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Towards a neural model of infant cry perception

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ABSTRACT

Previous work suggests that infant cry perception is supported by an evolutionary old neural network consisting of the auditory system, the thalamocingulate circuit, the frontoinsular system, the reward pathway and the medial prefrontal cortex. Furthermore, gender and parenthood have been proposed to modulate processing of infant cries. The present meta-analysis (N = 350) confirmed involvement of the auditory system, the thalamocingulate circuit, the dorsal anterior insula, the pre-supplementary motor area and dorsomedial prefrontal cortex and the inferior frontal gyrus in infant cry perception, but not of the reward pathway. Structures related to motoric processing, possibly supporting the preparation of a parenting response, were also involved. Finally, females (more than males) and parents (more than non-parents) recruited a cortico-limbic sensorimotor integration network, offering a neural explanation for previously observed enhanced processing of infant cries in these sub-groups. Based on the results, an updated neural model of infant cry perception is presented.

1. Introduction

For most young animals the primary way to express aversive states and call for help is by vocal communication, which corresponds to ‘crying’ among humans (Darwin, 1897). Since crying could decrease biological fitness (e.g., by attracting the attention of predators), efficient parental infant cry perception (and an adaptive response) likely has had surplus fitness value in mammalian evolution (Newman, 2007). Therefore, it has been suggested that the parental neural circuitry to detect and respond to infant crying has evolved relatively early in mammalian evolution and is conserved across mammals (Lingle et al., 2012). Indeed Bowlby (Bowlby, 1999) already proposed that caregiving behavior, including reacting to baby cries, is at least partially biologically prepared.

MacLean’s (MacLean, 1985) comparative neuroanatomic studies confirmed that the thalamocingulate circuit, an evolutionary old neural circuit, consisting of the thalamus and cingulate gyrus, is more differentiated in mammals than in evolutionary older vertebrates and suggested that this mammalian circuit might therefore be involved in parenting. With the advent of neuroimaging, it became subsequently possible to investigate non-invasively what network in humans is associated with infant cry perception. In a seminal fMRI study, Lorberbaum (Lorberbaum et al., 1999) indeed found activity of the cingulate gyrus during infant cry perception. Since then a sizable neuroimaging literature on the neural circuitry involved in infant cry perception has accumulated.

Synthesizing the neuroimaging literature of infant cry perception, Rilling (Rilling, 2013) proposed a multi-stage model with five sub-circuits supporting the various hypothesized stages of the infant cry perception process. First, auditory information is processed in the auditory cortex with right hemispheric specialization. Second, the thalamocingulate pathway (including the posterior cingulate) represents a neural ‘alarm signal’ that the offspring is in need of care. Third, a midbrain-dopaminergic pathway (including the ventral tegmental area and the substantia nigra) is involved in eliciting approach behavior despite the averseness of the cry sound. Fourth, the fronto-insular cortex is involved in ‘emotional empathy’. Last, the dorsomedial prefrontal cortex (dmPFC), is proposed to be involved in more cognitive aspects of empathy, such as ‘perspective taking’ and ‘theory of mind’. The dmPFC is located within the medial superior frontal gyrus (mSFG),

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which is hard to parcellate based on classical macroanatomical boundaries (Schurz et al., 2014). Therefore, in the present work we define sub-divisions within the mSFG as follows based on connectivity based parcellation: the dmPFC as anterior to MNI Y-coordinate 36 (Zhang et al., 2012), the pre-supplementary motor area (pre-SMA) as lying in between MNI-Y coordinate 36 (Zhang et al., 2012) and 0 (Kim et al., 2010; Zhang et al., 2012) and the supplementary motor area (SMA) as lying posteriorly to MNI-Y coordinate 0 (Kim et al., 2010; Zhang et al., 2012).

Regarding the auditory processing stage, developments in the cognitive neuroscience of speech processing seem compatible with the model outlined above, and may offer some extensions. The Dual Stream Model of speech perception (Hickok and Poeppel, 2007; Lima et al., 2016) proposes that human speech is decoded in two parallel processing streams analogously to visual perception: a bilateral ventral stream including the core, belt (Heschl's gyrus) and parabelt (superior temporal gyrus) auditory cortex that extracts auditory object identity (and hence has been called the 'what' pathway) and a parallel left lateralized dorsal pathway (including the inferior frontal gyrus and the premotor cortex) that integrates auditory with motor information. One of the proposed functions of the dorsal stream is to support perception of speech by linking the perceived speech sounds to the articulatory gestures required to produce the same speech sounds, and hence has been called the 'how' pathway.

Non-segmental speech (i.e., vocal auditory information that does not contain elementary speech sounds or 'phonemes', as is the case for infant cries) differs fundamentally from speech containing segments, requiring higher spectral resolution processing in order to extract information from the frequency domain, for which the right hemisphere auditory processing centers are better adapted (Hickok and Poeppel, 2007). A long line of research (Witteman et al., 2012, 2011) has therefore suggested that the right hemispheric homotopes of the segmental speech perception centers as proposed in the Dual Stream Model, and particularly the mid-superior temporal gyrus, might be specialized for such 'suprasegmental' processing. This emotional prosody network might then similarly be involved in the processing of other non-segmental emotional auditory signals such as infant cries.

Indeed, various authors (Lorberbaum et al., 2002; Seifritz et al., 2003) have proposed that right hemispheric specialization for infant cry perception might be explained by involvement of the emotional prosody perception network. Interestingly, a recent multimodal imaging study showed that the right larynx representation in the pre-motor cortex is involved in prosody perception (Sammler et al., 2015), suggesting that the dorsal 'how' stream might be right lateralized for non-segmental speech perception. Hence, right dorsal stream activation (i.e., the IFG and premotor cortex) might similarly be expected in infant cry perception.

As outlined above, evolutionary inspired theories of infant cry perception (Newman, 2007) suggest that there might be an additional final stage in the infant cry perception process that has not been formalized in Rilling's (Rilling, 2013) model but that has been proposed previously, i.e. preparation of caregiving behavior (Swain et al., 2007). Indeed, previous neuroimaging studies of infant cry perception report activation in structures involved in motor preparation such as the (pre-) SMA in the mSFG (Bornstein et al., 2017; Laurent and Ablow, 2012; Li et al., 2017; Swain et al., 2017; Venuti et al., 2012) and action execution in the precentral gyrus (Montoya et al., 2012). Hence, as has been suggested by some of these authors (Bornstein et al., 2017; Laurent and Ablow, 2012; Venuti et al., 2012) infant crying may elicit motor preparation for a parenting response in the (pre-)SMA. A non-mutually exclusive alternative possibility is that the (pre-)SMA might play a more general role in audiomotor integration within the dorsal auditory perception stream (Lima et al., 2016). The basal ganglia (specifically the putamen and caudate nucleus) form cortico-striatal motor loops with the cortical motor system to support motor preparation and hence may additionally be involved in this final stage.

