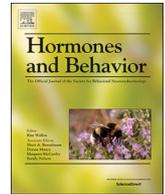




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Implicit associations to infant cry: Genetics and early care experiences influence caregiving propensities

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ABSTRACT

Adults' sensitive appraisal of and response to infant cry play a foundational role in child development. Employing a gene × environment (G × E) approach, this study investigated the interaction of genetic polymorphisms of the serotonin transporter gene (5-HTTLPR) and oxytocin receptor genes (OXTR; rs53576, rs2254298) with early parental care experiences in influencing adults' implicit associations to infant cry. Eighty nulliparous adults (40 females, 40 males) responded to the Parental Acceptance-Rejection Questionnaire (PARQ), a measure of early care experiences, and participated in a Single Category Implicit Association Task (SC-IAT) to measure implicit associations to infant cry. Independent of parental experience, the valence of the implicit response to infant cry is associated with the serotonin transporter gene polymorphism (5-HTTLPR), with LL-carriers showing more positive implicit associations than S-carriers. OXTR rs53576 moderated the relation between parental rejection and implicit appraisal of infant cry: A-carriers who experienced negative early care showed an implicit positive appraisal of infant cry, whereas in GG carriers, positive early care experiences were associated with an implicit positive reaction to infant cry. OXTR rs2254298 had no relation to implicit associations to infant cry or to early care experiences. These findings cast light on the possible interplay of genetic inheritance and early environment in influencing adults' responses to infant cry that may be incorporated into screening protocols aimed at identifying at-risk adult-infant interactions.

1. Introduction

1.1. Saliency of infant cry

Deficient in linguistic capacities at birth, infants first convey their distress and needs primarily by crying, rendering them largely dependent on caregivers to sensitively perceive these salient vocal cues (Cecchini et al., 2007; Newman, 2007; Soltis, 2004; Zeifman, 2001). Possessing a specific acoustic pattern (Esposito et al., 2013; Esposito and Venuti, 2010), infant cry carries enormous emotional and instrumental valence (Bell and Ainsworth, 1972; Soltis, 2004) that elicits caregiver proximity and triggers caregiving behaviours (Bornstein et al., 2017; Bornstein et al., 2016; Zeifman, 2001). Indeed, adults' re-

sponses to infant cry remain amongst the most biologically adaptive human behaviours (Bornstein et al., 2017). The possible evolutionary underpinnings of humans' predisposition to respond to infant cry are shown in the fact that cries activate specific brain areas involved in caregiving (Barrett and Fleming, 2011; Parsons et al., 2014; Rigo et al., 2017; Swain et al., 2014). The latter results led to the concept of the “parental brain” model (PBM; Swain et al., 2014). According to PBM, specific cortical and subcortical regions process salient infant vocalizations, regulate emotional responses to the stimuli, and elicit appropriate caregiving. Therefore, caregiving behaviour is regulated at different levels, from reflexive processes to controlled ones, which act separately and independently. One study that investigated the consistency of responses across levels showed that measures are only

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weakly correlated (Senese et al., 2019a), further confirming that adults' responsiveness to infant cues is a complex and multifactorial process. Nurturing behaviour in response to infant cry is paramount for the child's psychosocial development and is critical to a wholesome developmental trajectory (Bell and Ainsworth, 1972; Bowlby, 1982; Lorenz, 2010; Parsons et al., 2010; Salter Ainsworth et al., 2015; Zeifman, 2001). Given the adaptive relevance of responsiveness to infant stimuli, the existence of biological mechanisms (caregiving propensities) that prompt humans to care for infants, independent of parenthood status, have been hypothesized (Bornstein, 2015; Bornstein et al., 2017).

1.2. Early care experiences

Despite an evolutionarily seeded inclination to exhibit caregiving responses (Bornstein, 2015; Bowlby, 1969), sensitive caregiving is not universal, and adults do not always manifest adequate nurturing behaviours towards infants. Having been described as aversive (Zeifman, 2003), infant cry has been reported to incite maltreatment (Kadushin et al., 1981), neglect (see Barnow et al., 2005; Beck and Shaw, 2005; Putnick et al., 2012) or have otherwise been associated with childhood abuse (see Beck and Shaw, 2005; Leerkes et al., 2011; Putnick et al., 2012). Many adults interact with infants in a manner that is insensitive, neglectful, or hostile, leaving an adverse impact on the child's development (see Barnow et al., 2005; Beck and Shaw, 2005; Cicchetti and Rizley, 1981). Poor caregiving sensitivity can impair the quality of infant attachment and subsequently increase the risk of psychopathology later in life (Bowlby, 1969; Wright et al., 2017). At the same time, individuals may perceive themselves as rejected (i.e., not loved, as neglected, etc.) regardless of the actual behaviour of their caregivers, and this subjective perception of rejection or the caregiving environment has been universally shown to be a better predictor of psychological maladjustment than more objective indicators (see Rohner, 2016). As such, individual differences (see Boukydis and Burgess, 1982) in the quality of caregiving propensities have been extensively investigated (e.g. Belsky and Jaffee, 2015; Jaffee et al., 2006; Klahr and Alexandra Burt, 2014), but the sources of such differences have yet to be fully elucidated.

