFC engagement, with multiple comparison adjustments for the number of models tested. Third, it still remains elusive how puberty impacts our findings, and whether our fMRI findings from a negative emotion paradigm can generalize to positive emotions.

Conclusions

Our study highlights that family SES along with cortisol, a stress-sensitive hormone, plays a critical role in mediating children's emotion-related brain circuitry, with the most prominent effect in the left CMA functional coordination with

medial PFC and dorsolateral PFC circuits involved in negative emotion. Given that SES is predictive of a broad range of important life outcomes, understanding the neuroendocrinal and neurobiological underpinnings of SES disparities during childhood has important implications for how socioeconomic backgrounds shape child development, which is a critical public health concern.

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The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the State Key Laboratory of Cognitive Neuroscience and Learning & IDG/McGovern Institute for Brain Research (TT, YZ, JX, YH, MC, LH, MJ, SQ), Beijing; Beijing Key Laboratory of Brain Imaging and Connectomics (TT, JX, YH, MC, LH, MJ, SQ), Beijing Normal University, Beijing; Chinese Institute for Brain Research (SQ), Beijing; Key Laboratory of Cognition and Personality (JQ, XC), Ministry of Education, Chongqing; the Department of Psychology (JQ, XC), Southwest University, Chongqing; and College of Teacher Education (LH), Southwest University, Chongquing, China; Department of Neurology and Neurological Sciences (CBY), Stanford University School of Medicine, Stanford, California; and Donders Institute for Brain, Cognition and Behaviour (YZ), Radboud University Medical Center, Nijmegen, the Netherlands.

Address correspondence to Shaozheng Qin, Ph.D., at szqin@bnu.edu.cn.

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