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Effects of Vasopressin on Neural Processing of Infant Crying in Expectant Fathers

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Abstract

In a randomized, double blind, placebo-controlled, within-subject magnetic resonance imaging study, we examined the effect of 20 IU vasopressin on the neural processing of infant crying in 25 fathers-to-be. We explored whether familial background modulates vasopressin effects, and whether vasopressin differentially affects cry processing coupled with neutral or emotional contextual information. Participants listened to cries accompanied by neutral ('this is an infant') or emotional ('this infant is sick/bored') contextual information, and neutral control sounds ('this is a saw'). Additionally, participants reported on their childhood experiences of parental love-withdrawal and abuse. Infant crying (vs control sounds) was associated with increased activation in the bilateral auditory cortex and posterior medial cortex. No effects of vasopressin were found in this 'cry network'. Exploratory whole-brain analyses suggested that effects of vasopressin in the anterior cingulate cortex, paracingulate gyrus and supplemental motor area were stronger in fathers who experienced lower (vs higher) levels of love-withdrawal. No interaction was observed for abuse. Vasopressin increased activation in response to cries accompanied by emotional vs neutral contextual information in several brain regions, e.g. the cerebellum, brainstem, posterior medial cortex, hippocampus, putamen, and insula. Our results suggest that the experience of love-withdrawal may modulate the vasopressin system, influencing effects of vasopressin administration on cry processing. Results further suggest a role for vasopressin in the processing of cry sounds with emotional contextual information.

Introduction

Whether they are cold, sick, or tired, crying is one of the infant's most important means of soliciting parental attention and care. However, crying can also elicit aversion and anger in the parent, and can trigger child abuse and neglect (Barr, Trent, & Cross, 2006). How parents process infant cry sounds, therefore, constitutes an important area of study. In recent years, fathers have significantly increased their participation in child caretaking. Even though there remains large variation in paternal involvement (Hrdy, 2009) and quality of caregiving (Lucassen et al., 2011; van Ijzendoorn & DeWolff, 1997), a fathers' parental role is highly relevant for child development (Kok et al., 2015; Ramchandani, Stein, Evans, O'Connor, & Team, 2005). In the past decade, a relatively large literature on the neural underpinnings of the processing of infant crying in mothers has become available (e.g. Groh et al., 2015; Parsons et al., 2017; Wright, Laurent, & Ablow, 2017), however, little is known about the way fathers process these cues of infant distress (Li, Chen, Mascaro, Haroon, & Rilling, 2017; Mascaro, Hackett, Gouzoules, Lori, & Rilling, 2014; Seifritz et al., 2003). Following-up on the Li et al. (2017) study on the effects of neuropeptides oxytocin (OT) and vasopressin (AVP) on the processing of infant signals in fathers of toddlers, the present study examined the effect of AVP on expectant fathers' processing of infant cry sounds, and explored whether this effect of AVP is moderated by the father's childhood parenting experiences. Moreover, we examined whether accompanying contextual information affects expectant fathers' neural processing of cry sounds, and whether AVP administration modulates this effect of context.

Quality of parenting skills may in part be related to hormonal levels. In fathers, the neuropeptide vasopressin has been suggested to play a special role (S. E. Taylor, Saphire-Bernstein, & Seeman, 2010). Both in rodents and in non-human primates, the transition to fatherhood has been associated with changes in AVP signaling (Bamshad, Novak, & De

Vries, 1993; Kozorovitskiy, Hughes, Lee, & Gould, 2006; Z. X. Wang, Liu, Young, & Insel, 2000). In male prairie voles, AVP injections into the lateral septum elicit paternal behavior (i.e. crouching over pups, Z. Wang, Ferris, & De Vries, 1994), and AVP-immunoreactive staining in the bed nucleus of the stria terminalis has been associated with paternal behavior in California mice (Bester-Meredith & Marler, 2003; but see J. H. Taylor & French, 2015 who found no effects of intranasal AVP administration on responsiveness to infant stimuli in male marmosets).

Associations between AVP and parenting have also been observed in humans, but results have been inconsistent. In expectant fathers, vasopressin administration increased fathers' implicit caregiving interests (Cohen-Bendahan, Beijers, van Doornen, & de Weerth, 2015). However, in a sample of 15 fathers of 1-2-year-old children, AVP administration (compared to placebo administration) did not affect neural processing of infant cry sounds nor of own infant photos (Li et al., 2017). As this is one of the few studies examining AVP effects in human fathers—and with a relatively small sample—we revisit the questions posed in the Li et al. (2017) study (does AVP administration affect processing of infant crying and is its effect modulated by familial background?) with a larger sample in a different group of fathers (fathers-to-be instead of fathers of toddlers). Moreover, we extend the literature by examining the effect of contextual information on cry sound processing in fathers and by assessing whether AVP modulates such a 'context effect'.