One determinant of quality of caregiving is the responsiveness of cortico-limbic networks to infant cues, which in turn is influenced by current and early-life experiences, hormonal variables, and other factors (Bleker et al., 2017; McGuire et al., 2012; Renier et al., 2016; Romund et al., 2016; Truzzi et al., 2016). In the present study, we investigate the role of early care experiences in shaping how adults perceive infant cry. Negative early care experiences have an enduring effect on the individual and may lead to dysregulation in emotional processing and coping behaviours (Dalsant et al., 2015; Esposito et al., 2017a). An example that illustrates the effect of negative early care experiences is when mothers who have undergone early life trauma exhibit more intrusive interactions with their infants (Moehler et al., 2007). These poor emotional and behavioural coping mechanisms may have arisen due to altered functioning in cortico-limbic pathways and the hypothalamic-pituitary-adrenal (HPA) axis (Barrett and Fleming, 2011). For instance, mothers with a history of childhood abuse possess altered cortisol production (hypo- or hyper-secretion) and have been linked to insensitive parenting (Mills-Koonce et al., 2009). A possible deduction from this finding is that similar underlying cortico-limbic pathways and hormonal factors are implicated in both early care experiences and parenting quality, which contribute to individual differences in evaluating salient infant cues. As infant vocalizations trigger caregiving behaviours, this study aims to explore the link between adults' initial appraisal of infant cry and their early care experiences. Because we are interested in evaluating processes that regulate caregiving propensities, we investigated this relation in a sample of nulliparous adults.

1.3. Serotonin transporter gene (5-HTTLPR) and oxytocin receptor genes (OXTR)

Numerous studies have begun to report findings of specific genotypes involved in perceiving infant stimuli (Bakermans-Kranenburg and van IJzendoorn, 2008; Esposito et al., 2017b; Feldman et al., 2012; Rodrigues et al., 2009) and caregiving behaviours (e.g., Cents et al., 2014; Feldman et al., 2016; Henry et al., 2015; for a review see Feldman et al., 2016). Two well-known implicated genes are the serotonin transporter gene (5-HTTLPR) and the oxytocin receptor gene (OXTR). The 5-HTTLPR gene has two allelic forms, the short allele (S) and long allele (L) resulting in three possible combinations (genotype: SS, SL, LL), the OXTR gene possesses two prominent polymorphisms of interest: rs53576 (genotype: AA, AG, GG) and rs2254298 (genotype: AA, AG, GG).

Possessing two alleles, the serotonin transporter gene (5-HTTLPR) regulates the concentration of serotonin in the body. The S-allele is associated with lower reuptake of serotonin as it is less transcriptionally efficient as compared to the L-allele (Canli and Lesch, 2007). 5-HTTLPR moderates stressful experiences on future social behaviours (Canli and Lesch, 2007; Truzzi et al., 2017). Amongst S-carriers, life stress is negatively associated with amygdala and hippocampal activation in response to face stimuli, while L-carriers exhibit a positive association (Canli et al., 2006; Canli and Lesch, 2007). Additionally, Bakermans-Kranenburg and van IJzendoorn (2008) learned that mothers who are S-carriers display lower levels of sensitive parenting as compared to those who are L-carriers. However, contradictory findings were reported by Mileva-Seitz et al. (2013) and Cents et al. (2014), who observed that mothers carrying the S-allele display more sensitivity than L-carriers. In a $G \times E$ study, the genotype of 5-HTTLPR was found to moderate the effects of early care experiences on mothers' responses to infants (Mileva-Seitz et al., 2013). Specifically, in a measure of gaze orientation (implicit assessment), mothers with L-alleles who had adverse early care experiences showed more negative responses to their infants (oriented their gaze away from the infant), whereas mothers with S-allele who had positive early care experiences reported higher perceived attachment to their infant (Mileva-Seitz et al., 2013). To date, only one study conducted a $G \times E$ analysis, investigating the role of 5-HTTLPR in moderating responses to infant cry, but neither a main gene effect nor a $G \times E$ interaction was found (Truzzi et al., 2017). Although the study of Truzzi and colleagues has the merit of having investigated a $G \times E$ interaction in response to infant cry, it has some limitations and calls for additional investigations: (a) small sample ($N = 42$) composed exclusively of men limited the statistical power of the study and the generalizability of results; (b) physiological response (HRV) was measured but not the valence of the response; (c) only the polymorphism of serotonin was considered, whereas other genotypes have been shown to be involved in perception of infant stimuli; and (d) the measure of early parent-infant interaction (environment) was the Parental Bonding Inventory, a scale that evaluates only care and overprotection dimensions, but that does not capture aspects of rejection that in the literature have been associated with psychological adaptation and parenting.

Commonly known as a "social hormone", oxytocin governs a broad swathe of social and non-social functions in animal and human species, including reproduction (Mandelli and Serretti, 2013) and metabolism (Blevins and Baskin, 2015; Ho and Blevins, 2013; Klockars et al., 2015). OXTR also regulates complex social behaviours, including affiliation (Bakermans-Kranenburg and van IJzendoorn, 2008; Chen et al., 2011; Feldman et al., 2016; Mileva-Seitz et al., 2013; Smearman et al., 2016), forming interpersonal relationships (Bartz et al., 2011; Feldman et al., 2012; Insel and Young, 2001; Kumsta and Heinrichs, 2013; Krueger et al., 2012; Poulin et al., 2012; Kogan et al., 2011; Rodrigues et al., 2009), and parenting (Bush et al., 2017; Esposito et al., 2017b; Feldman et al., 2013; Klahr et al., 2015; Senese et al., 2017a; Smearman et al., 2016; Unternaehrer et al., 2015). The OXTR rs53576 GG genotype is associated with sensitive caregiving behaviours, although not all

studies have generated similar findings. For instance, Bakermans-Kranenburg and van IJzendoorn (2008) and Klahr et al. (2015) discovered that mothers who are GG homozygotes exhibit more sensitivity and warmth towards their infants as compared to those who are A-carriers. However, in Michalska et al. (2014), A-carriers were found to display more positive parenting. With regard to parenting attitudes, Senese et al. (2017a) found stronger positive implicit associations to infant faces in GG homozygotes than in A carriers. In the second single nucleotide polymorphism (SNP) of interest, parents who are GG homozygotes of OXTR rs2254298 displayed less touch during parent-infant interactions as compared to A-carriers. A gene \times environment ($G \times E$) interaction involving rs2254298 has also been shown to modulate adult reactivity to infant cues (Esposito et al., 2017a). Specifically, the rs2254298 polymorphism moderated the effect of early care experiences (remembrances of parental bonding) on facial skin temperature and heart rate activity in response to infant stimuli. A review by Cataldo et al. (2017) synthesized findings from numerous studies that reported an interaction between OXTR polymorphisms and early parental care in contributing to the development of psychiatric disorders later in life.

