Medial prefrontal-hippocampal concordance in child-parent dyads underlies children's psychological wellbeing

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Abstract

Negative family environment can be harmful for a child's psychological wellbeing through suboptimal child-parent interactions. The medial prefrontal cortex (mPFC) is implicated in socioemotional cognition within either child or parent's brain, but how interactions between child and parent brains within this region contribute to children's psychological wellbeing remains unknown. Across two studies examining 395 child-parent dyads, results showed that children from negative family environment experienced more psychopathological symptoms. Dyad-based analyses of movie-watching functional magnetic resonance imaging (fMRI) data revealed that children had higher inter-subject correlations in dorsal- and ventral-mPFC with parents than stranger controls, and increased concordance of activity with regions critical for socioemotional skills. Negative family environment reduced inter-subject connectivity of the ventral-MPFC with the hippocampus in child-parent dyads, which further mediated children's internalizing symptoms. The ventral-mPFC and hippocampus exhibited reciprocal activity concordance in child-parent dyads. Our findings suggest child-parent brain-to-brain concordance as a neurobiological mechanism of how family environment affects psychopathological symptoms.

Introduction

Family environment is fundamental to all aspects of child development. Positive family interactions provide a scaffold for children to learn socioemotional skills via shared experiences and reciprocal interactions with their parents (Morris et al., 2017). Conversely, negative family interactions are harmful to children's psychological wellbeing, causing and maintaining various psychopathological symptoms (Valiente et al., 2006; Volbrecht and Goldsmith, 2010) and altering emotional brain development (Dahl et al., 2018; Ugarte et al., 2021). Such adverse effects are thought to result from derailing the coordination of biobehavioral patterns in child-parent dyads (Feldman, 2020). Although well documented in behavioral studies, the underlying neurobiological mechanisms of how negative family environment may affect children's psychological wellbeing from child-parent dyad-based approaches remains unknown.

Psychosocial and bio-behavioral synchrony models posit that positive child-parent reciprocal interactions can foster children's emotional development and wellbeing (Feldman, 2012; Ratliff et al., 2022). Supportive parenting, for instance, is crucial for children to develop various skills and strategies which are necessary to regulate negative emotions (Feldman, 2007), thus promoting psychological wellbeing (Morris et al., 2017). Family members in a negative environment, however, are prone to experiencing more frequent conflicts, neglect, and threat (Eisenberg, 2020; Morris et al., 2017). As such, negative family environment increases the risk of endangering psychological wellbeing by derailing reciprocal interactions and dyadic concordance. Indeed, many studies have demonstrated that negative family environments compromise the effectiveness of reciprocal interactions in child-parent dyads and discourage supportive parenting (Hoyniak et al., 2021; Tarullo et al., 2017). Children who experienced maladaptive family interaction with parents are prone to develop psychopathological symptoms later in life (Feldman, 2007; Quinones-Camacho et al., 2019). Recently, several studies investigated the association between family risk factors (i.e., family conflicts and childhood maltreatment) and children's brain structure

and function using single-brain paradigms in which either the parent or child is examined (Gong et al., 2021; Noble et al., 2015; Teicher et al., 2016). Little, however, is known about how negative family environment affects children's psychopathological symptoms through altered reciprocal responses across child-parent brains.

One fundamental question in the neurobiology of family risk factors in mental health is to understand how negative family environment affects children's wellbeing via altered child-parent dyadic interactions at the neurobiological level. The medial prefrontal cortex (mPFC), a core node of the socioemotional networks, is recognized to play a critical role in transmission of shared socioemotional experiences across individuals (Krueger et al., 2009; Roy et al., 2012). Child-parent shared neural response in the PFC is also implicated in emotion regulation critical for one's psychological wellbeing (Lee et al., 2017; Quinones-Camacho et al., 2019; Vanessa Reindl et al., 2018), via its contributions to coordinated socioemotional behaviors including cooperation (V Reindl et al., 2018), joint attention and smiling (Piazza et al., 2020). Moreover, the acquisition and transmission of social experience and knowledge require multiple brain regions to interact and exchange information (Babiloni and Astolfi, 2014). Indeed, recent studies demonstrate that the mPFC works in concert with the hippocampus allowing individuals to learn and accumulate necessary knowledge and experience through social interactions (Hiser and Koenigs, 2018; Yeshurun et al., 2021). This is considered a neurocognitve model of solidifying socioemotional knowledge and skills to cope with ever-changing environmental demands. Family risk factors including parenting stress (Azhari et al., 2019), anxious attachment (Azhari et al., 2020), and sociodemographic risks (Hoyniak et al., 2021) could alter child-parent shared neural response in the PFC. These findings provide initial evidence to suggest that family risk factors can may impede the children's formation of socioemotional capability of coping with various stressful situations through altered prefrontal functional networks. The current study tests this hypothesis by examining whether and how child-parent shared brain

responses in the mPFC and related circuitry mediate the association between family risk factors and child's emotional wellbeing.

A new emerging approach of mapping brain-to-brain concordance has the potential to revolutionize our understanding on how shared socioemotional representations across brains arise from dyadic interactions between children and parents (Ratliff et al., 2022). These approaches compute functional activity concordance across brains (Nastase et al., 2019). Using functional near-infrared spectroscopy and electroencephalogram hyperscanning techniques, recent studies have demonstrated neural synchrony across brains critical for child-parent interactions (Perone et al., 2020; V Reindl et al., 2018; Spielberger, 1983). However, these techniques provide insufficient spatial resolution to assess shared neural signatures in the MPFC and related subcortical structures. Recently, inter-subject correlation (ISC) and inter-subject functional connectivity (ISFC) of functional magnetic resonance imaging (fMRI) data have been used to identify brain activity concordance in cortical and subcortical regions between strangers, and their related functional circuits during movie watching (Hasson et al., 2004; Simony et al., 2016). fMRI during movie watching is emerging as a powerful tool for exploring brain function and their concordance across individuals that allows us to identify: 1) shared neural responses across child-parent brains in reaction to emotions elicited by movie watching, 2) reactivity of related socioemotional knowledge in long-term memory to cope with elicited emotions, 3) child-parent dyadic brain predictors underlying the effects of negative family environment on children's psychological wellbeing. Based on models of socioemotional learning and bio-behavioral synchrony (Feldman, 2017; Morris et al., 2017), we hypothesize that child-parent dyads will exhibit an increase in brain-to-brain concordance (vs. child-stranger dyads) in the mPFC and related functional circuits, and such concordance would account for the effects of negative family environment on children's psychological wellbeing.

