International Journal of Psychophysiology 136 (2019) 39–48

Contents lists available at ScienceDirect

International Journal of Psychophysiology

journal homepage: www.elsevier.com/locate/ijpsycho

Interoception sensitivity in the parental brain during the first months of parenting modulates children's somatic symptoms six years later: The role of oxytocin

Eyal Abraham[a], Talma Hendler[b,c,d], Orna Zagoory-Sharon[a], Ruth Feldman[a,e,*]

[a] Baruch Ivcher School of Psychology, Interdisciplinary Center (IDC), Herzliya 46150, Israel.
[b] Functional Brain Center, Wohl Institute of Advanced Imaging, Tel-Aviv Sourasky Medical Center, Tel Aviv, Israel.
[c] School of Psychological Sciences, Faculty of Medicine, Tel Aviv University, 69978 Tel Aviv, Israel.
[d] Sagol School of Neuroscience, Tel Aviv University, 69978 Tel Aviv, Israel.
[e] Child Study Center, Yale University School of Medicine, New Haven, CT, United states.

A B S T R A C T

Interoception, the perception and interpretation of one's own bodily signals, is a key aspect of human caregiving that impacts infant health and well-being across life. Interoception relies on limbic structures, mainly the amygdala, and the agranular visceromotor cortex, particularly the anterior insula (AI), that integrate with the oxytocin (OT) system to support interoceptive sensitivity. Here, we used functional magnetic resonance imaging (fMRI) to examine whether interoception sensitivity in the parent's brain during the first months of parenting combines with sensitive parenting and OT-system functionality to predict children's somatic symptoms six years later. We followed 45 primary-caregiving first-time mothers and fathers and their infants across the first six years of parenting. In infancy (Time 1), parents' brain response to infant stimuli was imaged, salivary OT measured, and parent-infant interactions coded for parent sensitivity. In preschool (Time 2), parent and child's OT and parent sensitivity were measured again. At six years (Time 3), parents reported on children's somatic symptoms. Greater activation of the parent's AI bilaterally when his/her child was an infant predicted lower child somatic problems at six years. Parent sensitivity partially mediated the links between parental AI activation and child somatic symptoms. In addition, greater parental bilateral amygdala activity predicted higher child OT levels at 3 years and parental OT moderated the relations between preschoolers' OT and later somatic symptoms. Our findings chart two independent cross-generational pathways from interoception sensitivity in the parent's brain and child somatization. The first defines an evolutionary-ancient path including the amygdala and the OT system that support mammalian attention to arousal modulations in response to social cues; the second, via the AI, implicates higher-order interoceptive representations of bodily responses and affective states that underpins human embodiment.

1. Introduction

The caregiver's ability to rapidly detect and immediately respond to the infant's physical needs and emotional states depends on a fine balance between the awareness of bodily signals originating in the caregiver's own body and those belonging to the infant (Feldman, 2012a, 2015a, 2016a; Hofer, 1994; Lambert, 2012). Such two-pronged capacity to both detect online changes in one's own bodily states and use them to guide well-adapted caregiving carries a profound effect on the developing infant, supporting maturation of the child's social skills, empathic abilities, body awareness, and sense of well-being (Feldman, 2012a, 2012b, 2017). This parental ability relies on specific neural circuits, endocrine systems, and behavioral patterns that undergo significant reorganization with the birth of an infant and serve to orient the parent to the caregiving role (Feldman, 2015b; Numan and Young, 2016; Weaver et al., 2004).

Interoception – the representation of one's own bodily milieu - refers to the individual's online awareness of internal bodily signals, including proprioception, heart rate, state of arousal, temperature, pain, air supply, energy level, and signals of hunger and thirst. In addition to its immediate function in the regulation of physiological homeostasis, interoception plays a central role in the individual's sense of self and physical health by generating subjective feelings and self-awareness, affording readiness to changing situational demands, and supporting moment-by-moment adaptation to the environment (Craig, 2002, 2009; Critchley et al., 2004; Critchley and Harrison, 2013; Seth and Friston, 2016). Interoception relies on several neural circuits. Representations of the body is supported by the agranular visceromotor cortices, a complex network including the anterior insula (AI), cingulate cortex, and orbital frontal cortex, and this network is located at the top of the interoceptice hierarchy. These higher-order visceromotor structures receive ascending projections from viscerosensory areas, including the

* Corresponding author at: Simms-Mann Professor of Developmental Social Neuroscience, Baruch Ivcher School of Psychology, Interdisciplinary Center (IDC) Herzliya, P.O. Box 167, Herzliya 46150, Israel.
E-mail address: feldman@mail.biu.ac.il (R. Feldman).

https://doi.org/10.1016/j.ijpsycho.2018.02.001
Received 24 May 2017; Received in revised form 25 January 2018; Accepted 1 February 2018
Available online 24 February 2018
0167-8760/

posterior and mid-insula whose descending connections engage a range of subcortical and brainstem targets, such as the amygdala, thalamus, and hypothalamus that support viscemotor control and monitor autonomic signals (Craig, 2009; Friston, 2010; Kumagai et al., 2012; Quattrocki and Friston, 2014; Simmons et al., 2013).

The amygdala and the AI mark two key regions in the interoceptive circuit, one at the top, the other at the bottom of the interoceptive hierarchy. The amygdala and AI are involved in translating bodily homeostatic information into subjective feelings that are grounded in the present moment and can guide ongoing social behavior (Craig, 2009; Cameron, 2009; Critchley and Harrison, 2013; Herbert and Pollatos, 2012; Seth and Friston, 2016). For instance, greater AI activations and gray matter volume were linked with interoceptive accuracy, general visceral awareness, and subjective emotional experiences (Craig et al., 2000; Critchley et al., 2002; Critchley et al., 2004). Moreover, individuals showing stronger connectivity within the interoceptive circuit, specifically, between the insula and anterior midcingulate cortex, exhibited greater concordance between subjective and objective measures of bodily arousals (Kleckner et al., 2017). Interestingly, disruptions in amygdala-insula connectivity were found in adolescents with general anxiety disorder, a disorder characterized by hypervigilance to somatic sensations (Roy et al., 2013).

Theories on the neural basis of intersubjectivity (Gallese, 2014; Preston and De Waal, 2002) propose a link between the ability to perceive one's own bodily signals and the capacity to empathize with the physical states and emotions of others. It has been argued that detecting and understanding others' bodily and affective states require a sound representation of one's own body. Neuroimaging studies lend support to these models and show an overlap between brain regions implicated in self and bodily experiences and those underpinning mental inferences about the affective states of others, including the AI and amygdala (Decety, 2015; Fukushima et al., 2011; Jackson et al., 2006; Singer et al., 2009; Singer and Lamm, 2009). Of note, parenting a young nonverbal infant and attending to his/her physical needs is perhaps the experience most constantly activating the parent's interoceptive circuits and the one likely requiring reorganization and upregulation of the parent's interoceptive network. Indeed, it has been shown that the postpartum months mark the period of greatest plasticity in the adult brain, particularly in key nodes of the neural systems that coalesce into the global “human parental caregiving network” (Feldman, 2015a, 2017). Studies of human parents have repeatedly shown that the amygdala and AI are key structures of the parental caregiving network and activate when mothers and fathers are exposed to auditory, visual, or multimodal stimuli of their own infant (For reviews see: Feldman, 2015a, 2017). Furthermore, the degree of parental amygdala and AI activations have been associated with parental sensitive behavior, OT levels, lower psychopathology, and greater involvement in childcare (Atzil et al., 2011; Abraham et al., 2014, Abraham et al., 2016; Feldman, 2015a; Kim et al., 2016; Rilling and Young, 2014).

Oxytocin (OT), a nine-amino-acid neuropeptide hormone, triggers activation of the parental neural network in mammals and underpins the development of human parenting, affiliative behavior, and prosocial competencies (Feldman, 2012a; Francis et al., 2002; Feldman et al., 2016a). OT is also involves in interoception. OT receptors in limbic areas, including the amygdala, support OT's role in the transmission and regulation of interoceptive signals in neuronal circuits (Luminet et al., 2011; Riem et al., 2011a, 2011b; Ropper and Samuels, 2009). The participation of OT in interoceptive signal transmission has been associated with several bodily processes, including taste, light, touch, warmth, sexual desire, pain, thermoregulation, thirst, and appetite (Kontoangelos et al., 2012). OT attenuates the effects of stress and anxiety on nociceptive signaling, carrying an analgesic effect by modulating sensitivity to both physical and social pain (Bos et al., 2015; Ditzen et al., 2009; Olff et al., 2013; Singer et al., 2008; Tracy et al., 2015). In addition, OT is critical for the initiation and maintenance of affiliative bonds, including the parent-infant relationship. OT influences mothers' and fathers' physiology and behavior (Abraham et al., 2014, Abraham et al., 2016, 2017a; Atzil et al., 2011; Riem et al., 2011a, 2011b;Weisman et al., 2012) and supports social cognition, motivated behavior, emotion regulation, and empathy (Kim et al., 2011; Luminet et al., 2011; Quirin et al., 2011; Toepfer et al., 2016). Maternal amygdala response to infant cues has been linked with higher maternal plasma OT (Atzil et al., 2011) and while mothers generally show greater amygdala activations than fathers (Atzil et al., 2012), when fathers assume a primary-caregiving role for infant care comparable amygdala response is found in mothers and fathers (Abraham et al., 2014).