1.4. Aims of the present study

Previous studies have demonstrated that adults' responses to infant stimuli predict parental ideas, that is subjective views of parenting behaviours, or long-term developmental consequences for the child (see Leerkes et al., 2011; McElwain and Booth-LaForce, 2006; Senese et al., 2013) and influences attachment security later in adulthood (Leerkes et al., 2011). Given the importance of adults' emotional responses and appraisal of infant cries, the present study sheds light on the roles of individuals' past experiences and biological disposition in sensitively appraising salient cues of infants. A more holistic understanding of the biological and psychological mechanisms governing adult reactivity and regulation towards infant cry can mitigate instances of adverse adult-child interactions (see Belsky and Pluess, 2009; Bornstein et al., 2016) in various contexts, such as in parenting relationships or child-care settings. These findings may increase awareness amongst adults responding to infant distress, which may in turn inculcate sensitive responses to infant needs. Previous studies of adult responsiveness to infant cues have mainly been based on self-report measures that evaluate only conscious processes, and can be biased by social desirability (Bornstein, 2015), and/or fMRI measures that describe changes in neural activation but rarely clarify valence, and so still yield an incomplete picture of factors and processes that regulate the way adults respond to infant cues.

The aim of the present work is to investigate how adults' implicit response to infant cry is influenced by genetic polymorphism (G), by perceived early care experiences (E), and by their interaction. To our knowledge, only one study has directly investigated the roles of genetics, early care experiences, and their interaction on the valence of implicit associations to infant faces (Senese et al., 2017a). No study has investigated how adults' implicit responses to infant cry are influenced by genetic characteristics or earlier experiences in their family of origin, or an interaction of the two variables. In this study, a Single Category Implicit Association Task (SC-IAT) was employed to capture adults' implicit associations to infant cry. The SC-IAT is a behavioural paradigm that allows for the evaluation of positive or negative valence of adult associations to target stimuli without the limitation of self-report responses (Karpinski and Steinman, 2006). A study investigating the neural correlates of IAT scores (Stanley et al., 2008) found that implicit responses were associated with activation of subcortical structures, which, according to the Parental Brain Model (see Swain et al., 2014), influence the quality of infant caregiving. Moreover, it has been shown that explicit and implicit responses have differential, independent, and relevant impacts on processing of infant cues and beliefs about parenting behaviours (Senese et al., 2018), and that implicit responses

were only weakly related to physiological measures (Senese et al., 2019a). In previous studies, the SC-IAT was adapted to investigate the valence of implicit responses to visual and acoustical infant cues (Senese et al., 2013; Senese et al., 2017a, 2017b). Findings from those studies showed that infant faces are associated with specific and positive implicit reactions, whereas infant cries are associated with negative implicit associations. To understand the genetic contributions of different polymorphisms to adults' responses to infant cry, DNA samples were collected and sequenced, targeting three single nucleotide polymorphisms that have been associated with adult responsiveness to infants: the 5-HTTLPR marker (serotonin transporter gene polymorphism), OXTR rs53576 marker, and OXTR rs2254298 marker. As a measure of early care experiences, the Adults' Parental Acceptance and Rejection Questionnaire (Adult PARQ; Rohner and Khaleque, 2005) was utilized to assess participants' remembrances of parental acceptance/rejection in childhood. We used this scale because it is the measure in literature that best operationalizes the construct of parental rejection (Rohner, 2016; Rohner and Khaleque, 2005) that is critical for evaluating the perception of one's own childhood experiences. Non-parent adults were recruited because we were interested in the general caregiving propensity and we wanted to ensure that findings are independent of parental status and experience. Indeed, there is a growing literature on gene-environment correlations and parenting showing that children's genes also elicit different parenting behaviours (Kopala-Sibley et al., 2017; Kryski et al., 2014; Pener-Tessler et al., 2013).

According to the current literature (Senese et al., 2017b), we expected a negative implicit association towards infant cry, and that the considered genetic polymorphisms would moderate the association between early care experiences and implicit associations, showing a $G \times E$ interaction. To evaluate these possibilities, data analysis was conducted based on a theoretical model of differential susceptibility (Belsky and Pluess, 2009). Essentially, this model theorizes that differences in genetic polymorphisms confer sensitivity to environmental factors, such that genetic variants magnify the possibility of adverse outcomes in a negative environment, while enhancing the probability of optimistic effects in a positive environment.

2. Methods

2.1. Participants

A total of 80 non-parent adults (40 females, 40 males) participated in a within-subject experimental design. Their ages ranged from 18 to 25 years ($M = 22.5$, $SD = 2.2$), and their educational level varied from middle school to college. Males and females were matched on age, $F < 1$, and all the participants were tested individually. Prior to the start of the study, the sample size was ascertained by power analysis (minimum power of 0.80; Tabachnick and Fidell, 2001) using the software G*Power version 3.1.9.2 (Faul et al., 2009). In the power analysis, we considered a linear regression model with three predictors, fixed the alpha at 0.05, power ($1 - \beta$) at 0.80, and considered an expected "medium" effect size. The estimation of this effect size was based on data from a previous published study (Senese et al., 2017a) investigating the $G \times E$ interaction effects on implicit responses to infant faces. Approval from the University Ethics Committee was acquired before the study was conducted.