To test the above hypotheses, we conducted two separate studies integrating assessments of family emotional environment and children's psychopathological symptoms, as well as dyad-based analysis of movie-watching fMRI data for child-parent dyads. In study 1, we investigated how negative family environment relates to children's psychopathological symptoms including internalizing and externalizing problems in 395 child-parent dyads (**Fig 1a**). We assessed family environment using a well-validated scale of family emotional expressiveness that characterizes how often positive and negative emotions were expressed in a family (Halberstadt et al., 1995). Each child's internalizing and externalizing symptoms were measured by the widely used child behavior checklist (CBCL)(Achenbach, 1991). In study 2, we used a child-friendly naturalistic movie-watching paradigm in an fMRI experiment known for its ecological validity (Vanderwal et al., 2019) to measure child-parent shared brain responses in 50 child-parent dyads (**Fig 1b**). Brain-to-brain concordance metrics in response to movie watching were assessed through ISC and ISFC methods. Given the correlational nature of dyad-based brain concordance, we used an optimized linear mixed effect model with crossed random effects to achieve proper control for false positives and offer wider adaptability, more powerful interpretations than nonparametric methods (Chen et al., 2017) (**Fig 1c**). Mediation analyses were used to examine how child-parent shared brain response could account for the direct and/or indirect effects of negative family environment on children's internalizing problems.

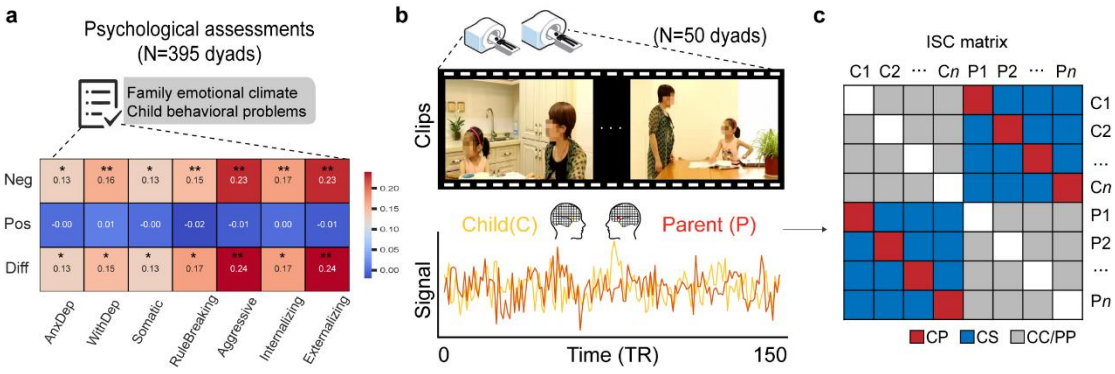

Figure 1. An illustration of experimental design and inter-subject correlation analysis (ISC). **a.** Correlations of negative ('Neg') and positive ('Pos') family environment with children's internalizing and externalizing problems respectively. And the difference between the row1 and row2 is significant. **b.** Representative frames of a 6-min movie

of a 7-year-old girl and her mother used as the fMRI paradigm. An illustration of voxel-wise ISC between two time series of a child-parent dyad for each voxel of the grey matter mask. **c.** A matrix represents pairwise correlations among child and parent subjects, resulting in child-parent dyads (red), child-stranger controls (grey), child-child & parent-parent pairs (blue). Each cell represents a ISC value.

Results:

Negative family environment affects children's internalizing/externalizing symptoms

First, we examined how family emotional environment, including positive and negative components, affects children's internalizing and externalizing symptoms in Study 1. Pearson's correlation analyses revealed that negative family environment was associated with more severe children's internalizing symptoms (r_{395} = 0.17, q < 0.001), including anxious/depressed (r_{395} = 0.13, q = 0.024), withdrawn/depressed (r_{395} = 0.16, q = 0.005), and somatic problems (r_{395} = 0.13, q < 0.001), as well as externalizing symptoms (r_{395} = 0.23, q < 0.001), including aggressive (r_{395} = 0.24, q < 0.001) and rule-breaking behaviors (r_{395} = 0.15, q = 0 .001) (*all q values were FDR corrected*) (***Fig 1a***). We did not observe any reliable associations of positive family environment and children's internalizing and externalizing symptoms (all rs_{395} < 0.01, qs > 0.70). Further tests for Fisher's z-transformed correlation coefficients revealed significant differences between negative and positive family environment components (all Z > 1.95, q < 0.05, FDR corrected). Notably, the positive associations of negative family environment with children's internalizing and externalizing symptoms still remained robust, even after regressing out each child's age, gender, and socioeconomic status (*Fig S2*). These results indicate that children from negative family environment exhibit more severe internalizing and externalizing symptoms.

Increased inter-subject correlation in vmPFC and dmPFC for child-parent dyads

Next, we identified systems across brains showing a shared pattern of temporal neural activity in response to viewing an emotionally negative movie clip. As a first step, the

ISC maps were computed to represent shared brain activity by correlating time series of the same voxel across participants (**Fig 2a*)***. As a second step, a linear mixed-effects (LME) model was conducted for ISC maps collapsing across children and parents to identify brain systems showing inter-subject synchrony during movie watching. This analysis revealed significant clusters in widespread occipital, temporal, parietal, and frontal regions, with the most prominent effects in unimodal and transmodal association areas, middle frontal gyrus, and medial prefrontal cortex (mPFC) (**Fig 2b**, q < 0.05 FDR-corrected). This pattern of results is consistent with ISC data from previous fMRI studies (Finn et al., 2018; U Hasson et al., 2004).

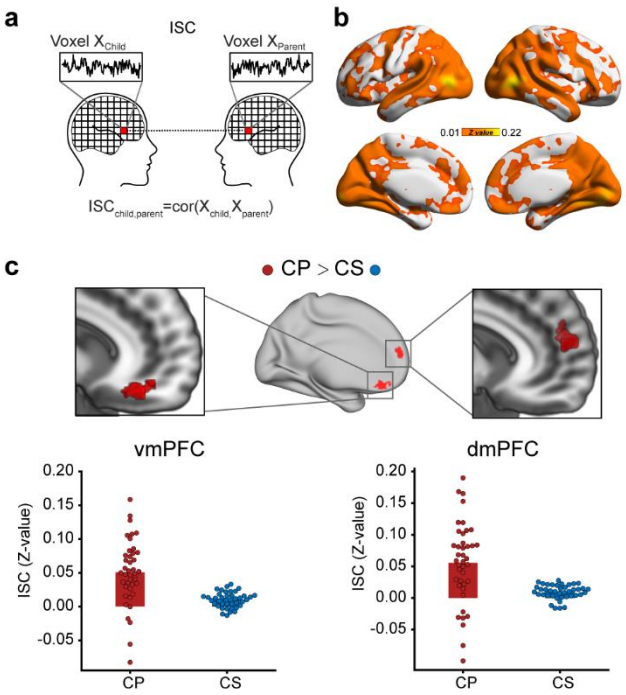

Figure 2. Primary results from inter-subject correlation (ISC) analysis. **a.** An illustration of inter-subject correlation (ISC) between time series of a given voxel in each child and his/her parent's brain. **b.** Brain regions show significant ISC during movie watching in general, with most prominent effect in the visual cortex followed by frontal, temporal, and parietal cortices. Significant clusters were thresholded using q < 0.05 FDR corrected. The color bar represents Fisher's-Z value. **c.** Representative views of the vmPFC and dmPFC show stronger inter-subject synchronized activity (ISC) in child-parent dyads as compared to child-stranger controls. Significant clusters were derived from a contrast between child-parent dyads and child-stranger controls, with an initial threshold p < 0.001 (two-tailed) and an extent threshold p < 0.05 corrected.