Imaging studies on the cross-generation transmission of human sociality indicate that functional connectivity within the parent's limbic network when the child was an infant, comprising the amygdala, hypothalamus, and subcortical dopamine-rich structures, predicted preschoolers' capacity to employ simple self-regulatory tactics to manage high positive arousal. In comparison, connectivity within the parent's embodied-simulation network, including the AI, predicted their ability to use complex regulatory strategies that rely on symbolization, introspection, and frustration tolerance and the link between the parent's embodied simulation network and child outcome was mediated by parent and child's OT (Abraham et al., 2016, 2017a, 2017b). These studies highlight the importance of amygdala and AI activity and connectivity patterns for shaping long-term child social and emotional outcomes. These findings are also consistent with recent studies in humans and animal models indicating that the cross-generation transmission of mammalian social adaptation relies on key structures in the parental brain, functionality of the parent's OT system, and the expression of species-specific caregiving behavior (Abraham et al., 2016; Champagne and Meaney, 2001, 2006; Curley and Champagne, 2016; Feldman et al., 2010, 2013; Perkeybile et al., 2015; Pratt et al., 2015).

The parent's interoceptive capacity is proposed by several developmental models as providing the foundation for the infant's lifelong ability to engage interoception in the service of emotion regulation, sensory modulation, and self-awareness (Bowlby, 1958; Fotopoulou and Tsakiris, 2017; Steele et al., 2017). To become a sensitive caregiver, the parent must first be aware of her/his own internal visceral and autonomic states and use them for inferences about the infant. Sensitive parenting involves both mammalian-general aspects that include physical proximity, touch, and the species-typical postpartum behavior such as vocalizations, gaze, and affect, and human-specific mental capacities, including reflection, empathy, and theory-of-mind and both are critical for the child's ability to achieve homeostasis and regulate emotions in social contexts (Feldman et al., 2014; Fonagy et al., 2002; Stern, 1985). While it is generally recognized that multiple factors influence children's somatic symptoms (Gilleland et al., 2009), developmental theories underscore the effects of early caregiver-child interactions in shaping somatic problems (Stuart and Noyes, 1999). Insensitive parenting may impair the child's ability to form accurate representations of bodily sensations as markers of specific feelings and mental states and such deficits may increase somatic symptoms in early childhood and later (Bowlby, 1977; Fonagy et al., 2002). Yet, no study to date explored the relations between activations of the interoceptive circuit in the parental brain during the child's infancy, combined with sensitive caregiving is longitudinally related to children's somatization.

Dysfunction in interoceptive processing is considered an important factor in the development of somatization - physical symptoms for which medical evaluation revealed no physical reason (Silber and Pao, 2003). Malfunctions in interoceptive awareness disrupt the capacity to detect, identify, and distinguish among somatic signals (Bruce, 1961; Schaefer et al., 2012; Cameron, 2001; Craig, 2003). Somatic symptoms in childhood often co-occur with increased alexithymia, difficulties in identifying and describing feelings (Jones et al., 2004; Nakao et al., 2002), higher levels of internalizing and externalizing symptoms (McCauley et al., 1991; Zwaigenbaum et al., 1999), and impairment in academic and social functioning (Forgeron et al., 2010; Hughes et al.,

2008; Konijnenberg et al., 2005). Furthermore, children with heightened somatic symptoms use fewer and less effective self-regulatory strategies and have poor emotional awareness (Stonnington et al., 2013). Genetic factors have also found to play a role in somatization, particularly in relation to the hypothalamic-pituitary-adrenal (HPA) axis (Gillespie et al., 2000; Hickie et al., 1999; Holliday et al., 2010; Torgersen, 1986; Veletza et al., 2009). It is thus of interest to understand the roots of child somatization in the context of the cross-generational transfer of well-being from parent to child.

In the current longitudinal study of first-time primary-caregiving mothers and fathers, we followed parent and children four times over the first six years of parenthood. During the first home visit in infancy (Time 1 = infancy), we videotaped parent-infant interactions and measured parents' OT. In the second visit, within the next few days, we imaged parents' brain (fMRI) observing their own interaction with the infant compared to a gender- and age-matched unfamiliar parent-infant interaction. In the third session, when children were approximately 4 years old (Time 2 = preschool), we revisited families, observed parent-preschoolers' interactions, and measured parent and child OT. In the fourth testing, when children were six years (Time 3 = school entry), parents completed self-report measures of children's somatic symptoms.

We hypothesized that two distinct cross-generation pathways may lead from parent brain functioning to child somatic symptoms. The first, an evolutionary-ancient path, which operates via amygdala activation and modulated by parent's and child's OT, allows the parent to perceive and immediately respond to bodily and affective infant signals and fulfill survival needs. The second, a more phylogenetically-recent pathway, relies on the later-evolving AI, directs parents to “here-and-now” bodily exchanges and integrates online biological and behavioral signals (Feldman, 2017; Hasson and Frith, 2016). Four hypotheses were proposed. First, activations of the AI in the parent's brain would directly predict children's somatic symptoms six years later (Hypothesis 1). Next, amygdala activity would be associated with children's OT in preschool (Hypothesis 2). On the basis of recent research highlighting the role of parental OT as a protective buffer against psychopathology in next generations (Pratt et al., 2015), we hypothesized that parental OT would moderate the relations between children's OT in preschool and somatic symptoms at six years (Hypothesis 3). Finally, the degree of parental sensitivity would mediate the links between parent's brain activation and child's somatic symptoms (Hypothesis 4).

2. Materials and methods

2.1. Participants

A total of 45 first-time primary-caregiving parents raising their infant within a committed two-parent family participated in the study [mean age: 36.4 years + 6.87 SD]. These included 20 heterosexual primary-caregiving biological mothers and 25 homosexual primary-caregiving biological fathers raising their infant without maternal involvement since birth through surrogacy. Infants [mean age at Time 1: 10.95 months + 6.87 SD; mean age at Time 2: 40.22 months + 4.45 SD; mean age at Time 3: 78 months + 2.32 SD] were all born at term and were healthy since birth with no history of physical illness. Parents were screened for high depression and anxiety symptoms using the Beck Inventory (BDI) (Beck, 1978) and the State-Trait Anxiety Inventory(STAI) (Spielberger et al., 1970). All parents were of middle-class background and participants completed 12 to 19 years of education [mean: 15.86 + 1.73 years]. No difference in socioeconomic status was found between primary-caregiving mothers and fathers. All participants, recruited through advertisement in the community, were healthy and free of medication. 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. In the first, we visited 45 families at home (Time 1 = Infancy), primary-caregiving parents were videotaped interacting with the infant and salivary samples were collected from parent for OT. A few days later, each parent underwent functional brain scanning with the individually-tailored home videotapes as fMRI stimuli. In the third session (Time 2 = Preschool), when children reached preschool age, we re-visited families at home. Visit included parent-child interactions and salivary samples were collected from parents and children for OT. One child and one parent OT samples were missing for insufficient saliva. In the fourth session (Time 3 = School entry), when children were six years parents completed self-report measures of children somatic symptoms during the last six months. Five parents were lost to attrition at Time 3 mainly due to inability to locate families or time constraints.

2.3. Oxytocin and collection and determination

Collection and determination of OT and were conducted in accordance with our prior research (Abraham et al., 2014, Abraham et al., 2016, 2017a; Weisman et al., 2013). Saliva was collected using Salivettes (Sarstedt, Rommelsdorf, Germany). Samples were stored at –20 °C until centrifuged twice, 2 days apart, at 4 °C at 1500*g* for 20 min. Liquid samples were kept at –80 °C, lyophilized for 10 days, and stored at 20 °C. On the assay day, the dry samples were reconstituted in water and concentrated ×4, before immunoassay. OT was assayed by ELISA (Enzo® (NY, USA) with careful sample preparation; samples were centrifuged twice; delicate lyophilization maintained constant refrigeration to slows the drying; and samples were reconstituted in water prior to assay. Measurements were performed in duplicate and the concentrations of samples were calculated using Matlab-7 according to relevant standard curves. The intra-assay and inter-assay coefficients of variability are < 15.4%. The average of the two assessments was used.

2.4. Behavioral coding

We used global rating scales for parent-child interaction at the preschool stage (Time 2).

Parent-child interactions (Times 2) were coded using the Coding Interactive Behavior (CIB) Manual (Feldman, 1998). This CIB is a well-validated global rating system for adult-child interactions includes42 scales, which aggregate into theoretically meaningful constructs. The system has been validated in multiple studies and shows good psychometric properties including test-retest reliability, individual stability across long developmental epochs, and construct validity (for review, see Feldman, 2012b). In preschool (Time 2), we used the *parental sensitivity* construct to index the central behavioral expression of attuned human caregiving. Construct's codes describe the expression of both human species-typical parental physical behavior (parent gaze, positive affect, affectionate touch) and high-order mental parental processes, including parent's acknowledgment, elaboration, resourcefulness during interaction, parental empathic responses to child emotional signals and the degree to which the parent's presence provides a “secure base” for child's play and exploration (Feldman, 2007a, 2007b). Trained raters blind to all other information the coding. Inter-rater reliability, measured on 20% of the sample, was intraclass $r = 0.94$ (range = 0.87–0.99). For the current study only parental behavioral measures from the second home visit were associated with both parent's neural responses to parent-infant interaction and child's somatic symptoms.

