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Trends and Perspectives

TRENDS AND PERSPECTIVES

Cry, Baby, Cry: Expression of Distress As a Biomarker and Modulator in Autism Spectrum Disorder

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Abstract

Background: Early diagnosis of autism spectrum disorder is critical, because early intensive treatment greatly improves its prognosis.
Methods: We review studies that examined vocalizations of infants with autism spectrum disorder and mouse models of autism spectrum disorder as a potential means to identify autism spectrum disorder before the symptomatic elements of autism spectrum disorder emerge. We further discuss clinical implications and future research priorities in the field.
Results: Atypical early vocal calls (i.e., cry) may represent an early biomarker for autism spectrum disorder (or at least for a subgroup of children with autism spectrum disorder), and thus can assist with early detection. Moreover, cry is likely more than an early biomarker of autism spectrum disorder; it is also an early causative factor in the development of the disorder. Specifically, atypical crying, as recently suggested, might induce a "self-generated environmental factor" that in turn, influences the prognosis of the disorder. Because atypical crying in autism spectrum disorder is difficult to understand, it may have a negative impact on the quality of care by the caregiver (see graphical abstract).
Conclusions: Evidence supports the hypothesis that atypical vocalization is an early, functionally integral component of autism spectrum disorder.

Keywords: cry, autism spectrum disorder, early biomarkers, animal models of ASD, ultrasonic vocalizations

Introduction

Since Kanner's description of autism (Kanner, 1943), impairment in social communication and social skills have been considered core symptoms of the disorder. Over the last decade, a large body of work has been produced to ontologically define the disorder, now defined as autism spectrum disorder (ASD) in the latest version of the Diagnostic and Statistical Manual of Mental Disorders, which especially highlights its heterogeneity. However, a clear understanding of the etiopathogenesis of ASD and its heterogeneity is still lacking.

There is an intense interest in identifying very early signs of ASD. Although it is possible to diagnose ASD by 2 years of age in humans, earlier identification of signs is critical, because early

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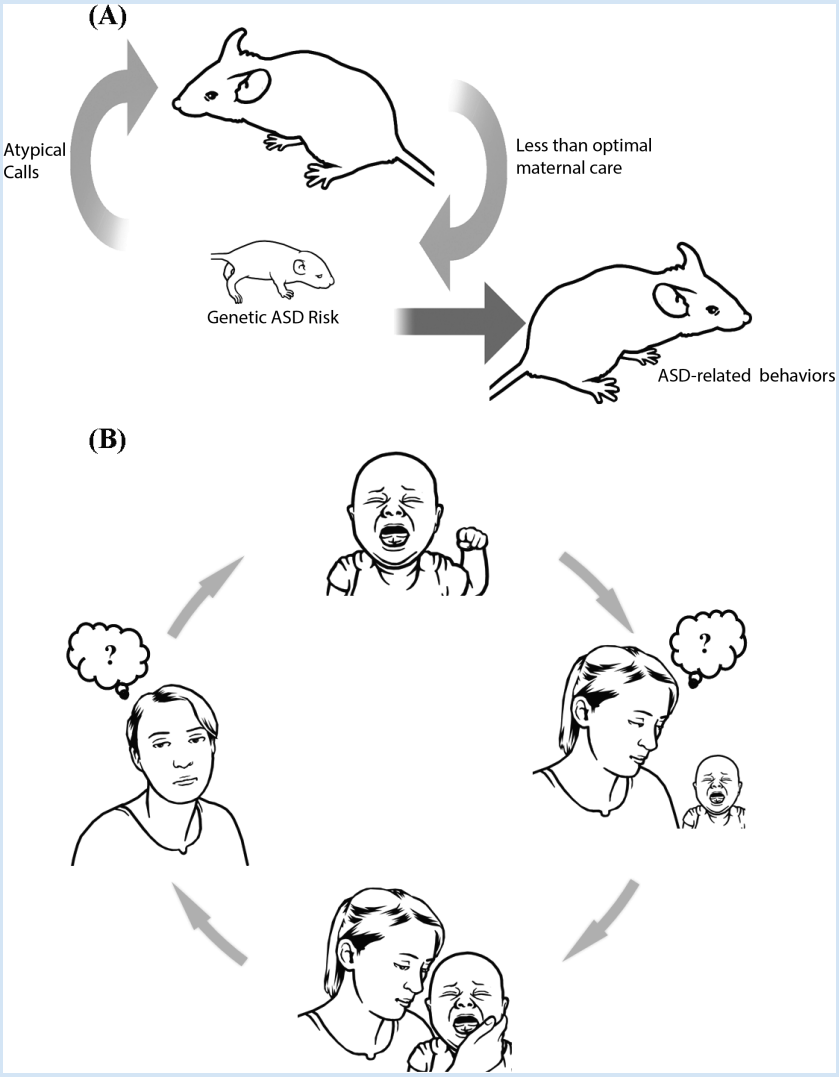
Significance Statement

