Empathy networks in the parental brain and their long-term effects on children's stress reactivity and behavior adaptation

Eyal Abraham, Gal Raz, Orna Zagoory-Sharon, Ruth Feldman

ARTICLE INFO

Keywords:
Parental Brain
Empathy
Network Integrity
Embodied Simulation
Mentalizing
Longitudinal Studies

ABSTRACT

Parental empathy is a key component of sensitive parenting that supports children's social adaptation throughout life. Consistent with a two dissociable network perspective on empathy, we measured within- and between-network integrity of two empathy-related networks in the parental brain as predictors of children's social outcomes across the first six years of life. We focused on two empathy networks; embodied simulation, which supports parents' capacity to resonate with infant state and emotions and implicates cingulo-insulary structures, and mentalizing, which underpins parents' theory-of-mind and mental attributions via prefrontal-temporo-parietal circuit. We followed 87 first-time parents across the first six years of family formation, including heterosexual and homosexual parents. In infancy, parents' brain response to own versus unfamiliar infant stimuli was imaged; in preschool, children's cortisol production and emotion regulation were assessed; and at six years, children's behavior problems were reported. Parents' intra- and inter-network integrity increased when viewing their own infant compared to unfamiliar infant, suggesting that attachment stimuli increase network coherence in the parental brain. Functional connectivity within the parent's embodied simulation network in infancy predicted lower child cortisol production while inter-network connectivity among the embodied simulation and mentalizing networks was associated with more advanced child emotion regulation skills in preschool and lower internalizing problems at six years. Children's emotion regulation capacities mediated the link between inter-network integrity in the parental brain and internalizing symptoms. Our findings, the first to demonstrate that integrity of empathy-related networks in the parental brain shape children's long-term stress reactivity and emotional adaptation, highlight the brain component of the parental empathy attribute, suggest that increased coherence within the 'parental caregiving network' marks a key feature of parent-infant attachment, and contribute to discussion on biobehavioral mechanisms underpinning the cross-generation transmission of human stress reactivity and sociality.

What does the baby see when he or she looks at the mother's face? I am suggesting, that ordinarily, what the baby sees is himself or herself. In other words the mother is looking at the baby and what she looks like is related to what she sees there.

(Winnicott, 1971, p.112).

1. Introduction

Theoretical perspectives consider the parent's empathic capacity - defined as the parental ability to share the child's feelings, thoughts, motives, and wishes - as a central component of sensitive parenting and as a cornerstone of children's social adaptation, including evolutionary theories (Hrdy, 1999), psychoanalytic theories of affect (Kohut, 1971; Winnicott, 1965), developmental theories (Feshbach, 1990), social learning theory (Iannotti, 1978), and attachment theory (Bowlby, 1973). Empirical studies within these conceptual frameworks have shown that the parent's empathic capacity plays a key role in children's socialization, affect regulation, symbolic competence, cognitive functioning, and the child's ultimate ability to internalize a moral code and empathize with others (Feldman, 2007a; Strayer and Roberts, 2004; Feshbach, 1990; Landry et al., 2006; Psychogiou et al., 2008; Eisenberg

http://dx.doi.org/10.1016/j.neuropsychologia.2017.04.015
Received 25 January 2017; Received in revised form 5 April 2017; Accepted 8 April 2017
0028-3932/ © 2017 Elsevier Ltd. All rights reserved.

Please cite this article as: Abraham, E., Neuropsychologia (2017), http://dx.doi.org/10.1016/j.neuropsychologia.2017.04.015
and McNally, 1993). The parent’s empathic orientation enables children to feel secure, recognize their own thoughts and feelings, show compassion toward others, and become competent members of social groups (Feldman, 2016; Fonagy et al., 2007).

Evolutionary models suggest that the capacity for empathy evolved within the mammalian parent-offspring bond to provide care that exceeds feeding and includes nurturing and comfort, thus maximizing offspring survival and reproduction (MacLean, 1985; De Waal, 2008; Gonzalez-Liencres et al., 2013). Across mammalian evolution the “parental caregiving system” extended to include other group members and the “empathic” capacity to other social relationships (Bell and Richard, 2000; Hrdy, 2009; De Waal, 2007; Feldman, 2015a, 2017). In mammals, the parent’s ability to detect motivationally salient and survival-related cues to recognize offspring’s distress is underpinned by the ancient limbic system (Feldman, 2015a; Lindquist et al., 2012; Shahrokh et al., 2010; Dulac et al., 2014), which enables parents to rapidly respond to infant physiological and emotional signals. Yet, across human evolution, there was a progressive increase in length of infant dependency and in the complexity of social networks that grew to include both biological and non-biological helpers (Clutton-brock, 2002). The parent’s automatic response to infant distress became insufficient, and abilities such as affect sharing, biobehavioral synchrony, self-other awareness, mental flexibility, and perspective-taking, supported by paralimbic and cortical networks, evolved to increase offspring’s adaptation (Decety, 2015; De Waal, 1996; Feldman, 2015b).