2.2. Procedure

Participants' signed informed consent was obtained before proceeding with the study. Each experimental session was divided into two parts. In the first part, behavioural questionnaires consisting of basic sociodemographic background information (i.e., sex, age, and socioeconomic status) and responses to the Adult PARQ scale (assessment of remembrances of parental rejection) were collected. In the second part, the auditory SC-IAT was administered to evaluate participants' implicit

association to infant cry. At the end of the experimental session, DNA samples were collected for sequencing of genetic polymorphisms of interest.

2.3. Measures

2.3.1. Adult parental acceptance rejection questionnaire (PARQ)

The Adult PARQ is a 60-item culturally invariant self-report scale (Rohner and Khaleque, 2005; Senese et al., 2016) developed within Interpersonal Acceptance-Rejection Theory (IPARTheory; Rohner, 2016) to measure adults' remembrances of parental (maternal or paternal) acceptance–rejection in childhood, on a 4-point Likert scale (from 4 “almost always true” to 1 “almost never true”). The scale measures four dimensions: (1) warmth/affection, example item is “My (mother/father) made me feel wanted and needed”; (2) hostility/aggression, example item is “My (mother/father) hurt my feelings”; (3) indifference/neglect, example item is “My (mother/father) paid no attention to me”; and (4) undifferentiated rejection, example item is “My (mother/father) let me know I was not wanted”. In this study, all scales had adequate reliability ($\alpha > 0.75$) as did the two total scores ($\alpha > 0.83$). In our sample maternal rejection total scores ranged from 70 to 213 ($M = 97.9$, $SD = 27.3$), whereas paternal rejection total scores ranged from 67 to 203 ($M = 104.6$, $SD = 28.7$), showing adequate variability to evaluate relations between perceived parental experiences and responses to infant stimuli. The total scores of the two parents were summed to obtain a single measure of parental rejection.

2.3.2. DNA genotyping

Using buccal swab brushes, DNA samples from all participants were obtained. The DNA purification kit QIAamp DNA Mini Kit (Qiagen Inc., Tokyo, Japan) was used to extract DNA from buccal epithelial cells. The three polymorphisms of interest were the serotonin transporter polymorphism (5-HTTLPR) and SNP markers rs2254298 (OXTR) and rs53576 (OXTR). 5-HTTLPR gene was amplified from 10 ng genomic DNA using these primers: forward 5'-GGCGTTGCCGCTCTGAATGC-3' and reverse 5'-GAGGGACTGAGCTGGACAACCAC-3', before polymerase chain reaction (PCR) was conducted using KOD FX Neo DNA polymerase (Toyobo, Osaka, Japan). PCR was performed on GeneAmpPCR System 9700 (Applied Biosystems, CA, USA) with 1 cycle at 94 °C for 2 min followed by 35 cycles of 94 °C for 10 s, 63 °C for 30 s, 68 °C for 30 s. Products from PCR, the short (S) allele (484 bp) and long (L) allele (528 bp), were separated on a 3% agarose gel via gel electrophoresis. OXTR SNPs rs2254298 and rs53576 were amplified from 10 ng of DNA, and PCR was performed in 10-IL reaction volumes in 48-well plates. PCR was conducted using Light-Cycler 480 Real-Time PCR Instrument (Roche Ltd) at the following conditions: 95 °C for 10 min and then 40 cycles of 95 °C for 15 s and 60 °C for 1 min. To check for quality of analysis, a random 10% of the sample was reanalysed, and genotypes were found to be concordant with initial results. The genotypic frequency for rs2254298 marker is AG = 23 (28.8%) and GG = 57 (71.2%); for rs53576 marker is AA = 7 (8.8%), AG = 39 (48.8%), and GG = 34 (42.4%); for 5-HTTLPR is SS = 20 (25%), SL = 36 (45%), and LL = 24 (30%). Each of the OXTR SNPs were further divided into two groups, with G variant was treated as dominant: AG/AA = 46 (57.5%) and GG = 34 (42.5%). With respect to 5-HTTLPR, samples were separated into two groups: SS/SL = 56 (70%) and LL = 24 (30%).

2.3.3. Single category-implicit association test (SC-IAT)

The Single Category Implicit Association Test (SC-IAT) in the present study was adapted from (Karpinski and Steinman, 2006) and (Senese et al., 2013; Senese et al., 2017a, 2017b) to investigate participants' implicit associations to infant cry. The SC-IAT is a two-phase measure with a positive condition in one phase and a negative condition in the other phase. In each SC-IAT task, auditory stimuli, either infant cry or words, are played through a set of headphones in a randomized order. One item was presented at a time, and participants were

