Structural and Functional Aberrations of the Auditory Brainstem in Autism Spectrum Disorder

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Autism spectrum disorder (ASD) is a neurodevelopmental condition associated with difficulties in the social, communicative, and behavioral domains. Most cases of ASD arise from an unknown etiologic process, but there are numerous risk factors, including comorbidities and maternal exposures. Although it is not part of the diagnostic criteria, hearing difficulties ranging from deafness to hyperacusis are present in the majority of persons with ASD. High-functioning children with ASD have been found to have significantly slower and asymmetric auditory brainstem reflexes. Additionally, histopathological studies of postmortem brainstems in decedents who had ASD have consistently revealed significantly fewer neurons in auditory nuclei compared with those in people who did not have ASD. The authors review the literature implicating auditory dysfunction in ASD along with results from human study participants and postmortem human brain tissue. Together, these results implicate significant structural and functional abnormalities in the auditory brainstem in ASD and support the utility of auditory testing to screen for ASD.

The Auditory System

The mammalian auditory system consists of a peripherally located sound-collecting device (the pinna), a sound-conducting system (the tympanic membrane and middle ear
ossicles), mechanoreceptive hair cells in the cochlea, the auditory nerve, and a complex neural circuitry in the central nervous system. The primary functions of the auditory system are to detect and convert sound pressure waves into action potentials and, through an elaborate neural circuitry, to characterize the sound’s frequency, intensity, envelope, and origin. The auditory system is organized according to frequency; this organizing principle is established in the cochlea and is maintained throughout the auditory pathways.

The central auditory circuitry begins with bipolar neurons in the spiral ganglion. These bipolar neurons send a peripheral projection to the organ of Corti to innervate inner hair cells and a central projection into the cochlear nuclei (Figure 1). Each type I axon arising from the spiral ganglion terminates widely in the ipsilateral cochlear nuclei (CN). The major targets of ascending projections from the ventral CN are the superior olivary complex (SOC) and the inferior colliculus. The SOC is a conglomerate of nuclei in the caudal pons and plays important roles in sound source localization and encoding temporal features of sound. Humans are excellent low-frequency listeners: our SOC is dominated by the medial superior olive (MSO). The human MSO is composed of a thin column of neurons that each give rise to a medial and lateral dendrite (Figure 2A and Figure 2B). Upon these dendrites is a massive convergence of information from the cochlear nuclei: the lateral dendrite receives input from the ipsilateral ear, and the medial dendrite receives input from the contralateral ear. The MSO neurons are referred to as coincidence detectors because they function to encode differences in arrival time of sounds between the 2 ears. This interaural time difference is essential in the localization of sound sources. Thus, normal structure and function of the

**Figure 1.**
Illustration of the auditory pathway. The central auditory circuit begins with the spiral ganglion and central projections comprising the auditory nerve. The auditory nerve innervates the subdivisions of the cochlear nucleus. The cochlear nucleus projects bilaterally to the nuclei of the superior olivary complex and to the contralateral inferior colliculus. The superior olivary complex projects bilaterally to the inferior colliculus through the lateral lemniscus. The inferior colliculus projects to the medial geniculate, which in turn projects to the auditory cortex.
MSO is required for normal hearing, and hypoplasia and dysmorphology in the MSO results in hearing difficulties. Axons from the MSO ascend in the lateral lemniscus to reach the inferior colliculus. Axons from the inferior colliculus target subnuclei in the medial geniculate body in the thalamus. From the medial geniculate, information ascends through the internal capsule to reach the auditory cortex.

Superimposed on this ascending pathway is a descending pathway that originates in the cerebral cortex, involves neurons at each level of the pathway, and terminates in the cochlea (Schofield provides a detailed review). The final neurons in this descending system are situated in the SOC and comprise 2 systems: a medial olivocochlear system and a lateral olivocochlear system. Neurons of the medial olivocochlear system are situated mainly in the ventral nucleus of the trapezoid body and send a major projection to innervate outer hair cells in the contralateral organ of Corti. This system is believed to filter out background noise when listening in noisy environments. Neurons of the lateral olivocochlear system are located in or around the lateral superior olive. Lateral olivocochlear system neurons send axons to the ipsilateral cochlea and innervate auditory nerve axons that innervate inner hair cells. At the very least, olivocochlear neurons modulate function of the cochlea, which appears necessary to protect the cochlea from damage from loud sounds and for selective listening in the presence of background noise.