A hypothetical causative chain of events involving atypical vocalizations in mice and humans. Striking similarities have emerged from human and mouse data indicating how genetic components may lead to the production of atypical distress vocalizations, which in turn jeopardizes effective neonatal social communication between infants and mothers. A) Atypical vocal call sequences of pups with an autism spectrum disorder (ASD) risk gene evoke less maternal approach in mothers in mice. The suboptimal maternal care acts as a self-generated environmental factor to exacerbate the phenotypic expression of ASD-related behaviors in the risk carriers, resulting in ASD-related behaviors later. B) In humans, atypical vocalization in infants with an ASD risk factor diminishes mothers' ability to appropriately respond to babies' specific needs because such cries are not well understood or are negatively perceived by mothers. This might lead to a vicious cycle of confusion and negative perception as to how to appropriately respond to baby's atypical cries.



intervention is highly effective (Wallace and Rogers, 2010; Rogers et al., 2014; Wetherby et al., 2014; Green et al., 2015). Many anatomical, functional, and behavioral features predictive of later ASD diagnosis have been examined (Elsabbagh and Johnson, 2016; Varcin and Jeste, 2017). Brain imaging studies have identified alterations of brain structures and regional activities among infants in their first year of life who are later diagnosed with ASD (Varcin and Nelson, 2016; Varcin and Jeste, 2017). Moreover, atypical development of behavioral features serve as markers of later diagnosis of ASD in infants (Ozonoff et al., 2010; 2014; Zwaigenbaum et al., 2015), including a reduced attention to eyes (Jones and Klin, 2013; Moriuchi et al., 2017), poor postural control (Flanagan et al., 2012), early motor asymmetry (Teitelbaum et al., 1998; Esposito et al., 2009, 2011), increased perceptual sensitivity (Clifford et al., 2013), and atypical preverbal vocalizations (Esposito and Venuti, 2010b; Ozonoff et al., 2010; 2014).

Among these behavioral features, neonatal vocalization has been examined in mice as a potential proxy of one aspect of ASD. In mice, pup vocal calls are thought to be a form of social communication similar in function to the nonverbal calls of infants

(Scattoni et al., 2009). When separated from dams, rodent pups emit vocal calls that the dams use to locate and retrieve the pups (Ehret and Bernecker, 1986; D'Amato et al., 2005; Uematsu et al., 2007; Wöhr et al., 2010). Atypical neonatal calls have been identified in a number of genetic mouse models of ASD, some of which show ASD-related behaviors (i.e., lack of reciprocal social interaction and repetitive behavioral traits) during adolescence and adulthood (Michetti et al., 2012; Lai et al., 2014; Nishi and Hiroi, 2016). More importantly, a recent observation indicates that pups with an ASD risk gene variant emit atypical vocal sequences, which in turn induce less than optimal maternal care, thereby establishing atypical vocal call sequences of a genetic ASD mouse model as a functionally integral phenotype of ASD-associated gene variants (Takahashi et al., 2016; Kikusui and Hiroi, 2017).