2.5. Self-report measures

The Child Behavior Checklist (CBCL) 6–18(Achenbach, 1991) is the most widely-used instrument identifying behavior problems in 6–18-

year old children as reported by their parents. There are two broad-band subscales: the Internalizing Behavior Problems scale and the Externalizing Behavior Problems scale. Several narrow-band subscales also can be calculated. One of these, the Somatic Symptoms scale, was used in this study. It includes item referring to somatic symptoms such as nausea, headaches, nightmares, dizziness, chronic pains, fatigue and exhaustion, eye problems, skin disorders, vomiting and stomach problems. Children's Somatic Symptoms scale scores ranged from 0 (non-clinical range) to 6 (subclinical range). None of the children scored above the cutoff for clinical somatic symptoms (> 7).Achenbach and Edelbrock (1981) reported that the somatic symptoms factor has emerged from different behavioral checklist studies by four different groups of researchers. In addition, since no differences emerged between boys and girls on somatic symptoms, both genders were collapsed into one group ($t_{(1,38)} = -0.272$, $P > 0.7$).

2.6. Functional MRI data acquisition and analyses

Imaging was performed on a GE-3 T Sigma Horizon echo-speed scanner with resonant gradient echoplanar imaging system. Functional T2*-weighted images were obtained using field of view = 220 mm, matrix size = 96 × 96, repetition time = 3000 ms, echo time = 35 ms, flip angle = 90°, acquisition orientation of the fourth ventricle plane, 39 axial slices of 3-mm thickness, and gap = 0. Additionally, each functional scan was accompanied by a three-dimensional (3D) anatomical scan using anatomical 3D sequence spoiled gradient echo sequences obtained with high-resolution of 1 × 1 × 1 mm. The fMRI data were analyzed with the BrainVoyager analysis package (version 2.1; Brain Innovation). After standard preprocessing (see Supplementary Methods) statistical maps were prepared for each participant using a general linear model (GLM), in which the various blocks were defined as distinct predictors. Single-participant analysis was followed by multi-participant analysis computed with random effects using gray matter mask. Regressors were convolved with canonical two-gamma hemodynamic response function. The baseline was considered as the averaged BOLD signal collected at all rest periods throughout the paradigm. Additional nuisance regressors included the head movement realignment parameters and the time course of averaged activity in cortical white-matter. We also incorporated a gray-matter mask and corrected for temporal autocorrelations using second-order autoregressive model.

2.7. fMRI experimental design

While lying in the scanner, participants were instructed to watch a series of attachment-related vignettes presented on the screen. All videos included multi-modal, dynamic, and realistic stimuli of bonding-related stimuli in the home ecology. Each parent's video set was individually tailored, comprising three 2-minute infant- parent related videos with alternating rest fixation periods of 15 or 18 s between stimuli, preceded by a 1-minute rest with fixation period. The two clips included vignettes of: (i) each parent interacting with her/his own infant ('Self—Infant Interaction'); (ii) video clip of the unfamiliar parent interacting with unfamiliar infant ('Unfamiliar Parent—Infant Interaction') (where the parent was the same sex as the participant). Order of stimuli presentation was counterbalanced into three possible sequences. To ensure that parents' and infants' affective states did not differ between parent-infant interaction vignettes (Self—Infant, Unfamiliar Parent-Infant), we selected only clips where infants and parents were in neutral affective state (coded by CIB). To examine generalizable brain responses at the group level, analysis combined 45 different self-infant interaction videos as one 'Self—Infant Interaction' condition and 45unfamiliar parent-infant interaction videos as one 'Unfamiliar Parent-Infant Interaction' condition.

2.8. Regions-of-interest

We extracted mean parameter estimates (beta values) for our analyses for region of interest (ROIs) of a priori predictions: bilateral amygdala and bilateral AI. Beta values were averaged across ROI voxels and for each experimental condition separately. We used an index of 'Self—Infant Interaction' minus 'Unfamiliar Parent—Infant Interaction' beta in attempt to pinpoint parents' attachment-specific fMRI brain activations stimulated specifically by watching themselves interact with their infant, while controlling for activations in response to observing any unfamiliar infant and social interaction. Region-of-Interest (ROI) selection was a priori and theory-based. ROI analysis was conducted on brain areas which were repeatedly shown in research on the parental brain to activate in response to infant cues (auditory, visual or multimodal infant stimuli, such as infant crying, pictures or movies, often comprising "own" infant to standard infant or control condition) (Feldman, 2015a, 2017; Kim et al., 2016; Rilling and Young, 2014). The amygdala was defined on the basis of a meta-analysis, which clustered emotion-related brain structured according to their co-activity across studies (Kober et al., 2008). The AI was defined on the basis of recent meta-analysis on empathy and mentalizing (Bzdok et al., 2012) (Supplementary Table 1). MNI to Talairach transformations were performed using a Lancaster transformation (Lancaster et al., 2007). Specifically, for each region, a box-shaped volume of 5-voxel diameter was placed around the peak of activation. To evaluate lateralization of ROI's activations, paired sample *t*-tests were conducted between two hemispheres, and found no significant lateralization of the amygdala and AI activations in response to 'Self—Infant Interaction' minus 'Unfamiliar Parent—Infant Interaction' contrast. Thus, the beta values calculated from each hemisphere were averaged together (amygdala: $t_{(1,44)} = -0.982$, $P > 0.3$; AI: $t_{(1,44)} = 0.834$, $P > 0.4$).

Associations between ROI's activation and participants' behavioral and hormonal data were assessed using Pearson correlations and reported at $P < 0.05$(Bonferroni-corrected for multiple comparisons).

3. Results

We defined the selected ROI's on the basis of prior research on the human parental brain (Fig. 1; Supplementary Table 1). Before conducting our analyses we examined activation differences between the primary-caregiving mothers and fathers in each selected brain region and found no differences between the two groups while parents viewed their own interaction with the infant minus an unfamiliar parent and infant interaction (bilateral amygdala: $t_{(1,43)} = 0.505$, $P > 0.5$;

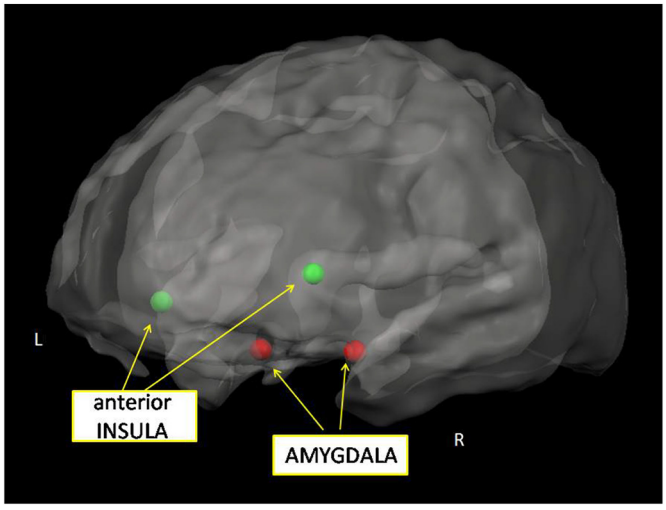

Fig. 1. Location of regions-of-interest comprising the bilateral amygdala and bilateral anterior Insula, from sagittal view. L, left; R, right.

Table 1
Correlations matrix for all the variables.

INFANCY (TIME 1)	1	2	3	4	5	6
1. AMYGDALA	1 (45)	-0.02 (45)	-0.037 (40)	0.547** (44)	-0.034 (45)	0.208 (40)
2. A. INSULA		1 (45)	-0.121 (40)	0.070 (44)	0.568** (45)	-0.573** (40)
3. PARENTAL OT			1 (40)	0.226 (39)	0.072 (40)	-0.19 (40)
PRESCHOOL (TIME 2)						
4. CHILD OT				1 (44)	0.356* (44)	-0.209 (39)
5. PARENTAL SENSITIVITY					1	-0.553** (40)
SCHOOL-ENTRY (TIME 3)						
6. CHILD'S SOMATIC SYMPTOMS						1 (40)

*P<0.05; ***p<0.001

bilateral AI: $t_{(1,43)} = -0.131$, $P > 0.8$). Thus, we collapsed the parents groups. Correlations of all the variables are presented in Table 1.