We conducted additional dyad-based analysis using dyadic ISC maps between each child and their parent in comparison to each child and a stranger's parent as a control. We implemented an optimized LME model with crossed random effects to control for co-linearity and false positives, as this approach can achieve proper control for false positives, and offers wider adaptability, more powerful interpretations than conventional methods(Gang Chen et al., 2017). We then examined brain systems showing shared temporal neural responses during movie watching that unique to child-parent dyads as relative to child-stranger controls. This analysis revealed significant clusters (voxel-wise $p < 0.001$ two-tailed, cluster-wise $p < 0.05$ corrected) in the vmPFC [peak MNI coordinate at (2,38, -18); cluster size $k = 116$ voxels; **Fig 2c**] and the dorsal mPFC (dmPFC) [peak at (0, 52, 12), $k = 122$ voxels]. There were no significant clusters when examining greater activity in child-stranger versus child-parent differences. To verify whether this effect is specific to movie stimulus, we also performed parallel analysis for resting state fMRI data, and we didn't find any reliable ISC effects in the vmPFC and dmPFC (Table S2). These results indicate higher inter-subject correlation in vmPFC and dmPFC for child-parent dyads than controls.

Increased child-parent vmPFC connectivity with social and emotional systems

Given that mPFC-centric circuitry and networks are implicated in human emotion and social cognition (Krueger et al., 2009; Lieberman et al., 2019), we used vmPFC and dmPFC clusters identified above as separate seeds to perform inter-subject functional connectivity analysis at the whole brain level. The LME model for vmPFC-seeded ISFC map was examined to identify functional circuits showing higher inter-subject connectivity in child-parent versus child-stranger dyads (Fig 3a). This analysis revealed significant clusters in widespread regions in the frontal, temporal and occipital lobes, including the hippocampus [peak MNI coordinates (-16, -30, -8)], amygdala [peak MNI coordinates (18,2, -16)], and fusiform gyrus [peak MNI coordinates (-32, -48, -8), FDR<0.05] (Fig 3b-d, Table S5). Parallel analysis for dmPFC-seeded ISFC

maps revealed that child-parent dyads exhibited higher connectivity with the angular gyrus [peak MNI coordinates (-46, -64, 24)] and medial prefrontal gyrus [peak MNI coordinates (0,54,14). FDR<0.05] (Fig S6a, Table S5) than child-stranger dyads. To verify whether this effect is specific to movie watching, we also performed paralell analysis for resting-state fMRI data, and we did not find no any reliable ISFC effect in child-parent dyads than child-stranger controls (Table S5).

We then used a meta-analytic decoding approach based on a widely used Neurosynth platform (Yarkoni et al., 2011) to determine psychological functions associated with the above clusters that showed higher inter-subject connectivity with the vmPFC and dmPFC in child-parent than child-stranger dyads. This analysis revealed that child-parent dyads shared vmPFC-based connectivity patterns with widespread regions that are implicated in episodic memory, emotion, and social functions **(Fig 3c)**, whereas dmPFC-based connectivity didn't exhibit apparent relationship with 15 psychological functions (Fig S6c). These results indicate higher vmPFC connectivity with social and emotional systems in child-parent dyads than child-stranger controls.

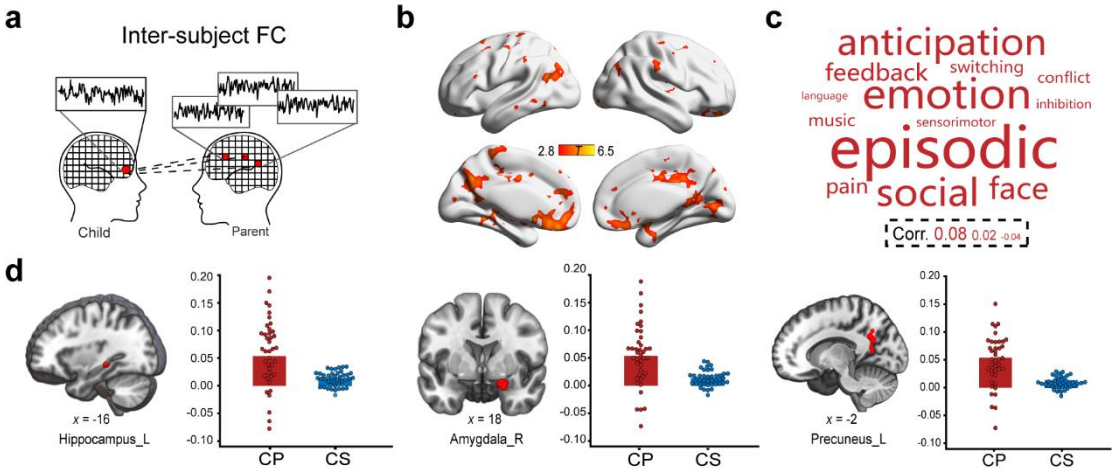

Figure 3. Major results from inter-subject functional connectivity (ISFC) analysis. **a.** An illustration of seed-based ISFC that computes the correlation between a seed's time series in a child brain and all other voxel's time series of his/her parent brain. **b.** Child-parent dyads showed stronger ISFC of the vmPFC seed with these regions than child-stranger controls. Lateral and medial view of significant clusters in the inferior

frontal gyrus, middle cingulum gyrus, precuneus, fusiform, hippocampus and middle occipital gyrus (q < 0.05 FDR corrected). **c.** Word cloud depicting commonly used terminology associated with regions showing vmPFC connectivity. **d**. Representative slices of significant clusters in the hippocampus, amygdala and precuneus that show stronger ISFC in child-parent dyads then child-stranger control dyads.