Several factors have been proposed to moderate activation within the infant cry perception network. First, infant cry perception studies typically contrast a recorded infant cry to a control sound, varying from white noise to spectrally and intensity matched scrambled control sounds. With an increasing acoustic match between the cry and control sound, more lower level auditory processing areas would be expected to fall below the statistical detection threshold (Rilling, 2013).

Second, parental status has been suggested to moderate neural processing of infant cries, with parents purportedly showing enhanced processing as compared to non-parents (Bos et al., 2010; Luo, 2015; Parsons et al., 2014; Proverbio et al., 2006; Seifritz et al., 2003) specifically in the amygdala, mid cingulate gyrus, middle temporal gyrus, insulae, middle frontal gyrus, orbitofrontal cortex, inferior frontal gyrus, and the SMA (Parsons et al., 2014; Seifritz et al., 2003). Others (Mascaro et al., 2014) have additionally proposed that amygdala and ventral tegmental activation might be specific for mothers. One possibility is that such purported specificity is explained by neuro-endocrine induced neuroplastic changes caused by pregnancy and the partus (Hoekzema et al., 2017; Rilling, 2013).

Last, it has been proposed that females may show enhanced processing of infant sounds as compared to males (Dhatri et al., 2018; Messina et al., 2016; Proverbio et al., 2006; Sander et al., 2007; Seifritz et al., 2003; Zeifman, 2001), with increased activation for females as compared to males in the amygdala and the anterior cingulate (Sander et al., 2007). On the other hand, more pronounced *de*activation for females as compared to males has also been found (Seifritz et al., 2003) in the anterior cingulate and the medial prefrontal cortex for infant cry perception, which was interpreted as a role for the anterior cingulate in suppressing irrelevant information. Electrophysiological studies suggest that enhanced processing of infant emotional expressions among females may arise relatively early in the perception process (Dhatri et al., 2018; Proverbio et al., 2006), namely at the sensory processing stage. These gender effects have been interpreted as physiological predispositions for enhanced responding to infant cries among females (Dhatri et al., 2018; Proverbio et al., 2006; Sander et al., 2007; Zeifman, 2001).

Although qualitative syntheses of the previous infant cry perception literature have been performed (Rilling, 2013; Swain et al., 2014), it has been noted that there is significant variability between neuroimaging studies of cry perception in the location of activations reported (Rilling, 2013), raising the question what network is robustly involved in infant cry perception. Quantitative meta-analysis offers the advantage to formally test what network is robustly involved in infant cry perception across studies. Recent developments in meta-analysis of neuro-imaging data (Radua and Mataix-Cols, 2009) allow for the inclusion of (part of the) original imaging data, dramatically increasing sensitivity as compared to previous meta-analytic methods and to formally test the influence of moderators. Therefore, the present work used a novel meta-analytic technique to investigate what neural network is reliably involved in infant cry perception among human adults, to what extent (and where) it is lateralized, and whether activation in response to infant cries is moderated by the acoustic match between cry and control stimulus, parenthood, and gender.

2. Methods

2.1. Study selection

The PubMed database (www.ncbi.nlm.nih.gov/pubmed/) was searched for relevant publications until January 2018 using the following search string (where the asterisk denotes a wildcard and 'tiab' indicates searching for keywords in the title and the abstract): (infant [tiab] OR baby [tiab]) AND (cry [tiab] OR crying [tiab] OR cries [tiab]) AND (*MRI [tiab] OR PET [tiab] OR *imaging [tiab]). This search yielded 33 publications. Additionally, the reference lists of relevant articles and reviews (Rilling, 2013; Swain et al., 2014) were checked for potentially relevant publications. This search yielded 44 eligible publications. The following inclusion criteria were then applied: (1) an infant cry stimulus was contrasted to an auditory control stimulus (2) participants were healthy adults and not administered a psychoactive substance before scanning (3) whole brain analyses were reported (papers including only ROI analyses were excluded) (4) peak coordinates of significantly activated areas were reported in MNI or Talairach standard stereotactic space (5) the sample size was at least 10 participants (6) the article had been published in an international peer-reviewed journal. Application of these criteria resulted in 10 publications (14 experiments) that were included in the meta-analysis (See Supplementary Fig. 1).

For each study contrasts were selected as follows. The active condition had to be an infant cry and the control a (matched) control sound. If a study reported multiple contrasts that were eligible for inclusion, the most conservative contrast was chosen (e.g., when foci were presented for infant cries vs. a pure tone and vs. a matched control sound, the latter was chosen because it yields a more conservative estimation of the network activity involved in the perception of infant crying).

All included studies used fMRI (see Supplementary Table 1, a total of 14 studies (total N = 350 subjects) were included in the meta-analysis. All of the included studies compared infant cries to a (matched) control sound. Furthermore, we obtained the original statistical parametric maps (SPMs) for 6 out of 14 included studies (Bos et al., 2014, 2010; Li et al., 2017; Mascaro et al., 2014; Riem et al., 2014, 2011).

2.2. Seed-based d-Mapping

Seed-based d-mapping (formerly known as Signed Differential Mapping) is a validated voxel based meta-analytic method (Radua et al., 2012) that has been used in previous (Fullana et al., 2016; Gabay et al., 2014) meta-analyses of neuro-imaging studies. In brief, d-mapping calculates meta-analytic maps of (de-)activation effect sizes for a contrast based on the effect size (T-values) of peak coordinates of activation clusters as reported in primary studies. Activation effect sizes of voxels surrounding the voxel within a distance of 20 mm containing the activation peak are estimated using an anisotropic Gaussian kernel. Hence, the method is conceptually similar to coordinate based meta-analysis such as Activation Likelihood Estimation (ALE) meta-analysis (Eickhoff et al., 2009a) but with the advantage that (de-)activation effect sizes are used in addition to the coordinates of activation clusters, increasing the validity of meta-analytic estimates of the true signal (Radua et al., 2012). Additionally, d-mapping allows for the inclusion of original statistical parametric maps (SPMs), dramatically increasing the amount of information that is used to calculate meta-analytic statistical maps. Indeed, it has been shown that including only 20% SPMs can increase sensitivity from 55% to 87% (Radua et al., 2012). Next, individual voxel-wise effect size maps are combined into a meta-analytic effect size map using a random effects model with individual studies weighted by their inverse variance and sample size (Radua et al., 2012). Last, significance of meta-analytical effect size clusters is determined by testing against a null-distribution obtained from a Monte Carlo simulation that randomizes effect sizes over the grey matter voxel template. A combination of an uncorrected *p*-value of 0.005 and an SDM *Z*-value of $> = 1$ (note that the SDM-Z distribution does not correspond to a standard normal distribution because null effect sizes are relatively common) and a cluster extent of $> = 10$ voxels has been shown to correspond to a corrected *p*-value of 0.05. For a full technical discussion of Seed-based d-Mapping see (Radua et al., 2012).