3.1. Direct and indirect longitudinal links between parent's brain activation and child somatic symptoms

First, we sought to examine longitudinal associations between each parent ROI's activation (Time 1) and child's somatic symptoms in school years (Time 3) (Hypothesis 1). As expected, we found that activity in the AI negatively correlated with child's somatic symptoms ($r = -0.573$, $P < 0.001$), but not in amygdala ($r = 0.208$, $P > 0.2$) (Fig. 2A). In addition, to test Hypothesis 4 on indirect effects via parenting sensitivity, we examined whether parental sensitivity mediated the relationship between parent's brain activity and child's somatic symptoms. Using Sobel's (1982) test, we found partial mediation by parental sensitivity for the link between parent's AI activity and child's somatic symptoms ($z = 2.002$, $p = 0.044$; Fig. 2B). Baron and Kenny's (1986) steps were computed. In Step 1, association between the predictor (parent's AI activity) and outcome (child somatic symptoms) was found significant (path C; $\beta = -0.570$, $t = -4.277$, $p < 0.001$). In Step 2, association between predictor and mediator (parental sensitivity) was significant (path A; $\beta = 0.605$, $t = 4.681$, $p < 0.001$). In Step 3, association between mediator and outcome controlling for predictor was significant (path B, $\beta = -0.360$, $t = -2.266$, $p < 0.05$). In Step 4, the association between the predictor and the outcome variable, controlling for the mediator was significant ($\beta' = -0.360$, $t = 2.266$, $p < 0.05$). Sobel's test for mediation, $z = 2.002$, $p < 0.05$, indicated a significant indirect effect of parent's AI activity on the child's somatic symptoms six year later, partially mediated by parental sensitivity during preschool years.

3.2. Longitudinal associations between parent's brain activity, parental oxytocin, child's oxytocin and child's somatic symptoms

To tap brain-hormone-behavior constellations (Hypotheses 2 and 3), we explored whether the functionality of the human parent's brain response to parent-infant interaction may be associated with children OT profile in preschool years, and whether children OT in preschool years is linked to somatic symptoms in school years. As expected, results indicated that parent's amygdala activity (Time 1) predicted child's OT levels at preschool (Time 2) ($r = 0.547$, $P = 0.001$; Fig. 3A) (Hypothesis 2).In addition, while correlation between child's OT levels and somatic symptoms was not found to be significant ($r = -0.209$, $P > 0.2$), we did find that parent's OT level during the child's infancy (Time 1) moderated the relation between child's OT levels in preschool (Time 2) and the child's somatic symptoms in school years (Time 3) (Hypothesis 3) (R^2 Total = 0.170; $F_{1,35} = 4.455$, $P < 0.01$; Fig. 3B; Supplementary Table 2). A hierarchical multiple regression predicting children's somatic symptoms by child's OT, parent's OT, and their interaction showed children's somatic symptoms were predicted by child's and parent's OT interaction. Under the condition of low parental OT levels (above and below the median split, Median = 30.6) a significant negative correlation emerged between child's OT levels and child's

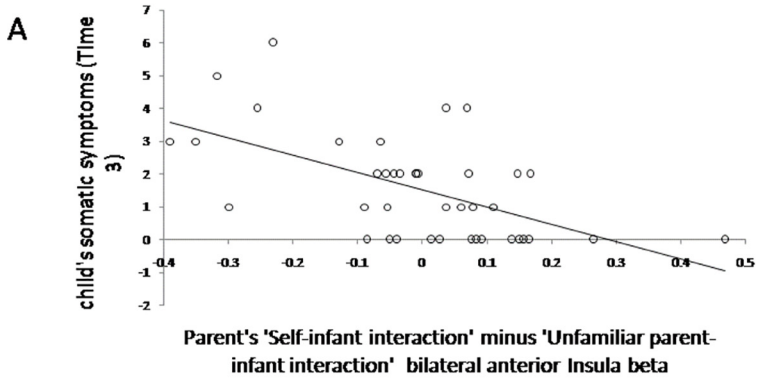

Fig. 2. (A) Scatter plots show significant negative correlations between activation of the parent's AI bilaterally when his/her child was an infant during 'Parent-Infant Interaction' minus 'Unfamiliar Parent-Infant Interaction' contrast (Time 1 = infancy) and child's somatic symptoms in school-entry (Time 3 = school-entry) ($r = -0.573$, $P < 0.001$). (B) Standardized regression coefficient for the relations between parent's AI activity and child's somatic symptoms as partially mediated by parental sensitivity. Path c shows the standardized regression coefficient for the total (β) and direct (β') effects of AI activity on child's somatic symptoms. AI, anterior insula.

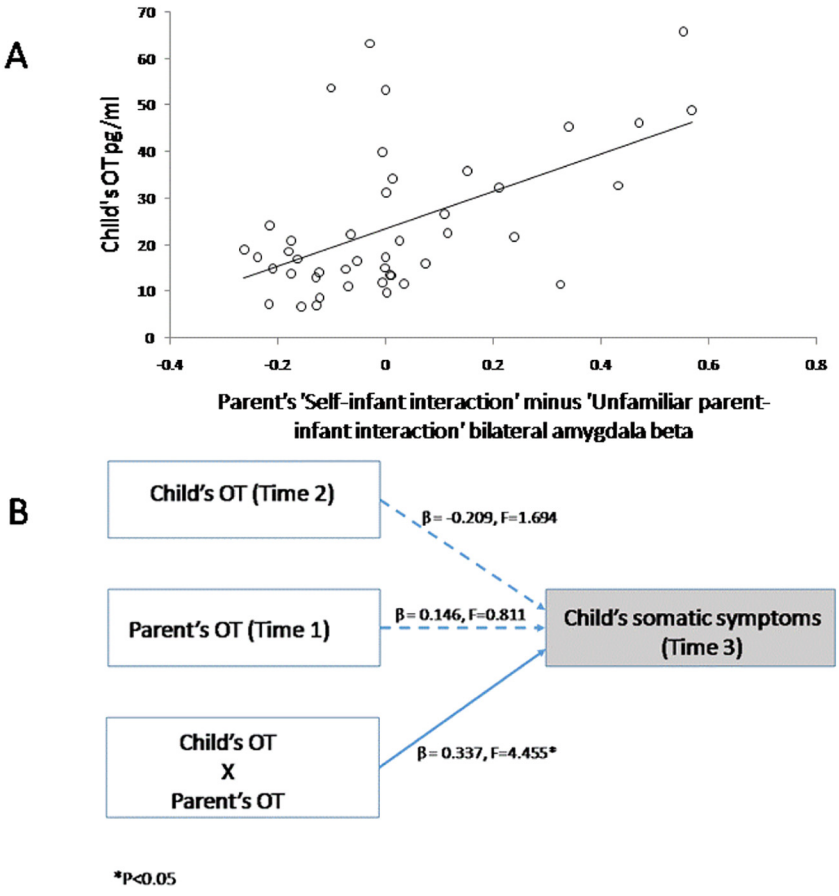

Fig. 3. (A) Scatter plots show significant positive correlations between parent's activation of amygdala bilaterally when his/her child was an infant during 'Parent-Infant Interaction' minus 'Unfamiliar Parent-Infant Interaction' condition (Time 1 = infancy) and child's OT levels in preschool (Time 2 = preschool) ($r = 0.547$, $P < 0.001$). (B) Moderation model of parental OT levels (Time 1) on child's OT levels (Time2) and child's somatic symptoms (Time 3 = school-entry).Under condition of low parental OT levels, significant negative correlation emerged between child's OT levels and child's somatic symptoms ($r = -0.735$, $P = 0.001$), but such correlation was not found under high parent's OT ($r = 0.209$, $P > 0.2$). Solid lines indicate significant coefficients and broken lines non-significant coefficients. *$P < 0.05$.

somatic symptoms ($r = -0.735$, $P = 0.001$), but such a correlation was not found under high parent's OT condition ($r = 0.209$, $P > 0.2$). We also found that parental sensitivity, measured during parent-preschooler play interaction, was positively associated with preschooler's OT level ($r = 0.356$, $P < 0.05$).

4. Discussion

Results of the current study are the first, to our knowledge, to provide neurobiological evidence for the long-term association between interoception sensitivity in the parent's brain in the postpartum period and the development of children's somatic symptoms. We found that the link between the parent's interoceptive circuit and child somatization is described by two independent paths; the first, a more evolutionarily-ancient path related to the amygdala and OT system, the second involving the AI, a key node of the human viceromotor cortex. Overall, our results highlight three important findings. First, increased activation in the parent's bilateral AI in response to a video of self interacting with his/her infant predicted lower somatic problems in the child six years later and this link was mediated by the parent's sensitive behavior at age four. Second, parents' bilateral amygdala activation when children were infants predicted higher OT levels in their preschool-aged children. Finally, parental OT moderated the link between preschoolers' OT and somatic symptoms at six years. Overall, our findings are consistent with animal and human imaging studies that highlight the importance of specific nodes in the parental brain and OT functionality during the child's infancy for consolidating the neurohormonal systems that support offsrping sociality, well-being, and health (Abraham et al., 2016, 2017a, 2017b; Champagne and Meaney, 2006; Feldman et al., 2016; Kundakovic and Champagne, 2015; Perkeybile et al., 2015).

Since humans are highly social creatures who form the most complex social networks of all species, the infant's ability to organize subjective bodily experiences into a mental sense of "selfhood" is rooted in early social interactions, primarily the caregiver-infant relationship (Loman and Gunnar, 2010; Schore, 2001). Interoception plays an important role in sensitive human caregiving. The parent's rapid and accurate identification of internal and external somatic signals assists children in reading their own bodily signals and the parent's neural functioning and sensitive behavior enables the consolidation of the child's interoceptive systems that support their ability to map and represent internal bodily states (Fotopoulou and Tsakiris, 2017). This ability provides the basis for the child's self-awareness, the maturation of embodied mechanisms in the child, and the consolidation of a healthy sense of bodily self and competencies that depend on embodiment, including theory-of-mind, empathy, and social synchrony. Here, we identified two parallel neuronal pathways that may play a role in the cross-generational transfer of human somatization.

The first pathway leading from functionality of the parent's neurobiological systems to child somatization defines an evolutionary-ancient path involving the parent's amygdala response to a video of self interacting with his/her infant and by parent's and child's OT levels. While previous imaging studies found associations between maternal amygdala activation and maternal plasma OT (Atzil et al., 2011, Abraham et al., 2014), we show here for the first time that parental amygdala response is longitudinally predictive of preschooler's OT levels and similar correlations emerged for primary-caregiving mothers and fathers. This is consistent with studies in animal models showing that adult offspring reared by high licking-and-grooming rat dams exhibited increased OT receptors (OTR) binding in the central nucleus of the amygdala (Francis et al., 2002), that sensitive parenting increased OTR binding in the amygdala of female prairie voles offspring (Bales et al., 2011), and that daily separation reduced OTR binding in the amygdala of male rats offspring (Lukas et al., 2010).

The link between child OT and somatic symptoms was moderated

by parental OT. A possible explanation for this cross-generational pathway leading from the parent's amygdala activity to the child's somatic symptoms as mediated by the child's OT and moderated by the parent's OT may relate to the central role of the amygdala and OT system for the initiation of the species-typical postpartum parenting behaviors across mammalian species. The amygdala enables a rapid arousal-sensitive processing of emotional signals (Pessoa and Adolphs, 2010) and participates in guiding parental attention to biologically-relevant social stimuli (Fleming and Korsmit, 1996; Lee et al., 2000; Oxley and Fleming, 2000), vigilance for social signals (Öhman, 2002), adjustment of social orienting value, and detection of reward-salient and survival-related cues (Janak and Tye, 2015). These functions enable the caregiver to automatically and accurately identify and respond to infant bodily and affective signals without being overly preoccupied and distracted by own bodily signals (Barrett and Fleming, 2011; Lindquist et al., 2012). Such parental capacities allow the infant to develop arousal regulation via mechanisms of co-regulation which are supported by the parent's amygdala and OT and have shown longitudinal links with children's emotion-regulation, empathy, and well-being (Feldman, 2003, 2012a). Since somatization is considered to be a disturbance of affect regulation (Cacioppo et al., 2000; Subic-Wrana, 2011; Taylor et al., 1997; Waller and Scheidt, 2004, 2006), it is reasonable to conclude that lower functionality of the amygdala and oxytocinergic system in the context of early attachment may play a role in child somatic symptoms. Moreover, the effect of child OT on later somatic symptoms was moderated by parental OT; when parent OT was high children's somatic symptoms were not impacted by their own OT levels. These findings suggest that parental OT may buffer against the development of somatic symptoms in the next generations. We have previously shown that high maternal OT in chronically depressed mothers provides a protective buffer against the effects of maternal depression on 6-year old children's OT response and the current findings suggest a similar mechanism (Pratt et al., 2015).

The second cross-generational link defines a more phylogenetically-recent pathway, relies on the later-evolving AI, and charts both direct and indirect longitudinal link from the parent's AI activation to the child's somatic symptoms as mediated by parental sensitivity. One possible interpretation is that the higher AI activity was related to the parents' recognition of themselves in the videos and re-experiencing their own bodily and affective states during interaction with the infant. This interpretation highlights the centrality of the parent's own interoceptive sensitivity and its long-term effects on children's well-being and health. Another possibility is that during observation the parent's empathically experiences the infant's states as his/her own interoceptive state, increasing AI activity. Such explanation is corroborated by our finding of the role of parental sensitivity, which includes the parent's empathic response to child emotional signals, as a mediator of the relation between parental AI activation and child somatic symptoms, and by previous studies showing greater insula activation when mothers and fathers observe their own infant alone compared to a strange infant (Swain et al., 2014).

The AI, a higher-order structure (Craig, 2009), modulates autonomic reactivity to salient stimuli (Menon and Uddin, 2010), computes a meta-representation of the primary interoceptive activity in relation to self-awareness (Craig, 2002; Critchley et al., 2004; Gu et al., 2013), and underpins the individual's sense of "self" that integrates ongoing awareness of bodily and emotional state (Damasio, 1999; Damasio et al., 1996). Together with other later-evolving structures, the inferior frontal gyrus (IFG) and the middle anterior cingulate cortex (ACC), the AI is involved in *embodied simulation* - a bottom-up process guided by higher-order interoceptive representations of another person's bodily and affective states that are based on one's own physiological sensations (Craig, 2009; Gallese, 2014). It is suggested that processes of embodied simulation enable the parent to draw on information from their own experiences to interpret the infant's emotional and bodily states by representing them in the parent's brain, thus grounding experience in the here-and-now (Decety, 2015; Keysers et al., 2010; Keysers et al., 2013). The Von Economo neurons (VENs), found in the AI and ACC, enable fast communication between the two sides of the cortex, leading to an integrated representation of emotional moments and their behavioral expressions (Allman et al., 2005; Craig, 2009). Furthermore, dysfunction of the AI is implicated in chronic stress and pain (De Greck et al., 2011; Smallwood et al., 2013; Valet et al., 2009). For instance, patients with high somatization failed to use emotion-based biasing signals generated from the body when appraising response options and had empathy and mentalizing deficits due to AI abnormalities (Reker et al., 2010; Silani et al., 2008; Singer and Leiberg, 2009; Stonnington et al., 2013).

Our findings suggest a higher-order cross-generational transmission pathway of human somatization via simulation processes in the parent's brain, which tune the infant's brain to interoception processes possibly via mechanisms of *brain-to-brain synchrony* (Feldman, 2017; Hasson et al., 2012; Hasson and Frith, 2016; Kinreich et al., 2017). Such parent-child neural and behavioral synchrony is based on repeated experiences during parent-infant interactions that afford practice in the matching of non-verbal cues and symbolic expression (Feldman, 2007a, 2007b, 2017). With the maturation of the insular cortex, the early synchronous biobehavioral matrix enables the child to develop subjective awareness of emotional state and experiences of embodied self and body ownership (Feldman, 2016b), which may reduce the likelihood of the child's being on the somatization continuum ranging from mild bodily misperceptions to severe and disabling somatoform symptoms (Critchley et al., 2002).

Limitations of the study are important to consider for the interpretation of the findings. First, we did not measure parents' and children's interoceptive sensitivity, state- and trait-empathy indices, or the parents' somatic symptoms. Second, children's somatic symptoms were rated by their parents, the same participants whose brain activity was measured during the fMRI scans and not by objective raters. In addition, we did not assessed genetic factors that may have contributed to the longitudinal effects of somatization. Our inability to infer causality only relationships among variables is another limitation of the current study. Other possible limitations is the fact that OT was sampled in the periphery and not centrally and no physiological measures were collected during or immediately after the fMRI scans. While growing number of studies have utilized peripheral OT measurements, the links between central and peripheral OT are still not fully clear and this is a clear study limitation. Yet, studies in animals (Carter et al., 2007; Wotjak et al., 1998) and human's adults and children (Carson et al., 2015) suggest that central and peripheral activity of the OT system is likely to be coordinated. For instance, OT administration, which impacts central OT, is associated with marked increases in salivary OT (Weisman et al., 2012), salivary OT correlates with genetic variability on the *OXTR* (Feldman et al., 2013), parallel increases were found in maternal plasma OT and in fMRI BOLD response in brain areas rich in OT receptors (Strathearn et al., 2009); and salivary OT measured across multiple ages and labs show parallel findings to those observed for central OT in animals. In addition, future studies are needed to characterize interoception sensitivity in parent's brain in response to "infant alone" stimuli in order to control for the effect of viewing the self. Finally, it in light of inconsistency with findings of a previous study (Strathearn et al., 2009) showing greater insula activations in insecure/dismissing mothers in response to their own infant's sad faces which was not associated with parental e empathy scores, future studies are needed to generalize to populations with various attachment styles and to those with mental disorders such as anxiety disorders and somatization known to impair interoceptive awareness.

Identifying the cross-generational mechanisms of human somatization is important for advancing understanding, prevention, and management of somatization in children and adults. Much further research within the framework of a "two-person neuroscience" (Hari et al., 2015) is required to integrate longitudinal data including brain

imaging, hormonal analysis, and careful behavioral assessment of parent and child to describe how reorganization of the parent's brain in the postpartum shapes children's long-term well-being.

Acknowledgement

Supported by the German-Israel Foundation (GIF) and the Simms-Mann Foundation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpsycho.2018.02.001.

References

Abraham, E., Hendler, T., Zagoory-Sharon, O., Feldman, R., 2016. Network integrity of the parental brain in infancy supports the development of children's social competencies. Soc. Cogn. Affect. Neurosci. nsw090.

Abraham, E., Gilam, G., Kanat-Maymon, Y., Jacob, Y., Zagoory-Sharon, O., Hendler, T., Feldman, R., 2017a. The human coparental bond implicates distinct corticostriatal pathways; longitudinal impact on family formation and child well-being. Neuropsychopharmacology.

Abraham, E., Raz, G., Zagoory-Sharon, O., Feldman, R., 2017b. Empathy networks in the parental brain and their long-term effects on children's stress reactivity and behavior adaptation. Neuropsychologia.

Achenbach, T.M., 1991. Child Behavior Checklist/4–18. University of Vermont, Psychiatry.

Achenbach, T.M., Edelbrock, C.S., 1981. Behavioral problems and competencies reported by parents of normal and disturbed children aged four through sixteen. Monogr. Soc. Res. Child Dev. 1–82.

Allman, J.M., Watson, K.K., Tetreault, N.A., Hakeem, A.Y., 2005. Intuition and autism: a possible role for Von Economo neurons. Trends in cognitive sciences 9 (8), 367–373.

Atzil, S., Hendler, T., Feldman, R., 2011. Specifying the neurobiological basis of human attachment: brain, hormones, and behavior in synchronous and intrusive mothers. Neuropsychopharmacology 36 (13), 2603–2615.

Atzil, S., Hendler, T., Zagoory-Sharon, O., Winetraub, Y., Feldman, R., 2012. Synchrony and specificity in the maternal and the paternal brain: relations to oxytocin and vasopressin. J. Am. Acad. Child Adolesc. Psychiatry 51 (8), 798–811.

Bales, K.L., Boone, E., Epperson, P., Hoffman, G., Carter, C.S., 2011. Are behavioral effects of early experience mediated by oxytocin? Front. Psych. 2, 24.

Baron, R.M., Kenny, D.A., 1986. The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. J. Pers. Soc. Psychol. 51 (6), 1173.

Barrett, J., Fleming, A.S., 2011. Annual research review: All mothers are not created equal: Neural and psychobiological perspectives on mothering and the importance of individual differences. J. Child Psychol. Psychiatry 52 (4), 368–397.

Beck, A.T., 1978. Cognitive Therapy of Depression: a Treatment Manual. Beck.

Bos, P.A., Montoya, E.R., Hermans, E.J., Keysers, C., van Honk, J., 2015. Oxytocin reduces neural activity in the pain circuitry when seeing pain in others. NeuroImage 113, 217–224.

Bowlby, J., 1958. The nature of the child's tie to his mother. Int. J. Psychoanal. 39, 350.

Bowlby, J., 1977. The making and breaking of affectional bonds. II. Some principles of psychotherapy. The fiftieth Maudsley Lecture. Br. J. Psychiatry 130 (5), 421–431.

Bruce, H., 1961. Conceptual confusion in eating disorders. J. Nerv. Ment. Dis. 133 (1), 46–54.

Bzdok, D., Schilbach, L., Vogeley, K., Schneider, K., Laird, A.R., Langner, R., Eickhoff, S.B., 2012. Parsing the neural correlates of moral cognition: ALE meta-analysis on morality, theory of mind, and empathy. Brain Struct. Funct. 217 (4), 783–796.

Cacioppo, J.T., Berntson, G.G., Larsen, J.T., Poehlmann, K.M., Ito, T.A., 2000. The psychophysiology of emotion. In: Handbook of Emotions. 2. pp. 173–191.

Cameron, O.G., 2001. Interoception: the inside story—a model for psychosomatic processes. Psychosom. Med. 63 (5), 697–710.

Cameron, O.G., 2009. Visceral brain–body information transfer. Neuroimage 47 (3), 787–794.

Champagne, F., Meaney, M.J., 2001. Like mother, like daughter: evidence for non-genomic transmission of parental behavior and stress responsivity. Prog. Brain Res. 133, 287–302.

Champagne, F.A., Meaney, M.J., 2006. Stress during gestation alters postpartum maternal care and the development of the offspring in a rodent model. Biol. Psychiatry 59 (12), 1227–1235.

Craig, A.D., 2002. How do you feel? Interoception: the sense of the physiological condition of the body. Nat. Rev. Neurosci. 3 (8), 655–666.

Craig, A.D., 2003. Interoception: the sense of the physiological condition of the body. Curr. Opin. Neurol. 13 (4), 500–505.

Craig, A.D., 2009. How do you feel–now? The anterior insula and human awareness. Nat. Rev. Neurosci. 10 (1).

Craig, A.D., Chen, K., Bandy, D., Reiman, E.M., 2000. Thermosensory activation of insular cortex. Nat. Neurosci. 3 (2), 184–190.

Critchley, H.D., Harrison, N.A., 2013. Visceral influences on brain and behavior. Neuron 77 (4), 624–638.

Critchley, H.D., Mathias, C.J., Dolan, R.J., 2002. Fear conditioning in humans: the influence of awareness and autonomic arousal on functional neuroanatomy. Neuron 33 (4), 653–663.

Critchley, H.D., Wiens, S., Rotshtein, P., Öhman, A., Dolan, R.J., 2004. Neural systems supporting interoceptive awareness. Nat. Neurosci. 7 (2), 189–195.

Curley, J.P., Champagne, F.A., 2016. Influence of maternal care on the developing brain: Mechanisms, temporal dynamics and sensitive periods. Front. Neuroendocrinol. 40, 52–66.

Damasio, A., 1999. The feeling of what happens. In: Body and Emotion in the Making of Consciousness.

Damasio, A.R., Everitt, B.J., Bishop, D., 1996. The somatic marker hypothesis and the possible functions of the prefrontal cortex [and discussion]. Philos. Trans. R. Soc., B 351 (1346), 1413–1420.

De Greck, M., Scheidt, L., Bölter, A.F., Frommer, J., Ulrich, C., Stockum, E., ... Northoff, G., 2011. Multimodal psychodynamic psychotherapy induces normalization of reward related activity in somatoform disorder. World J. Biol. Psychiatry 12 (4), 296–308.

Decety, J., 2015. The neural pathways, development and functions of empathy. Curr. Opin. Behav. Sci. 3, 1–6.

Ditzen, B., Schaer, M., Gabriel, B., Bodenmann, G., Ehlert, U., Heinrichs, M., 2009. Intranasal oxytocin increases positive communication and reduces cortisol levels during couple conflict. Biol. Psychiatry 65 (9), 728–731.

Feldman, R., 1998. Mother-Newborn Coding System Manual. Bar-Ilan Univ. Press, Tel Aviv, Israel.

Feldman, R., 2003. Infant–mother and infant–father synchrony: The coregulation of positive arousal. Infant Ment. Health J. 24 (1), 1–23.

Feldman, R., 2007a. On the origins of background emotions: from affect synchrony to symbolic expression. Emotion 7 (3), 601.

Feldman, R., 2007b. Mother-infant synchrony and the development of moral orientation in childhood and adolescence: Direct and indirect mechanisms of developmental continuity. Am. J. Orthopsychiatry 77 (4), 582.

Feldman, R., 2012a. Oxytocin and social affiliation in humans. Hormones and behavior 61 (3), 380–391.

Feldman, R., 2012b. Parent–infant synchrony: A biobehavioral model of mutual influences in the formation of affiliative bonds. Monogr. Soc. Res. Child Dev. 77 (2), 42–51.

Feldman, R., 2015a. The adaptive human parental brain: implications for children's social development. Trends Neurosci. 38 (6), 387–399.

Feldman, R., 2015b. Sensitive periods in human social development: New insights from research on oxytocin, synchrony, and high-risk parenting. Dev. Psychopathol. 27 (02), 369–395.

Feldman, R., 2016a. The neurobiology of mammalian parenting and the biosocial context of human caregiving. Horm. Behav. 77, 3–17.

Feldman, R., 2016b. Bio-behavioral Synchrony and the Cross-generation Transmission of Well-being and Psychopathology. Int. J. Psychol. 51, 357.

Feldman, R., 2017. The neurobiology of human attachments. Trends Cogn. Sci.

Feldman, R., Gordon, I., Zagoory-Sharon, O., 2010. The cross-generation transmission of oxytocin in humans. Horm. Behav. 58 (4), 669–676.

Feldman, R., Gordon, I., Influs, M., Gutbir, T., Ebstein, R.P., 2013. Parental oxytocin and early caregiving jointly shape children's oxytocin response and social reciprocity. Neuropsychopharmacology 38 (7), 1154–1162.

Feldman, R., Rosenthal, Z., Eidelman, A.I., 2014. Maternal-preterm skin-to-skin contact enhances child physiologic organization and cognitive control across the first 10 years of life. Biol. Psychiatry 75 (1), 56–64.

Feldman, R., Monakhov, M., Pratt, M., Ebstein, R.P., 2016. Oxytocin pathway genes: evolutionary ancient system impacting on human affiliation, sociality, and psychopathology. Biol. Psychiatry 79 (3), 174–184.

Fleming, A.S., Korsmit, M., 1996. Plasticity in the maternal circuit: effects of maternal experience on Fos-Lir in hypothalamic, limbic, and cortical structures in the postpartum rat. Behav. Neurosci. 110 (3), 567.

Fonagy, P., Gergely, G., Jurist, E., Target, M., 2002. Affect Regulation, Mentalization, and the Development of the Self.

Forgeron, P.A., King, S., Stinson, J.N., McGrath, P.J., MacDonald, A.J., Chambers, C.T., 2010. Social functioning and peer relationships in children and adolescents with chronic pain: a systematic review. Pain Res. Manag. 15 (1), 27–41.

Fotopoulou, A., Tsakiris, M., 2017. Mentalizing homeostasis: the social origins of interoceptive inference. Neuropsychoanalysis 19 (1), 3–28.