Research in human neuroscience supports a two-system model of empathy; an emotional and a cognitive system that implicate dissociate brain networks (Shamay-Tsoory, 2011). The emotional system not only supports affective sharing, but also serves a more fundamental embodied simulation function. Embodied simulation is a phylogenetically-early, bottom-up process that enables vicarious sharing of the bodily states of others and is supported by an assemblage of brain structures, including the anterior insula (AI), anterior cingulated cortex (ACC), and inferior frontal gyrus (IFG). The embodied simulation network enables parents to respond to infant pain and emotions by representing them in the self (Fan et al., 2011; Feldman, 2015a), ground emotional experiences in the present moment on the basis of interoceptive representations (Craig, 2009; Gallee, 2014), and afford perceptual-motor coupling of infant action to better understand infant communications (Rizzolatti and Craighero, 2004). Cognitive empathy is a more advanced top-down mentalizing system that supports inferences on others’ mental states (Shamay-Tsoory, 2011) and imaginative transposing of self into the thoughts and feelings of others (Decety and Jackson, 2006). It includes structures such as the dorsomedial prefrontal cortex (dmPFC), ventromedial prefrontal cortex (vmPFC), temporal parietal junction (TPJ), temporal pole, superior temporal sulcus (STS), and frontopolar cortex, and enables parents to understand the infant’s non-verbal intentions from actions, represent infant state, and plan future caregiving (Feldman, 2017; Frith and Frith, 2006, 2012; Decety and Cacioppo, 2012). Importantly, parental empathy, like empathy in general, requires self-other differentiation to allow parents to distinguish their own thoughts and feelings from those of the infant’s (Feshbach, 1990).

The aforementioned empathy-related networks - embodied simulation and mentalizing- have been consistently found to activate in paradigms that elicit empathy (Raz et al., 2014). Since empathy is a multidimensional construct ranging from emotional contagion to cognitive perspective-taking, it is assumed that sensitive parenting requires the integration of both networks into the “parental caregiving network”. Indeed, fMRI studies of the human parental brain have repeatedly shown activation of embodied-simulation and mentalizing structures when parents are exposed to auditory, visual, or multimodal stimuli of their infants compared to unfamiliar infants (Abraham et al., 2014, 2016; Atzil et al., 2011, 2012; Feldman, 2015a, 2017; Swain, 2011, Swain et al., 2014), suggesting that activation of these two networks in the parental context index attachment-specific responses. This is consistent with research in humans and animals indicating that social closeness or distance, that is, familiarity, kinship, and group membership, modulate the degree of empathy (Singer, 2006; Engert et al., 2014; Wang et al., 2016; Gonzalez-Liencres et al., 2013; Decety, 2015; Mellon et al., 2014). Yet, despite the centrality of empathy to parenting, no our knowledge, has tested the degree to which these empathy-related brain structures cohere into dissociable networks when parents view their own, as compared to unfamiliar infants. It is also unknown whether intra- and inter-connectivity of the two networks in the parental brain bear long-term consequences for children’s development. In the current study we examined within and between network integrity of the two empathy-related networks in the parental brain as predictors of children’s development across the first six years of life focusing on three outcomes: stress reactivity as measured by cortisol production, emotion regulation strategies, and externalizing and internalizing symptoms.

Cortisol (CT), the end product of the hypothalamic pituitary adrenal (HPA) axis, marks the body’s central response to stress and plays a key role in establishing homeostasis after threat is removed (Ponzi et al., 2016). The HPA system has well-known effects on growth, reproduction, physiological homeostasis, and socio-emotional response, including empathy (Schneiderman et al., 2014; Rubin et al., 2005; Anderson and Galinsky, 2006). Individual differences in HPA activity are associated with children’s internalizing and externalizing problems (Cicchetti and Dawson, 2002). Higher basal CT may reflect a failure to effectively regulate physiological and emotional arousal and is linked with low empathy (Reinhard et al., 2012), internalizing problems (Smider et al., 2002; El-Sheikh et al., 2008; Goodyer et al., 2001; Lopez-Duran et al., 2009), aggressive behavior (Dettling et al., 1999), and depressive symptoms in children, adolescents, and adults (Bhagwagar et al., 2005; Ruttle et al., 2011; Dietrich et al., 2013), as well as with increased attention to threat (Vasey et al., 1996), conduct disorder, and anxiety (McBurnett et al., 1991).