2.3. Meta-analyses

In the main analysis, we tested what neural regions were significantly activated across studies by infant cry sounds as compared to control sounds. The SDM-Z null distribution was calculated using 50 whole-brain permutations. If original SPMs used Z scores or Talairach space, the images were first converted to T scores or MNI, respectively. Similarly, if effect size (activation) was reported as Z values, they were first converted to T values. Next, preprocessing was performed by applying a kernel with a width of 20 mm FWHM and an anisotropy of 1 (assigning more weight to voxels that are spatially correlated with the peak). The reproduction of T-maps by SDM based on study coordinates was manually checked by comparing the SDM estimated T-map to figures displaying activation clusters in the respective study. Voxels outside the MNI grey matter mask were excluded. Voxels were considered significant at a *p*-value of 0.005. Clusters were considered significant when containing an SDM-Z peak value of $> = 1$ and having an extent of $> = 10$ voxels. As outlined above, these thresholding parameters correspond to a corrected *p*-value of 0.05.

We additionally analyzed whether there was evidence for lateralization of activation in response to infant cries by multiplying the x-coordinates of the input coordinates and maps by -1 (effectively left-right flipping each coordinate) and subtracting the flipped meta-analytical map from the original (unflipped) map (Turkeltaub and Coslett, 2010) using the general linear model function in Seed-based d-Mapping.

2.4. Heterogeneity, sensitivity and publication bias analyses

The following supplemental analyses were performed to assess the robustness of the main analyses. First, jackknife sensitivity analyses were performed to analyze which activation clusters were stable across studies. This analysis re-calculates the results of the analysis for the k studies k times, each time removing one study, allowing for an analysis of robustness of the meta-analytic results (i.e., what clusters remain significant after removal of each study). If a brain region remains significant in all or most of the analyses, the result can be considered rather robust. In the results section, only clusters that replicate across all studies are discussed, but all significant clusters (and their robustness across studies) are reported in the accompanying tables. Furthermore, the full jackknife analyses can be found in the Appendix.

Second, for each meta-analytic activation cluster funnel-plots of effect size against measurement precision were inspected and Egger's tests were performed to test whether there were signs of publication bias.

Last, areas of significant between-study heterogeneity were identified by computing the Q-statistic. Subsequently, sub-group analyses were performed using the general linear model function of SDM to explain heterogeneity in regional activations. Three moderators that varied sufficiently across studies were considered: (1) the level of acoustic matching between the infant cry and control stimulus: spectrally + intensity matched (k = 7) vs. matched on less than spectrum and intensity (k = 7); (2) gender of the participants: male (k = 3) vs. female (k = 11); (3) parental status of the participants: non-parent (k = 5) vs. parent (k = 7). Note (see Supplementary Table 1 in the Appendix) that for gender and parenthood one and two studies, respectively, had a mixed sample that therefore were excluded from the respective moderator analysis. Sub-group analyses were performed at the same statistical threshold as the main analyses. For gender and parenthood sub-group analyses, parenthood and gender respectively were entered as covariate of no interest in the general linear model to investigate effects of gender controlling for parenthood and vice versa.

3. Results

3.1. Main analysis

3.1.1. Main analysis - results

The main meta-analysis revealed seven clusters (see Table 1 and Fig. 1) that were replicated across all studies. The first cluster had a peak in the R mid STG/STS but extended along the anterior-posterior

Table 1
Main meta analysis of [cry > control] for n = 14 experiments. All clusters were thresholded at the p = 0.005 voxel level and a minimum extent of 10 voxels. Bold regions are robust across all jackknife folds.

Peak voxel						Cluster	
Region	MNI			SDM-Z value	p-value	No. voxels	Local peaks
	x	y	z				
R mid STG	62	−22	0	10.28	˜0	7128	R mid superior temporal gyrus, R anterior superior temporal gyrus, R temporal pole, R middle frontal gyrus, R inferior frontal gyrus triangular, R precentral gyrus, R inferior frontal gyrus opercular, R inferior frontal gyrus orbital, R temporal pole, R dorsal anterior insula, R angular gyrus
L ant STG	−64	−14	−2	8.90	˜0	4509	L anterior superior temporal gyrus (ant STG), L anterior superior temporal sulcus, L mid superior temporal gyrus, L striatum, L medial inferior frontal gyrus triangular, L inferior frontal gyrus orbital, L temporal pole, L inferior parietal
R mSFG	6	8	60	5.96	˜0	1799	R pre-supplementary motor area (pre-SMA), L pre SMA, R SMA, L dorsomedial prefrontal cortex (dmPFC), R dmPFC
Posterior cingulate	0	−46	24	3.91	4.1e-5	1035	L posterior cingulate gyrus, R posterior cingulate gyrus
L medial cerebellum (VIIa, Crus I)	−16	−80	−22	3.76	7.4e-5	450	L medial Cerebellum VIIa crus I, L medial Cerebellum lobule VI
L putamen	−26	0	4	4.44	4.6e-6	377	L putamen, L dorsal anterior insula
R caudate body	14	6	19	3.4	3.1e-4	129	R caudate body, R dorsal anterior thalamus
R Cerebellum (crus I)	14	−80	−26	3.53	1.8e-4	110	R medial cerebellum VIIa crus I, R medial Cerebellum VIIa crus II, Cerebellum lobule VI
L thalamus	−12	2	10	3.17	7.3e-4	71	L thalamus
L MFG	−44	18	26	3.00	1.4e-3	39	L middle frontal gyrus (MFG)
R thalamus	6	−8	2	3.10	9.5e-4	26	R thalamus
Thalamus	0	−8	8	2.87	2.3e-3	10	Medial thalamus
L IFG	−56	16	2	2.88	2.2e-3	10	L inferior frontal gyrus triangular part