Francis, D.D., Young, L.J., Meaney, M.J., Insel, T.R., 2002. Naturally occurring differences in maternal care are associated with the expression of oxytocin and vasopressin (V1a) receptors: gender differences. J. Neuroendocrinol. 14 (5), 349–353.

Friston, K., 2010. The free-energy principle: a unified brain theory? Nat. Rev. Neurosci. 11 (2), 127–138.

Fukushima, H., Terasawa, Y., Umeda, S., 2011. Association between interoception and empathy: evidence from heartbeat-evoked brain potential. Int. J. Psychophysiol. 79 (2), 259–265.

Gallese, V., 2014. Bodily selves in relation: embodied simulation as second-person perspective on intersubjectivity. Philos. Trans. R. Soc. B 369 (1644), 20130177.

Gilleland, J., Suveg, C., Jacob, M.L., Thomassin, K., 2009. Understanding the medically unexplained: emotional and familial influences on children's somatic functioning. Child Care Health Dev. 35 (3), 383–390.

Gillespie, N.A., Zhu, G., Heath, A.C., Hickie, I.B., Martin, N.G., 2000. The genetic aetiology of somatic distress. Psychol. Med. 30 (05), 1051–1061.

Gu, X., Hof, P.R., Friston, K.J., Fan, J., 2013. Anterior insular cortex and emotional awareness. J. Comp. Neurol. 521 (15), 3371–3388.

Hari, R., Henriksson, L., Malinen, S., Parkkonen, L., 2015. Centrality of social interaction in human brain function. Neuron 88 (1), 181–193.

Hasson, U., Frith, C.D., 2016. Mirroring and beyond: coupled dynamics as a generalized framework for modelling social interactions. Phil. Trans. R. Soc. B 371 (1693), 20150366.
Hasson, U., Ghazanfar, A.A., Galantucci, B., Garrod, S., Keysers, C., 2012. Brain-to-brain coupling: a mechanism for creating and sharing a social world. Trends Cogn. Sci. 16 (2), 114–121.
Herbert, B.M., Pollatos, O., 2012. The body in the mind: on the relationship between interoception and embodiment. Top. Cogn. Sci. 4 (4), 692–704.
Hickie, I., Kirk, K., Martin, N., 1999. Unique genetic and environmental determinants of prolonged fatigue: a twin study. Psychol. Med. 29 (02), 259–268.
Hofer, M.A., 1994. Early relationships as regulators of infant physiology and behavior. Acta Paediatr. 83 (s397), 9–18.
Holliday, K.L., Macfarlane, G.J., Nicholl, B.I., Creed, F., Thomson, W., McBeth, J., 2010. Genetic variation in neuroendocrine genes associates with somatic symptoms in the general population: results from the EPIFUND study. J. Psychosom. Res. 68 (5), 469–474.
Hughes, A.A., Lourea-Waddell, B., Kendall, P.C., 2008. Somatic symptoms in children with anxiety disorders and their unique prediction of poorer academic performance. Child Psychiatry Hum. Dev. 39 (2), 211–220.
Jackson, P.L., Brunet, E., Meltzoff, A.N., Decety, J., 2006. Empathy examined through the neural mechanisms involved in imagining how I feel versus how you feel pain. Neuropsychologia 44 (5), 752–761.
Janak, P.H., Tye, K.M., 2015. From circuits to behaviour in the amygdala. Nature 517 (7534), 284–292.
Jones, M.P., Schettler, R.A., Olden, K., Crowell, M.D., 2004. Alexithymia and somatosensory amplification in functional dyspepsia. Psychosomatics 45 (6), 508–516.
Keysers, C., Kaas, J.H., Gazzola, V., 2010. Somatosensation in social perception. Nat. Rev. Neurosci. 11 (6), 417–428.
Keysers, C., Thioux, M., Gazzola, V., 2013. Mirror neuron system and social cognition. In: In Understanding Other Minds: Perspectives from Developmental Social Neuroscience, pp. 233–263.
Kim, H.S., Sherman, D.K., Mojaverian, T., Sasaki, J.Y., Park, J., Suh, E.M., Taylor, S.E., 2011. Gene–culture interaction: oxytocin receptor polymorphism (OXTR) and emotion regulation. Soc. Psychol. Personal. Sci. 2 (6), 665–672.
Kim, P., Strathearn, L., Swain, J.E., 2016. The maternal brain and its plasticity in humans. Horm. Behav. 77, 113–123.
Kinreich, S., Djalovski, A., Kraus, L., Louzoun, Y., Feldman, R., 2017. Brain-to-brain synchrony during naturalistic social interactions. Sci. Rep. https://doi.org/10.1038/s41598-017-17339-5.
Kleckner, I., Zhang, J., Touroutoglou, A., Chanes, L., Xia, C., Simmons, W.K., ... Barrett, L., 2017. Evidence for a large-scale brain system supporting allostasis and interoception in humans. bioRxiv, 098970.
Kober, H., Barrett, L.F., Joseph, J., Bliss-Moreau, E., Lindquist, K., Wager, T.D., 2008. Functional grouping and cortical–subcortical interactions in emotion: a meta-analysis of neuroimaging studies. Neuroimage 42 (2), 998–1031.
Konijnenberg, A.Y., Uiterwaal, C.S.P.M., Kimpen, J.L.L., van der Hoeven, J., Buitelaar, J.K., de Graeff-Meeder, E.R., 2005. Children with unexplained chronic pain: substantial impairment in everyday life. Arch. Dis. Child. 90 (7), 680–686.
Kontoangelos, K., Raptis, A.E., Papageorgiou, C.C., Tsiotra, P.C., Papadimitriou, G.N., Rabavilas, A.D., ... Raptis, S.A., 2012. Oxytocin and psychological factors affecting type 2 diabetes mellitus. Exp. Diabetes Res. 2012.
Kumagai, H., Oshima, N., Matsuura, T., Iigaya, K., Imai, M., Onimaru, H., ... Kamayachi, T., 2012. Importance of rostral ventrolateral medulla neurons in determining efferent sympathetic nerve activity and blood pressure. Hypertens. Res. 35 (2), 132–141.
Kundakovic, M., Champagne, F.A., 2015. Early-life experience, epigenetics, and the developing brain. Neuropsychopharmacology 40 (1), 141–153.
Lambert, K.G., 2012. The parental brain: transformations and adaptations. Physiol. Behav. 107 (5), 792–800.
Lancaster, J.L., Tordesillas-Gutiérrez, D., Martinez, M., Salinas, F., Evans, A., Zilles, K., ... Fox, P.T., 2007. Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template. Hum. Brain Mapp. 28 (11), 1194–1205.
Lee, A., Clancy, S., Fleming, A.S., 2000. Mother rats bar-press for pups: effects of lesions of the mpoa and limbic sites on maternal behavior and operant responding for pup-reinforcement. Behav. Brain Res. 108 (2), 215–231.
Lindquist, K.A., Wager, T.D., Kober, H., Bliss-Moreau, E., Barrett, L.F., 2012. The brain basis of emotion: a meta-analytic review. Behav. Brain Sci. 35 (03), 121–143.
Loman, M.M., Gunnar, M.R., 2010. Early experience and the development of stress reactivity and regulation in children. Neurosci. Biobehav. Rev. 34 (6), 867–876.
Lukas, M., Bredewold, R., Neumann, I.D., Veenema, A.H., 2010. Maternal separation interferes with developmental changes in brain vasopressin and oxytocin receptor binding in male rats. Neuropharmacology 58 (1), 78–87.
Luminet, O., Grynberg, D., Ruzette, N., Mikolajczak, M., 2011. Personality-dependent effects of oxytocin: greater social benefits for high alexithymia scorers. Biol. Psychol. 87 (3), 401–406.
McCauley, E., Carlson, G.A., Calderon, R., 1991. The role of somatic symptoms in the diagnosis of depression in children and adolescents. J. Am. Acad. Child Adolesc. Psychiatry 30 (4), 631–635.
Menon, V., Uddin, L.Q., 2010. Saliency, switching, attention and control: a network model of insula function. Brain Struct. Funct. 214 (5–6), 655–667.
Nakao, M., Barsky, A.J., Kumano, H., Kuboki, T., 2002. Relationship between somatosensory amplification and alexithymia in a Japanese psychosomatic clinic. Psychosomatics 43 (1), 55–60.
Numan, M., Young, L.J., 2016. Neural mechanisms of mother–infant bonding and pair bonding: similarities, differences, and broader implications. Horm. Behav. 77, 98–112.
Öhman, A., 2002. Automaticity and the amygdala: nonconscious responses to emotional faces. Curr. Dir. Psychol. Sci. 11 (2), 62–66.
Olff, M., Frijling, J.L., Kubzansky, L.D., Bradley, B., Ellenbogen, M.A., Cardoso, C., ... van Zuiden, M., 2013. The role of oxytocin in social bonding, stress regulation and mental health: an update on the moderating effects of context and interindividual differences. Psychoneuroendocrinology 38 (9), 1883–1894.
Oxley, G., Fleming, A.S., 2000. The effects of medial preoptic area and amygdala lesions on maternal behavior in the juvenile rat. Dev. Psychobiol. 37 (4), 253–265.
Perkeybile, A.M., Delaney-Busch, N., Hartman, S., Grimm, K.J., Bales, K.L., 2015. Intergenerational transmission of alloparental behavior and oxytocin and vasopressin receptor distribution in the prairie vole. Front. Behav. Neurosci. 9.
Pessoa, L., Adolphs, R., 2010. Emotion processing and the amygdala: from a 'low road' to 'many roads' of evaluating biological significance. Nat. Rev. Neurosci. 11 (11), 773–783.
Pratt, M., Apter-Levi, Y., Vakart, A., Feldman, M., Fishman, R., Feldman, T., ... Feldman, R., 2015. Maternal depression and child oxytocin response; moderation by maternal oxytocin and relational behavior. Depress. Anxiety 32 (9), 635–646.
Preston, S.D., De Waal, F.B., 2002. Empathy: Its ultimate and proximate bases. Behav. Brain Sci. 25 (1), 1–20.
Quattrocki, E., Friston, K., 2014. Autism, oxytocin and interoception. Behav. Brain Sci. 47, 410–430.
Quirin, M., Kuhl, J., Düsing, R., 2011. Oxytocin buffers cortisol responses to stress in individuals with impaired emotion regulation abilities. Psychoneuroendocrinology 36 (6), 898–904.
Reker, M., Ohrmann, P., Rauch, A.V., Kugel, H., Bauer, J., Dannlowski, U., ... Suslow, T., 2010. Individual differences in alexithymia and brain response to masked emotion faces. Cortex 46 (5), 658–667.
Riem, M.M., Bakermans-Kranenburg, M.J., Pieper, S., Tops, M., Boksem, M.A., Vermeiren, R.R., ... Rombouts, S.A., 2011a. Oxytocin modulates amygdala, insula, and inferior frontal gyrus responses to infant crying: a randomized controlled trial. Biol. Psychiatry 70 (3), 291–297.
Riem, M.M., Pieper, S., Out, D., Bakermans-Kranenburg, M.J., van IJzendoorn, M. H., 2011b. Oxytocin receptor gene and depressive symptoms associated with physiological reactivity to infant crying. Soc. Cogn. Affect. Neurosci. 6 (3), 294–300.
Rilling, J.K., Young, L.J., 2014. The biology of mammalian parenting and its effect on offspring social development. Science 345 (6198), 771–776.
Ropper, A.H., Samuels, M.A., 2009. The hypothalamus and neuroendocrine disorders. In: Adams and Victor's Principles of Neurology. McGraw-Hill, New York, NY.
Roy, A.K., Fudge, J.L., Kelly, C., Perry, J.S., Daniele, T., Carlisi, C., ... Ernst, M., 2013. Intrinsic functional connectivity of amygdala-based networks in adolescent generalized anxiety disorder. J. Am. Acad. Child Adolesc. Psychiatry 52 (3), 290–299.
Schaefer, M., Egloff, B., Witthöft, M., 2012. Is interoceptive awareness really altered in somatoform disorders? Testing competing theories with two paradigms of heartbeat perception. J. Abnorm. Psychol. 121 (3), 719.
Schore, A.N., 2001. Effects of a secure attachment relationship on right brain development, affect regulation, and infant mental health. Infant Ment. Health J. 22 (1–2), 7–66.
Seth, A.K., Friston, K.J., 2016. Active interoceptive inference and the emotional brain. Phil. Trans. R. Soc. B 371 (1708), 20160007.
Silani, G., Bird, G., Brindley, R., Singer, T., Frith, C., Frith, U., 2008. Levels of emotional awareness and autism: an fMRI study. Soc. Neurosci. 3 (2), 97–112.
Silber, T.J., Pao, M., 2003. Somatization disorders in children and adolescents. Pediatr. Rev. 24 (8), 255–261.
Simmons, W.K., Avery, J.A., Barcalow, J.C., Bodurka, J., Drevets, W.C., Bellgowan, P., 2013. Keeping the body in mind: insula functional organization and functional connectivity integrate interoceptive, exteroceptive, and emotional awareness. Hum. Brain Mapp. 34 (11), 2944–2958.
Singer, T., Lamm, C., 2009. The social neuroscience of empathy. Ann. N. Y. Acad. Sci. 1156 (1), 81–96.
Singer, T., Leiberg, S., 2009. Sharing the emotions of others: The neural bases of empathy. In: The Cognitive Neurosciences IV. MIT Press, pp. 971–984.
Singer, T., Critchley, H.D., Preuschoff, K., 2009. A common role of insula in feelings, empathy and uncertainty. Trends Cogn. Sci. 13 (8), 334–340.
Smallwood, R.F., Laird, A.R., Ramage, A.E., Parkinson, A.L., Lewis, J., Clauw, D.J., ... Robin, D.A., 2013. Structural brain anomalies and chronic pain: a quantitative meta-analysis of gray matter volume. J. Pain 14 (7), 663–675.
Sobel, M.E., 1982. Asymptotic confidence intervals for indirect effects in structural equation models. Sociol. Methodol. 13, 290–312.
Spielberger, C.D., Gorsuch, R.L., Lushene, R.E., 1970. Manual for the State-Trait Anxiety Inventory.
Steele, M., Steele, H., Beebe, B., 2017. Applying an attachment and microanalytic lens to "embodied mentalization": commentary on "Mentalizing homeostasis: the social origins of interoceptive inference" by Fotopoulou and Tsakiris. Neuropsychoanalysis 19 (1), 59–66.
Stern, D.N., 1985. The Interpersonal World of the Infant: a View from Psychoanalysis and Developmental Psychology. Karnac Books.
Stonnington, C.M., Locke, D.E., Hsu, C.H., Ritenbaugh, C., Lane, R.D., 2013. Somatization is associated with deficits in affective theory of mind. J. Psychosom. Res. 74 (6), 479–485.
Strathearn, L., Fonagy, P., Amico, J., Montague, P.R., 2009. Adult attachment predicts maternal brain and oxytocin response to infant cues. Neuropsychopharmacology 34 (13), 2655–2666.
Stuart, S., Noyes, R., 1999. Attachment and interpersonal communication in somatization. Psychosomatics 40 (1), 34–43.
Subic-Wrana, C., 2011. Emotion regulation and mentalization in somatoform disorders. In: Emotion Regulation and Well-Being. Springer, New York, pp. 245–260.
Swain, J.E., Kim, P., Spicer, J., Ho, S.S., Dayton, C.J., Elmadih, A., Abel, K.M., 2014.