Previous studies from our lab have shown that effects of OT are dependent on experienced care, such that positive effects of OT are found in individuals coming from a supportive background only (Bakermans-Kranenburg, van Ijzendoorn, Riem, Tops, & Alink, 2012; M. M. Riem, Bakermans-Kranenburg, Huffmeijer, & van Ijzendoorn, 2013; van IJzendoorn, Huffmeijer, Alink, Bakermans-Kranenburg, & Tops, 2011). For example, OT administration decreased excessive force on a hand-grip dynamometer when listening to

infant cry sounds, but only in individuals who experienced low levels of harsh discipline (Bakermans-Kranenburg et al., 2012). Although there is no direct evidence that effects of AVP may also be dependent on experiences of childhood care, the association between experienced care and own caregiving skills suggest that these experiences affect biological properties important to parenting (Kovan, Chung, & Sroufe, 2009; Madden et al., 2015). There may be a variety of biological mechanisms explaining increased or decreased susceptibility to extraneous hormones, for example, endogenous hormone levels or receptor properties. Through gene methylation, experiences of harsh and neglectful care may affect properties of systems involved in parenting such as OT, but also AVP (Mulder, Rijlaarsdam, & Van IJzendoorn, 2017).

As the cause of the infant's distress may be difficult to discern from the infant's cry, contextual information can be an important determinant of parental action. For example, the parental response to crying is delayed when the infant has just been fed (Leger, Thompson, Merritt, & Benz, 1996), or when the adult is told that the infant needs sleep (Wood & Gustafson, 2001). Effects of contextual information have also been found on the neural processing of cry sounds (M. M. Riem, Voorthuis, Bakermans-Kranenburg, & van Ijzendoorn, 2014). In a sample of nulliparous women, the amygdalae showed an increased response to the same cry sound labeled as originating from a sick infant compared to a bored infant. In the insula and inferior frontal gyrus, a comparable effect was found after administration of OT, a neuropeptide similar to AVP in molecular structure but with different behavioral correlates. However, similarly to OT, AVP has been found to alter the interpretation of social stimuli (Thompson, Gupta, Miller, Mills, & Orr, 2004), and therefore, modulating effects on the processing of contextual information may also be expected of AVP administration.

The present study assessed the effect of AVP administration on the neural processing of infant cry sounds in 25 fathers-to-be. Based on the previous literature in females, we expected expectant fathers to show increased activation in response to infant crying (compared to control sounds) in regions associated with social information processing, such as the amygdala, insula, cingulate cortex and inferior frontal gyrus (Laurent & Ablow, 2012a, 2012b; Riem et al., 2014; Riem, Pieper, Out, Bakermans-Kranenburg, & van IJzendoorn, 2011). We hypothesized that activation in these regions would be affected by AVP administration and by contextual information accompanying the cry sound. Finally, we explored whether experiences of harsh and neglectful parenting modulate the effect of AVP administration on the processing of infant cry sounds.

Methods

Participants

Participants were recruited through midwives and ads on Leiden University affiliated webpages. They cohabitated with their pregnant partners, spoke Dutch, were in good health, without psychiatric, neuroendocrine or neurological disorders, and were screened for alcohol and drug use. Twenty-five first time expectant fathers participated in the study. The mean age of the participants was 31.9 years (SD = 4.30), and the mean gestational age of the unborn infants was 27.02 weeks (SD = 4.91). All participants provided informed consent. This study was approved by the Ethics Committees of the Institute for Education and Child Studies at Leiden University and the Leiden University Medical Centre, as well as the Dutch Central Committee on Research Involving Human Subjects.

Procedure

In a randomized, double blind, placebo-controlled, within-subject trial, fathers-to-be participated in two sessions in which they self-administered either a nasal spray containing

AVP (20 IU) or placebo (PL) using a syringe with a MAD Nasal™ Device. After nasal spray administration, participants completed several questionnaires and were familiarized with the fMRI protocol outside of the MRI environment. Prior to the cry paradigm, participants performed a working memory fMRI paradigm also involving cry sounds as well as a paradigm aimed at measuring protective parenting, to be reported separately. The cry sound paradigm commenced approximately 94 minutes after nasal spray administration in both the AVP and placebo sessions. In a study examining cerebrospinal fluid (CSF) AVP concentrations up to 80 minutes after intranasal administration of AVP, 80 and 40 IU of intranasal AVP resulted in a significant increase in CSF AVP after 10, and 60 minutes, respectively (Born et al., 2002). For both dosages, AVP was still significantly increased after 80 minutes. We, therefore, believe that the 94 minutes delay after administration of 20 IU of AVP in the present study is an appropriate delay.