instructed to categorize words or sounds as accurately and as fast as possible. The same two response keys on the keyboard were used for both classification tasks: the “e” and the “i” keys for left and right responses, respectively. For each item, a response window of 1500 ms was given to force participants to make a rapid response. Prior to data collection, words were characterized as either “positive” or “negative” and had to be classified into a positive or negative category, accordingly. Ten positive words (e.g., love, beautiful, luck, joy, etc.), ten negative words (e.g., bad, pain, negative, unpleasant, etc.), and four acoustic stimuli from the infant cry category were used in the SC-IAT. The infant stimuli used in this study are the same as those used in a previous study (for more details see Senese et al., 2017b). Infant cries were extracted from home videos of 10 typical firstborn 13-month-olds (5 girls/5 boys). The average fundamental frequency of cries was 363.07 Hz ($SD = 35.82$), whereas the average peak amplitude of the infant cries was 73.98 dB ($SD = 2.20$). The classification task was repeated two times (two conditions). In the first SC-IAT phase, target sounds, and positive words were categorized using the same response key, “e”, and negative words with a different key, “i” (positive condition). In the second phase, target sounds and negative words were classified with the same response key, “i”, and positive words with a different key, “e” (negative condition). Each condition consisted of 23 practice trials (3 filler trials plus one block of 20 trials) followed by 63 test trials (3 fillers trials plus three blocks of 20 trials each). For each block, the first three trials (one for each category) were fillers and omitted from analysis. To measure participants' implicit associations towards the target stimuli, otherwise known as the IAT effect, the difference in response latencies between the two SC-IAT phases is computed. SC-IAT scores showed adequate reliability ($\alpha > 0.73$). An object-attribute pair classified at faster rates is considered to be more strongly ingrained in memory as compared to pairs classified at slower rates. If a stimulus was classified faster in the positive as compared to the negative condition, the score for that stimulus is positive and the participant is interpreted to possess a positive implicit attitude to that particular target stimulus. Conversely, if the stimulus is categorized more quickly in the negative than in the positive condition, a negative score is assigned, and the participant is deemed to have a negative implicit attitude towards the stimulus. To compute the SC-IAT score, the difference between the response latencies of the stimuli in the negative and the positive conditions is divided by the standard deviation of latencies in the two conditions (D-score; Greenwald et al., 2003). According to the D-score algorithm (Greenwald et al., 2003), values around 0 denote no specific implicit attitude towards the target, values from 0.2 to 0.3 indicate a “slight” effect, values around 0.5 a “medium” effect, and values of 0.8 to infinity a “large” effect.

2.4. Data analysis

Preliminary descriptive analyses were conducted to examine missing values in the data and to generate variable distributions. Univariate distributions of observed variables were examined for normality. To investigate if implicit reactions to infant cry were affected by early parental care experience, genetic polymorphisms of interest, and their interaction, three hierarchical multiple regression analyses were executed on the implicit responses to infant cry as a function of the three genetic polymorphisms (5-HTTLPR, rs53576, and rs2254298). In all hierarchical regression models, genetic polymorphism was entered into the first block (coded: SS/SL = 0 and LL = 1, AG/AA = 0 and GG = 1, GG = 0 and AG/AA = 1, for the 5-HTTLPR, rs53576, and rs2254298 markers, respectively), remembrance of early parental care experiences (PARQ z-score) was entered in the second block, and PARQ \times Genetic polymorphism interaction was entered in the third block. To control the robustness of the significant effects, we also computed adjusted *p*-values using the False Discovery Rate as a correction (FDR; Benjamini and Hochberg, 1995). Moreover, to check if the effect were independent of Gender and Age, the regressions were

Table 1

Hierarchical multiple regression analysis predicting Implicit Associations to Infant Cry (SC-IAT) as a function of Parental Rejection and Serotonin Transporter Gene polymorphism (5-HTTLPR).

Predictors	B	Beta
Step 1		
Constant	-0.06	-
Parental rejection	-0.01	-0.02
Gene (LL = 1)	0.24	0.30*** [‡]
R ²	0.089*	
Step 2		
Constant	-0.06	-
Parental rejection	-0.02	-0.04
Gene (LL = 1)	0.25	0.30*** [‡]
Gene × parental rejection	0.03	0.04
R ²	0.090	

Note: ****p* < .001; ***p* < .01; **p* < .05; [‡]FDR corrected *p*-value < .05; Gene: “LL” = 1, “LS/SS” = 0.

repeated by considering these two variables in a preliminary control step.

2.5. Results

2.5.1. Parental experience and 5-HTTLPR on implicit responses

Results from hierarchical regression analysis of implicit associations to infant cry as a function of parental experience and serotonin transporter gene polymorphism (5-HTTLPR) are reported in Table 1.

The 5-HTTLPR genetic polymorphism was associated with the implicit association to infant cry, $\beta = 0.30, p < .01$; this effect was also observed when controlling for the remembrance of parental rejection (PARQ z-score), $R^2 = 0.089, p < .05$. The effects of remembered early care experiences (PARQ) and the PARQ × Genetic polymorphism interaction were not significant. Parameter analysis of the genetic polymorphism main effect revealed that the participants with an LL polymorphism had a more positive implicit association to infant cry than S-carriers (see Fig. 1). The same results were observed when correcting the *p*-value with the FDR method or controlling for Gender and Age.

2.5.2. Parental experience and OXTR on implicit responses

Results from hierarchical regression analysis of implicit associations to infant cry as a function of parental experience and oxytocin genetic

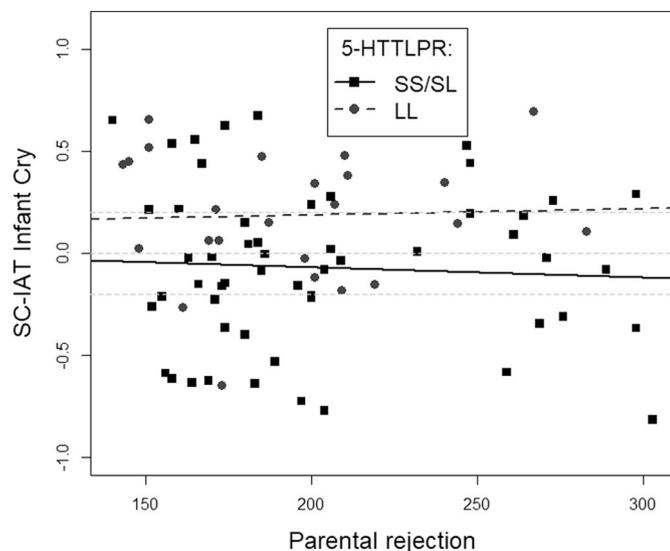


Fig. 1. Relation between Parental Rejection and Implicit Associations to Infant Cry (SC-IAT) as a function of Serotonin Transporter Gene polymorphism (5-HTTLPR).