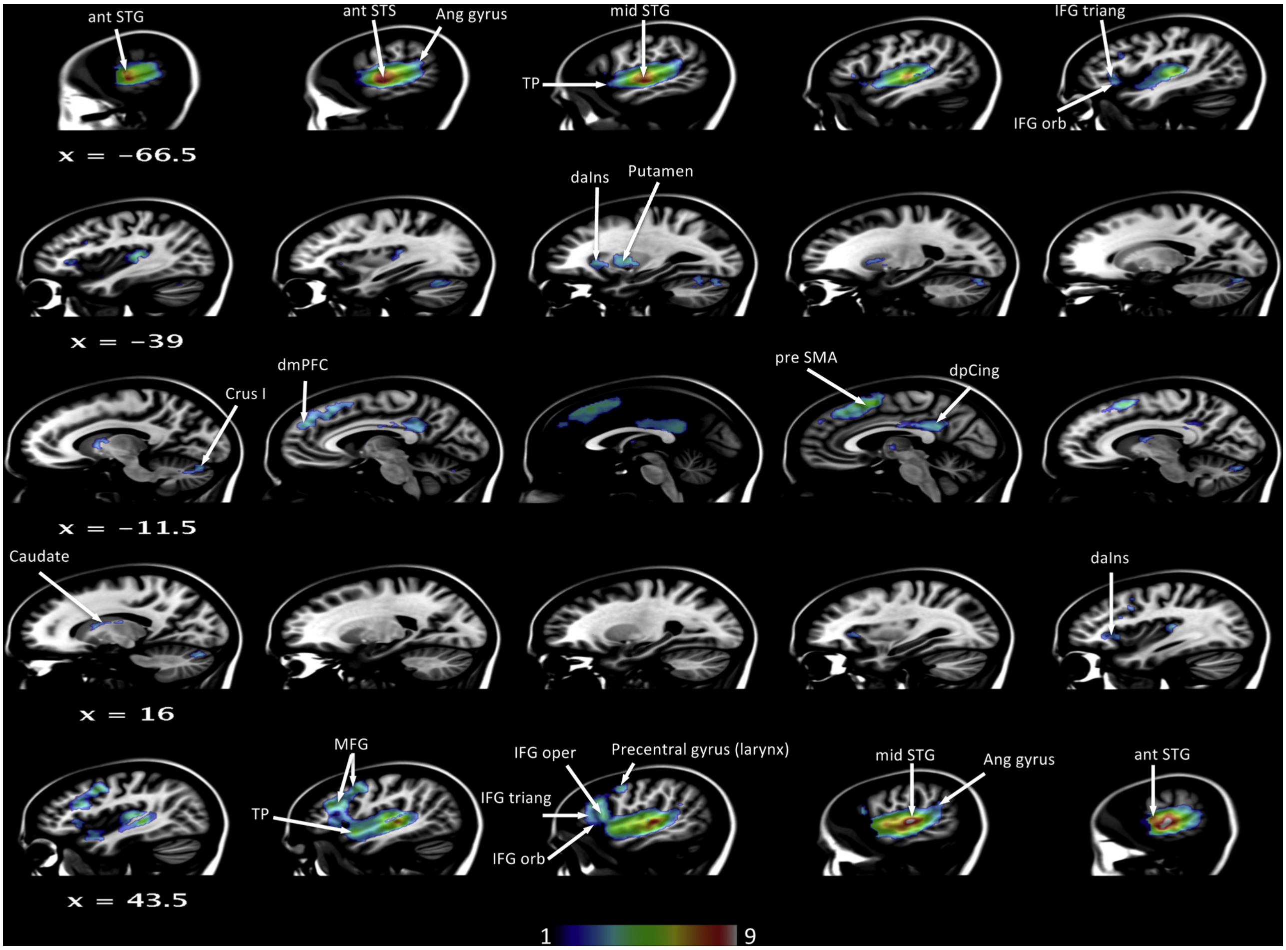

Fig. 1. Main meta-analysis of [cry > control]. Arrows indicate the peak voxel and local peaks for robust clusters reported in the associated table. IFG triang = inferior frontal gyrus triangular part, IFG orb = inferior frontal gyrus orbital part, IFG oper = inferior frontal gyrus opercular part, daIns = dorsal anterior insula, TP = temporal pole, ant STG = anterior superior temporal gyrus, mid STG = middle part of the superior temporal gyrus, ant STS = anterior superior temporal sulcus, MTG = middle temporal gyrus, ang gyrus = angular gyrus, PM = premotor cortex, dmPFC = dorsomedial prefrontal cortex, thal = thalamus, dpCing = dorsal posterior cingulate gyrus, Crus 1 = Crus I of the neocerebellum, pre SMA = pre-supplementary motor area, MFG = middle frontal gyrus.

Table 2
Lateralization analysis (x flipped map subtracted from original map) of n = 14 experiments. All clusters were thresholded at the p = 0.005 voxel level and a minimum extent of 10 voxels. Regions in bold were robust across all jackknife folds.

Peak voxel						Cluster	
Region	MNI			SDM-Z value	p-value	No. voxels	Local peaks
	x	y	z				
R precentral gyrus	**52**	**2**	**42**	**2.61**	**2.6e-4**	**166**	**R precentral gyrus**
R ant STG	64	−2	6	2.83	5.7e-4	23	R anterior superior temporal gyrus (ant STG)
R medial post STG/STS	46	−34	−4	2.80	6.4e-4	12	R medial posterior superior temporal gyrus and sulcus (medial post STG/STS)
L Cerebellum	−28	−64	−20	2.41	2.9e-3	12	L Cerebellum, hemispheric lobule VI

axis with local peaks in the TP, anterior STG, and the angular gyrus. The cluster extended into the frontal cortex with local peaks in the lateral IFG (triangular, opercular and orbital) and the middle frontal gyrus (MFG) and precentral gyrus (the premotor and primary motor cortex), including the larynx representation (Brown et al., 2008). Medially the cluster extended into HG (including the core and belt auditory cortex) and the insula with a local peak in the dorsal anterior insula.