Measures

fMRI paradigm

For a visual representation of the cry paradigm, see Figure 1. Contextual information (emotional: 'this infant is sick' or 'this infant is bored', neutral: 'this is an infant') was presented as a white text on a black screen for a duration of 2s. In order to assure that participants remained attentive throughout the task, they were instructed to press a button with their index right finger when they finished reading the context information. The context information was followed by the presentation of a fixation cross hair. After 500 ms, the auditory stimulus was presented (10s), while the fixation cross hair remained on the screen. Trials were separated by an inter stimulus interval (ISI) of variable length ranging from 4.5-5.5s. The fixation cross remained visible during the ISI.

A total of three cry sounds were recorded from two infants, one male (two sounds) and one female (one sound) using a TasCam DR-05 solid state recorder with at a 44.1 Khz sampling rate and 16 bit. All sounds were recorded within the first two postnatal days. Individual sounds were scaled, the intensity was normalized to the same mean intensity and sounds were edited to last for 10s using PRAAT software (Boersma & Weenink, 2017). For each cry sound, a neutral auditory control stimulus was created by calculating the average spectral density over the entire duration of the original sound. A continuous sound of equal duration was re-synthesized from the average spectral density and amplitude modulated by the amplitude envelope, extracted from the original sound. After this procedure, all auditory stimuli and control stimuli were intensity matched. The neutral auditory control stimuli were identical to the original auditory stimuli in terms of duration, intensity, spectral content, and amplitude envelope, but lacking the emotional meaning associated with a cry sound. Control sounds were presented as the sound of a saw (i.e., 'this is a saw').

Participants received one of four pre-programmed semi-random orders. The three infant cry sounds were presented four times with each of the three contextual information labels (36 trials). The three corresponding control sounds were also presented four times, leading to a total of 48 trials. The task was programmed in E-Prime (Schneider, Eschman, & Zuccolotto, 2002). A projector outside of the MRI suite was used to display the task on a large screen located at the back of the MRI bore, that was viewable through a mirror mounted on the top of the head coil. All responses were registered using a fiber optic response box (Current Designs, Philadelphia, PA, USA).

For one participant, responses in the AVP condition were logged for the first 22 trials only. Although the participant did not report having fallen asleep, it is unclear whether the lack of responses was due to the participant's inattention or due to a technical problem. Therefore, analyses assessing the effect of AVP on neural processing were performed both

including and excluding his data (See Supplemental text 1, Supplemental Figure 1, and Supplemental Table 1). As exclusion did not affect the results, the analyses including this participant are reported.

fMRI parameters

MRI scanning was performed on a 3T Philips Achieva TXMRI system (Philips Medical Systems, Best, the Netherlands). For registration purposes, a T1-weighted anatomical scan was acquired (TR = 9.7 ms, TE = 4.6 ms, flip angle = 8°, 140 transverse slices, voxel size .875 × .875 × 1.2 mm). The fMRI-task utilized a gradient-echo blood oxygen level dependent (BOLD) EPI sequence with: TR = 2200 ms, TE = 30 ms, flip angle = 80°, 38 transverse slices, and voxel resolution of 2.75 × 2.75 × 3.025 mm (including a 10% interslice gap). The duration of the fMRI paradigm was 14 min 19s (387 volumes). Participants listened to the cry and control sounds through MRI-compatible headphones.

Questionnaires

The questionnaires used in the present study were sent to the participant's e-mail address a few days after the first session.

Conflict Tactics Scale Participants completed the Conflict Tactics Scale – Parent Child (CTS), a questionnaire assessing maltreating behaviors that occur in a parent-child relationship (Straus, Hamby, Finkelhor, Moore, & Runyan, 1998). In the present study, participants were asked whether one or both of their parents behaved in an abusive way towards them during their childhood. Only items from the subscales Psychological aggression (e.g., "My mother or father cursed or swore at me"), Minor physical assault (e.g., "My mother or father spanked me on the bottom with her/his hand"), Severe physical assault (e.g., "My mother or father threw or knocked me down"), and Neglect (e.g., "My mother or father wasn't able to give me the food I needed") were used, resulting in a total of 18 items. Items were

answered on a 7-point scale (0 = ‘never’, 1 = ‘once’, 2 = ‘twice’, 3 = ‘3-5 times’, 4 = ‘6-10 times’, 5 = ‘11-20 times’, 6 = ‘more than 20 times’). Scores on the minor and severe physical assault scales were averaged to compute a Physical assault score. An Abuse score was computed by averaging the scores on the Psychological aggression and Physical assault scales. An overall CTS score was computed by averaging the Abuse and Neglect scales (M = 0.53, SD = 0.34), which was used for further analysis. One outlier (Z = 4.09) was winsorized to match the second highest score. The CTS total was positively correlated with the Abuse scale, r = .92, p < .001, and with the Neglect scale, r = .53, p = .006.