The parent-child relationship is among the central contributors to the consolidation of children’s CT response (Gunnar and Donzea, 2002; Repetti et al., 2002; Gunnar et al., 2015; Hostinar et al., 2014a, 2014b; Jessop and Turner-Cobb, 2009). Sensitive parenting, including parental empathic responses to child emotional signals, attenuates children’s CT response to social stressors (Feldman et al., 2010a, 2010b; Weisman et al., 2013; Ahnert et al., 2004; Albers et al., 2008; Blair et al., 2008; Berry et al., 2016; Hostinar et al., 2014a, 2014b). In contrast, insensitive parenting alters the development of children’s stress response and threat-detection neurobiological circuits (Hostinar et al., 2014a, 2014b), and correlates with higher CT production (Marceau et al., 2015a, 2015b; Ahnert et al., 2004; Berry et al., 2016; Enlow et al., 2014) and inflexible response (Apter-Levi et al., 2016). However, to date, imaging studies have not explored the relationship between the parental brain and children’s CT reactivity.

Emotion regulation (ER), defined as the ability to manage states of increased positive and negative arousals to organize goal-directed behaviors (Rothbart and Posner, 1985; Cole et al., 2004; Eisenberg and Morris, 2002), is a key predictor of social-emotional and mental-health outcomes throughout life (Eisenberg, 2000; Moffitt et al., 2011). During the preschool years, children make important strides in ER abilities (Feldman, 2009; Zeman et al., 2006; Hirschler-Guttenberg et al., 2015). ER deficits have been linked with internalizing and externalizing symptoms (Eisenberg et al., 2009; Buchholdt, 2013; Morris et al., 2010; Aldao et al., 2010), low empathy and conscience (Feldman, 2015b; Kochanska et al., 2000), peer rejection, and antisocial behavior (Trentacosta and Shaw, 2009). Sensitive parenting that externally-regulate infant distress through empathic and supportive responses help children develop ER strategies for accurately labeling emotions, coping with distress and happiness, and communicating affect in socially-accepted ways by the preschool years (Batson, 2011; Feldman, 2003, 2007). It has been shown that sensitive early parenting promotes both ER skills (Eisenberg et al., 1998; Morris et al., 2007) and lower behavior problems in the preschool years (Cicchetti and
2. Materials and method

2.1. Participants

A total of 87 first-time parents raising their infant within a partnered relationship participated in the study [mean age Time 1: 36.1 ± 3.43 (SD)]; 41 heterosexual biological parents comprising 20 mothers and 21 fathers, and 48 homosexual fathers who were living within a committed two-parent family who had a child through surrogacy and were raising infants without maternal involvement since birth. In each father couple, one father was the biological father and the other was the adoptive, non-biological father. Infants [mean age at Time 1 ± 2: 11 ± 6.67 (SD); mean age at Time 2: 43 ± 4.45 (SD); Time 3: 79 ± 4.12 (SD)] were all born at term and healthy since birth. Parents were screened for high depression and anxiety symptoms using the Beck Inventory (BDI) (Beck, 1978) and the State-Trait Anxiety Inventory (Spielberger et al., 1970). Data of two fathers were excluded due to strong movement artifacts. No differences in socioeconomic status emerged between groups. Participants were compensated for their time and gave written informed consent. The study was approved by the Ethics Committee of the Tel Aviv Sourasky Medical Center.

2.2. Procedure

The experimental procedure included four sessions with each family (Fig. 1). In the first, we visited families at home (Time1 = Infancy; 11 ± 6.67 (mo)), parents were instructed to play with the infant “as they usually do” and were videotaped. In the second session, several days later (Time2 = infancy), parents underwent functional brain scanning with the individually-tailored home videotapes used as fMRI stimuli. In the third session (Time3 = Preschool; 43 ± 4.45 (mo)), when children reached preschool age, we re-visited families at home, salivary samples were collected from parent and child for CT, and visit included parent-child interactions and several child emotion-regulation procedures with a stranger videotaped for later coding when parent was in the room. We carefully selected well-validated emotion-regulation procedures that tap children’s use of emotion-regulatory strategies, as follows.

2.2.1. Regulation of negative emotions – Masks

In this procedure, adapted from the LAB-TAB (Goldsmith and Rothbart, 1996), child sits in front of the experimenter who puts on four increasingly fear-eliciting masks: rabbit, lion, alligator, and monster. After putting on each mask, the experimenter called the child’s name and left the mask on for 15 s.

2.2.2. Regulation of positive emotions – Bubbles

Similarly adapted from the LAB-TAB (Goldsmith and Rothbart, 1996), the experimenter blew soap bubbles for the child to play for 5 min and invited the child to play together.

In the fourth session (School entry; 79 ± 4.12 (mo)), when children were six years each parent completed self-report measures of child behavior problems.