The second cluster had a peak in the L anterior STG, extending along the anterior-posterior axis with local peaks in the TP, anterior STS, mid-STG and angular gyrus. The cluster extended into the frontal cortex with local peaks in the lateral IFG (triangular, opercular and orbital). Medially the cluster extended into HG (including the core and belt auditory cortex) and the insula, with a local peak in the dorsal anterior insula.

The third cluster had a peak in the mSFG (L and R), including the (pre-) SMA (particularly in the right hemisphere) with a peak in the posterior pre-SMA but continuing anteriorly into the dmPFC. The fourth cluster had a peak in the dorsal posterior cingulate (L and R). The fifth cluster had a peak in the L cerebellum (crus I). The sixth cluster had a peak in the L putamen, extending into the claustrum and anterior insula. The seventh cluster had a peak in the R caudate nucleus (body), extending into the dorsal anterior thalamus.

For none of the peaks there was evidence of publication bias (for all: Egger's test $P > = 0.079$).

3.1.2. Main analysis – moderation analysis

Inspection of the map of the normalized Q (heterogeneity) statistic revealed significant ($p < 0.005$, extent = 10 voxels) between-study variation with a peak in the Heschl's gyri (including the core and belt auditory cortex) and surrounding parabelt auditory cortex (mid-STG), extending into the parietal operculum laterally and the posterior insula medially (left and right). Exploratory sub-group analyses were performed in an attempt to explain inter-study variation. These sub-group analyses should be interpreted with caution since the number of studies per sub-group is relatively small (however, note that only areas that are activated across all jackknife folds are discussed).

First, studies varied in the level of acoustic matching between the infant cry and the control sound. As can be observed in Supplementary Table 2 and Supplementary Fig. 2, studies that matched on fewer acoustic dimensions found activity in the left mSFG, with a peak in the dmPFC but continuing posteriorly into the pre-SMA.

Second, some studies only had female participants while others only had male participants. As can be observed in Supplementary Table 3 and Supplementary Figs. 3 and 4, when females were directly compared to males (controlling for parenthood), statistically robust larger activations were observed with a peak in the bilateral dorsal posterior insulae (extending into the bilateral HG, both core and belt), extending into the bilateral frontoparietal opercula and with clear local peaks in the ventral bilateral postcentral gyri, close to the larynx representation (Roux et al., 2018). Males showed statistically robust larger activation than females in the right IFG (triangular), extending into the temporal pole, and left angular gyrus.

Third, studies varied in whether parents vs. non-parents were included. As can be observed in Supplementary Table 4 and Supplementary Fig. 6, when parents were directly compared to non-parents (controlling for gender) statistically robust larger activation was observed in a cluster with a peak in the right supramarginal gyrus, however, this activation extended all over the frontoparietal operculum and STG laterally and to the HG (both core and belt) and insula medially, with local peaks in the dorsal posterior insula, HG, ventral posterior insula, dorsal anterior insula, postcentral gyrus, precentral gyrus and the putamen. Again, the location of activation in the postcentral gyrus included the larynx representation (Roux et al., 2018). Secondly, a robust cluster was found with a peak at the border of the left HG (both core and belt) and dorsal posterior insula, extending laterally over the frontoparietal operculum and the STG and medially into the insula, with local peaks in the dorsal posterior insula, ventral posterior insula, dorsal anterior insula, precentral gyrus, postcentral gyrus and supramarginal gyrus. When comparing non-parents directly to parents there was one statistically robust cluster with larger activation, with a peak in the right caudate nucleus (head).

3.2. Lateralization analysis

Lateralization analysis revealed one right lateralized cluster that was replicated across all studies (see Table 2 and Fig. 2). This cluster had a peak in the right dorsal precentral gyrus (the premotor cortex, BA 6), at the level of the larynx representation (Brown et al., 2008) extending into the middle frontal gyrus. A significant right lateralized cluster was also observed in the right anterior superior temporal gyrus (the temporal pole) that was replicated in all but one jackknife fold.

4. Discussion

Evolutionary inspired theories of human parenting suggest that a relatively old mammalian neural circuit supports efficient perception and responding to infant cries (MacLean, 1985; Newman, 2007). In the present work, we examined what neural network is involved in infant cry perception, to what extent it is lateralized (and where), and whether neural processing is moderated by the acoustic match between cry and control stimulus, parental status, and gender, using a novel meta-analytic technique that included a significant body of original imaging data from the previous literature. This allowed for a relatively rigorous test of the neural circuitry previously proposed to be involved in infant cry perception (Rilling, 2013; Swain et al., 2014)

Most components of the rudimentary neural models of infant cry perception as outlined in the introduction were indeed supported by the current work. First, robust meta-analytic activation was observed across the whole anterior-posterior axis of the superior temporal lobe, including the core and belt primary auditory cortex (HG) and the parabelt (STG). Furthermore, activation extended into the anterior and posterior border of the STG and to the middle temporal gyrus (MTG). These activations therefore seem to be compatible with an auditory (HG, STG) and semantic (temporal pole, MTG) processing stage (such as

