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Receptive Language Organization in High-Functioning Autism

Richard E. Frye, MD, PhD, and Michael S. Beauchamp, PhD

One of the core defining components of autism is impairment in communication, typically manifested as a delay in speech development. To date, neuroimaging studies have shed limited light on the mechanisms behind delay in speech development in autism. We performed magnetoencephalographic-based auditory language mapping in 2 cases of high-functioning autism. Overall, 2 distinct characteristics were found, such as the use of atypical language pathways and cortical

hyperexcitability. These neurophysiological findings parallel those reported in 2 other developmental disorders, developmental dyslexia and Rett syndrome. We discuss common mechanisms that may account for cognitive delays across these developmental disorders.

Keywords: autism; language reorganization; magnetoencephalography

The neurobiological mechanisms underlying autism remain largely unknown. Although preventing or curing autism is the ultimate goal, such a possibility does not appear to be within our grasp at this time. Thus, optimizing cognitive functioning may be a more pragmatic, but important, goal. To design optimal cognitive rehabilitation treatments, the organization of neural networks as well as the dynamic changes in the structure of these neural networks with cognitive development and remediation needs to be better understood. Because language is such an important aspect of human development, much interest is focused on remediating the language deficits found in autism.

Neuroimaging has provided some insight into the organization of the cognitive language processing network in individuals with autism. Functional magnetic resonance

imaging (MRI) and magnetoencephalography studies suggest that the brain may not process language in the same way in typically developing individuals and individuals with autism. During language tasks, functional MRI activation is abnormally decreased or increased in typical language areas and increased in atypical cortical areas in individuals with autism as compared with typically developing individuals.¹⁻⁵

Magnetoencephalography has advantages over functional MRI. Because it directly measures the magnetic fields emitted by active synapses, instead of the indirect blood-oxygen signal measured with functional MRI, it allows the millisecond-by-millisecond temporal evolution of cortical activation pattern to be studied. This may be important because the timing of cortical activation is different in individuals with developmental cognitive disorders as compared with typically developing individuals. Second, the morphology and neurophysiological characteristics of the evoked magnetic field can be examined.

Previous magnetoencephalography studies have shown that the auditory evoked field follows an opposite pattern of hemispheric dominance maturation in individuals with autism as compared with typically developing individuals. Although both typically developing individuals and individuals with autism demonstrated reduced lateralization to syllable stimuli in childhood, as age increases cortical activation has been shown to become left lateralized in typically developing individuals and right lateralized in individuals with autism.⁶ This suggests that individuals with autism eventually overuse the right hemisphere to process language, but that this language dominance does not develop until adolescence. Interestingly, evoked potential studies demonstrate similar findings for older children with Asperger syndrome.⁷

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Table 1. N1m Component Characteristics for a Typically Developing Adolescent and 2 Individuals With High-functioning Autism

	Left Hemisphere		Right Hemisphere	
	Amplitude (fT)	Peak Latency (ms)	Amplitude (fT)	Peak Latency (ms)
Participant A	-112	135	122	130
Participant B	-512	234	380	266
Control	-45	114	79	110

None of the magnetoencephalography studies that have examined individuals with autism have used functional mapping to examine the spatiotemporal dynamics of cortical activation during language tasks. We provide 2 examples of the spatiotemporal dynamics of cortical activation during simple auditory receptive language tasks in an older child and an adolescent with high-functioning autism. Our results suggest that children with autism may demonstrate patterns of cortical reorganization similar to those identified in developmental dyslexia,^{8,9} and cortical hyperexcitability, not unlike the neurophysiological characteristics described in Rett syndrome.¹⁰

Methods

Participant A

Participant A was a 16-year-old male with an unremarkable medical history and family history significant for a brother of learning disabilities. He experienced language and social regression with development of stereotypic behavior at 18 months of age. Elements of his childhood developmental history were diagnostic of autistic disorder.¹¹ Intensive speech therapy resulted in slow, but gradual, improvement in speech. He continues to have poor social skills, obsessive and repetitive behaviors, sensory adversities, and cognitive perseveration. He was diagnosed with attention deficit disorder at 8 years of age, but stimulants were ineffective. Electroencephalogram and sleep study were normal. At 14 years of age, he was reevaluated and received the diagnoses of Learning Disorder, Not Otherwise Specified and Pervasive Developmental Disorder, Not Otherwise Specified. His full scale intelligence quotient, as determined by the Wechsler Intelligence Scale for Children, 4th edition, was 84 and considered in the low average range. On examination, he demonstrated reduced initiation and maintenance of eye contact and social interactions, mild to moderate psychomotor delay, and flat monotone dysfluent speech. At times, he smiled, laughed, and giggled spontaneously but inappropriately.

Participant B

Participant B was an 8-year-old boy with marked speech and social delay. Elements of his childhood developmental history were diagnostic of autistic disorder.¹¹ A generalized seizure disorder was diagnosed at approximately 1 year of age and was controlled by valproic acid. He had particular difficulties with reading and following auditory directions, and is described as a visual learner. He had perseverative interests and did not understand peer-to-peer relationships. Electroencephalogram demonstrated

intermittent focal slowing and intermittent sharp waves over the right posterior quadrant. On examination, he demonstrated speech that was poorly modulated in rate and volume, and he used repetitive stereotypic phrases. He had good eye contact but decreased reciprocity. Prior to the magnetoencephalography scan, the participant completed the Comprehensive Test of Nonverbal Intelligence that revealed a score of 85, which is 1 standard deviation below average and is considered in the low average range.

Magnetoencephalography Procedures

After description of the study to the participant and parent, written informed consent was obtained in accordance with our institutional review board regulations for the protection of human participants. A whole-head 248-channel axial gradiometer system (MAGNES 3600 WH, 4-D Neuroimaging, San Diego, California) was used for magnetoencephalography recording in both cases. Standard procedures for participant preparation and stimulus delivery were used.¹² Participant A performed the continuous recognition memory task twice.¹² This task required the participant to indicate whether any of the 135 sequentially presented aural words matched words on a pretest list. Participant B performed 2 auditory word rhyme tasks. In each task, the participant heard 64 sequentially presented word pairs and indicated if the pairs rhymed. Equivalent results were found for both runs for both participants. Auditory evoked field waveforms¹³ and the significant functional mapped current estimates¹⁴ are presented. An example of an auditory evoked field from a typically developing adolescent is provided for comparison to our participants.

Results

Participant A

Although the early N1m component is within reasonable limits (Table 1), the late components are abnormal. Instead of a normal N400m that is typically characterized by a slowly increasing field with a peak between 400 and 500 ms, a very sharp peak occurred at 350 ms and 358 ms in the left and right hemispheres, respectively. In addition, a third prominent peak occurred at 544 ms in the right hemisphere (Figure 1A). Functional localization demonstrated bilateral activation of the superior temporal gyrus near the auditory cortices and the right, but not the left, inferior frontal gyrus. The current estimate waveforms from the right superior temporal gyrus clearly demonstrated peculiar recurrent activation (Figure 2A).

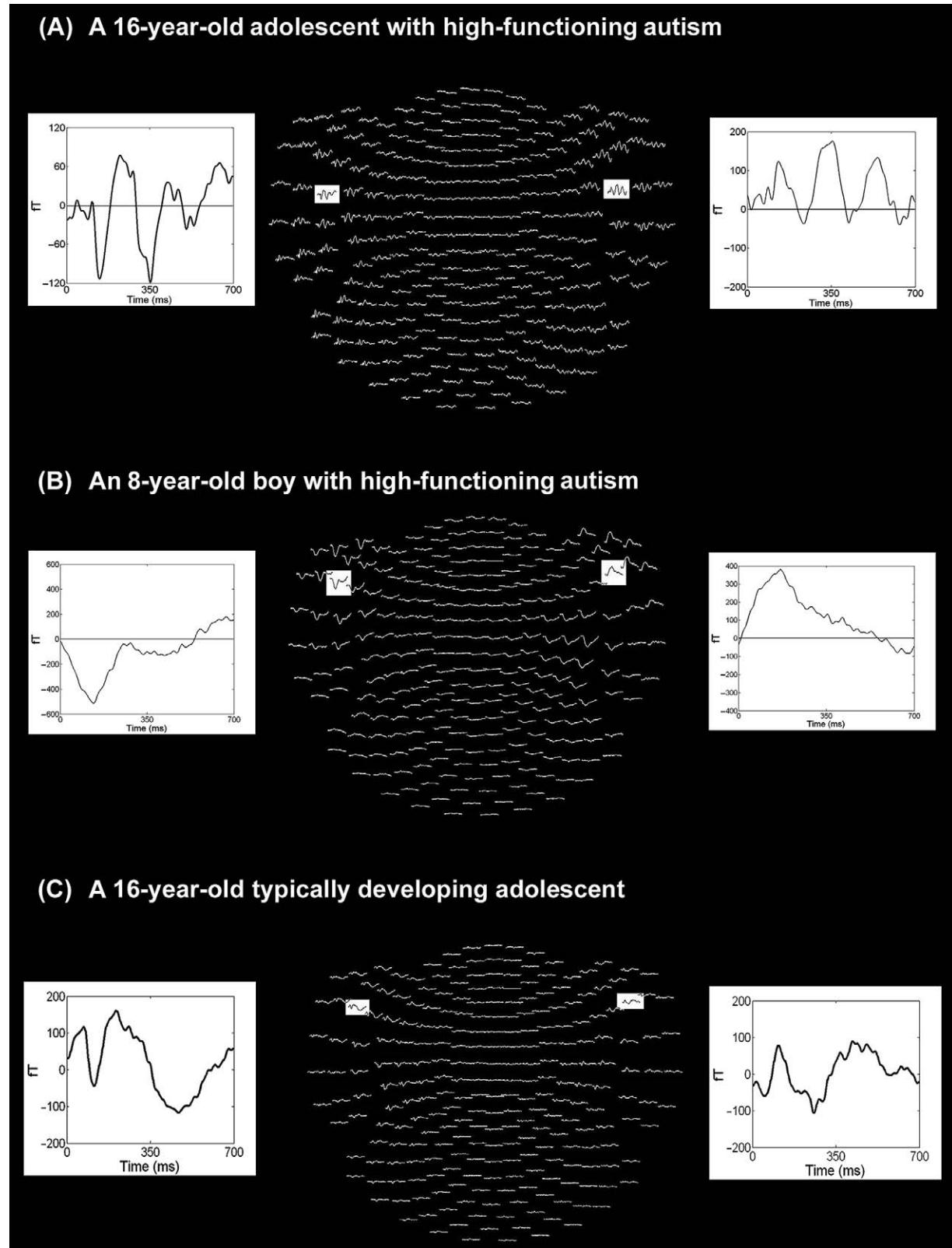


Figure 1. Auditory evoked fields for 2 individuals with high-functioning autism (A, B) and a normal participant (C). Representative waveforms are selected from the left and right hemisphere for each participant. Amplitude scales are adjusted to provide an optimal view of the waveform. A, The auditory evoked field waveform is clearly abnormal in its morphology, having sharply peaked late components and multiple late components in the right hemisphere. B, A clearly abnormally high-amplitude (3-4× normal) early component (N1m) is seen in both hemispheres. C, Normal auditory evoked field waveform morphology with both an early and late component.

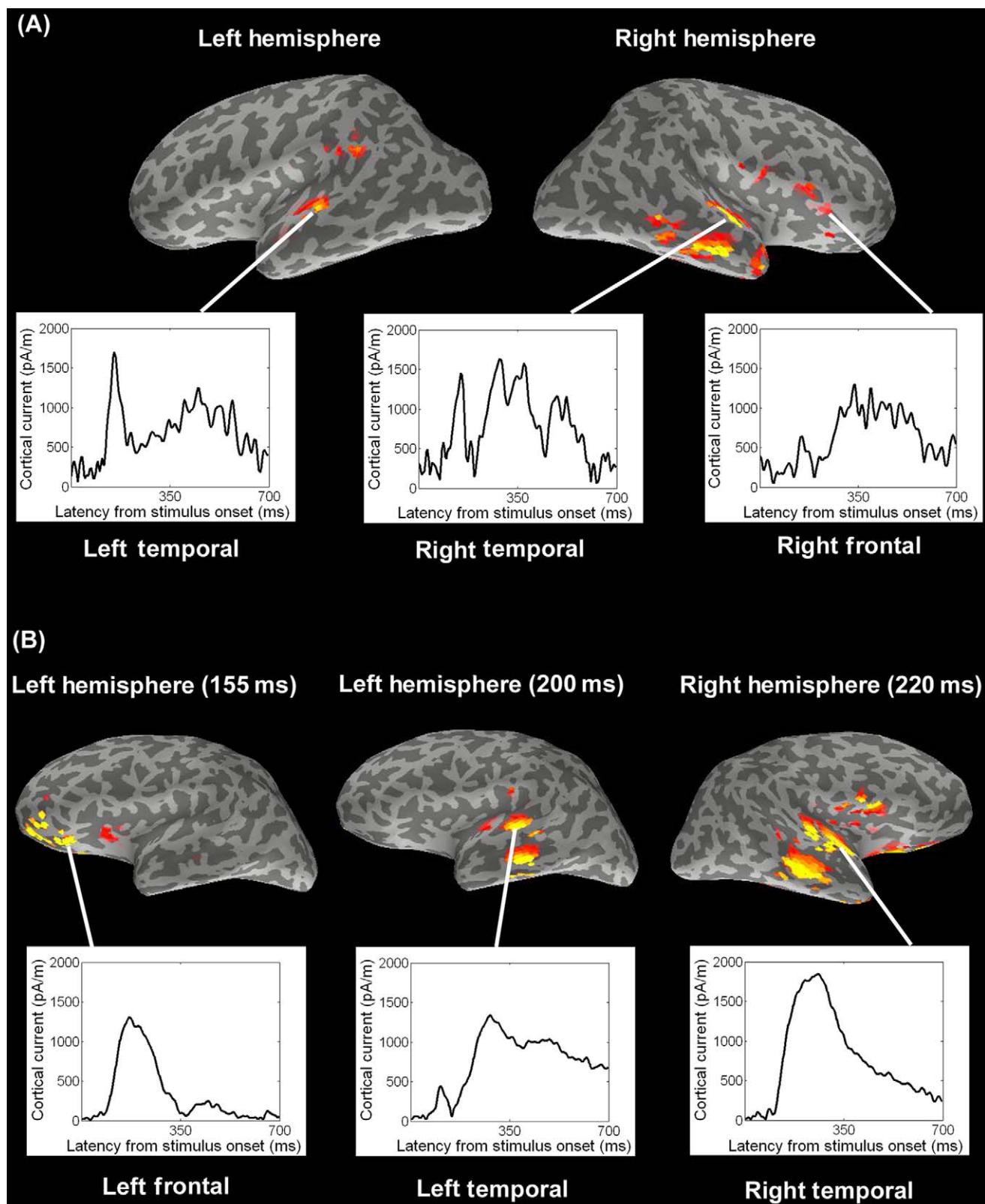


Figure 2. Functional localization of auditory evoked fields for (A) 16-year-old and (B) 8-year-old boys with high-functioning autism. A, Cortical activation lateralizes to the right hemisphere as latency from stimulus onset increases. Recurrent activation of the right temporal cortex occurs at least several times as demonstrated by unusual high-amplitude late waveform components. Activation of the right inferior frontal cortex also occurs late. B, A large amplitude delayed N1m occurs but with the initial activation occurring in the frontal lobe rather than the temporal lobe. Activation in the superior temporal cortex in the vicinity of the auditory cortex does occur, but after frontal activation.

This pattern of activation suggests overuse of right hemisphere language pathways.

Participant B

The auditory evoked field demonstrated a very high-amplitude N1m peak in the left and right hemispheres (Table 1; Figure 1B) with no discernible late component. Functional localization demonstrated significant activation of the left superior temporal gyrus and inferior frontal gyrus. Current estimates from these areas demonstrated earlier activation in the left inferior frontal gyrus (~155 ms) with later activation of the left (~200 ms) and right (~220 ms) superior temporal gyrus—a reverse of the typical pattern of activation (Figure 2B).

Discussion

This report outlines 2 cases of autism with 2 neurophysiological abnormalities in common. First, the auditory evoked field waveforms demonstrated clearly abnormal morphology. Second, functional localization demonstrated cortical reorganization of the language system in both cases. Despite these commonalities, these cases also demonstrate the heterogeneity in cortical responses to auditory language stimuli in autism.

The Significance of Cortical Reorganization

The abnormal functional localization demonstrated in these 2 cases of autism may be significant in 2 ways. First, the functional patterns described above are not unlike patterns seen in developmental dyslexia, in 2 ways. Neuroimaging studies have suggested that young adults with compensated developmental dyslexia overuse right temporoparietal and inferior frontal gyrus areas during reading tasks to compensate for weak left hemisphere language areas.⁸ Likewise, individuals with autism could also be overusing right hemisphere areas. This would be consistent with the pattern of activation demonstrated in participant A and previous neurophysiological studies.^{6,7}

Children with developmental dyslexia demonstrate a different abnormal pattern of cortical activation as compared with young adults with compensated developmental dyslexia. Magnetoencephalography studies have shown that children with developmental dyslexia demonstrate a reverse sequence of left hemisphere activation with the left inferior frontal gyrus activating prior to left temporo-parietal.⁹ This is similar to Participant B who demonstrated a reverse in the typical sequence of superior temporal gyrus and inferior frontal gyrus activation. Thus, these 2 developmental disorders, developmental dyslexia and autism, may share common patterns of cortical reorganization. Studying this overlap in reorganization may

help us better understand neurodevelopmental disorders and how to apply research knowledge and treatments from other neurodevelopmental disorders to autism.

Second, abnormal cortical localization of language has implications for the developmental of multisensory integration and speech prosody—areas in which individuals with autism have difficulties. The posterior superior temporal gyrus, a brain area involved in verbal language processing, appears to be critical for multisensory integration.¹⁵ Thus, posterior superior temporal gyrus abnormalities may affect the development of language and multisensory integration. Second, speech prosody is typically processed by the right superior temporal gyrus and inferior frontal gyrus.¹⁶ If these areas are compensating for dysfunctional left hemisphere language areas, they may be unable to process speech prosody simultaneously, leading to speech that is poorly modulated in volume, inflection and emotional content.

The Significance of Cortical Hyperexcitability

The auditory evoked fields in the cases above demonstrate indications of cortical hyperexcitability. For example, Participant A demonstrated multiple late components and Participant B demonstrated high-amplitude early waveforms. Several lines of evidence support the idea of cortical hyperexcitability in autism, including an abnormally high number of excitatory pyramidal cells and underconnectivity in long-distance frontoposterior reciprocal pathways.¹⁷ Rett syndrome is characterized by autistic behavior and cortical hyperexcitability.¹⁰ Animal models of Rett syndrome demonstrate decreased cortical inhibitory¹⁸ and reduced long-term potentiation and depression.¹⁹ The auditory evoked fields in this report support the notion that cortical hyperexcitability could be a factor that links the deficits in cognitive development in the various forms of autism.

Implications for the Study of Autism

This report confirms and clarifies previous neurophysiological findings in autism and outlines parallels between autism and other developmental disorders. Uncovering these parallels may help us understand the neurological basis of autism. Such information will no doubt be of great benefit in furthering diagnosis and treatment of this devastating disease.

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