Parental love withdrawal To measure parental use of love-withdrawal, the participants completed a questionnaire consisting of 11 items. Seven items from the Withdrawal of Relations subscale of the Children’s Report of Parental Behavior Inventory were used, of which two items were slightly adapted for a smoother translation (CRPBI, Beyers & Goossens, 2003; Schludermann & Schludermann, 1983). To obtain a more comprehensive measurement of parental love-withdrawal, the questionnaire was complemented with four items from the Parental Discipline Questionnaire (PDQ, Patrick & Gibbs, 2007). See (Huffmeijer, Tops, Alink, Bakermans-Kranenburg, & van Ijzendoorn, 2011; van IJzendoorn et al., 2011) for the resulting scale. Participants rated how well each of the statements described their mother's or father’s behavior (e.g., “My mother is a person who, when I disappoint her, tells me how sad I make her”) on a 5-point scale ranging from 1 (not at all) to 5 (very well). The 11 items referring to mother’s behavior were averaged to create a maternal love-withdrawal score. The same was done for the items referring to the father’s behavior. A parental love-withdrawal score was computed by averaging the maternal and paternal score (M = 1.72, SD = 0.47*)*. The maternal and paternal scores correlated with the total score r = .74, p < .001, and r = .67, p < .001, respectively.

Analysis

Preprocessing

Preprocessing and statistical analysis of the imaging data were performed using FSL (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012; Smith et al., 2004). Brain extraction was performed via BET, and motion correction using MCFLIRT. Spatial smoothing was applied with a Gaussian kernel of 5 mm (FWHM). FMRI data from each participant were spatially normalized to their own high resolution T1 image (boundary-based registration (BBR, Greve & Fischl, 2009), 90 degree search) and then to MNI space (12 degrees of freedom (DOF), 90 degree search) using FSL's FLIRT registration tool.

Statistical analysis

After preprocessing, statistical analyses were performed at the single-subject level using the general linear model (GLM) within FSL's FEAT. A total of five EVs (explanatory variables) were created, one for each differently labelled sound ('sick' cries, 'bored' cries, 'infant cries', and white noise 'saw' sounds), and one referring to the presentation of the contextual information. For each of the differently labelled sounds, temporal derivatives were added to the model, as well as both standard motion parameters and additional motion confound EVs as obtained from fsl_motion_outliers (DVARS, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLMotionOutliers) to address common problems resulting from motion (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). For the GLM, we contrasted baby cries with the label 'this is an infant' ('infant' cry sounds) to saw control sounds, and both 'sick' and 'bored' cries were contrasted against 'infant' cry sounds. In a group-level analysis, we tested the difference between cry sounds with label 'this is an infant' and 'saw' control sounds to assess the network of regions involved in the processing of infant crying in the placebo data only. Subsequently, in a within-subject higher-level analysis, effects of AVP on the processing of 'infant' crying vs control sounds were tested within this

infant cry network. The interaction between AVP administration and (demeaned) parental love-withdrawal or CTS Total scores were examined in third-level analyses. Additionally, in a second-level analysis, participant specific COPES (contrasts of parameter estimates) were created for the contrast [(‘infant’ cry – control)AVP – (‘infant’ cry – control)PL]. These COPES were then used as the input for a third-level analysis in which caregiving experience was used as a covariate.

In order to examine the effect of contextual information and its interaction with AVP administration, a 2 [sick(-infant) vs bored(-infant)] x 2 [AVP vs PL] high-order within-subject analysis was performed in regions of the infant cry network using lower-level COPES of contrasts [‘sick’-‘infant’] and [‘bored’-‘infant’] as input. Given the exploratory nature of our study, we did not examine whether this effect depended upon experiences of harsh and neglectful care, as to limit the overall number of tests.

All analyses in the infant cry network were followed up by exploratory whole-brain analyses. As Li et al. (2017) found stronger effects when the hormone (OT) was administered in the first rather than the second session, we also assessed whether order of administration modulated AVP effects on the processing of ‘infant’ cry sounds vs control sounds in a third-level analysis.

Results

Sample characteristics can be found in Table 1. Thirteen of the 25 participants (52%) received AVP during their first session. Our two measures of experienced parental care were positively correlated, $r = .41$, $p = .04$.

Neural correlates of infant crying

Results of the comparison of cry sounds labelled as ‘infant’ versus control sounds are described in Table 2 and Figure 2. This comparison resulted in three significant clusters, corresponding to the left ($p < .001$) and right ($p < .001$) auditory cortex (i.e. Heschl’s gyrus and the superior temporal gyrus), and the bilateral posterior cingulate cortex and precuneus ($p = .047$), further referred to as the infant cry network. AVP administration did not affect activation in these regions, nor did we find significant effects of AVP for this contrast in the whole brain. Order of administration did not affect the effect of AVP on the processing of ‘infant’ cry sounds versus control sounds.