Reduced child-parent vmPFC connectivity with the hippocampus accounts for negative family environment's effects on children's internalizing symptoms

Given our central hypothesis that neural mechanisms link negative family environment and psychological wellbeing, we further investigated how negative family environment shapes inter-subject correlation of brain activity and connectivity during movie watching in child-parent dyads, which then affects children's psychopathological symptoms. Brain-behavior association analyses were conducted for ISC and ISFC metrics of the vmPFC and dmPFC. Among these metrics, we found that negative family environment was significantly correlated with lower child-parent shared vmPFC connectivity with the left hippocampus (**Fig 4b**) and the right precuneus (q = 0.03, FDR corrected; Table S5). Next, we observed a negative correlation of child-parent vmPFC-hippocampal dyadic connectivity with children's internalizing symptoms, especially for anxious/depressed components (Fig 4b, FDR correction, q = 0.06).

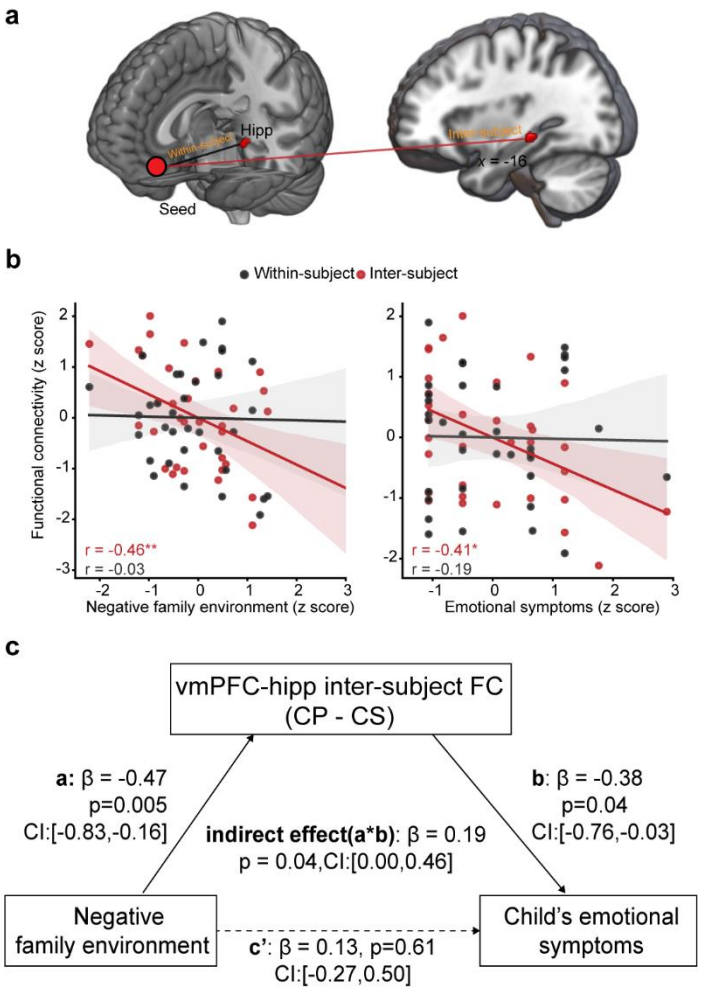

Figure 4. The relationships among negative family environment, ISFC and anxious/depressed symptoms. a. Representative view of vmPFC seed and its connectivity with the hippocampus within subject, with inter-subject vmPFC-hippocampus connectivity. **b.** Scatter plots depict the negative correlations (FDR corrected) of inter-subject vmPFC-hippocampal connectivity (red color) with negative family environment and children's anxious/depressed symptoms. This pattern is not observed within-subject (grey color) in the vmPFC-hippocampal connectivity pathway. **c.** Mediation model depicts the indirect pathway of negative family environment on children's anxious/depressed symptoms via the shared vmPFC-hippocampal inter-subject connectivity. Standardized coefficients are depicted. The solid lines represent significant effect. Notes: *p < 0.05; **p < 0.01. All statistical tests here are two-tailed and pass the FDR correction.

Since child-parent vmPFC-hippocampal connectivity was associated with both negative family environment and children's internalizing symptoms, we conducted a mediation analysis to examine whether this inter-subject functional pathway could

account for the association between negative family environment and children's internalizing problems. This analysis revealed an indirect pathway of negative family environment mediating higher children's internalizing symptoms via reduced vmPFC connectivity with the hippocampus in child-parent dyads than child-stranger controls (B = 0.17, SE = 0.10, p = 0.028, bootstrapped 95% CI = [0.01,0.42], 56.7% of the total effect size). Parallel analysis also revealed an indirect pathway of negative family environment accounting for children's anxious/depressed symptoms via child-parent vmPFC-hippocampal connectivity (**Fig 4c,** B = 0.19, SE = 0.12, p = 0.04, bootstrapped 95% CI = [0.00,0.46], 59.4% of the total effect size). Notably, such mediation effect was significant even when regressing out child-parent's age and gender (Fig S8a). Since children's emotional problems could influence family environment (Rothenberg et al., 2020), we tested an alternative model with children's internalizing symptoms as input variable and negative family environment as outcome predictor. Although this model also survives (*Fig S8c&d*), model comparison with Akaike Information Criterion (AIC) favors the initial model with family environment affecting child internalizing symptoms (AIC = 2.70) over the alternative one of the reverse (AIC = 2.66).

To verify whether negative family environment affects children's internalizing problem through their shared vmPFC-hippocampus responses rather than within individual/single brain metrics, we performed vmPFC-seeded functional connectivity within children's brains to examine its relationship with negative family environment and children's internalizing symptoms **(Fig 4a)**. However, we did not find any reliable effects pertaining to such within-brain metrics **(Fig 4b, S9).** In addition, we conducted time-lagged analysis for vmPFC-based ISFC to verify whether child-parent dyads exhibited the highest ISFC at other timepoints. This analysis revealed that child-parent dyads exhibited highest vmPFC-hippocampal functional correlation at lag zero (Figure S7). Together, these results indicate that reduced child-parent vmPFC connectivity with the hippocampus accounts for the adverse effects of negative family environment on children's internalizing symptoms.

Child-parent vmPFC and hippocampal activity concordance in event boundaries

According to recent neurocognitive models of continuous event segregation and integration, the hippocampus and vmPFC are recognized to support segregation of important event boundaries and integration of episodic events into structured representations (Baldassano et al., 2017; Ben-Yakov and Henson, 2018; Ezzyat and Davachi, 2021; Liu et al., 2021). Our perception and process of such events are actively shaped by existing memories and schematic scripts about experiences in the world (Baldassano et al., 2018). Living in the same family environment, child-parent dyads often have reciprocal interactions during various social and emotional scenarios, and thus they tend to form shared mental schemas on how to understand, cope and respond to key events. Thus, we expected that children would exhibit a similar pattern of hippocampal responses to the moments of shift between meaningful events (boundary timepoints) with their parents. Based on our observed higher child-parent inter-subject coupling of the vmPFC with the hippocampus during movie watching, we further expect that the vmPFC would work together with the hippocampus to integrate boundary and non-boundary events into structured representations.