Here, we argue that atypical early cry may represent an early biomarker for a subgroup of children with ASD (Esposito, 2016) and, moreover, may also represent an early causative factor in the development of the disorder. Specifically, atypical crying likely induces a "self-generated environmental factor" in caregivers (Kikusui and Hiroi, 2017).

Cry as an Early Biomarker

Forcing air through the vocal tract and over the larynx produces cry. The process of controlling the air passing through the larynx is regulated, through the cranial nerves, by the brainstem and limbic system, functions of which are thought to be compromised in individuals with ASD (Amaral et al., 2008). Assessment of the spectrographic characteristics of crying can thus give investigators important information about function of those brain areas that are involved in the pathogenesis of ASD.

The cry sound can be described by a variety of parameters, including loudness (i.e., amplitude), the timing of onset, and inter-utterance intervals. Other aspects of cry can be represented acoustically by fundamental frequency (F0), voicing, and formant frequencies. F0 is the base frequency of a cry and is perceived as pitch. Voicing is a phonation that results from harmonic vibration of the vocal folds (Sheinkopf et al., 2012). Formant frequency is a cluster of sound waves at a particular frequency and is produced by resonance of the vocal tract. ASD is associated with atypical vocal quality (i.e., atypical pitch production and shorter duration) and different developmental trajectories (Esposito and Venuti, 2010a).

These vocal parameters may also help to identify incipient ASD infants, who are likely to be diagnosed in the future with ASD (Sheinkopf et al., 2000, 2012; Esposito et al., 2014a). Sheinkopf et al. (2012) investigated the acoustic properties of cries of 6-month-old infants at risk for autism and of a typically developing low-risk group. The at-risk group produced pain-related cries with higher pitch with greater variability than low-risk infants; those at-risk infants later diagnosed with ASD produced the widest frequency range and most poorly phonated cries. Thus, differences in cries may be an early manifestation of an atypical affective state, which may play a role in the development of poor social communication.

A subsequent study (Esposito et al., 2014a) examined the acoustic characteristics of cries extracted from the separation phase of the Strange Situation Procedure, a procedure devised to observe attachment relationships between a caregiver and a child, in child siblings of an older child with ASD defined as high-risk (HR, the incidence of ASD is higher than in the general population) and low-risk (LR) for ASD. Higher fundamental frequency (f0) and maximum f0 (highest pitch) of the first utterance of crying was found in the HR compared with the LR toddlers. HR toddlers had shorter duration of crying than LR toddlers. Finally, HR toddlers who were later diagnosed with ASD had the highest f0 and the shortest cry duration. Since the onset of crying is thought to be under direct neural control, these findings suggest poor central control of crying in HR toddlers.

As early as the first months of age, infants later diagnosed with autism show a different pattern of cry compared with those with other types of developmental delays and typically developing infants (Esposito and Venuti, 2010a). Specifically, episodes of cry in ASD showed higher fundamental frequencies, higher formant frequencies, and a decreased number of pauses.

Mouse Models

Over the last decade, researchers interested in the mechanisms of early distress vocalization in ASD have focused on mouse models. When separated from mother during the first few weeks of life, mouse and rat pups emit distress calls as ultrasonic vocalizations (USVs), ranging from 30 to >100 kHz (Scattoni et al., 2009). Mouse pups increase the number of ultrasonic vocal calls during the first week and decrease calls thereafter. This rodent period corresponds to a period up to 2 years old in humans (Semple et al., 2013).

A compromised ability to emit USVs during the neonatal period has been seen in various animal models of autism. This bears resemblance to observations made in infants at high risk for ASD (Leonard et al., 2013; Mody et al., 2016), as well as those diagnosed with ASD (Mody et al., 2016). An altered number of neonatal USVs has been reported for mouse models with various genetic variants (Michetti et al., 2012; Lai et al., 2014; Nishi and Hiroi, 2016). In addition, mouse models of ASD exhibit spectrographic deviations (Schmeisser et al., 2012; Michetti et al., 2012; Belagodu et al., 2016) and altered vocal repertoire (Scattoni et al., 2008; Young et al., 2010; Hiramoto et al., 2011; Ey et al. 2013; Hiroi et al., 2013; Romano et al., 2013; Burkett et al., 2015; Yang et al., 2015; Fraley et al., 2016).