Table 2

Hierarchical multiple regression analysis predicting Implicit Associations to Infant Cry (SC-IAT) as a function of Parental Rejection and Oxytocin receptor gene polymorphism (rs53576).

Predictors	B	Beta
Step 1		
Constant	-0.00	-
Parental rejection	-0.02	-0.06
Gene (GG = 1)	0.04	0.05
R ²	0.005	
Step 2		
Constant	0.01	-
Parental rejection	0.10	0.26
Gene (GG = 1)	0.03	0.04
Gene × parental rejection	-0.20	-0.41*
R ²	0.069	

Note: ****p* < .001; ***p* < .01; **p* < .05; Gene: “GG” = 1; “AG/AA” = 0.

polymorphism rs53576 are reported in Table 2.

The rs53576 polymorphism results showed that genetic polymorphism moderated the association between parental rejection and the implicit association to infant cry, $R^2_{diff} = 0.064, p < .05$. Parameter analysis of the final model revealed that in the A-carrier group the remembrance of parental rejection was positively associated with implicit associations to infant cry, whereas in the GG group the PARQ scores and IAT scores were negatively related (see Fig. 2). Therefore, in the A-carrier group a negative early care experience was associated with adult implicit positive association to infant cry, whereas in the GG group positive early care experience was associated with an implicit positive reaction to infant cry. The same results were observed when controlling for Gender and Age, whereas the effect was not significant when correcting the *p*-value with the FDR method.

Finally, with regards to oxytocin genetic polymorphism rs2254298, results showed that implicit association to infant cry was not related to the genetic polymorphism, to parental experiences, or to their interaction.

3. Discussion

This study employs an SC-IAT paradigm, a technique that has been shown to be sensitive to subtle cues and to minimize bias of social desirability (McElwain and Booth-LaForce, 2006; Senese et al., 2013; Senese et al., 2017b), to explore the interplay between genes and

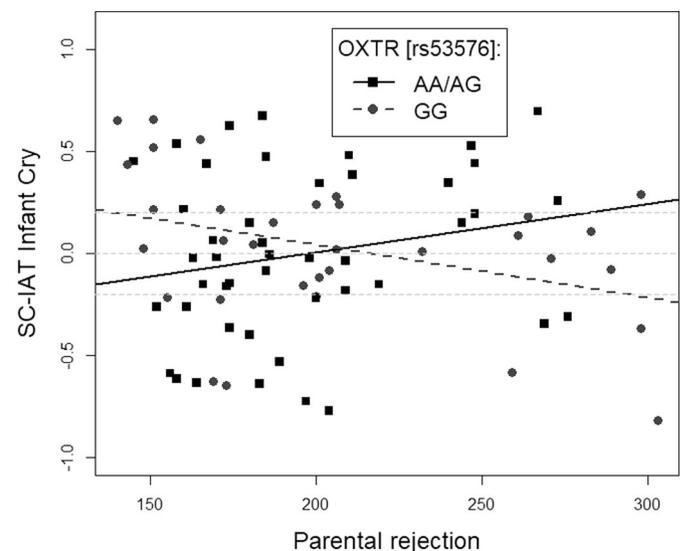


Fig. 2. Relation between Parental Rejection and Implicit Associations to Infant Cry (SC-IAT) as a function of Oxytocin receptor gene polymorphism (rs53576).

perceived early parental care experiences on adults' implicit associations to infant cry. As expected (see Leerkens et al., 2011; Senese et al., 2013; Senese et al., 2017b; Truzzi et al., 2017), results from the present work confirmed that 5-HTTLPR and OXTR are both associated with adults' responses to infant cues, despite bearing some differences. Although a main effect rather than a moderation effect was observed for 5-HTTLPR, OXTR SNP rs53576 was found to moderate participants' appraisal of infant cry, even if the effect disappeared when we applied the corrections to the *p*-values. No direct or moderation effect was observed as regards the oxytocin genetic polymorphism rs2254298.

3.1. 5-HTTLPR and early care experiences

In line with the extant literature (Bakermans-Kranenburg and van IJzendoorn, 2008; Cents et al., 2014; Henry et al., 2015; Mileva-Seitz et al., 2013; Senese et al., 2017a), the serotonin transporter gene has a specific role in the regulation of adult responsiveness to infant cry that, in turn, is related to caregiving propensity and behaviours (see Leerkens et al., 2011; Senese et al., 2013; Senese et al., 2017a). Participants with an LL genotype possess a more positive implicit association to infant cry than S-carriers. This result contrasts with Truzzi et al. (2017) who did not observe a main effect of 5-HTTLPR polymorphism on the response to infant cry. A possible explanation of this divergence may be methodological differences between the two studies. Truzzi et al. employed only a small sample of only men and, more germane here, measured physiological responses. A recent study has shown that physiological and implicit measures show a weak association (Senese et al., 2019a). From this perspective, therefore, the results seem to confirm the idea that the response to child stimuli is regulated at different levels, as advanced by the Parental Brain Model (Swain et al., 2014), and that to achieve a clearer picture of processes that regulate caregiving propensity, it is necessary to consider measures that take into account different levels of processing.