Approaching the biology of human parental attachment: Brain imaging, oxytocin and coordinated assessments of mothers and fathers. Brain Res. 1580, 78–101.
Taylor, G.J., Bagby, R.M., Parker, J.D.A., 1997. Disorders of Affect Regulation: Alexithymia in Medical and Psychiatric Illness. 10.1017 CBO9780511526831.
Toepfer, P., Heim, C.M., Entringer, S., Wadhwa, P.D., Provencal, N., Binder, E.B., Buss, C., 2016. A variation in the oxytocin receptor gene moderates the relationship between early maternal care in childhood and interleukin 6 (IL-6) concentrations during pregnancy. Psychoneuroendocrinology 71, 15.
Torgersen, S., 1986. Genetics of somatoform disorders. Arch. Gen. Psychiatry 43 (5), 502–505.
Tracy, L.M., Georgiou-Karistianis, N., Gibson, S.J., Giummarra, M.J., 2015. Oxytocin and the modulation of pain experience: implications for chronic pain management. Neurosci. Biobehav. Rev. 55, 53–67.
Valet, M., Gündel, H., Sprenger, T., Sorg, C., Mühlau, M., Zimmer, C., ... Tölle, T.R., 2009. Patients with pain disorder show gray-matter loss in pain-processing structures: a voxel-based morphometric study. Psychosom. Med. 71 (1), 49–56.
Veletza, S., Samakouri, M., Emmanouil, G., Trypsianis, G., Kourmouli, N., Livaditis, M., 2009. Psychological vulnerability differences in students—carriers or not of the serotonin transporter promoter allele S: effect of adverse experiences. Synapse 63 (3), 193–200.
Waller, E., Scheidt, C.E., 2004. Somatoform disorders as disorders of affect regulation: a study comparing the TAS-20 with non-self-report measures of alexithymia. J. Psychosom. Res. 57 (3), 239–247.
Waller, E., Scheidt, C.E., 2006. Somatoform disorders as disorders of affect regulation: a development perspective. Int. Rev. Psychiatry 18 (1), 13–24.
Weaver, I.C., Cervoni, N., Champagne, F.A., D'Alessio, A.C., Sharma, S., Seckl, J.R., ... Meaney, M.J., 2004. Epigenetic programming by maternal behavior. Nat. Neurosci. 7 (8), 847–854.
Weisman, O., Zagoory-Sharon, O., Feldman, R., 2012. Oxytocin administration to parent enhances infant physiological and behavioral readiness for social engagement. Biol. Psychiatry 72 (12), 982–989.
Weisman, O., Delaherche, E., Rondeau, M., Chetouani, M., Cohen, D., Feldman, R., 2013. Oxytocin shapes parental motion during father–infant interaction. Biol. Lett. 9 (6), 20130828.
Zwaigenbaum, L., Szatmari, P., Boyle, M.H., Offord, D.R., 1999. Highly somatizing young adolescents and the risk of depression. Pediatrics 103 (6), 1203–1209.