2.3. Cortisol collection and determination

Saliva was collected during home visits at preschool period (Time 3) between 3P.M. and 6P.M. Children were asked to chew on a roll of cotton for 1 min until it became saturated and then was placed in a Salivette (Sarstedt, Rommelsdorf, Germany). Saliva samples were collected at three time-points during home visit: At arrival (baseline), 30 min later - prior to the fear paradigm (masks), and 20 min thereafter. Parents were instructed to make sure children weren’t involved in exceptional physical activities and weren’t exposed to any stressors prior home visits. Salivates were kept cool and then stored at −20 °C until centrifuged at 4 °C at 1500 x g for 20 min. Cortisol levels were then assayed using a commercial ELISA kit (Assay Design, MI).
A. INFANCY > B. PRESCHOOL > C. SCHOOL-ENTRY


2. Parental Brain 3. Saliva Cortisol Sampling

Fig. 1. Experimental procedure. During the infancy stage (A), we videotaped first-time parents at home interacting with infants (A1). Several days later, each parent underwent functional brain scanning using the home videotapes as fMRI stimuli (A2). During the preschool stage (B), we revisited families and administered a social battery to assess children's positive and negative emotion regulation (B1-2), and collected salivary cortisol samples from children (B3). During school-entry (C), parent's filled out child behavior checklist to identify child’s behavioral problems.

Measurements were performed according to the kit's instructions. CT levels were calculated by using MatLab-7 according to relevant standard curves. The intra-assay and inter-assay coefficients are less than 10.5% and 13.4%, respectively.

Children's salivary CT was measured, consistent with prior research, by computing area under the curve with respect to the ground (AUCg; Pruessner et al., 2003). The AUCg was used as a measure of total CT production (in pg/mL) over a time-period (Pruessner et al., 2003). We have previously measured CT during a home visit in children of that age (Ostfeld-Etzion et al., 2015) and utilized the index of AUCg during a home visit as a measure of overall CT production in children of that age (Apter-Levi et al., 2016; Halevi et al., 2017).

2.4. Coding

2.4.1. Child emotion regulation

The Masks and Bubbles paradigms were each micro-coded for the child's regulatory skills, consistent with our prior research (Hirschler-Guttenberg et al., 2015; Ostfeld-Etzion et al., 2015; Feldman et al., 2011). In light of these studies of preschool-aged children we focused on complex, age-appropriate regulatory behaviors that are not inherently self-regulatory but may be used for emotion regulation during moments of increased stress, such as substitutive-symbolic play (e.g. ‘dolly’s hungry’), functional play (for example, moving a toy train back-and-forth), using executive skills to divert attention, or talking to parent or experimenter. Scores from the two paradigms were averaged into a ‘child regulatory skills’ construct. Coding was conducted on a computerized system (The Observer, Noldus Information Technology, Wageningen, The Netherlands). Two blind trained observers coded while the tape progressed at normal speed, shifting to slow motion when shift in behavior occurred. Coders were trained to 90% reliability. Inter-rater reliability, measured on 20% of the sample, was intraclass, $r = 0.86$ for the masks, and $r = 0.89$ for the bubbles. Proportion and frequency variables were used.

2.4.2. Self-report measures

The Child Behavior Checklist (CBCL) 6–18 (CBCL; Achenbach, 1991) is the most widely-used instrument. The CBCL is a 118-items instrument that measures behavior and emotional problems over the past 6 months. Items are rated on a 3-point scale ranging from 0 (not true) to 2 (very true or often true). Standard scores from the externalizing scale, which includes 35 items for two subscales (aggressive behavior and delinquent behavior; $\alpha = 0.89$), and the internalizing scale, which includes 32 items from three subscales (anxious/depressed, withdrawn, and somatic complaints; $\alpha = 0.87$), were used in these analyses. None of the children were scored above the cutoff criterion for clinical externalizing and internalizing problems (> 64). In addition, since no differences emerged between boys and girls on externalizing and internalizing symptoms, both genders were collapsed into one group ($t(1,38) = -1.168$, $P > 0.2$; $t(1,38) = -0.089$, $P > 0.9$, respectively; Supplementary Table 2).

2.5. fMRI data acquisition and analyses

Imaging was performed on a GE-3T Sigma Horizon echo-speed scanner with a resonant gradient echoplanar imaging system. Functional T2*-weighted images were obtained using field of view $= 220 \text{ mm}$, matrix size $= 96 \times 96$, repetition time $= 3000 \text{ ms}$, echo time $= 35 \text{ ms}$, flip angle $= 90^\circ$, acquisition orientation of the fourth ventricle plane, 39 axial slices of 3-mm thickness, and gap $= 0$. In addition, each functional scan was accompanied by a three-dimensional (3D) anatomical scan using anatomical 3D sequence spoiled gradient (SPGR) echo sequences that were obtained with high-resolution of $1 \times 1 \times 1 \text{ mm}$. Functional MRI data were analyzed with the BrainVoyager analysis package (version 2.1; Brain Innovation).

2.6. fMRI data preprocessing

The first six volumes, before signal stabilization, were discarded to allow for T1 equilibrium. Preprocessing of functional scans included 3D motion correction, slice scan time correction, spatial smoothing [a full width at half maximum (FWHM) 4-mm Gaussian Kernel], linear trend removal, and high-pass filtering (fast Fourier transform based with a cutoff of two cycles per time course). The functional images were then superimposed on 2D anatomical images (a 3D spoiled gradient echo sequence, field of view $= 220 \text{ mm}$, matrix size $= 96 \times 96$, axial slices of...
3 mm thickness, gap = 0) and incorporated into the 3D datasets through trilinear interpolation. Exclusion criteria of head motion greater than 1.5 mm and rotation greater than 1.5 degrees during fMRI scanning. The complete dataset was transformed into Talairach space.