Moderating effects of experienced care

No moderating effects of harsh parenting or love-withdrawal were found in the infant cry network. However, whole-brain analyses suggested that in expectant fathers who experienced less (relative to more) parental love withdrawal, AVP had a stronger effect on the neural response to ‘infant’ cry sounds versus control sounds in the bilateral anterior cingulate cortex, paracingulate gyrus and supplemental motor area ($p = .023$, see Table 3 and Figure 3).

Effect of contextual information on the processing of infant crying

In order to assess the effect of emotional contextual information, lower-level COPES of the [‘sick’-‘infant’] contrast and the [‘bored’-‘infant’] contrast were analyzed and compared for the AVP and PL sessions. When analyses were restricted to the cry network, neither the higher-level main effect of emotional contextual information (controlled for neutral contextual information), nor the higher-level main effect of hormone nor their interaction were significant. The exploratory whole-brain analyses resulted in a significant main effect of AVP in a cluster including the cerebellum, precuneus, posterior cingulate cortex, brainstem, lingual gyrus, fusiform cortex parahippocampal gyrus, and hippocampus ($p < .001$), as well as in a cluster including the putamen, insula, and central opercular cortex ($p =$

.004). In these regions, irrespective of the specific emotional contextual information, infant cry sounds with emotional contextual information were associated with increased activation compared to the 'infant' cry sound (Table 4, Figure 4) in the AVP condition relative to the PL condition. The higher-level main effect of emotional contextual information and the hormone × context higher-level interaction effect were not significant.

Discussion

The present study examined the neural processing of infant crying in expectant fathers. Specifically, we assessed the effect of AVP administration on the neural response to infant cry sounds, and examined whether this effect was modulated by the father's experienced care. Comparable to previous studies, listening to infant cry sounds vs. control sounds was associated with increased activation in the bilateral auditory cortex and posterior cingulate. Activation in this infant cry network was not affected by AVP administration. However, exploratory whole-brain analyses suggest that AVP increases activation in response to cry sounds (relative to control sounds) in the ACC, paracingulate gyrus, and supplemental motor area. This effect of AVP depended upon the father's familial background, i.e., AVP had a stronger effect in fathers who experienced low levels of parental love-withdrawal.

While Li et al. (2017) did not find support for a moderating effect of familial background on AVP administration, here we report a stronger effect of AVP on the processing of infant cry sounds in expectant fathers from a more supportive (relative to a less supportive) background. These diverging results could be related to differences in sample characteristics or differences in sample size. The present study examined expectant fathers, who had no prior exposure to crying of their own child, while Li et al. (2017) studied fathers of 1-to 2-year old children. Moreover, the present study presents an increase in sample size of

60% relative to the Li et al. (2017) study. While both sample size may be considered small, the present study may simply have more power to find this interaction effect.

The stronger effect of AVP in fathers from a more supportive background were found in the ACC, paracingualte gyrus, and supplemental motor area. The ACC and paracingulate gyrus have been associated with decision making and empathic behavior, and theory of mind, respectively (Lavin et al., 2013; Walter et al., 2004), while the supplemental motor area has been associated with motivation and initiation of action (Nachev, Kennard, & Husain, 2008). Increased activation in these regions in response to infant crying could, however in the absence of a behavioral measure admittedly speculatively, be interpreted as an increased empathic response and motivation to relieve the infant's distress.

When examining the neural processing of sick and bored cry sounds, no effects of contextual information, AVP administration or their interaction were found in the cry network. A main effect of AVP was found in exploratory whole-brain analyses, suggesting that AVP administration may increase activation in response to emotionally labelled cry sounds (versus the same but neutrally labelled cry sounds) in the cerebellum, precuneus, posterior cingulate cortex, brainstem, lingual gyrus, fusiform cortex, parahippocampal gyrus, and hippocampus, as well as in a cluster including the putamen, insula, and central opercular cortex. As especially the first cluster encompasses many different structures which all have been implicated in a variety of functions, interpretation would be speculative. Distribution of AVP receptors in the human brain has not been fully characterized, but human and animal literature suggests availability of receptors in (amongst other regions) the hippocampus, thalamus, cerebellum and brainstem (Hernando, Schoots, Lolait, & Burbach, 2001; Loup, Tribollet, Duboisdauphin, & Dreifuss, 1991), which may in part explain why findings are localized here. Our results do suggest that AVP may play a role in processing of cry sounds but only when the father understands the emotional context of the infant's crying. Of note,

AVP effects were hypothesized only in regions involved in processing of infant cry sounds. Our findings were exploratory and need confirmation by replication.

Contrary to Riem et al. (2014), we did not find evidence of differential processing of the same cry sound presented as a cry due to sickness or as a cry out of boredom, nor did AVP administration result in differential processing of such cries. Riem et al. (2014) examined nulliparous women. In general, women are reported to be more empathetic than men (Eisenberg & Lennon, 1983), which could result in larger differences in response to cry contexts in women compared to men. Moreover, although Riem et al. (2014) found evidence for differential processing in the amygdalae in the placebo condition, in the insulae and IFG this effect was only found after OT administration. Natural differences in processing of sick vs. bored cries may thus be small, and potentially more pronounced after OT administration. Here, we find no such evidence for AVP administration.

Several limitations of the present study should be noted. Participants self-administered 20 IU of AVP, and the time delay was 94 minutes. This dose is in accordance with prior research (e.g. Li et al., 2017; Thompson et al., 2004; Thompson et al., 2006; Uzefovsky et al., 2012). However, to our knowledge, there are no systematic studies comparing the efficacy of different doses and timing of AVP, and it therefore is currently unclear whether this dose and time delay were appropriate to find the hypothesized effects. The present sample included expectant fathers. The experience of the child's birth and the exposure to and interaction with the child may affect a man's hormonal levels (Gettler, McDade, Feranil, & Kuzawa, 2011), and brain anatomy (Kim et al., 2014), and ultimately his neural response to his own infant's cry sounds. Finally, as noted above, the AVP effects were found in exploratory analyses and warrant replication. Despite the powerful within-subject design—which has more power than a between-subject design with twice the number of participants (van IJzendoorn &

Bakermans-Kranenburg, 2016)—the performance of several exploratory whole-brain analyses may increase the risk of false-positive findings.

In conclusion, the present study reports stronger effects of AVP administration in response to infant crying (versus control sounds) in the medial prefrontal cortex in fathers from a more supportive, relative to a less supportive, background. As similar findings have been reported for OT, experiences of childhood care may broadly and persistently affect systems involved in parental care. Our study complements and extends Li et al. (2017), who did not find evidence for a role of AVP in the processing of infant signals. We also report a specific role for AVP in the processing of cry sounds of which the emotional contextual information is known. Compared to the same cry sounds accompanied by an uninformative, neutral label, AVP increased the response to cry sounds described as 'sick' or 'bored' cries. AVP, thus, seems to play a role in the processing of cry sounds particularly when the father understands the emotional context of the infant's crying. While the present results await replication, in order to understand what it means for a father to show increased activation in response to AVP, behavioral correlates of the neural response to cry sounds and its implications for paternal caregiving constitute important areas of future research.

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Table 1. Sample characteristics

		M(SD)/N(%)	Min	Max
Age		31.91 (4.30)	24.65	43.04
Gestational age		27.01 (4.91)	20.43	36.14
Education	Secondary	5 (20%)		
	Higher	20 (80%)		
Income	< €3200	6 (24.00%)		
	€3200 – €4000	10 (40.00%)		
	> €4000	9 (36.00%)		
Handedness	Right handed	23 (92.00%)		
Condition session 1	AVP	13 (52%)		
Time since nasal spray cry sound paradigm	Placebo	1:34 (0:05)	1:25	1:58
	AVP	1:34 (0:07)	1:22	1:50
Harsh parenting		0.56 (0.36)	0.00	1.13
Love withdrawal		1.72 (0.47)	1.05	2.55

Table 2. The 'infant cry network'

Cluster number	Region	Cluster size	MNI coordinates (mm)			*z*	*p* (corr.)
			x	y	z		
	'Infant' cry sounds > control sounds						
1	R STG	2221	62	-16	2	5.64	< .001
	R planum porale		56	4	-2	5.61	
	R Heschl's gyrus		52	-12	4	5.57	
	R planum porale		54	2	0	5.51	
	R STG		62	4	-4	5.36	
	R STG		66	-20	2	5.28	
2	L planum porale	1479	-54	-6	2	5.68	< .001
	L planum porale		-58	-20	10	5.30	
	L STG		-60	-2	-4	5.07	
	L precentral gyrus		-54	6	8	5.03	
	L Heschl's gyrus		-48	-18	6	4.83	
	L planum temporale		-62	-28	12	4.05	
3	L WM/precuneus	446	-14	-50	24	3.20	.047
	L WM/precuneus		-12	-58	36	3.20	
	L precuneus		-6	-62	26	3.19	
	R PCC		6	-46	32	3.09	
	L WM/precuneus		-10	-60	26	3.08	
	L WM/precuneus		-10	-56	28	3.07	
	'Infant' cry sounds < control sounds: n.s.						