We therefore implemented dyad-based analysis of brain responses to event segmentation during movie watching to examine whether children's vmPFC and hippocampal responses to event boundary and non-boundary timepoints are correlated with their parents. As expected, this analysis revealed that children's hippocampal responses to event boundaries were indeed positively associated with their parent's responses (r = 0.27, p = 0.04). This concordance, however, did not emerge for within-event time points (r = -0.13, p = 0.21). Further Z-test analysis for Fisher's z-transformed correlation coefficients reveals a significant difference (Z = 1.84, p = 0.03). Interestingly, parallel analysis revealed an opposite pattern of child-parent concordance for the vmPFC activity. That is, children's vmPFC responses to non-boundary timepoints were positively correlated with their parents (r = 0.33, p = 0.02),

but not for event boundaries (r = 0.03, p = 0.42). Further test revealed a marginally significant difference between the two correlations (Z = -1.39, p = 0.08). Taken together, these results indicate that the vmPFC and hippocampus exhibit interactive activity concordance in child-parent dyads in response to non-boundary and boundary events during movie watching.

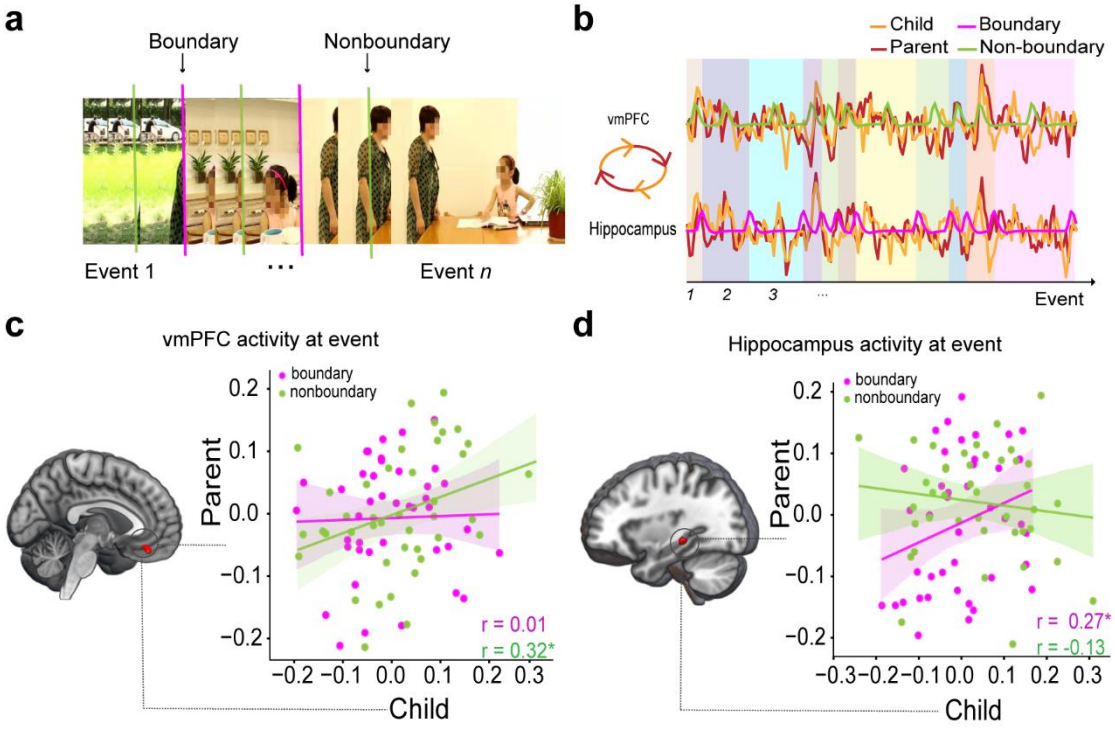

Figure 5. Child-parent hippocampal and vmPFC activity concordance in movie watching. a. An illustration of between- and within-event boundaries for major episodic events during movie watching. **b.** The magenta and green lines represent expected signals of event boundaries and non-boundaries respectively. The yellow and red lines represent neural signals in children and parents separately. Child-parent dyads showed higher vmPFC-hippocampus functional coupling during movie watching, and their vmPFC and hippocampal activity concordance were modulated by segmentation of event boundaries. **c.** Child-parent hippocampal activity concordance was significantly higher for boundary than non-boundary event time series (Z = 1.84, p = 0.03). **d.** Child-parent vmPFC activity concordance was marginally significant higher for boundary than non-boundary timeseries (Z = -1.39, p = 0.08).

Discussion

By leveraging dyad-based analysis of fMRI data during naturalistic movie watching, we investigated the neural substrates of how negative family environment affects

children's psychopathological symptoms through child-parent brain-to-brain activity and connectivity concordance. As compare with child-stranger dyads, child-parent dyads exhibited higher inter-subject correlation in the vmPFC and dmPFC, and higher inter-subject connectivity of the vmPFC with widespread regions critical for socioemotional cognition. Critically, reduced child-parent vmPFC-hippocampal connectivity could account for the association between negative family environment and children's internalizing symptoms, with distinct contributions of the vmPFC and hippocampus to non-boundary and boundary boundaries during movie watching. Our findings provide a neurobehavioral model of how negative family environment affects children's internalizing symptoms through reduced child-parent brain-to-brain concordance in the vmPFC-hippocampal circuitry.

Behaviorally, children in negative family environments experienced more severe psychopathological symptoms. This is in line with previous findings showing positive associations between family risk factors (e.g., maternal maltreatment, family conflicts) and children's internalizing symptoms (Cummings et al., 2013; Gong et al., 2021; Schleider and Weisz, 2017). According to social learning and bio-behavioral synchrony models (Feldman, 2020, 2017; Justyna, 2017), child-parent shared experiences are indispensable for children to learn and develop emotional skills through socialization from their parents in daily life. This may inform family systems therapy (Alexander et al., 2013; Minuchin, 1985) which targets relationships within the family to help remedy childhood anxiety/depression. Through child-parent reciprocal interactions such as affective synchrony and empathic dialogues, for instance, children regulate themselves to attune each other's minds, which helps them develop socioemotional skills such as emotion regulation and theory of mind (Feldman, 2020). Socioemotional interactions in a family have been demonstrated to help child-parent dyads build a shared or synchronous pattern of brain responses (Piazza et al., 2020; Wass et al., 2020). Such shared neural responses can serve as a scaffold for children's socialization to learn necessary skills and form memories via reciprocal interactions

with their parents in daily life (Reindl et al., 2018). As such, negative family environment may impede child-parent brains from forming effective socioemotional skills, and even leads to the emergence of children's psychopathological symptoms, due to suboptimal dyadic interactions and lacking of shared socioemotional experiences. As discussed below, this account is supported by three aspects of our observed concordance across child-parent brains.