As regards the $G \times E$ effect, contrary to our expectations (but see Truzzi et al., 2017), no moderation effect of 5-HTTLPR polymorphism on the relation between early parental care experiences and the valence of implicit reactions to infant cry was observed. Senese et al. (2017a) discovered that the 5-HTTLPR variant moderated the effect of remembrance of parental rejection on implicit attitudes of participants to infant faces. Specifically, S-carriers who had negative early care experiences exhibited an implicit positive association to infant faces. In the LL group, positive early care experience was linked to positive implicit attitudes to infant faces instead. Therefore, comparing our results with that literature (Senese et al., 2017a), it seems that processes that regulate adult responsiveness to infant cry are not completely equivalent to those observed for infant faces. It is likely that these differences arise due to different mechanisms involved when processing salient infant cues in different modalities. Infant cry encompasses acoustic and visual cues, such as facial signals and body language (Wolff, 1987). Green et al. (1995) showed that information from the visual modality influenced perception of infant cry. Therefore, a possible explanation for differences in moderation effects of 5-HTTLPR towards implicit associations to infant cry and face could be ascribable to different processing and regulatory mechanisms set in motion when appraising infant cues of different modalities. Another possible explanation is that the level of distress elicited by neutral infant faces in Senese et al. (2017a) is not comparable to the infant cry employed in this study. In a previous study of infant facial expression, Messinger (2002) found that participants rated negative emotions in infant cry faces of greater intensity when they displayed stronger eye constriction and lip movement. As compared to infant cry vocalizations, which convey distinct auditory distress, neutral infant faces which lack the above expressive components would have been evaluated to be less distressing. Consequently, different levels of distress could provoke differences in the association between genetic polymorphism and implicit attitudes towards infant cues across these two studies. Specifically, in a “higher distress

context”, any moderation effect of 5-HTTLPR polymorphism on the relation between early parental care experiences and implicit association to infant cry could have been diminished. In comparison, within a “lower distress context”, the implicit association to infant faces of neutral valence was moderated by 5-HTTLPR polymorphisms and early care experiences. To verify whether the modality of infant cues, or the distress level, influenced the differences in the moderation of 5-HTTLPR, future studies should systematically compare implicit associations across both modalities of infant cues (i.e. faces and cries) at different distress intensities.

3.2. OXTR and early care experiences

Unlike 5-HTTLPR, the rs53576 (OXTR) polymorphism moderated the effect of parental rejection on participants' implicit association to infant cry. Specifically, in the A-carrier group, a negative early care experience is associated with an implicit positive association to infant cry, whereas in the GG group, a positive early care experience is associated with an implicit positive reaction to infant cry. It is important to note that the significance of the interaction effect is lost when correcting the *p*-values with the FDR method. This result seems to indicate the importance of replicating this study to verify the robustness of the observed effect. If confirmed, this finding could reinforce our understanding that OXTR plays a role in processing infant cues linking in a specific way environmental experiences and parenting (Klahr et al., 2015; McQuaid et al., 2013). Although an unequivocal consensus about the differential susceptibility conferred by the G and A polymorphisms in OXTR rs53576 has not been attained, generally, numerous studies suggested that rs53576 might reflect a sensitivity to the familial environment in early life (Bethlehem et al., 2013; Bradley et al., 2013; Chen et al., 2011; Ebstein et al., 2012; Hostinar et al., 2014; Kim et al., 2010; Meyer-Lindenberg and Tost, 2012; Myers et al., 2014; Rodrigues et al., 2009). With respect to parental perceptions of infant cues, Senese et al. (2017a) found that GG homozygotes, as compared to A-carriers, showed more positive implicit associations to infant faces, and Bakermans-Kranenburg and van IJzendoorn (2008) found that adults with a GG genotype displayed greater parental sensitivity.

Contrasting our results with the extant literature, our findings suggest that A-carriers do not necessarily exhibit more negative implicit associations to infant stimuli as compared to persons homozygous for the GG genotype. Indeed, this study indicates that A-carriers, similar to GG homozygotes, show positive implicit associations to infant cues despite the former being previously exposed to parental rejection. One possible speculation is that negative early care experiences are less likely to affect A-carriers as people with the GG genotype, as A-carriers might be less sensitive to early environmental influences. Previously, amongst those who have experienced negative environmental conditions, A-carriers have been shown to exhibit better emotion regulation, as compared to GG homozygotes (Bethlehem et al., 2013; Bradley et al., 2011; Ebstein et al., 2012; McQuaid et al., 2013; Meyer-Lindenberg and Tost, 2012). From this $G \times E$ interaction, one may deduce that differential sensitivity to early environments, due to different genetic polymorphisms, could result in positive implicit associations to infant cry in both OXTR rs53576 allelic groups. This latter result seems to further confirm the existence of a compensatory positive implicit reaction to negative early care environments, and that the valence of implicit reactions to infant cues is related to the genetic polymorphism, early care experiences, stimulus specificity and their interactions (Senese et al., 2017a).

Finally, as regards the oxytocin genetic polymorphism rs2254298, in line with previous literature considering implicit measures (Senese et al., 2017a), our results showed that implicit association to infant cry was not related to the genetic polymorphism, to early parental care experiences, or to their interaction. Yet, this latter result contrasts with what was observed by Esposito et al. (2017a). In their study, the oxytocin genetic polymorphism rs2254298 interacted with early parental

experiences on facial skin temperature and HRV (i.e., physiological measures). Probably, in this case also, it is possible that the differences in the results relate to the different measures. Future studies should therefore consider multilevel measures to disentangle these interpretations.