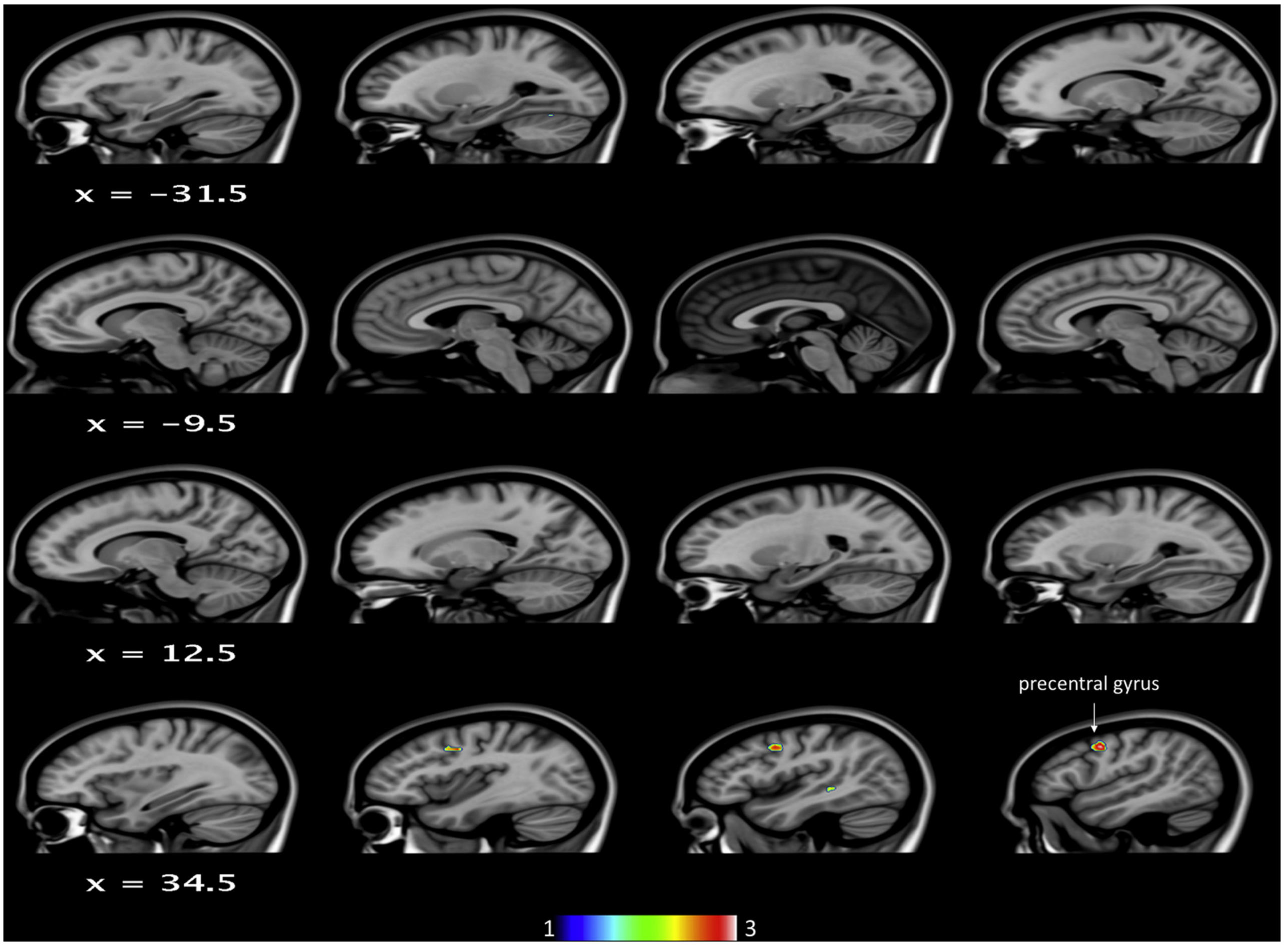

Fig. 2. Lateralization analysis: [unflipped map > flipped map]. Activated areas are more active in the respective hemisphere than the opposite hemisphere. Robustly lateralized clusters are indicated with an arrow].

evaluating the level and quality of discomfort as communicated with the cry) within a bilateral ventral auditory 'what' pathway (Hickok and Poeppel, 2007; Lima et al., 2016) to identify incoming auditory information as infant cries. Indeed the present results converge with a previous meta-analysis of emotional prosody perception studies suggesting that the bilateral STG supports auditory processing of emotional speech (Witteman et al., 2012).

Additionally, robust activation was observed in key nodes of the dorsal auditory 'how' pathway, including the bilateral opercular IFG and the right premotor cortex (Hickok and Poeppel, 2007) and the bilateral (pre-) SMA (Lima et al., 2016), suggesting that the dorsal stream is involved in infant cry perception. Moderator analysis furthermore indicated that the dmPFC and pre-SMA were more activated when the acoustic match of infant cries vs. the control sound was low rather than high, supporting an acoustic processing role of the (pre-) SMA in infant cry perception. Indeed, previous work suggests that these parts of the mSFG are involved in audio-motor integration and action monitoring (Amodio and Frith, 2006) and hence may be part of the auditory dorsal processing stream (Lima et al., 2016).

Moreover, lateralization analysis revealed only one robustly lateralized cluster within the cry perception network, located in the right premotor cortex at the level of the larynx representation, replicating a recent finding for prosody perception suggesting that this area is involved in motor simulation of incoming auditory information (Sammler et al., 2015). This suggests that the dorsal auditory processing stream might similarly be right lateralized for infant cry perception and may support accurate infant cry perception by audio-motor integration in the frequency domain (i.e., pitch).

Second, robust activation was observed in the dorsal anterior thalamus and the dorsal posterior cingulate gyrus, confirming the involvement of the thalamocingulate circuit (MacLean, 1985) in infant cry perception. This circuit has been previously proposed to function as a 'neural alarm signal' (Rilling, 2013) that the infant is in need. Indeed, this suggestion is compatible with a proposal that the thalamocingulate circuit might be a multisensory integration hub that, together with the anterior insula, can shift attention to motivationally salient sensory events (Leech and Sharp, 2014) such as infant crying.

Third, the anterior insula was predicted to be involved in infant cry perception, purportedly due to its role in emotional/affective empathy (Rilling, 2013). Indeed, robust activation in the fronto-insular cortex was observed, particularly in the dorsal anterior insula. Recent work suggests that the dorsal anterior insula might be involved in cognitive control and salience detection, due to its connectivity with the prefrontal cortex, SMA and lateral motor areas (Deen et al., 2011; Uddin et al., 2014; Zhang et al., 2018). This more fundamental purported function of the dorsal anterior insula may be compatible with a role in emotional empathy, since the anterior dorsal insula (together with the thalamocingulate pathway) seems well positioned to contribute to the ability to experience the emotions of others by detecting motivationally salient information (e.g., infant cries) and focusing attention on emotions as expressed through the voice, allowing for enhanced processing of emotional information.

Last, the dorsomedial prefrontal cortex (dmPFC), has been hypothesized to be involved in cognitive empathy (Rilling, 2013; Swain et al., 2014). Indeed, robust activation across studies was found in the mSFG, particularly in the pre-SMA, but continuing anteriorly into dorsomedial prefrontal cortex (dmPFC). Previous work suggests that there is an anterior to posterior gradient within the mSFG from the dmPFC to the (pre-)SMA from more abstract action monitoring in the dmPFC (Amodio and Frith, 2006) to increasingly more concrete motor processing in the (pre-)SMA (Kim et al., 2010; Zhang et al., 2012). Therefore, these regions seem well suited to initiate and plan a parenting response (Swain et al., 2007). However, through connectivity with the insula (Deen et al., 2011; Zhang et al., 2012) these regions might additionally be involved in evaluating emotional relevance of sensory stimuli (Schurz et al., 2014) and particularly emotion from the voice (Lima et al., 2016). These more fundamental functional roles of the mSFG in evaluation of emotional information and (motivated) action initiation may be compatible with a role in cognitive empathy.