Our movie-watching fMRI results show that children-parent dyads exhibited higher inter-subject correlation in the vmPFC and dmPFC than control child-stranger dyads. This is reminiscent of previous findings showing that the mPFC plays a critical role in characterizing shared neurocognitive processes between children and their parents (Hoyniak et al., 2021; Itahashi et al., 2020; Piazza et al., 2020; V Reindl et al., 2018). The mPFC is thought to act as a simulator for social event schemas that allows us to integrate and summarize social, self and emotional information as events unfold over time (Krueger et al., 2009). When processing socioemotional events, the dmPFC is important for inferring other's goal-oriented actions, whereas the vmPFC is crucial for appraisal, evaluation and regulation of values involved in self and affective processes (Bzdok et al., 2013). Such processes could serve as a neurocognitive basis to understand the intentions and mental states of others. Thus, higher inter-subject correlation in the dmPFC and vmPFC across child-parent dyads likely reflect similarities in how child-parent dyads perceive and react emotionally to the socioemotional world.

Our results also show that child-parent dyads exhibited higher inter-subject correlation of vmPFC- and dmPFC-based functional connectivity with widespread regions of social and emotional brain networks in comparison with child-stranger dyads. Specifically, child-parent dyads shared vmPFC coupling with distributed regions crucial for episodic memory, emotion and social processing (Lieberman et al., 2019; Phillips et al., 2019), while dmPFC shared with relatively uniform coupling with regions such as TPJ during movie watching. These inferences were drawn from a widely used

reverse inference database (Yarkoni et al., 2011). The vmPFC and its coordination with the hippocampus, precuneus, amygdala and among others are recognized to support appraisal of perceived socioemotional events (Hiser and Koenigs, 2018) and reinstatement of existing knowledge and strategies formed over the course of child-parent interactions (Feldman, 2017, 2015) about how to cope with negative emotions (Nawa and Ando, 2019; Roy et al., 2012). Our data suggest that vmPFC circuitry is critical for integration of disparate events shared by child-parent dyads when viewing emotionally negative movies, likely by promoting transmission of affectivity and sociality across child-parent dyads.

Our fMRI results additionally show that reduced neural concordance in the vmPFC-hippocampal pathway in child-parent dyads could account for the association between negative family environment and more severe internalizing symptoms in the child. In other words, higher child-parent shared vmPFC-hippocampal connectivity is associated with lower children's internalizing symptoms. Based on influential models of parental emotional socialization, child-parent shared brain responses could act as a scaffold for promoting children's psychological wellbeing (Ratliff et al., 2022), and the vmPFC-hippocampal circuitry is important for constructing the meaning of emotional events (Nawa and Ando, 2019; Roy et al., 2012). It is conceivable that child-parent concordance of vmPFC-hippocampal coupling during movie-watching likely reflects their co-construction of socioemotional events according to shared and/or embodied relationships. Constructing the meaning of emotional events can be a useful way to regulate children's internalizing states to achieve psychological balance (Carpendale and Lewis, 2004). It is possible that children with higher parental concordance of vmPFC-hippocampal connectivity may develop better socioemotional skills and thus exhibit lower levels of internalizing symptoms.

Critically, reduced child-parent concordance in the vmPFC-hippocampal pathway mediated the association between negative family environment and children's

internalizing symptoms. This data suggest that negative family environment may affect children's mental health due to lack of child-parent brain-to-train concordance. Thus, our results shed light on a possible mechanism for how negative family environment impacts the emotional wellbeing of a child. Namely, shared vmPFC-hippocampal connectivity in child-parent dyads may be as a potential marker of resilience against the harmful effects of negative family environment. It is worth noting that we also observed child-parent shared brain responses mediating the association of children's internalizing problems with negative family environment. It is thus possible that such relationships are bidirectional (Gong et al., 2021; Nelemans et al., 2020; Zvara et al., 2018). Longitudinal designs are required to disentangle the directionality effects. Our observed mediation effect suggests that child-parent vmPFC-hippocampal concordance could serve as a potential biomarker for children in families with emotional disorders. Future work may use neurofeedback techniques to explore the impact of upregulating vmPFC-hippocampus coordination with parents on children's emotional health.

Moreover, vmPFC-hippocampal circuitry is crucial in updating and integrating new events into existing memory schemas (Gilboa and Marlatte, 2017; Zeithamova et al., 2012). Increased vmPFC-hippocampal concordance could reflect child-parent dyads with lower negative family environment updating their internal schemas when socioemotional events are incongruent with existing schemas. Although we cannot rule out this possibility, analysis of event boundary-evoked response revealed that children's hippocampal responses to event boundaries were positively related to their parent's responses. Given segmenting continuous events into meaning units is driven by our experience and mental schemas (Baldassano et al., 2018), child-parent hippocampal activity concordance on boundary-evoked response suggests that child-parent dyads utilize their shared episodic memories and schemas to understand and interpret socioemotional events during movie watching. Together with stronger inter-subject vmPFC- hippocampal connectivity that we observed in child-parent dyads, the

vmPFC may signal child-parent hippocampal activity concordance in order to orchestrate long-term memory, emotional and social systems in support of their understanding of events during movie watching.

Several limitations should be considered in our study. First, we assessed child-parent neural concordance at activity and connectivity levels when viewing emotionally negative movies. Whether our findings can be generalized into positively valenced situations still remains open for future studies. Second, although we leveraged a naturalistic movie-watching fMRI paradigm, dedicated task designs are needed to complement the interpretation of child-parent shared neural responses in vmPFC and related circuits. Finally, real-time brain imaging or hyperscanning techniques with longitudinal designs would be critical to address how child-parent interactions foster emotional development through brain-to-brain synchrony.