2.7. fMRI experimental design

While lying in the scanner, participants were instructed to watch a series of attachment-related video vignettes presented on the screen. For ecological validity, we examined parents’ brain response to natural interactions and attachment-related stimuli videotaped in the home environment, the context where parental-infant bonding takes place. All videos included multi-modal, dynamic, and realistic stimuli. Each parent's video set was individually tailored, comprising three 2-min infant- and parent-related videos with alternating rest fixation periods of 15 or 18 s between stimuli, preceded by a1-minute rest with fixation period. For the NCI analysis we used a 2 min vignette of each parent interacting with her/his own infant during a free play (‘Self—Infant Interaction’). Stimuli were counterbalanced and were randomly presented in three different order patterns. In addition, NCI for a 2 min ‘Unfamiliar Parent-Infant Interaction’ condition (where the parent was the same sex as the participant) was calculated. To ensure that parents and infants’ affective states did not differ between participants, we selected only clips in which the infants and the parents were in neutral affective states, as coded using the CIB rating system (Feldman, 1998).

2.8. Computation of network cohesion indices

To analyzing the dynamic functional network connectivity of the three brain networks of interest, we used a NCI index (for details, see Raz et al., 2012, 2014) probing the coordination both within defined network (intra-network cohesion index; intra-NCI) and between networks (inter-network cohesion index; inter-NCI). Cohesion is measured here in a way that reflects both the strength of the average correlations between signals in a group of regions and the variation about this average, with higher values for correlations that are narrowly distributed about a high average. First, the average signal of each region-of-interest was extracted using a Gaussian mask with 3 mm radius around the seed coordinates in a selected time window of 114 s (38 TRs), for both 'Self-Infant Interaction' and 'Unfamiliar Parent-Infant Interaction' conditions, incorporating a hemodynamic delay of two TRs. Next, for each network $k$, and participant $p$, the set of all pairwise Pearson correlations was computed at the selected time-window $t$ as follows

$$NCl_{ij}(t) = t\text{-statistic} \left\{ p_{ij}(t) \mid i, j \in \text{network} \right\}$$

Thus, the NCI resulted from a right tailed Student’s $t$-test with a null hypothesis of $\mu_R = 0$ performed on the population of the Fisher Z-transformed coefficients. In this test, the $t$-statistic serves as a probe for the connectivity within the network with high values when the mean correlation is high and variance is low. Inter-NCI was calculated in the same manner, except that the population of the $t$-tested pairwise correlations includes pairs of ROIs in different networks.

2.9. Definition of networks of interest

Relevant comprehensive and updated meta-analyses of neuroimaging studies were used to define the embodied-simulation and mentalizing networks. The embodied simulation network was defined on the basis of recent meta-analyses on empathy (Fan et al., 2011) and mirror properties (Molenberghs et al., 2012). The definition of the mentalizing network relied on studies in which participants were instructed to infer other’s intentions, thoughts and future actions (Bzdok et al., 2012). For details, see Fig. 2 and Supplementary Table 1. MNI to Talairach transformations were performed using a Lancaster transformation (Lancaster et al., 2007).

2.10. Statistical analyses

Paired sample $t$-tests were done to compare parents’ intra- and inter-NCIs between ‘Self-Own Infant Interaction’ condition and ‘Unfamiliar Parent-Infant Interaction’ condition. Independent two-tailed $t$-test was used to compare children's CT ACC levels which have been divided into two groups: children of parents with low embodied simulation-NCI and children of parents with high embodied simulation-NCI. Longitudinal associations between parent’s intra-NCI, inter-NCI in infancy and child’s behavioral data in childhood assessed using Pearson correlation. The level of significance for all analyses was set at $P < 0.05$.