Note. Table displays the 6 most significant voxels per contrast and is not a conclusive list of significant regions. STG = superior temporal gyrus; PCC = posterior cingulate cortex; WM = white matter

Table 3. Experienced care by AVP interaction effect on processing of infant crying

Cluster number	Region	Cluster size	MNI coordinates (mm)			*z*	*p* (corr.)
			x	y	z		
	CRPBI positive: n.s.						
	CRPBI negative						
1	L ACC	499	-4	20	32	3.38	.023
	L ACC		-6	18	36	3.36	
	L WM		-12	10	48	3.33	
	L paracingulate gyrus		-8	18	42	3.07	
	L WM		-16	4	48	2.98	
	SMA		0	4	54	2.90	
	CTS positive: n.s.						
	CTS negative: n.s.						

Note. Table displays the 6 most significant voxels per contrast and is not a conclusive list of significant regions. ACC = anterior cingulate cortex; WM = white matter; SMA = supplemental motor area.

Table 4. Effects of emotional contextual information and AVP administration on neural processing of cry sounds

Cluster number	Region	Cluster size	MNI coordinates (mm)			*z*	*p* (corr.)
			x	y	z		
	Main effect hormone						
1	R parahippocampal gyrus	4317	24	-36	-12	4.39	<.001
	R lingual gyrus		12	-40	-4	4.34	
	R PCC		16	-48	4	4.20	
	PCC		0	-22	34	4.14	
	R hippocampus		12	-10	-22	4.10	
	R brainstem		-2	-20	-20	4.00	
2	L WM/putamen	599	-22	-2	12	4.67	.005
	L WM		-22	-12	18	3.83	
	L WM/caudate		-20	6	16	3.74	
	L WM/putamen		-28	8	8	3.65	
	L insula		-36	8	-4	3.45	
	L putamen		-28	-12	8	3.41	
	Main effect context: n.s.						
	Interaction effect hormone x context: n.s.						

Note. Table displays the 6 most significant voxels per contrast and is not a conclusive list of significant regions. PCC = posterior cingulate cortex; WM = white matter