One interpretative caution here is that the genetic background of mutant and wild-type littermates is not controlled (i.e., noncongenic mice) in some studies, and alleles surrounding the targeted gene are expected to systematically differ between mutant and their wild-type littermates. As different inbred mouse lines have distinct vocal patterns (Scattoni et al., 2008), any phenotypic difference in vocal calls between noncongenic mutant and wild-type littermates might not genuinely reflect the impact of the targeted ASD-linked gene mutation.

Crying As a Modulator of the Environment

Crying is evolutionarily shaped to elicit parental responses. Parental responses to infant cries are the results of cultural norms, caregiver characteristics, and characteristics of the infant cry (Gustafson and Green, 1989; Bakeman et al., 1990; Zeifman, 2003). Over the last several decades, many studies have focused on how the frequency and duration of crying episodes modulates adult responses. Cry pitch can influence caregivers' perception: higher frequency cries are often perceived as more aversive and distressing than lower frequency cries.

Parents often report they had great difficulty decoding the emotional signals of their infants with ASD diagnosis, especially during the first year of the child's life. They report, in particular, problems understanding the causes of crying episodes (Esposito and Venuti, 2008; Esposito and Venuti, 2010b; Bornstein et al., 2016). Such a lack of understanding regarding why their infants are crying can initiate a vicious cycle; the mother fails to recognize the infant's needs, which in turn results in an inadequate feedback to the infant.

To understand the precise acoustic parameters that negatively influence perception of crying, some studies (Esposito et al., 2013, 2014b) deconstructed ratings of distress, as perceived by parents, in cries of infants with ASD. These studies identified that pause lengths (duration of inhalation), compared with the number of utterances or fundamental frequency, had the strongest impact on the perception of distress in 2 contrasting cultural groups. These findings underscore the importance of acoustic parameters other than the commonly researched fundamental frequency in analyzing caregiver perception of infant cry.

Episodes of crying in infants with ASD are interpreted by adults as high levels of distress in the infant and thus cause increased distress in adult listeners (Esposito et al., 2013). Overestimated levels of distress expressed in an episode of crying may jeopardize caregiver responsiveness, because accurate evaluation of infant's vocalizations can be critical for appropriate bonding and for offspring well-being and survival (Seifritz et al., 2003).

The adult brain responds to the acoustic characteristics of infant cries. An fMRI-based study measured brain activity during adult processing of cries of infants with ASD and of matching control infants. For ASD infant cries, in addition to higher activations in the primary and secondary auditory cortex, higher levels of activation were observed in the inferior frontal gyrus (Venuti et al., 2012), a region known to play a critical role in processing emotional information and evaluating the affective salience of speech. This suggests that listening to the cries of infants with ASD calls for deeper and more effortful auditory attention and comprehension, and in particular comprehension of "emotional content," which may be compromised in the cries of infants with ASD.

Consistent with the notion that ASD cries are more distressful, ASD cries elicited higher activations in the left inferior frontal gyrus/anterior insula, which are known to mediate brain responses to aversive and arousing stimuli. Additionally, activity in the supplementary motor cortex and precentral gyri emerged, suggesting preparation for care behaviors. ASD cries appear to activate adults' intentions to reduce infant distress.

A more recent study (Esposito et al., 2015) assessed activation of the autonomic nervous system of fathers of typically developing children and non-fathers in response to typical and atypical (i.e., those of ASD) infant vocalizations. Galvanic Skin Response, cardiac dynamics via Inter-Beat Interval, and right hand temperature change were measured. Both groups showed greater negative responses (i.e., increased Galvanic Skin Response) while listening to cries of infants with ASD compared with typical cries and laughter. In contrast, fathers showed higher Inter-Beat Interval and greater temperature increases in right hand temperature change than non-fathers while listening to typical and atypical ASD cries. These findings point to similarities and differences in fathers' and non-fathers' physiological responsiveness to cries of infants with ASD and might guide specific intervention programs for parents of children at risk for ASD.

Expression of distress in ASD is not only evident in the vocal domain. Indeed, when female adults were made to judge the distress and typicality (expected normality) of isolated vocal, facial, and bodily cues of 18-month-old ASD developmentally delayed or typically developing infants, vocal cries of ASD and developmentally delayed infants were perceived as equally distressing, but cries were perceived as more atypical for infants who were later diagnosed with ASD as they had higher frequency cries (Esposito and Venuti, 2008). Facial cues of ASD infants were perceived as less typical and less distressed, consistent with the lack of emotional expressivity. ASD children's bodily movements were perceived as more distressed and less typical compared with those of infants with other types of developmental delay or with typical development (Esposito et al., 2011).

All of these differences in distress cues may account for adults' bias in interpreting their infant's states of uneasiness. This bias may in turn jeopardize adequate parental responsiveness. Indeed, qualitatively different responses were shown in response to crying episodes. While mothers of typically developing infants or those with other types of developmental delays were more likely to use tactile or vestibular stimulation to soothe their infants, mothers of infants with ASD used more verbal soothing (Esposito and Venuti 2010c). A possible explanation of this is that when parents cannot understand the meaning of a crying episode, they use more verbal interactions.

Mouse Models

Pups' distress vocalizations have some communicative value for mothers. Pups' USVs are thought to be essential for the development of social bonds between the mother and young, making USVs vital for the pup's survival (Zippelius and Schleidt, 1956). Pups' calls alone are demonstrated to elicit maternal approach behaviors (Uematsu et al., 2007; Okabe et al. 2013). A more recent study (Takahashi et al., 2016) demonstrated that USVs of pups that carry heterozygous deletion of the gene *Tbx1*, an ASD risk gene encoded in the 22q11.2 region (Hiramoto et al., 2011; Hiroi et al., 2013) and itself a monogenic ASD risk gene (Gong, 2001; Paylor et al., 2006; Ogata et al., 2014), elicits less maternal approach compared with those of wild-type pups. The USVs of *Tbx1* heterozygous pups were also characterized by less individually variable call sequences and less complex call types compared with those of wild-type littermate pups. Randomized sequences of calls of wild-type pups induced less maternal approach behaviors, indicating that mutation of this ASD risk gene alters the neonatal call sequence, which renders the pup's social communication with mothers ineffective and maternal care less efficient (Takahashi et al., 2016; Kikusui and Hiroi, 2017).

Where Should We Head Next?

To date, human and mouse studies have shown that assessment of early distress vocalization can offer insights into the behavioral and brain mechanisms behind the earliest stages of development in infants with ASD. Striking similarities have emerged from human and mouse data pointing to how genetic components may create a specific physiological deficit that leads to the production of atypical distress vocalizations, which in turn jeopardizes the effective communicative power of the distress vocalization and finally hinders caregiver-infant interaction. In other words, a genetic component plays a major role in producing a specific phenotype (atypical crying) that modulates the environment in which the phenotype is expressed (hindering caregiver understanding and responsiveness, see also graphical abstract). This can thus be seen as a complex dynamic of gene × environment effect in which the environmental factor is positively created, instead of being passively perceived (e.g., accidental environmental insults), by risk carriers (Kikusui and Hiroi, 2017). Here, the environmental factor results from the behavioral phenotype of a genetic risk carrier and at the same time results in the augmentation of the genetic impact.

Finally, we would like to highlight 3 directions for research studies in these fields. First, considering that ASD is a spectrum of disorders characterized by wide heterogeneity, a biomarker detectable during early development (such as the acoustic features of cries) in incipient infants with ASD and their siblings could potentially inform ASD subtype identification and clinical population

stratification. Second, training of the caregiver to interpret atypical crying episodes is likely to improve social communication between incipient ASD infants and their parents. Third, both human and rodent studies should quantitatively evaluate the predictive prognostic value of early vocal abnormalities in incipient ASD. Infant cries in both humans and mouse models of ASD can be capitalized on to advance our understanding of the developmental origin of ASD and to devise effective therapeutic options.

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Statement of Interest

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