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Atypical hemispheric asymmetry in the arcuate fasciculus of completely nonverbal children with autism

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Despite the fact that as many as 25% of the children diagnosed with autism spectrum disorders are nonverbal, surprisingly little research has been conducted on this population. In particular, the mechanisms that underlie their absence of speech remain unknown. Using diffusion tensor imaging, we compared the structure of a language-related white matter tract (the arcuate fasciculus, AF) in five completely nonverbal children with autism to that of typically developing children. We found that, as a group, the nonverbal children did not show the expected left–right AF asymmetry—rather, four of the five nonverbal children actually showed the reversed pattern. It is possible that this unusual pattern of asymmetry may underlie some of the severe language deficits commonly found in autism, particularly in children whose speech fails to develop. Furthermore, novel interventions (such as auditory-motor mapping training) designed to engage brain regions that are connected via the AF may have important clinical potential for facilitating expressive language in nonverbal children with autism.

Keywords: autism; nonverbal; language; arcuate fasciculus; asymmetry; auditory-motor mapping training

Introduction

Autism spectrum disorder (ASD) is a developmental condition that affects one in 110 children. One of the core diagnostic features of ASD relates to impairments in language and communication. It has been estimated that up to 25% of the individuals with ASD lack the ability to communicate with others using speech sounds, and many of them have limited vocabulary in any modality, including sign language.[1,2] Severe deficits in communication not only diminish the quality of life for affected individuals, but also present a lifelong challenge for their families.

The ability to communicate verbally is considered to be a positive prognostic indicator for children with ASD.[3] Unfortunately, few techniques are available that can reliably produce improvements in speech output in nonverbal children with ASD.[4] Recently, our laboratory has developed a novel intonation-based intervention, auditory-motor mapping training (AMMT), which aims to facilitate speech output and vocal production in nonverbal children with ASD.[5,6] One of the unique features of this intervention is that it promotes speech production directly. The acquisition of basic vocal output will allow these children to eventually participate in speech therapy that focuses on verbal expression as a primary means of communication.

In addition to the behavioral data collected as part of the ongoing treatment study, we have also acquired neuroimaging data in a subset of our nonverbal participants to identify potentially atypical language-related characteristics in this understudied population. Previous neuroimaging studies have shown that high-functioning verbal individuals with autism typically have larger brains, more gray matter, and possibly more local connections, but fewer long-range connections than typically developing controls.[7,8] Interestingly, a reversal of the usual left–right asymmetry (found in typically developing individuals) is present in the inferior frontal gyrus, with larger volumes in the right

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hemisphere of individuals with autism.[9,10] In contrast, a smaller right volume in autism has also been reported.[11] Some studies have shown smaller volumes of the left planum temporale,[12,13] whereas other studies have reported a reduction in volume in both hemispheres.[14] A recent report suggested a general loss of typical lateralization in tracts that interact with the fusiform gyrus.[15] Furthermore, functional imaging studies of high-functioning verbal individuals with autism have shown relatively normal temporal lobe activation, but reduced inferior frontal activation during semantic language tasks.[16] However, no studies to date have examined the brains of nonverbal children with ASD.

Here, we report preliminary data from our neuroimaging study on completely nonverbal children with autism. We investigated possible differences in a language-related white matter tract, the arcuate fasciculus (AF), using diffusion tensor imaging (DTI) and comparing their results to those of age-matched, typically developing children. Specifically, the AF is a language-related tract that connects brain regions involved in feedforward and feedback control of vocal output, and the mapping of sounds to articulatory motor actions.[17–21] Because of its role in speech production, we investigated structural differences in the AF of nonverbal children with autism with those of typically developing children.

Method

Participants

A total of 10 children underwent MRI scanning. There were five completely nonverbal children with ASD and five typically developing children (see Table 1 for participant characteristics). For the nonverbal children, the diagnosis of autism was made by pediatric neurologists and neuropsychologists prior to enrollment. We confirmed the participants' diagnoses using the childhood autism rating scale (CARS). "Nonverbal" was defined as having the complete absence of intelligible words. All participants had previously received speech therapy for at least 18 months and demonstrated minimal progress in speech acquisition (i.e., no intelligible words) based on speech-language pathologist and parent reports. Their minimal speech production was also confirmed by our intake assessment, based on clinical observations, and results from a phonetic inventory and the expressive vocabulary test.[22] The typically developing children were recruited as part of the laboratory's longitudinal study on children,[23] and all of them were classified as nonmusicians at the time of the scan. The study was approved by the Institutional Review Board of Beth Israel Deaconess Medical Center. The parents of all children gave written informed consent prior to their participation, and all procedures were conducted according to the approved protocol.