Noninvasive Tests of Cochlear and Auditory Brainstem Function

There are a number of commonly used, noninvasive tests to assess integrity of the cochlea and auditory brainstem. The utility of these tests is that they provide an objective measure of auditory function and can quickly provide assessment of hearing in young children and neonates.

The acoustic stapedial reflex (ASR) test is initiated by loud sounds and uses a 3- or 4-neuron brainstem circuit that involves the spiral ganglion, the CN, the SOC, and stapedial motor neurons within or near the facial nucleus. Activation of this circuit results in reflexive contraction of the stapedius muscle, which impedes transmission of vibrations along the ossicular chain. Contraction of the stapedius muscle is believed to protect the organ of Corti from damage and filter out background noise. The ASR is therefore a simple, noninvasive, and objective measure of auditory brainstem function.
The auditory brainstem response (ABR) test is used to assess functional integrity of the auditory pathway extending from the spiral ganglion to the medial geniculate. Normal ABR responses are present at birth and are unaffected by attention or anesthesia and therefore provide a simple, noninvasive measure of brainstem function. The ABR response, which is measured using electrodes that detect brainwave activity, normally includes 7 waves, numbered I through VII. These waves are believed to result from synchronous activity within the major auditory brainstem fiber tracts (Figure 1). Specifically, waves I and II are believed to result from activity in the auditory nerve, wave III is believed to correspond to activity in the CN and SOC, wave IV appears to arise from activity in the nuclei of the lateral lemniscus, wave V corresponds to activity in the inferior colliculus, and waves VI and VII appear to correlate with activity in the medial geniculate and related thalamocortical projections. Levels above or below normal in the latency and amplitude of ABR waves are associated with brainstem dysfunction.

In 1978, it was discovered that the human cochlea is capable of producing sound pressure waves and that these sounds could be recorded from the external ear. These sounds, termed otoacoustic emissions (OAEs), are produced by contraction of outer hair cells and require normal structure and function of the external ear, middle ear, and cochlea. Thus, OAEs serve as an additional simple, objective, and noninvasive measure of cochlear function.

Introduction to ASD

Autism spectrum disorder is a neurodevelopmental disorder characterized by difficulties in social, communicative, and behavioral domains. According to the most recent data, ASD affects 1 in 36 children and has a strong male predominance (5 males:1 female). Additionally, sensory sensitivity is a common feature of ASD and may involve somatic sensations (touch) and/or special senses (smell, taste, vision, and hearing). Indeed, abnormalities in auditory processing and perception are present to some degree in most, if not all, persons with ASD. Auditory dysfunction in persons with ASD may include deafness, hyperacusis, difficulty listening with background noise, and problems encoding speech sounds. Of particular importance is the observation that auditory dysfunction is often a cardinal indicator of ASD.

The concept that ASD might be a neurologic disorder is rooted in observations from the 1970s that persons with ASD had abnormal electroencephalogram recordings and increased incidence of seizures. Furthermore, it was proposed rather early in the history of ASD that this condition arises from lesions or dysfunction in brainstem centers. This suspicion was supported by an anatomical study that revealed dysmorphology in the cerebellum, though abnormalities were also identified in the forebrain. Additional support for hypoplasia in the cerebellum in persons with ASD was provided by Courchesne et al. Using magnetic resonance imaging to study the brainstem, Hashimoto et al. found significant hypoplasia of the brainstem and cerebellum in children with ASD. Since these early pioneering studies, many other researchers have revealed a wide range of pathological changes throughout the brain in persons with ASD.

The precise developmental changes that cause ASD are unclear. At present, the majority of ASD cases are idiopathic, but up to 20% of cases are comorbid with another neurodevelopmental disorder such as Angelman syndrome, Fragile X syndrome, tuberous sclerosis, genetic mutations/epigenetic factors, or chromosomal copy number variations, such as chromosome 15q duplication. Although only about 1% to 3% of ASD cases are associated with chromosome 15 abnormalities, duplications in the 15q region are the most common chromosomal duplications associated with ASD. Furthermore, maternal exposure to teratogenic drugs can increase ASD risk. Valproic acid (VPA) is a commonly prescribed antiepileptic drug, but it is used also in the management of bipolar disorder and migraine. Even though VPA is contraindicated during pregnancy, there is abundant evidence
that in utero VPA exposure significantly increases the risk of ASD.37,38 Notably, a diagnosis of ASD is 8 to 18 times higher in children exposed to VPA in utero compared with unexposed children37 and is 2.4 times more likely in males.38 However, the absolute risk of having a child with a diagnosis of ASD after in utero VPA exposure at therapeutic levels is less than 5%.38 Regardless, in utero VPA exposure is responsible for at least a small percentage of ASD cases.

The third tenet of osteopathic medicine states that structure and function are interrelated.39 An obvious correlate of this tenet is that neuronal dysmorphology will result in dysfunction. In the following sections, we summarize the literature on auditory brainstem dysmorphology and dysfunction in ASD and highlight findings on ASD obtained from the Auditory Research Center at the LECOM. Based on these findings, we propose how auditory dysfunction might be used to screen for ASD during the first postnatal week.

Auditory Dysmorphology in ASD

Several imaging studies24-26,40-42 have identified cerebellar and brainstem hypoplasia in persons with ASD. Furthermore, postmortem examination of brain tissue from persons with ASD has consistently revealed neuroanatomical changes involving the brainstem and cerebellum,23,43,44 including a loss of cerebellar Purkinje cells and hypoplasia of the facial nucleus and SOC. In the past decade, Wegiel et al.45,46 have found multifocal heterotopias and dysplasias in the forebrain and cerebellum and fewer Purkinje cells in the cerebellum. Together, these findings have been interpreted to suggest that in ASD, there are multiregional defects in neurogenesis, migration, and maturation of neurons.45,46

Adding to the mounting evidence for brainstem involvement in ASD was the work of Rodier et al.44 These researchers studied the brain of a 21-year-old woman with ASD and found marked hypoplasia of the facial nucleus and SOC, abnormal bundles of axons related to the hypoglossal nucleus, and marked shortening of the pons. With this and the aforementioned findings, we (researchers at LECOM, including R.L. and R.J.K.) proposed that the auditory difficulties in ASD were directly related to dysmorphology of auditory brainstem centers. Specifically, we hypothesized that hypoplasia, dysmorphic neurons, and abnormal cytoarchitecture were present in the SOC in persons with ASD. To investigate this hypothesis, 3 cohorts were examined that altogether included 19 participants without ASD in the control group (mean [SD] age, 16 [2.9] years) and 39 participants with ASD (mean [SD] age, 20 [2.3] years).57-40 The difference in ages was not statistically significant (t test, P=.29). We first examined neuronal morphology of the MSO in 6 participants with ASD (age 5-32 years) and 6 neurotypical controls (age 4-48 years; no difference in age, P=.79).47 In our study of more than 70 brains, the human MSO was composed of a thin column of 13,000 to 14,000 neurons (Figure 2A and Figure 2B).1,48,49 Persons with ASD were found to have fewer and smaller MSO neurons, and the majority of these neurons had round/oval soma (Figure 2B and Figure 2C). We also found that MSO neurons were abnormally oriented. We then examined a larger cohort of brainstems, from 9 participants with ASD (age 2-36 years) and 4 neurotypical control participants (age 4-32 years; no difference in age, P=.97).48 After examining all SOC nuclei, significantly smaller neurons were identified in 5 of the 6 constituent nuclei and dysmorphology in all 6. Furthermore, in persons with ASD, we found extracellular eosinophilic fibers, hypergliosis around the MSO, and, in 2 of the 9 participants (22%), clusters of ectopic neurons in the pons.