In conclusion, our study demonstrates brain-to-brain concordance across child-parent dyads during movie watching that was localized to the mPFC and its connectivity with regions in socioemotional networks. Inter-brain concordance in ventral mPFC-hippocampal circuitry, rather than within-brain metrics, emerges as a key locus that mediates the adverse effect of negative family environment on children's internalizing symptoms. Our study provides a neurobiological account for how family risk factors influence children's internalizing symptoms via shared socioemotional representations across brains in child-parent dyads, and can inform the development of dyad-based prevention and interventions designed to improve children's internalizing problem.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (32130045, 31522028, 82021004, 81571056), the Major Project of National Social Science Foundation (19ZDA363, 20&ZD153), the Open Research Fund of the State Key Laboratory of Cognitive Neuroscience and Learning (CNLZD1503) and the Fundamental Research Funds for the Central Universities. We thank Xuan Yang for assistant with collecting data, Jinfeng Wu for assistance with data analysis, and thank Yin Wang for comments on the manuscript.

Disclosures

We declare no biomedical financial interests or potential conflicts of interest.

Data availability.

All of the necessary behavioral and brain imaging data are available from the corresponding author upon reasonable request.

Code availability

All of the necessary behavioral and brain imaging codes are available from https://github.com/QinBrainLab/2022_ChildParent_MovieWatching.

Methods and Materials

Participants

A total of 395 family participated in Study 1. After removing missing values in behavioral measures, data of 395 child-parent dyads (children: mean ± S.D. = 9.35 ± 1.64 years old, range 6.28-12.51, 50% boys; parents: mean ± S.D. = 37.42 ± 4.62 years old, range = 27-57, 33% father) were analyzed. All participants had normal or corrected-to-normal vision, and none reported history of any psychiatric or neurobiological disorders. A subset of 50 child-parent dyads completed fMRI scanning while watching a negative movie clip in Study 2. Ninechild-parent dyads were excluded due to children's head motion with mean framewise displacement larger than 0.5 mm

during scanning. The final sample consists of 41 child-parent dyads (children: mean ± S.D. = 10.15± 1.41 years old, range 7-12, 46.3% boys; parents: mean ± S.D. = 38.91 ± 5.34years old, range=29-49, 24.4% father). In the rest sample, after excluding subjects with mean framewise displacement larger than 0.5mm, data of 25 pairs of children and parents were analyzed in the ISC and ISFC (children: mean ± S.D. = 7.8 ± 1.33 years old, range 7.80-12.26, 40% boys; parents: mean ± S.D. = 39.31 ± 5.51years old, range=29 - 49, 16% father). Six child-parent dyads were further excluded for the mediation analyses due to the incomplete family emotional expressiveness questionnaires. all subjects provided written informed consent before their participation and received monetary compensation. The study was approved by the Institutional Review Board (IRB) of the Beijing Normal University.

Materials and movie watching

A 6-minute video that was unfamiliar to all participants was used. This video showed a 7-year-old girl arguing with her mother（Figure1b）. The critical moments of this video clip are provided in Supplementary Materials S1. Children and their parents underwent fMRI when they were passively viewed the video. This video was silently (no subtitles and no voices) played inside the MRI scanner in order to mitigate potential confounds and individual differences in auditory perception and language comprehension. Participants were instructed to watch what happened between the child and her mother in the video and complete a quiz outside of the scanner to ensure that they were viewing on the movie clip.

Children's psychological wellbeing assessment

Children's internalizing problems and externalizing symptoms were assessed by the parent-reported CBCL scores based on parent surveys (Achenbach, 1991). It consists of five subscales, including anxious/depressed syndrome scale, withdrawn/depressed syndrome scale, somatic syndrome scale, aggressive scale and rule-breaking scale. The internalizing problem score is the composite score of three subscales

(anxious/depressed syndrome, withdrawn/depressed syndrome, somatic syndrome and the externalizing symptom score is the composite score of two subscales (aggressive and rule-breaking). The Chinese version of the CBCL has been used widely (Crijnen et al., 1999), and it has exhibited good test–retest reliability and validity. The internalizing problem score is the composite score of three subscales with a high score indicating a more severe behavioral problem (Leung et al., 2006). The internal consistency of the parent-reported CBCL broadband scales in the present study was a = 0.81 for internalizing problems and a = 0.84 for externalizing problems.

Family environment

Negative family environment was measured by the subscale of Halberstadt's Self Expressiveness in the Family Questionnaire, short form (SEFQ; Halberstadt et al., 1995). Parents reported how often positive (e.g. "Thank your family for everything they do") and negative emotions (e.g. "showing contempt for another's action") were expressed in their family on a 9-point Likert scale (1 = not at all frequently; 9 = very frequently in my family). The positive and negative family expressivity subscales consisted of 12 items separately, and the negative and positive expressivity scores were the mean of 12 items. This questionnaire had adequate reliability and validity, with internal consistency ranges from 0.75 to 0.88 and test–retest reliability ranges from 0.89 to 0.91 (Halberstadt et al., 1995). Coefficient alphas in the present sample were (α = 0.89) and (α = 0.85) for the positive and negative subscales.

fMRI Data Acquisition

Whole-brain images were acquired from Siemens 3.0T scanner (Siemens Magnetom Trio TIM, Erlangen, Germany), using a 12-channel head coil with a T2*-sensitive echo-planar imaging (EPI) sequence based on blood oxygenation level-dependent (BOLD) contrast. Thirty-three axial slices (4 mm thickness, 0.6 mm skip) parallel to the anterior and posterior commissure (AC-PC) line and covering the whole brain with the following parameters: repetition time (TR) 2000 ms, echo time (TE) 30 ms, flip angle (FA) 90°;

voxel size 3.0 x 3.0 x 4.0 mm3, field of view (FOV) 200x200 mm2. In addition, each participant's high-resolution anatomical images were acquired through three-dimensional sagittal T1-weighted magnetization-prepared rapid gradient echo (MPRGE) with a total of 192 slices (TR 2530 ms, TE 3.45 ms, FA 9°, inversion time (TI) 1100ms, voxel size 1.0 x 1.0 x 1.0 mm3, acquisition matrix 256 × 256, FOV 256 x 256 mm2, BW 190Hz/Px, slice thickness 1 mm). 17 child-parent dyads scanned at site 1 and the remaining 24 child-parent dyads were scanned at site 2. Both scanners were 3.0T Trio TIM with the same types of head coils and sequence parameters.

Imaging Data Analysis

Preprocessing.

Based on previous studies on ISC pre-processing pipelines (Nastase et al., 2019), brain images were preprocessed using statistical parametric mapping (SPM12, https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Images were corrected for slice acquisition timing and realigned for head motion correction. Subsequently, functional images were co-registered to each participant's gray matter image segmented from their corresponding high-resolution T1-weighted image, then spatially normalized into a common stereotactic Montreal Neurological Institute (MNI) space and resampled into 2-mm isotropic voxels. Images were subsequently smoothed by an isotropic 3D gaussian kernel with 6-mm full-width half-maximum (FWHM). The preprocessed images were regressed on a set of nuisance covariates (i.e., six motion parameters, the average signal of white matter and cerebrospinal fluid) and 140-sec high-pass filtered using toolbox Nilearn version 0.6.2. Finally, the first 5 volumes and the last 5 volumes were removed to minimize stimulus onset and offset effects and the data were z-scored overtime.