Image acquisition

All participants underwent scanning using a 3-tesla General Electric (Fairfield, CT) scanner, which included T1-weighted, gradient-echo anatomical images (resolution: $0.93 \times 0.93 \times 1.5$ mm3), and diffusion tensor images. Diffusion-weighted images were acquired using single-shot, spin-echo, echo-planar imaging sequence (TE = 86.9 ms, TR = 10,000 ms, FOV = 240 mm, matrix size = 128×128 voxels, slice thickness = 5 mm (resolution: $1.87 \times 1.87 \times 5.0$ mm^3), no skip, NEX = 1, axial acquisition, 25 noncollinear directions with b-value = 1000 s/mm^2, 1 image with b-value = 0 s/mm^2).

Preprocessing of DTI data

The diffusion data were preprocessed using FSL version 4.1.4 (www.fmrib.ox.ac.uk/fsl). Using FSL's FMRIB diffusion toolbox (FDT), we first corrected the diffusion data for eddy current and head motion artifacts by affine multiscale two-dimensional registration. We then fitted a diffusion tensor model at each voxel, which yielded lambda values for each principal eigenvector and fractional anisotropy.

Table 1. Participant characteristics

	Nonverbal ASD ($n = 5$)			Typically developing ($n = 5$)			Comparison
	Mean	SD	Range	Mean	SD	Range	P-value
Age (years)	6.7	1.2	5.8–8.8	7.0	0.9	6.2–8.5	0.175
Gender	3 males, 2 females			3 males, 2 females			

Fiber tracking parameters were estimated using a probabilistic tractography method based on a multifiber model, and applied using tractography routines implemented in FSL's FDT toolkit (5,000 streamline samples, 0.5-mm step lengths, curvature threshold of 0.2, and modeling 2 fibers per voxel to take into account crossing fibers).[24,25]

Tractography of the arcuate fasciculus.

A single rater drew the regions of interest (ROI) of the arcuate fasciculus—a curved fiber bundle that connects the posterior portion of the temporal lobe and the temporo-parietal junction with the inferior frontal lobe[26]—on both hemispheres in diffusion space. This rater was blind to whether participants were typically developing or had autism. The seed ROI was drawn in the white matter underlying the pars opercularis of the posterior inferior frontal gyrus on a sagittal slice of the FA map. Two waypoint ROIs were drawn: one on a coronal slice in the sensory-motor region covering the superior longitudinal fasciculus and another on a sagittal slice in the white matter underlying the posterior middle temporal gyrus. Exclusion masks were drawn axially in the external capsule, coronally in the region posterior to the temporal gyrus, and sagittally in the region medial to the fiber bundle in order to exclude fiber projections that were not part of the AF. The volume of each anatomical ROI was constrained such that a similar size ROI was used across the two hemispheres to minimize potential bias ($P > 0.9$).

Results

Fiber tracking reliably identified the arcuate fasciculus on both the left and right hemispheres of all 10 children. Figure 1 shows the average volumes of the left and right AF for the two groups of children. For each child, we calculated a laterality index (LI) = (left AF volume – right AF volume)/(left AF volume + right AF volume), where indices greater than zero indicate leftward asymmetry, and indices less than zero indicate rightward asymmetry. Consistent with the literature on the AF,[27] the typically developing children in our sample exhibited the usual leftward asymmetry (median LI = 0.166, range = 0.013 to 0.586). The nonverbal children, however, did not show the usual leftward pattern of asymmetry (median LI = –0.168, range = –0.940 to 0.120). To confirm that the two groups showed different patterns of laterality, a nonparameteric Mann–Whitney test was conducted, which revealed significant distributions of the two groups ($P = 0.016$). As illustrated in Figure 2, all five typically developing children showed greater AF tract volume in the left hemisphere compared to the right hemisphere, whereas four of the five nonverbal children with autism showed the reversed pattern of asymmetry (larger right than left AF volumes).

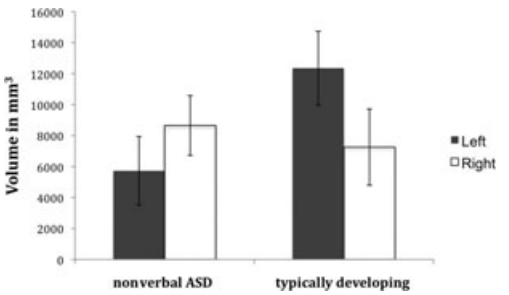

Figure 1. Total average volumes of the left and right AF of the nonverbal children with ASD and the typically developing children.

Discussion

In this study, we sought to examine potential structural brain abnormalities in completely nonverbal children with autism. Using DTI, we found that the arcuate fasciculus, a major language-related white-matter pathway in the brain, showed an overall hemispheric asymmetry reversal in a group of completely nonverbal children with autism compared to typically developing children. This abnormal structure of the AF may underlie some of the severe language deficits in autism, particularly in children who never develop speech.

Results from the present study converge with some of the previous imaging studies on high-functioning verbal individuals with autism. Using structural MRI, a reversal of the usual left–right asymmetry has been observed in the right inferior frontal gyrus of high-functioning individuals with autism, although smaller right frontal volumes in autism have also been reported. Similarly, smaller volumes of the left planum temporale have been observed, but other research has reported a reduction in both hemispheres.[13,28] The inconsistent findings reported by these structural imaging studies may be attributable, in part, to the heterogeneity in linguistic abilities among individuals included in these studies. Indeed, individuals with Asperger's

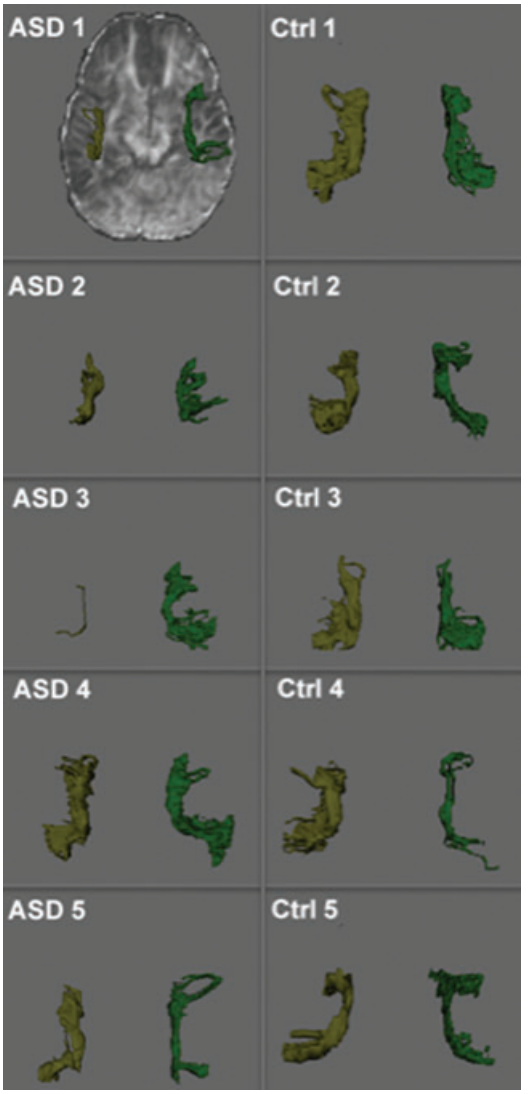

Figure 2. **Images showing the left (yellow) and right (green) AF of all 10 children (left panel = nonverbal ASD; right panel = typically developing controls). For display purposes, only the tracts of one child are superimposed onto their own FA image.**

syndrome (who have no language delay) have been found to have less gray matter than individuals with autism (who have atypical language development).[29] Thus, this finding highlights the importance of assessing language skills as a differentiating variable.

Two recent studies have also investigated the role of the arcuate fasciculus in autism. However, one study scanned a more heterogeneous group of children, including those who were not only verbal but also carried the diagnosis of Asperger's syndrome,[30] while another study scanned only verbal high-functioning adolescents.[31] Relative to controls, individuals on the autism spectrum were found to have longer fibers in the right arcuate fasciculus[30] and less lateralized fractional anisotropy,[31] but no differences in volume were observed. Our study extends these previous findings in two important ways. First, we recruited a relatively homogenous group of individuals who were completely nonverbal. Second, we used a probabilistic (rather than a deterministic) algorithm, which is less susceptible to regional measurement artifacts and problems concerning crossing fibers.[24] Probabilistic tractography approaches have been shown to produce better results in areas of crossing fibers, with superior reconstruction of fibers at borders of anatomical structures, and significantly more sensitive than deterministic approaches.[32]

The AF is a major white-matter tract involved in language and speech processing, and thus, may also be associated with the integration of auditory and motor functions. Because it runs through the premotor and motor cortex, it has been implicated in the mapping of sounds to articulatory actions, the coordination and planning of motor actions for speech production, as well as the monitoring of speech production and language learning.[19,33] Based on observations made in our laboratory, many nonverbal children with autism have speech–motor planning difficulties, and their deficits could be explained, in part, by the abnormal asymmetry of the AF found in the present study. More importantly, because AMMT is an intervention that trains the association between sounds and articulatory actions through rhythmic bilateral motor activities and repetitions of intoned words,[5] its potential in facilitating speech output in nonverbal children with autism may lie in its ability to engage a network of brain regions (e.g., the AF) that may be dysfunctional in autism.[34,35]

In the present study, a relatively short DTI sequence (less than 5 min) was used to minimize movement artifacts in our group of nonverbal children with autism. The resulting voxels from this sequence were nonisotropic, which means that partial volume effects and angular resolution could vary along different axes, thus limiting the degree to which comparisons can be made between tracts

that are oriented along these different axes. