Neurobiological Bases of Autism Spectrum Disorders and Implications for Early Intervention: A Brief Overview

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Keywords

Neurobiology · Autism spectrum disorder · Joint attention · Eye gaze · Early intervention

Abstract

Objectives: To better understand the pathogenesis of autism spectrum disorder (ASD) and implications for intervention, the current paper reports on research related to the neurobiological underpinnings of ASD and the implication for early intervention with a focus on the importance of joint attention and eye gaze behaviors. **Participants and Methods:** An overview is provided on the available research findings from the fields of social neuroscience and experimental psychology specific to brain development, brain pathology, eye gaze, and joint attention behaviors. **Results:** The results of the review converge towards the existence of aberrant brain connections and atypical brain morphology areas, which in complex and dynamic ways hinder the prioritization of social information. Consequently, the atypical social interaction skills exhibited by infants at risk for developing ASD are traced in the malformation of respective brain connections. **Conclusions:** Given the importance of neurobiological findings and their mapping onto early social pragmatic skills, early intervention goals need to focus on increasing appropriate eye gaze skills and joint attention. Such

goals could potentially improve intervention outcomes in terms of improving social communication skills in youngsters with ASD.

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Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental impairment that affects children and families regardless of language background, religion, and socioeconomic status around the world. ASD presents as one of the most prevalent neurobiological disorders of early childhood with affected individuals forming a heterogeneous group with severity and manifestation of symptoms varying from mild to severe [1]. Based on the *Diagnostic and Statistical Manual of Mental Disorders V* (DSM-5) [2], one area of particular challenge for children with ASD deals with social pragmatic skills and issues related to theory of mind (ToM) which is defined as the ability to reflect and decode what others know and believe [3, 4]. Furthermore, individuals with ASD exhibit problems in the linguistic subdomain of pragmatics described as the ability to exhibit appropriate use of language for social purposes (e.g., turn taking, humor appreciation, processing of metaphorical versus concrete language, us-

age of greetings, reading facial expression, etc.) [2, 5]. A recent review by Westby [6] discussed the neurobiological underpinnings related to ASD vis-à-vis affective and social ToM under the umbrella term of social neuroscience as advanced by Cacioppo and Bertson [7] and Baron-Cohen [8].

In the last 10 years, the field of social neuroscience has highlighted the relationship between neuroanatomical brain regions and their involvement in atypical social behavior as evidenced in ASD pathogenesis and symptomatology [9–11]. Such a relationship appears to operate in a bidirectional manner. That is, the ability to exhibit appropriate social behavior skills (i.e., using appropriate eye contact behaviors) influences neurobiological events. In turn, neuroanatomical, neurochemical, and neurophysiological events occurring in cortical and subcortical brain areas trigger and determine the person's ability to understand the meaning behind pragmatic aspects of communication. Such skills include the decoding of facial expressions, the appropriate use of eye contact, and joint attention [12, 13]. Data suggest that the infant's attention to a person's face is mediated by the subcortical area of the visual neural pathway (e.g., from the retina to the occipital lobe) [11, 14]. It appears that appropriate use of eye contact in infancy strengthens the establishment of such neural pathways. In turn, reciprocal use of eye contact contributes to the appropriate response by the child during joint attention instances occurring when 2 people share interest in an object or event. Findings from neuroscience research map directly onto the early diagnostic markers evident in ASD high-risk infants even as early as in the first months of the child's life. Diagnostic biomarkers include poor eye contact, lack of affective reciprocity, atypical eye gaze behavior, and lack of joint attention skills [11, 13–15]. This information proves to be an invaluable diagnostic criterion for clinical assessment and intervention; specifically, joint attention skills which emerge during the first year of life (around the age of 9 months) and become established by the age of 18 months are important. Note that such skills appear to be among the earliest diagnostic markers for possible ASD diagnosis in high-risk infants [12, 14, 16].

On a par with research reports, theory-motivated and evidenced-based findings can be adopted when developing specific therapy intervention goals targeting the improvement of eye contact, eye gaze, and joint attention skills. In the sections to follow we provide (a) a brief overview of research findings related to brain development, eye gaze skills, and joint attention in toddlers with ASD and (b) suggestions related to early intervention goals for

improving social communication skills via joint attention and eye contact. It is noted that the current report provides general rather than exhaustive information related to the neurobiological and intervention interphase in ASD.

Research Related to Brain Development, Eye Gaze Skills, and Joint Attention in ASD

Neuroscience findings serve to elucidate the development of ASD over time. To date, research has shown that aberrant brain activity and atypical brain morphology during infancy appear to underline the manifestation of ASD symptomatology. Deviant brain growth in ASD occurs during a critical age period of development when the formation and connectivity of cerebral circuits are at their prime, in the most productive and optimum stage of synaptic activity. Aberrant brain growth might disrupt the formation of typical cerebral connectivity necessary for the operation of optimum neural pathways, a process that might eventually lead to autism [9, 10, 17].

Information on brain development in children with ASD stems from systematic research developed in the last 10 years. These findings provide information regarding the neurobiological, neuroanatomical, and genetic underpinnings of ASD. Findings from functional magnetic resonance imaging (fMRI) studies have shed light on the nature and pattern of brain activity and growth in ASD infants [18]. Specifically, Weigelt et al. [17] and Courchesne et al. [18] detected remarkable growth patterns and changes in cerebellar brain areas, including the size of the cerebral vermis, defined as a region of the brain responsible for motor control and cognitive functions. Specifically, toddlers with ASD showed occurrences of atypical brain overgrowth during the first and second year of life. Aberrant brain overgrowth was noted in the cerebellar, cerebral, and limbic structures. These areas are responsible for the process and the use of higher-order cognitive, pragmatic, emotional, social, and language functions. In subsequent investigations, Courchesne and colleagues [10, 18] and Weigelt et al. [17] revealed that excessive brain growth was followed by abnormal deceleration of cerebral areas [18]. These findings seem to provide evidence for the existence of complex and multiple modalities that are abnormal in ASD, possibly due to neuroanatomical lesions in multiple brain regions involving the number of cell bodies in the prefrontal cortex. Interestingly, the role of the prefrontal cortex and temporal parietal junction has been shown to be active during ex-

perimental tasks that require processing of events related to people's emotions, thoughts, and beliefs (affective and cognitive ToM, respectively) [15]. Support for the contribution of specific areas in the brain responsible for prioritizing social information comes from research projects focusing on the involvement of the corpus callosum [9, 19]. One property that underlies the initial steps of social interaction is that of appropriate reciprocal eye contact followed by skills of joint attention. In these 2 areas, infants who develop ASD and infants at risk for developing ASD (e.g., with a significant familial history for ASD) appeared to lag behind on the expression and development of appropriate prelinguistic social skills [1, 2]. Based on diffusion tensor imaging, Wolff et al. [19] in 2012 indicated that the expression of ASD "communication-social" phenotypes is possibly preceded by atypical development of cerebral white matter pathways during infancy [14]. Such findings offer insight regarding the gradual rather than the sudden onset of ASD pathogenesis. This gradual occurrence appears to be "unfolding" during infancy rather than emerging during the second year of life after a period of unremarkable development. Furthermore, recent data on the importance of cerebellar pathways predicted later sensory responsiveness in toddlers with ASD symptoms [20]. Specifically, the findings suggested that restricted and repetitive behaviors on a par with ASD symptomatology at age 2 years were associated with structural properties of callosal and cerebellar white matter pathways measured during infancy and toddlerhood. They further suggested that repetitive behaviors seen in ASD and atypical sensory integration response patterns co-occurred and share common brain-behavior relationships.

Appropriate attention shifting in early infancy is paramount to later social pragmatic and cognitive development. In addition, joint attention skills that emerge as early as at 10 months of age are the "building blocks" for later social, pragmatic, and cognitive development [5, 8, 20]. One of the most significant prelinguistic social communicative challenges seen in youngsters with ASD is the inappropriate use of eye contact, eye gaze, and joint attention [11, 12, 21]. Pierce et al. [21] have shown that toddlers with ASD exhibited atypical patterns of visual preference as indexed by eye tracking behaviors. Furthermore, when compared to their neurotypical peers, children with ASD preferred watching geometric as opposed to social interaction vignettes projected on a screen [20, 21]. The authors proposed that unusual looking preferences and the lack of typical visual fixation behaviors might act as early biomarkers of ASD, despite the vari-

ability of factors that might contribute to language outcomes (e.g., cognitive ability, presence of familial history). On parallel lines, reports from MRI studies indicated that high-risk ASD infants showed delayed responses when shifting eye gaze during tasks that measure eye movements and eye contact. The researchers attributed this delay to atypical connectivity patterns observed in the splenium, a brain structure found in the area of the corpus callosum responsible for connecting the right and left cerebral hemispheres [19]. Comparable investigations related to eye gaze behaviors in infants who were high risk for developing ASD have been reported by Jones and Klin in 2013 [14] and Klin and Jones in 2008 [22]. The investigators indicated that the young high-risk participants preferred looking at a person's mouth rather than looking at the eyes, a pattern not observed in the neurotypical controls. Overall, eye gaze and eye fixation behaviors differentiate high-risk from low-risk ASD infants after the age of 2 months. The findings suggested that neurobiological reorganization followed different patterns in the 2 study groups. In summary, neuroimaging investigations of ASD have advanced our understanding of atypical brain structure, morphology, and function. Researchers have identified abnormalities in brain regions involved in social behavior, eye gaze, and eye contact. Recent reports have also proposed new ways of identifying ASD behaviors through the use of optometry, since this method allows the examination of specific visual behaviors consistent with ASD symptomatology. Given the difficulties regarding visual processing difficulties and atypical eye gaze and eye contact behaviors manifested in ASD, the authors supported such aberrant visual difficulties to occur in ASD toddlers during the process of optometric examination [23].

Collectively, experimental paradigms using MRI and neuroimaging have shed light on the aberrant behaviors manifested in ASD, as well as have improved our understanding of early symptomatology of ASD. Overall, converging evidence supports the neurobiological underpinning regarding the pathogenesis, etiology, and integrated functional and structural measures across brain regions in ASD high-risk infants and toddlers [7]. We know from research data that there is a clear difference between ASD and non-ASD subjects regarding the response of integrated brain regions responsible for eye gaze and joint attention processing. The following section discusses possible clinical implications related to brain behaviors in children with ASD with a particular focus on eye gaze and joint attention, as these skills are considered developmental precursors to affective ToM.

Clinical Implications and Early Intervention

Despite contradictory and unequivocal findings, data converge towards the existence of brain regions that contribute to the lack of social skills and social prioritizing skills seen in ASD. Future longitudinal studies on brain development can contribute to clarifying the mechanisms regarding ASD etiology, symptomatology, and variability of social behaviors. Consequently, evidence-based information can lead to best clinical practices with a major focus on bringing about positive and promising communication outcomes. Given the plethora of available information regarding the neurobiological substrate of ASD, targeted early intervention becomes imperative. Advances in neuroimaging methods and large-scale collaborations will also allow for an integrated approach via linking neurobiological information and early intervention regimes.

Given the early communication challenges associated with possible manifestations of ASD, one might hypothesize that by targeting the improvement of eye contact and joint attention skills during infancy positive neurodevelopmental and linguistic outcomes could emerge. Atypical patterns of visual fixation, visual preference, and visual shifting can be used as both clinical markers and clinical goals for ASD. This is because research findings suggest that these behaviors map onto specific brain areas and affect cerebral connectivity [23]. Based on what we know on social pragmatic deficits and current pragmatics-based language development theory, clinicians can use natural settings to elicit and motivate communication with emphasis on interaction involving shared control, turn taking, and reciprocity in a rich and positive manner. Given that the most significant behavioral impact of ASD is in the processing of social information, such as eye gaze, facial expression, and speech, a primary focus of interventions should be on facilitating these behaviors. Among these social behaviors, joint attention is a particularly challenging interactive behavior for toddlers with ASD. These children exhibit difficulty orienting and attending to a social partner, shifting gaze between people and objects, sharing affect or emotional state with another person, following the gaze and point of another person, and being able to draw another person's attention to objects or events for the purpose of sharing experiences [21, 22]. Clearly, a high priority in the early intervention of children with ASD is for them to learn to engage and respond and react to joint attention routines. As clinicians we are interested in joint attention skills when targeting early intervention goals because these skills form a critical foundation for social, cognitive, and language development.

However, it is important that clinicians become aware of different types of joint attention and eye contact skills. Discerning the different types of communication acts becomes of paramount importance. Since, in general, children with ASD are not particularly interested in these kinds of social communication behaviors, early focused intervention might increase their ability to begin to prioritize social information [5, 6]. Consequently, when dealing with ASD, it is important to be aware of the non-exhibited behaviors in addition to those behaviors exhibited by the child. The present overview of the neurobiological bases of ASD suggests that equivocality exists in the early diagnosis and early intervention of this pervasive disorder. Through continued research into the pathogenesis of ASD, maximum positive outcomes can be realized as characterized by a positive impact on the child, the family, and the educational/social system.

Consequently, early intervention goals may focus on increasing social skills through joint attention in a way that the child's communicative potential is maximized and brain connectivity is improved. Clinical opportunities arising from current neurobiological findings should be implemented in terms of improving assessment and intervention practices to improve long-term language outcomes [23].

Conclusion

Overall, neuroscience research findings have shed light on how the brain functions during processing tasks requiring social and cognitive affective behaviors. As a result, the neurobiological underpinnings of ASD, even though not very well understood, point towards the existence of certain brain areas which are responsible for early developing communication skills, including eye contact, eye gaze, and joint attention behaviors, which pose a particular challenge to youngsters with ASD. Given the aberrant brain functions which map onto early social pragmatic behaviors in humans, early intervention might eventually allow neurobiological reorganization that could reverse the negative developmental outcomes related with ASD [24]. Such areas of research await further investigation as this arena of research and clinical framework remains underinvestigated, albeit promising in terms of favorable communication outcomes [25].

Disclosure Statement

The authors declare that they have no conflicts of interest.

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