3. Results

3.1. Differences in parent's intra- and inter-empathy network integrity to 'Own' and 'Unfamiliar' Infants

Empathy networks were defined on the basis of prior research (Fig. 2, Supplementary Table 1). To examine parents’ functional connectivity within and between networks during the observation of ‘self-own infant interaction’ and ‘unfamiliar parent-infant interaction’, we applied network cohesion analysis (NCI; Raz et al., 2012, 2014) to derive intra- and inter-network indices. Before conducting our analyses we examined within and between networks functional connectivity differences between the three groups of parents in each condition and found no gender and sexual orientation differences in brain networks supporting empathy between the groups while viewing their own or unfamiliar infants ($P > 0.05$; Supplementary Table 3). Thus, we collapsed the parent groups. First, to evaluate the effects of viewing ‘Self-Own Infant Interaction’ video (condition 1) compared with ‘Unfamiliar Parent-Infant Interaction’ video (condition 2) on Intra-embodied simulation-NCI, mentalizing-NCI and Inter-embodied simulation-mentalizing-NCI (Hypothesis 1), paired samples $t$-tests were conducted between the two conditions (‘Self-Own Infant Interaction’ and ‘Unfamiliar Parent-Infant Interaction’). Results indicate that parents showed significantly greater connectivity within the embodied simulation network (intra-NCI), mentalizing network (intra-NCI), and between the two networks (inter-NCI) in the ‘Self-Own Infant Interaction’ condition than in the ‘Unfamiliar Parent-Infant Interaction’ condition (Fig. 3a; embodied simulation-NCI: $t = 3.125, P < 0.05$; B: mentalizing-NCI: $t = 2.799$,
P 0.05; C: embodied simulation-mentalizing-NCI: t=2.673, P 0.05, Bonferroni-corrected), confirming our first hypothesis. In addition, we found positive correlations between parent’s embodied simulation-NCI, mentalizing-NCI and embodied simulation-mentalizing-NCI in the ‘Self-Own Infant Interaction’ condition, but no associations between these variables were found in ‘Unfamiliar Parent-Infant Interaction’ condition (see Supplementary Table 4).

3.2. Longitudinal links between parent’s intra- and inter-empathy network integrity and children’s stress reactivity

To explore the implications of individual differences in the parent’s intra- and inter-empathy network integrity to child’s outcomes, we used fMRI data of the primary-caregiver parent in each couple. We first tested direct links between the degree of parent intra- and inter-empathy networks connectivity in infancy and child’s CT production at Time 3 (Preschool) (Hypothesis 2). Independent samples t-tests measured differences in child’s CT production among parents with high versus low NCI using the median split. As expected, results indicate that preschoolers being raised by parents with greater connectivity in the embodied simulation network (median=0.28) has significantly higher levels of CT during home visit (Fig. 4; t=2.379, P < 0.05; Supplementary Table 5). No differences emerged between the high and low parents groups in mentalizing-NCI and embodied simulation-mentalizing networks-NCI (mentalizing-NCI t=−0.676, P > 0.5; embodied simulation-mentalizing-NCI: t=−0.513, P > 0.5).

Next, we explored whether parents’ individual differences in neural crosstalk between the two networks would support child’s long-term behavioral adaptation in preschool (Time 3) and inschool-entry (Time 4) (Hypothesis 3). Parent’s embodied simulation- mentalizing-NCI
positively correlated with child's regulatory skills in preschool (Fig. 5A; $r=0.669, P > 0.001$) and was negatively associated with child's internalizing behavior problems in school-entry (Fig. 5B; $r=-0.564, P < 0.001$), but not associated with child's externalizing problems ($r=0.081, P > 0.5$). We also examined parents' intra-connectivity and children's outcomes, and found positive correlation between parent's embodied simulation-NCI and child's regulatory skills in preschool ($r=0.479, P < 0.01$), but no associations with behavioral problems in school age (internalizing: $-0.183, P > 0.2$, externalizing: $-0.059, P > 0.5$). However, mentalizing-NCI was not correlated with any child's outcomes: regulatory skills in preschool ($r=0.153, P > 0.3$), internalizing ($-0.067, P > 0.5$) and externalizing problems in school age ($r=0.130, P > 0.3$). To test Hypothesis 4 on indirect effects via child's regulatory behavior in preschool years, we examined whether preschooler's regulatory behavior mediated the relationship between parent's inter-embodied simulation and child's internalizing behavior in school years. As predicted, using Sobel's (1982) test, we found full mediation by preschooler's regulatory behavior for the link between parent's embodied simulation-mentalizing-NCI and children's internalizing behavior during school-entry ($z=-2.2003, P < 0.05$; Fig. 5C). Baron and Kenny's (1986) steps were computed. In Step 1, associations between the predictor (parent's embodied simulation-mentalizing-NCI) and outcome (child internalizing behavior) was found significant (path C; $\beta=0.564, t=-3.346, P < 0.01$). In Step 2, associations between predictor and mediator (preschooler's regulatory behavior) were significant (path A; $\beta=0.669, t=7.197, P < 0.001$). In Step 3, associations between mediator and outcome controlling for predictor were significant (path B, $\beta=-0.480, t=-2.311, P < 0.05$). In Step 4, we examined the association (Path C) between the predictor (parent's embodied simulation-mentalizing-NCI) and the outcome (child's internalizing behavior), controlling for child's regulatory skills in preschool years, and found the path to be non-significant ($\beta'=0.113, t=-0.543, P > 0.5$). We conducted a Sobel's test of mediation effect. This effect was significant ($z=-2.2003, P < 0.05$), suggesting that children's regulatory behavior in preschool years mediated the negative association between parent's embodied simulation-mentalizing-NCI and child's internalizing behaviors in school years. These findings provide support to our third hypothesis that the multidimensional nature of parental empathy, as express in cohesion between the two empathy-related networks, bears long-term effect on child's regulatory competencies and internalizing symptoms.

4. Discussion

Results of the current study are the first, to our knowledge, to address functionality of empathy-related networks in the parental brain in infancy and assess its long-term implications for children's stress reactivity and social-emotional development across the first years of life. Our data highlight three important findings. First, we found increased connectivity within and between empathy-related networks when parents are exposed to their own infant stimuli compared to unfamiliar infant. Second, we demonstrate that greater inter-connectivity in the parent's embodied simulation network, implicating increased emotional empathy, predicted lower cortisol reactivity in their preschool-aged children. Finally, we showed that greater connectivity between the two empathy networks - embodied simulation and mentalizing - predicted lower child internalizing symptoms at six years as mediated by the child's ER capacities. Overall, our findings are in line with recent social neuroscience models that highlight the importance of testing the functional and integrative properties of core networks, rather than the activations of discrete structures, as predictors of abilities that support human social life (Stanley and Adolphs, 2013; Abraham et al., 2014, 2016; Raz et al., 2014, 2016a, 2016b; Young et al., 2016).

The parent's empathic capacity is a key feature of sensitive parenting. We found greater coherence within the embodied simulation and mentalizing networks, as well as stronger connectivity between these two networks when parents observed their own infant. This is...
consistent with human and non-human studies showing that chimpanzees yawn more when watching a familiar conspecific yawning compared to unfamiliar one (Campbell and DeWaal, 2011), prairie voles exhibit "consolation" behaviors towards familiar conspecifics (Burkett, 2016), and humans display enhanced neural activity in ACC and AI when viewing loved ones in physical pain compared to strangers (Cheng et al., 2010). Ours is the first study to explore the parent's functional connectivity within and between empathy-related networks in the context of the parent-child attachment and are consistent with studies indicating greater activations of the 'human parent caregiving' network to own-infant stimuli (for review, see Feldman, 2015a, 2017; Rilling and Young, 2014). We suggest that such increased coherence to attachment stimuli marks an important feature of the parental brain at health. Research has indeed shown that depressed mothers did not show increased activations to their own infant compared to unfamiliar infant's cry and substance abusing mothers showed lower AI activations to their own infant cries compared to healthy mothers (Laurent and Ablow, 2012; Landi et al., 2011).

Importantly, imaging data does not show a consistent pattern of findings with regards to gender differences in relation to the neural mechanisms of empathy in humans and studies differ widely in the definition of empathy and the paradigm used. Few neuroimaging studies reported gender differences in brain activations while participants observed pain to others (Singer, 2006) or facial expression (Schulte-Rüther et al., 2008) and it is thus assumed that females and males may rely on different cognitive and emotional strategies when emphasizing to others' pain. However, this may not relate to parental empathy; much research has shown similar levels of parental sensitivity and reciprocity in mothers and fathers in research spanning infancy to adolescence (Feldman, 2000; Feldman et al., 2013; Feldman and Masalha, 2010). Our findings similarly show no gender differences between primary-caregiving mothers and fathers in the degree of network coherence within the embodied simulation and mentalizing networks, nor did we found gender differences in the connectivity between these networks. Thus, the neural underpinnings of "parental empathy" may relate more to caregiving experiences and individual differences than to parent gender.

These findings are consistent with the cooperative care hypothesis, which suggests that humans' unique ability to share emotions, imagine mental states, and identify with others evolved from the a uniform neural pathways underlying sensitive nurturance, response to offspring cues, and anticipation of infant physiological needs in multiple cooperative caregivers; mothers, fathers, siblings, and grandparents, as well as non-biologically related adults (Hrdy, 2009).

We found that preschoolers of parents with greater internal connectivity within the embodied simulation network showed lower stress reactivity and had lower CT production. These findings extend research on the links between empathic parental behavior and lower child stress reactivity and between parental insensitivity, lack of empathy, and reduced self-other differentiation with dysregulated stress response (Feldman, 2015b). We show here that not only parental behavior but also the parental "empathic brain" predicts children's cortisol production several years later. Animal models described the non-genomic cross-generation transmission of stress reactivity of both maternal and paternal care on offspring's HPA stress regulation (Hennessy et al., 2009; Hostinar et al., 2014a, 2014b; Rodgers et al., 2013; Champagne and Meaney, 2001). Maternal separation increases offspring corticotrophin-releasing factor (CRF) gene expression in the paraventricular nucleus of the hypothalamus (PVNh) and the central nucleus of the amygdala (CnAmy), and have major effects on systems that regulate CRF expression in the PVNh and CnAmy. These include glucocorticoid (GR) receptors that inhibit CRF synthesis and release in the PVNh neurons, as well as GABAergic/central benzodiazepine (CBZ) levels that regulate both amygdaloid CRF activity and levels of noradrenergic neurons in the locus ceruleus (LC) and nucleus tractus solitarius (NTS)(Caldji et al., 2000). In addition, maternal separation alters development of ascending serotonergic systems, and increases CSF measures of the central noradrenaline and serotonin (5-HT) responses to stress (Kraemer et al., 1989; Higley et al., 1991). Such brain and hormonal changes increase offspring behavioral and neuroendocrine reactivity to stress and these, in turn, organize parenting behavior thereby shaping stress reactivity in the next generation (Francis et al., 1999; Champagne and Meaney, 2001; Meaney, 2001). Human imaging studies have shown that the AI and ACC – key nodes of the embodied simulation network - play a critical role in facilitating appropriate response to stress, and greater connectivity between these areas was found to modulate the stress response (McMenamin et al., 2014; Hermans et al., 2011). Moreover, mothers with lower CT reactivity showed increased activation in the ACC and insula to their infant's cry (Laurent et al., 2011). The ACC is involved not only in the regulation of HPA-axis functioning (Diòrio et al., 1993) but also in offspring's distress call during separation from mother (MacLean and Newman, 1988). Our results extend previous knowledge and are the first to show that functional properties of ACC connectivity in the parental brain shape offspring HPA-axis reactivity in humans.