Inter-subject correlation (ISC) and statistical analysis

ISC was used to capture shared responses of each voxel across participants by correlating the corresponding voxel's time series between each pair of participants.

Whole-brain ISC maps during movie watching were computed for all possible pairs of 41 participants in a gray-matter mask using BrainIAK's ISC function (Kumar et al., 2020), which resulted in a total of 3321 pairs (Fig. 1b). Voxel-wise ISC values reflected Pearson's correlation between each pair of time series extracted from participant pairs. Correlations were then z-transformed using Fisher's transformation.

The ISC maps were submitted to further statistical analyses to identify brain regions that show significantly synchronous (shared) neural response across the whole sample. We adopted a recently developed linear mixed-effects (LME) model using a crossed random-effects formulation which can accurately interpret the ISC data's correlation structure (Gang Chen et al., 2017). This method has been demonstrated to have the three following advantages: i) Compared to the non-parametric methods, this method can effectively control for false positives; ii) this method also has good power attainment; iii) this method can effectively dissociate fixed and mixed effects. Participant' gender, age, and scanning sites were treated as covariates of no interest in the LME model. Significant clusters among all subjects were determined using a threshold of $q < 0.05$ with false discovery rate (FDR) correction for spatial multiple comparisons on the whole brain level (Benjamini and Hochberg, 1995). Next, we used a two-group formulation of the LME model with three covariates (age, gender, and site) to identify whether there were voxels that were more synchronous in child-parent dyads than child-stranger pairs. Significant clusters were examined at an initial voxel-wise threshold of $p < 0.001$ (two-tailed) and an extent threshold $p < 0.05$ corrected for multiple comparisons with a minimum cluster size of 82 voxels using 3dClustSim module of AFNI (http://afni.nimh.nih.gov).

Inter-subject functional connectivity (ISFC) analysis

Inter-subject function connectivity (ISFC) analysis was implemented to identify stimulus-evoked functional connectivity patterns across participants. We used a seed-based ISFC approach by computing the correlation of a given seed's [i.e., 6-mm

sphere of the peak voxel at MNI coordinate (2, 38, -18) in the vmPFC and (0,56,12) in the dmPFC] time series in one participant with every other voxel's time series in another participant. The computation of ISFC produced two asymmetric matrices for $r_{(VMPFCsubject1,Ysubject2)}$ and $r_{(VMPFCsubject2,Ysubject1)}$. We then computed the average correlation, which was treated as the ISFC value between each participant pair where r represents Pearson's correlation and Y represent the time series of each given voxel from participants. The ISFC data structure was the same as the ISC data structure. We used the same LME model as the ISC analysis to determine which brain regions showed higher coordination with vmPFC and dmPFC in child-parent pairs than child-stranger pairs. Significant clusters among all subjects were determined by using a threshold of $q < 0.05$ with false discovery rate (FDR) correction for spatial multiple comparisons on the whole brain level (Benjamini and Hochberg, 1995).

Within brain functional connectivity (FC) analysis

In order to verify that child-parent vmPFC-hippocampal ISFC played a unique role in the relationship between negative family environment and children's internalizing problem, we also examined whether the single brain's vmPFC-seed FC is associated with negative family environment and children's internalizing problem. We examined single brain FC in children's and parent's brains, and ran multiple regressions with negative family environment and children's internalizing problems, as separate regressors, predicting vmPFC-seed function connectivity; these models included age, gender and site as covariates. Here, we found vmPFC-seeded FC within brain is not associated with negative family environment and children's internalizing problem after multiple comparisons (FDR = 0.05).

Meta-analytic decoding with neurosynth

The neurosynth framework provides a comprehensive dataset of whole-brain term-to-activation maps, which allow us infer the psychological domains involved in brain map of the shared vmPFC-circuits in child-parent dyads. Specifically, we correlated the

child-parent thresholded vmPFC and dmPFC ISFC map (FDR<0.05) to the topics map of 15 general psychological domains involving a range of possible brain processes during movie viewing using the Neurosynth's python notebook （[https://github.com/neurosynth/neurosynth]; commit version 948ce7).

Mediation Analysis

The mediation analysis was performed using the Mediation Toolbox developed by Tor Wager's group (https://github.com/canlab/MediationToolbox). Prior to the mediation analysis, average values representing intersubject functional connectivity strength with vmPFC and dmPFC were extracted from 13 significant clusters and 2 significant clusters identified in the above linear mixed model to examine the correlation with negative family environment using FDR corrections (Benjamini and Hochberg, 1995) to control the false-positives. Only the left hippocampus (r = -0.461, q value = 0.038). and the right precuneus cortex (r = -0.48, q value = 0.038) remained significant after correction. Based on previous studies that showed that the interaction between medial prefrontal cortex and hippocampus are more engaged in social and emotional functioning, we correlated the left hippocampus with children internalizing problems, anxious/depressed, withdrawn/depressed somatic, externalizing symptoms, aggressive and rule-breaking symptoms. After FDR corrections, children who were anxious/depressed (r = -0.42, q value = 0.06) and had internalizing problem (r = -0.40, q value = 0.06) showed marginally significant correlation with the left hippocampus. Next, a mediation model was constructed to investigate the mediating pathways between negative family environment, shared vmPFC-hippocampus ISFC strength (the contrast between child-parent dyads and child-stranger pairs), and children's anxious/depressed and internalizing problem. The indirect or mediated effect was tested by a bias-corrected bootstrapping method (n = 10000 resamples). The indirect effect was considered significant if the 95% confidence interval (CI) did not include zero.

Event boundary analysis.

The correlation between hippocampal, vmPFC responses and event rating. Event boundaries were collected by an independent group of 20 adult raters (10 males) who watched this 6-minute video. The rates were asked to press a key at the end of one meaningful event and the beginning of another, which is consistent with previous studies. In line with Reagh's studies (Reagh et al., 2020), we include the boundary timepoints and within timepoints of this video. Boundaries timepoints are agreed by at least half of the samples, and we find a total of 10 event boundaries of the time series. We also add the same number of within time points compared to the event boundaries. The boundary and within time points were next convolved with a canonical HRF to obtain the boundary and within timeseries. Then we correlated each participant's hippocampal and vmPFC timeseries with the event boundary and within timeseries derived from the independent raters. Finally, we examined whether children's hippocampal and vmPFC response to boundary and within timeseries were correlated with their parents' responses to boundary and within timeseries.

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