One sub-circuit previously hypothesized to be involved in infant cry perception was not robustly activated - the midbrain-dopaminergic reward pathway. The mesocorticolimbic reward pathway is activated by naturally (unconditioned-) rewarding stimuli such as food or drugs of abuse (Koob and Volkow, 2010). Indeed, it has been noted in previous work that reward pathway activation is not routinely observed in neuroimaging studies of infant cry perception (Rilling, 2013). It could be argued that the cry sound of a (un)familiar child as typically used in neuroimaging studies of infant cry perception is not a naturally rewarding stimulus but rather an aversive stimulus that elicits a response by negative reinforcement. Hence, reward pathway activation by cry stimuli might not be expected to begin with. Indeed, some of the meta-analytically robustly active regions observed in the present work (the temporal poles, the orbitofrontal cortex, the auditory cortex, the putamen and cerebellum) have previously been shown to be involved in the processing of aversive sounds (Zald and Pardo, 2002). Alternatively, reward pathway activation in response to infant cries may depend on the stage of parenthood (Rilling, 2013; Rilling and Young, 2014), whether a parent is involved in primary caregiving (Abraham et al., 2014), or on neuro-endocrine induced neuroplastic changes that might be specific to mothers (Hoekzema et al., 2017; Luo, 2015). Such heterogeneity could have resulted in sub-threshold activation of the reward pathway in the present meta-analysis.

Three neural systems were found to be robustly activated during infant cry perception but that were not formalized in Riling's (Rilling, 2013) model or the Dual Stream Model of speech perception (Hickok and Poeppel, 2007). First, robust activation was observed in the bilateral triangular and orbitofrontal IFG, but with a larger extent in the right hemisphere. A recent meta-analytic co-activation clustering analysis (Hartwigsen et al., 2018) suggests that there is a gradient in the right IFG with more anterior areas being involved in more abstract cognitive processing and the posterior IFG in motor processing, with the triangular IFG specifically involved in social cognition and 'mentalizing' and the OFC in semantic affective analysis. Hence, these regions may support amodal emotional analysis of infant cries. Indeed, this interpretation would be in line with a previous meta-analysis of emotional prosody perception studies (Witteman et al., 2012) suggesting that the anterior IFG is involved in abstract (amodal) evaluation of affective information as communicated through the voice. Second, robust activation was observed in the left Crus I of the neocerebellum. Although the cerebellum typically is not covered in cognitive neuroscience models of auditory processing, anatomically it is an integral part of the auditory system and robust involvement of the cerebellum (including Crus I) has indeed been observed in a meta-analysis of auditory perception studies (Petacchi et al., 2005). Hence, the cerebellum might support auditory processing during infant cry perception. Alternatively, the cerebellum may be part of the cognitive control network during emotional processing (Stoodley and Schmahmann, 2009) or may support motor preparation, particularly during preparation of vocalization (Eickhoff et al., 2009b) or may have both auditory, emotional and motor functions. Third, robust activation was observed in the basal ganglia, specifically the right caudate nucleus and the left putamen. The basal ganglia have previously been suggested to be involved in supporting 'ritualistic behaviors' when listening to infant cries (Swain et al., 2007). Anatomically, the caudate and putamen are part of the cortico-striatal motor loops that respectively support (motivated) action initiation (Provost et al., 2010; Tricomi et al., 2004) and planning (Booth et al., 2007; Grahn and Rowe, 2009; Hove et al., 2013) which may include relatively routine behaviors observed in parenting.

Activation in response to infant crying was robustly moderated by parental status. As compared to non-parents, parents robustly activated the bilateral auditory cortex (core, belt, and parabelt), posterior insula, dorsal anterior insula, pre- and postcentral gyrus and the right putamen. Of note, activation of the somatosensory cortex included the representation of the larynx (Roux et al., 2018), which is responsible for vocalization. Recent connectivity work suggests that there is a posterior to anterior gradient in the insula, with the posterior insula (situated in between the auditory cortex and the somatosensory cortex) integrating emotionally relevant auditory information (such as the F_0 contour that perceptually corresponds to pitch variation) with somatosensory and motor information, while the anterior insula (as noted above) might be involved in amodal emotional processing (Deen et al., 2011; Zhang et al., 2018). In the case of infant cries this may include simulation of incoming pitch information by activation of the own larynx representation (Sammler et al., 2015). Collectively, these networks may be well suited to encode the perception of 'how the self feels' in response to auditory emotional information (Zhang et al., 2018). Hence, the present results suggest that parents differentially engage a cortico-limbic sensorimotor integration network that may assist in efficient processing of and motivated (emotional) responding to infant cries. Non-parents only activated the right caudate more than parents, which as outlined above may underlie a tendency to initiate action in response to infant cries.

Females (controlling for parenthood) robustly activated a very similar network more than males, with peaks in the posterior insulae, the primary auditory cortices (core and belt) and the somatosensory cortex at the level of the larynx representation. Therefore, as outlined above, females may differentially recruit a multi-sensory integration circuit to extract emotionally relevant information from the incoming auditory signal. Males showed robust larger activation in response to infant cries in the right triangular IFG (extending into the temporal pole) and left angular gyrus. As outlined above, a recent meta-analysis suggests that the right IFG is involved in 'mentalizing' (Hartwigsen et al., 2018). A recent combined fMRI and lesion study furthermore suggests that the angular gyrus is involved in semantic (combinatorial) processing (Price et al., 2015). Hence, the present results suggest that males may differentially recruit these regions, which may be associated with relatively more (as compared to females) semantic processing to evaluate infant cries.