Connectivity between the two empathy networks in the parental brain predicted better ER skills in early childhood and less internalizing symptoms at six years. Furthermore, children's ER abilities mediated the link between parents' inter-network connectivity and internalizing symptoms. Ours is the first study to follow consequences of the parental brain in infancy across the first six years of the child’s life. At 5–6 years, important maturational changes occur in children's cognitive, social, and emotional abilities (Collins et al., 2002) as well as in children's brain maturation (Del Giudice, 2014). At this stage, children enter the social world and must learn to interact with non-kin peers and adults (Furman and Buhrmester, 1992; Hartup, 1996) and their ability to cooperate, manage conflicts, empathize, and regulate emotions increase (Feldman et al., 2010; Vaish and Warneken, 2012). Individual differences in empathic competencies at this age are associated with greater maturity, lower social withdrawal, and greater social cognition (Miller and de Haar, 1997; Eisenberg and Miller, 1987; Strayer and Schroeder, 1989; Hoffman, 1984; Findlay et al., 2006). Inhibited toddlers showed both internalizing symptoms and reduced empathy towards a stranger (Young et al., 1999), and children with internalizing symptoms displayed lower ER (Eisenberg et al., 2001a, 2001b; Blair et al., 2004). As internalizing behaviors in middle childhood were found to predict depressive symptoms, delinquency, and substance abuse throughout life (Marmorstein et al., 2010; Harrington et al., 1999), our findings charting a line from network integrity of the parental brain to ER and cortisol reactivity in preschool and finally to internalizing symptomatology upon school entry may have important implication for theory and intervention-building. We previously found (Abraham et al., 2016) that complex self-regulatory skills and socialization skills were linked with the parent's functional connectivity within the embodied simulation and mentalizing networks, respectively. Here we show that the development of children's behavior symptoms is shaped by interconnectedness of the two empathy-related networks in the parent's brain in infancy. Such finding highlights the integration of both networks and their functional connectivity as important predictors of children's adjustment.

It has long been recognized that mammalian social behavior is transmitted cross-generationally through reciprocal behavior within attachment bonds (Meaney, 2001; Braun and champagne, 2014; Tinbergen, 1963; Feldman, 2016; Putalaz et al., 1998). Yet, the mechanisms of cross-generational transmission are far from understood. Our findings suggest that the cross-generational transmission of human empathy and prosocial behavior occur within the parent-infant context and implicates two components: the first is a phylogenetically ancient, automatic, and contagion-like process that is expressed by motor and affective mimicry and interoceptive representations of other's state and is underpinned by the parent's embodied simulation network (Shamay-Tsoory et al., 2009; Galles, 2007; Bruneau et al.,
Maternal depression across the first years of life compromises child psychosocial adjustment; relations to child HPA-axis functioning. Psychoneuroendocrinology 64, 45–56.


Burkett, J., 2016. The Neurobiology of Consolation in the Prairie Vole. (Doctoral dissertation) EMORY UNIVERSITY.


Cicchetti, D., Dawson, G., 2002. Early attachment and social competence: implications for children's social functioning and behavior problems (Sanson et al., 1991), or genetic factors that may have contributed to the longitudinal effects. Finally, our sample includes nonclinical healthy parents and children and future studies are needed to generalize to high-risk parents and children. Our results may have several implications for intervention and are consistent with mentalization-based treatments (Allen and Fonagy, 2006), filial therapy (Guinney et al., 1966), and empathy-focused interventions for parents that focus on improving parental empathy. Much further research within the framework of a “two-person neuroscience” (Hari et al., 2015) is required to further understand how the parental brain provides the first template that introduces children to the social world and shapes their social adaptation throughout life.

Acknowledgement

Supported by the German-Israel Foundation (GIF) (Grant No. 1114-101.4/2010) and the Simms-Mann Foundation (Grant No. 001).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuropsychologia.2017.04.015.

References