Later at LECOM, we were able to study an even larger cohort of 10 neurotypical control participants (age 3-32 years), 16 participants with ASD (age 5-56 years), and 12 participants with ASD and duplications in the 15q region (dup[15q]; age 5-39 years; no difference in age, P=.12).49 In all participants with ASD and ASD/dup(15q), there were significantly fewer neurons in the SOC. Again, the MSO was the most severely affected: In control participants, there were about 13,000 neurons, whereas in participants with ASD or ASD + dup(15q), there were only about 5400
neurons. In ASD and ASD + dup(15q) participants, there were significantly smaller neurons, over 40% of these neurons had round/oval morphology, and these neurons were abnormally oriented in the nucleus. The appearance of round neurons in the MSO is more common in younger persons (age <10 years). Therefore, we interpret such appearances of MSO neurons in adults as indicative of immature neuronal morphology. Additionally, we again identified ectopic clusters of neurons in the caudal pontine tegmentum. We believe such ectopic clusters represent, at least in part, displaced SOC neurons. Furthermore, this observation supports the hypothesis that brainstem dysmorphology in ASD arises from developmental causes involving abnormal neuronal migration.

Altogether, our studies were limited to brain tissue from 39 participants with ASD and 19 age-matched neurotypical controls. While we found dysmorphology in all 39 participants with ASD, a larger study is warranted in which persons can be subdivided and brains can be more extensively studied. There are obvious limitations to including such a wide range of ages in our analysis of brain tissue. Indeed, age-related changes in size and morphology of human MSO neurons are observed. Further analysis of these differences is beyond the scope of this review. Regardless, this difference does not diminish our major findings of drastic and consistently fewer neurons in the MSO and identification of periolivary ectopic neuronal clusters. In none of these studies have we been able to examine the structure of the cochlear nuclei or inferior colliculus. Our observations of severe dysmorphology and neuronal loss in the MSO in persons as young as 2 years also implicate an in utero mechanism. Likewise, the loss of cerebellar Purkinje cells but normal inferior olive also implicates some event/mechanism before 28 to 30 weeks of gestation. Based on our consistent observations of dysmorphology in the MSO, we propose that this nucleus be added to the claustrum and cerebellar Purkinje cells as a hallmark neuropathological marker of ASD.

We believe that our observations of the SOC from persons with ASD correlate well with reported functional deficits. It is important to note that not all persons with ASD are affected the same way; our anatomical studies provide evidence that not all persons with ASD have the same degree of dysmorphology. We attribute hyposensitivity to sound to result from fewer neurons in the SOC and perhaps the CN and inferior colliculus. These changes undoubtedly contribute to changes in the ABR and ASR, contribute to problems with vocalizations and localization of sound sources, and likely contribute extensively to dysfunction of the auditory forebrain. We, the authors of the present review, believe that hypersensitivity and difficulty listening with background noise likely results from specific loss of olivocochlear neurons.

Auditory Dysfunction in ASD

In Kanner’s original description, a common feature among the 11 children with autism was difficulty with language and hypersensitivity to loud noises. Additionally, observations by Ornitz and coworkers using evoked potentials raised suspicion for auditory problems in ASD. However, many of the earliest studies implicating difficulties in hearing and language in ASD were observational. These studies identified difficulties in processing language, problems focusing on multiple sounds or stimuli, and hyposensitivity or hypersensitivity depending on the stimulus modality. Collet et al found hyperacusis in children with ASD, and it was attributed to dysfunction in the medial olivocochlear system. Other investigators found conductive hearing loss and elevated thresholds (less sensitivity to sounds or needing sounds to be louder to hear them) or frank hearing loss. Koegel and Schreibman studied a child with ASD who was reported to be deaf to certain sounds but responded normally to other nonspeech sounds. The child responded normally to the sounds of a candy machine at a lower threshold than white noise stimuli. These observations suggested difficulty processing more complex auditory stimuli, which was considered a factor in poor speech development in ASD.
children with ASD often failed to orient when their name was called. Additionally, there is evidence that children with ASD have a preference for noise or nonverbal sounds over vocalizations or marked impairment for hearing speech even when normal hearing existed for environmental sounds (e.g., phone ringing, alarm).

A number of authors have compared thresholds using the ASR with some conflicting results: there are reports of normal middle ear reflexes in ASD and a report of hypersensitivity. We (LECOM researchers, including R.L. and R.J.K.) performed a detailed quantitative study of the ASR in a group of 29 control participants (ages 7-17 years) and 54 participants with ASD (ages 4-23 years) who were verbal and cooperative with the examiner. We found that children with ASD had significantly lower thresholds and significantly longer latency responses. Longer latencies were most prominently observed for ipsilateral-driven responses to a 1-kHz stimulus. In all control participants, ipsilateral responses always occurred at shorter latency compared with contralateral responses. In participants with ASD, we observed a marked asymmetry in ASR responses. Specifically, when we stimulated the left ear, ipsilateral responses occurred at a significantly longer latency than the contralateral responses. Finally, in our study of the ASR, 97% of participants with ASD had at least 1 response outside the 95% CI of control responses.

Some researchers have used OAEs to study auditory function in participants with ASD. Participants with ASD exhibited abnormal responses, marked asymmetry, and hypersensitivity. In a 2017 study of young males with ASD, there were significantly reduced responses in the 1-kHz range. In a study that same year of transiently evoked OAE, there were significantly elevated responses from study participants with ASD. We interpret such findings to support auditory dysfunction in ASD and to also highlight the range of dysfunction in the disorder.

The ABR has been used by a number of authors to study function of the auditory brainstem in ASD. Some of the earliest ABR studies provided evidence of brainstem dysfunction in ASD. While there are some conflicting results in the study of ABR in ASD, many studies over the past 40 years provide evidence that persons with ASD have smaller amplitudes in waves I, II, III, IV, and V and longer latencies/slower responses. Using a forward masking paradigm, Källstrand et al. found reduced amplitude of wave III. With ABR, the amplitude can be decreased when the contralateral ear is presented a noise stimulus. Khalfa et al. found that in persons with ASD, there was a larger suppression in the right ear compared with the left ear. In a recent prospective study of ABRs in young children (birth to age 3 months), children later diagnosed as having ASD had significantly longer wave V and I-V interpeak latencies. Furthermore, they noticed prolonged III-V latencies when stimulating the right ear only. In their analysis of wave V, they reported a positive predictive validity of 78% and a negative predictive validity of 73%. A major finding of this prospective study was that the majority of children who later received a diagnosis of ASD had abnormal ABRs in the first 3 months, despite having clinically normal hearing thresholds.

Beyond differences in ASR, OAE, and ABRs, there is abundant evidence for additional problems in auditory processing in ASD. Persons with ASD have difficulties in temporal processing, difficulties listening in the presence of background noise, and problems with sound localization tasks. Finally, it should be noted that there are a number of reports of dysfunction in the auditory forebrain, though a review of this portion of the literature is beyond the scope of this review. It is unclear whether these forebrain issues are inherited from brainstem centers or if the auditory forebrain is an additional primary site of injury in ASD. Regardless, it seems very likely that the problems children with ASD have with language can be attributed, at least in part, to dysfunction in the auditory brainstem.

Recommendation and Conclusion
The literature provides an abundance of data supporting both abnormal structure and function in the
auditory brainstem in persons with ASD. Furthermore, there is evidence from a number of functional studies for asymmetries in brainstem processing of sound in ASD. Both functional and anatomical investigations indicate that auditory issues are present at birth. Current screening for ASD typically fails to identify ASD until social or verbal abnormalities are present. As we stated previously\(^6\) (in accordance with other researchers), we believe that future research should be focused on noninvasive, objective testing of auditory function to screen for ASD. At the very least, auditory function could be used to raise suspicion of ASD or identify children at high risk of ASD manifesting later in life. The goal of early detection and diagnosis is early intervention to improve the quality of life of persons with ASD. Early intervention for children with ASD focusing on eye contact, gesturing, and vocalizations can substantially improve the child with ASD focusing on eye contact, gesturing, and vocalizations can substantially improve the child’s language and social interactions.\(^9\) There is also evidence that auditory integration training normalizes brainstem responses in children with ASD and even improves behaviors.\(^12\) Additional research in these areas will result in better integration and outcomes for children with ASD.

Acknowledgments

We thank the Lake Erie Consortium for Osteopathic Medical Training, the Deafness Research Foundation, and Autism BrainNet for providing financial support of the LECOM studies discussed in this review. We also thank the Barber National Institute for assistance in our study of the stapedial reflex. We are forever grateful to the families of the tissue donors, who have made these studies possible.

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