The present work had some strengths and limitations. First, relative small sample size of individual fMRI studies has been shown to result in low statistical power and reporting of false positive foci, calling for robust large-scale analyses of neuroimaging work (David et al., 2013). Therefore, in the meta-analysis we aimed to keep a nominal false positive rate and to maximize statistical power by obtaining a large combined sample size ($N = 350$), using an empirically derived statistical discovery threshold (Radua and Mataix-Cols, 2009) not including studies with a very small sample size ($N < 10$), only including foci from whole brain analyses performed at the same statistical threshold, weighing the contribution of individual studies by sample size using a random effects model, and only discussing foci that were replicable across all included studies. Also, we formally checked for heterogeneity and publication bias for all reported foci. However, it should be noted that the number of studies included in each level of our moderation analyses was relatively small and hence these analyses should be taken as preliminary. Second, we only included studies that contrasted a cry stimulus with a high-level control sound to reduce heterogeneity in the underlying psychological process measured and obtain a conservative estimate of the network involved in cry perception. However, as a

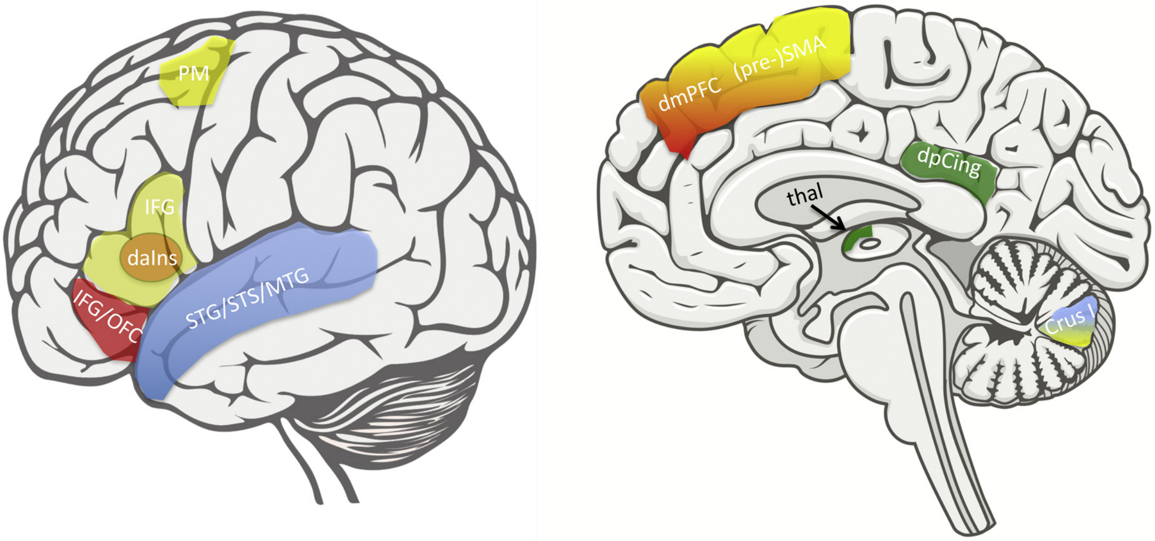

Fig. 3. Schematic illustration of the circuits involved in cry perception in the right hemisphere as confirmed in the present work (basal ganglia not shown, insula is hidden from view but indicated with a red circle). Blue = auditory object recognition in the ventral auditory stream, green = shifting of attention in the thalamocingulate circuit, red = amodal emotional/salience processing, yellow = (audio-)motor processing in the dorsal auditory stream and preparation of a caregiving response. Note that there is a gradient from amodal emotional processing to motor processing from the dmPFC to the (pre-)SMA and it is currently uncertain what the precise role (auditory or motor) of the cerebellum is in infant cry perception. IFG = inferior frontal gyrus, OFC = orbitofrontal cortex, daIns = dorsal anterior insula, STG = superior temporal gyrus, STS = superior temporal sulcus, MTG = middle temporal gyrus, PM = premotor cortex, dmPFC = dorsomedial prefrontal cortex, (pre-)SMA = (pre-) supplementary motor area, thal = thalamus, dpCing = dorsal posterior cingulate gyrus, Crus 1 = Crus I of the neocerebellum].

result, lower level areas involved in infant cry perception may have fallen below the statistical detection threshold. Third, because the included studies typically used the cry of an unfamiliar child as the active condition, areas involved in specifically processing the own child may not have been detected (Swain et al., 2007). However, note that others (Li et al., 2018) found little difference in neural activation between the own and other child (although it should be noted that this study only included fathers, and hence significant differences in the processing of the own vs. an unfamiliar child could be present in mothers). Last, we have suggested that the various neural structures robustly active in the present meta-analysis participate in neural circuits to support infant cry perception based on the previous connectivity literature but we did not test connectivity models of infant cry perception. Future connectivity studies could test whether there is indeed significant connectivity during infant cry perception in the pathways suggested in the present work.

The included studies involved a non-clinical population, and may be considered to provide a ‘normative’ baseline for comparison with clinical groups, for instance parents with perinatal depression or parents at risk for child maltreatment. Infant crying can also be an aversive stimulus that triggers child abuse (Reijneveld et al., 2004), which may be the case if depressed or stressed parents are overwhelmed by the sound of crying, or when it triggers negative childhood memories. Females with an insecure representation of attachment experiences in their childhood have been found to show heightened amygdala activation during exposure to infant crying compared to females with secure attachment representations (Riem et al., 2012), and higher heart rate reactivity to infant cry sounds was observed in individuals with a history of child neglect (Buisman et al., 2018). In a first study with a relatively small sample, mothers diagnosed with major depressive disorder showed reduced neural activation to infant crying (Laurent and Ablow, 2012). The present meta-analysis may serve as a baseline neural activation criterion to estimate deviation from the norm in these clinical groups.

In sum, the present meta-analysis largely confirms and extends previous models of infant cry perception (Fig. 3) and suggests that infant cry perception may be sub-served by at least four neural circuits. First, acoustic analysis of infant cries is performed in an auditory dual stream network, with a ventral stream including the primary and parabelt auditory cortex serving to identify incoming auditory information as infant cries (blue in Fig. 3), and a right lateralized dorsal stream consisting of the IFG, premotor cortex and the posterior dorsomedial prefrontal cortex to integrate auditory information with motor programs (yellow in Fig. 3), possibly assisted by the cerebellum. Second, the thalamocingulate pathway may assist in shifting attention to this potentially motivationally relevant signal (green in Fig. 3). Third, the dorsal anterior insula may further support detecting the salience of infant cries and focusing of attention while the mSFG (dmPFC) and the triangular and orbitofrontal cortex may assist in amodal evaluation of emotional information and mentalizing (red in Fig. 3). Last, a motor network consisting of the basal ganglia, the mSFG (pre-SMA, SMA) and the lateral motor areas may assist in initiating and planning (basal ganglia, pre-SMA, SMA) and execution (lateral cortical motor areas) of a motivated parental response (yellow in Fig. 3). Finally, moderator analyses suggest that previously purported enhanced processing of infant cries by females and parents could be related to differential recruitment of a relatively early sensorimotor integration circuit, involving the auditory cortex, posterior insula and somatosensory cortex to assist in efficient infant cry perception.

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Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2019.01.026.

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