As with other GxE endeavours, the results of this study should be interpreted with caution as it bears limitations which are characteristic of the challenges presented to other studies in this field (Dick, 2011; Dick et al., 2015). Although adequate from a statistical point of view, the sample size for the present study is still small; therefore, it is possible that small effects size were not captured in the results. Indeed, despite an abundant of publications derived from candidate-gene approaches, there is a lack of consistently reproducible findings reported across multiple experiments (Duncan and Keller, 2011). This issue stems from the small sample sizes that often characterize candidate-gene studies (< 1000 participants), which results in low statistical power in detecting GxE interactions with small effect sizes (for a review on GxE models, see Munafò et al., 2014). In this study, we were interested in investigating adults' responsiveness to infant cues independent of parental experience (non-parents); future research could obtain data from parents to obtain an additional interpretation of adults' processing of infant cry and to investigate the extent to which caregiving responses are associated with children's genetic characteristics. Childhood rejection experiences were evaluated by means of self-report measures that are known to be biased by the current psychological state, by the functioning of memory, and by social desirability (Hardt and Rutter, 2004; Reuben et al., 2016). Future studies should replicate our findings with a longitudinal design or with alternative measures of childhood adversity with objective indices and before evaluating the outcome variable (implicit responses). A unimodal methodology focusing on acoustic features of infant cry was used, whereas a multimodal approach might reveal more about individual responses to infant cry (Iachini et al., 2012). Here, we have only considered three single nucleotide polymorphism (SNPs), but given the polygenic nature of complex phenotypes, where multiple genes function together to shape behaviour (see Kraft and Aschard, 2015), other genetic factors could be involved in the appraisal of infant stimuli. Future studies may consider adopting a polygenic analysis approach by tabulating the number of alleles for each SNP and weighting the sum by the effect size obtained from a genome-wide association study (GWAS). Alternatively, cluster-analysis of SNPs can be conducted to reach a clearer understanding of the multiple genetic factors involved in adult responsiveness to infant cry. In addition, although our findings reproduced some results from previous studies, only a small percentage of studies focused on specific polymorphisms are repeated (Duncan and Keller, 2011); therefore, our results should be further replicated. We measured implicit reactions only, whereas caregiving behaviours are regulated at different levels of processing (Barrett and Fleming, 2011; Swain et al., 2014); future studies should replicate our findings by adopting a multilevel approach. A multilevel approach recognizes that caregiving propensity, in response to infant cues, is influenced by multiple interacting systems, at the biopsychosocial levels. Specifically, factors which have been found to be integral to the caregiving response include environmental, temperament and genetic variables, and physiological reactivity factors (Esposito et al., 2015). We measured implicit associations as an index of caregiving propensity, but future studies might directly investigate how valence of implicit associations to infant auditory cues relates to the quality of adult-infant interaction or to long-term child outcomes. Even if previous studies showed that the association between implicit associations and related behaviours is “small”, if confirmed, this effect is not trivial because it cumulates over repeated occurrences of caregiver-infant interactions (see Greenwald et al., 2015). We adopted a correlational design; therefore, we could not test the causal effects amongst our variables or separate genetic contributions from the environment in a valid way. The FDR correction of the *p*-values showed that the OXTR G × E effect was no longer

significant after the correction, therefore, a replication of the observed effect is needed before concluding that it is robust.

4. Conclusions

The importance of a securely attached parent-infant dyad was made evident decades ago (Ainsworth et al., 2015; Bell and Ainsworth, 1972; Bowlby, 1982; Parsons et al., 2010), and this knowledge has continued to propel discoveries in the field of parenting and child development. The advent of advanced molecular techniques has now allowed scientists to delve below the surface of behavioural observations and glean greater insight into the genetic components that might influence this social phenomenon. In summary, findings from this study suggest that polymorphisms can confer differential genetic sensitivity in adults' response to social cues. Furthermore, different genetic polymorphisms exert different influences on adults' implicit associations to infant cry, with 5-HTTLPR having a direct relation with appraisal of infant cry, and OXTR rs53576 interacting with early care experiences to play a moderating role in affecting implicit associations towards infant cry. Results from the analysis of OXTR rs53576 also converge to suggest a compensatory protective effect amongst A-carriers, such that the presence of negative early care experiences is associated with positive implicit appraisals of infant cry. The effect cannot be considered robust because it did not remain after FDR *p*-value correction was applied. Further studies are required to verify the reliability and robustness of these findings. Finally, if compared with the previous literature on the role of genetics and early care experiences on implicit responsiveness to infant cues, the results of this study suggest that the different infant cues (face and cry) activate specific associations that in turn are sensitive to different genetics characteristics, environmental experiences, and their interaction. While the sample size used to examine two genes and three polymorphisms may be small, the novel concept brought forth by our study, regarding the potential effects of genetic polymorphisms to different infant modalities, presents a significant contribution to the field of infant research. Indeed, past research has gathered evidence of different, albeit complementary, processing mechanisms of infant cries and faces. For instance, a study that investigated the association between implicit associations to different infant cues (face and cry) showed substantial independence between responses (Senese et al., 2019b). The implication of this latter result is that modulation of genetic polymorphisms to infant cues of different modalities may affect caregiving propensities in a different way. Further studies directly comparing responses to different infant cues are needed to better understand the extent to which responsiveness to different infant stimuli is an expression of a general caregiving propensity or reflects different components, and which of these aspects is more strongly related to actual behaviour.

The significance of the present work is also found in the importance of adults' implicit associations to infant cry in processing and responding to infant's needs (Bornstein et al., 2017; Cecchini et al., 2007; Newman, 2007; Soltis, 2004; Zeifman, 2001). The implicit appraisal of infant distress may shape the quality of adult-infant interaction, and consequently, affect child development. If we assume that implicit associations to infant cues influence the quality of adult caregiving, then we can suggest that SC-IAT measures should be included in screening protocols to obtain a clearer understanding of risk factors to the quality of adult-infant interaction.

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