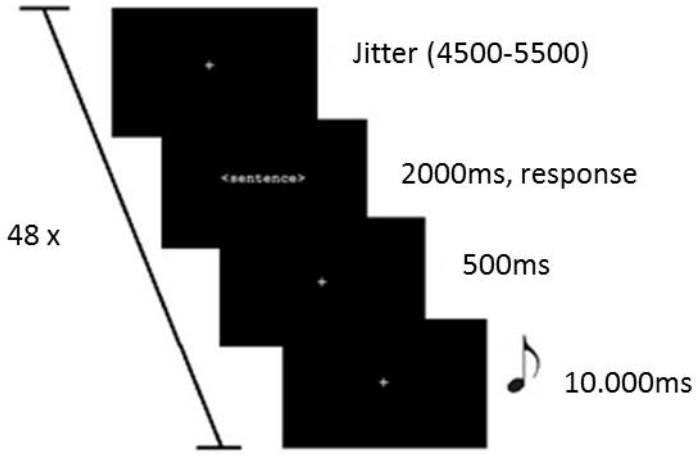

Figure 1. Task design and timing

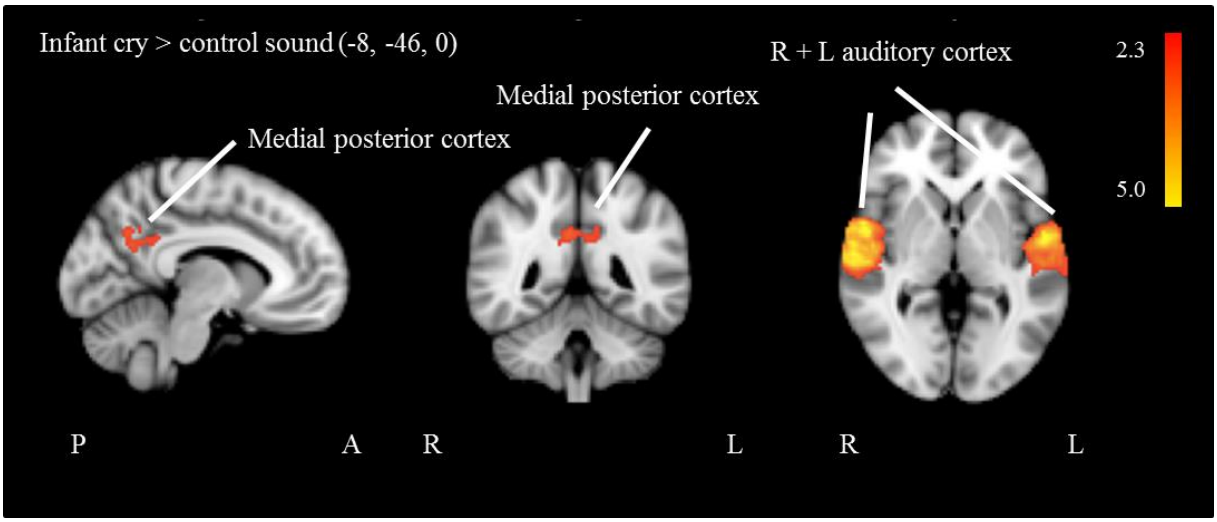

Figure 2. Neural correlates of infant crying vs control sounds

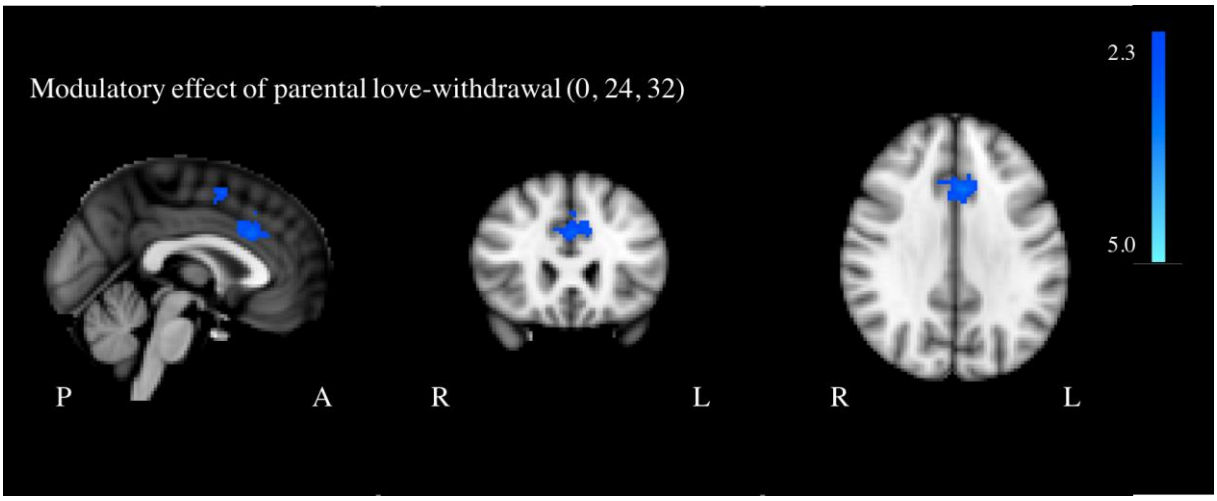

Figure 3. Modulatory effect of parental love-withdrawal on AVP effect on cry sounds processing

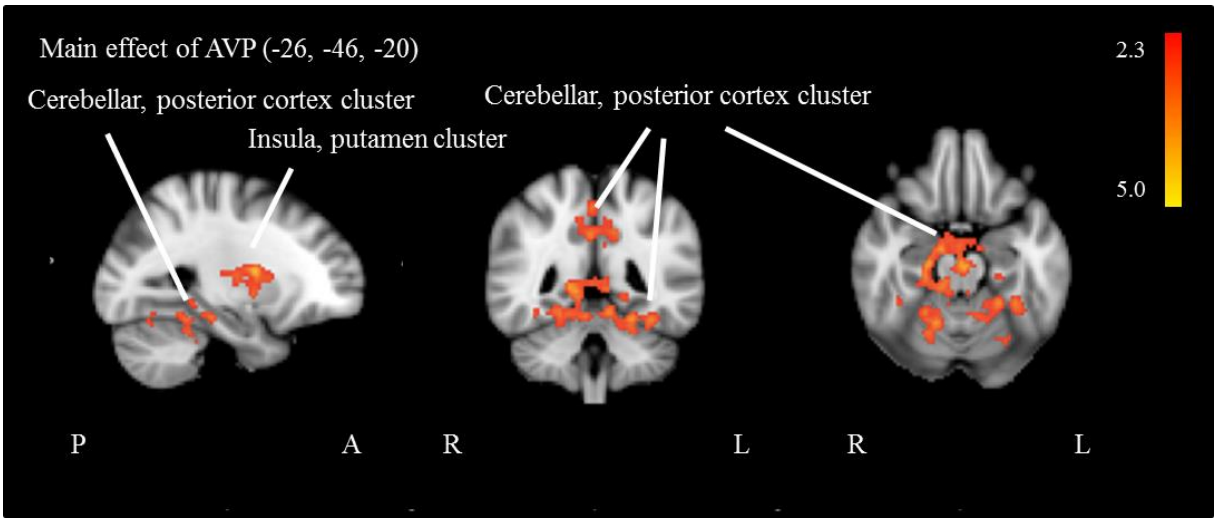

Figure 4. Effect of AVP on processing of cry sounds with emotional contextual information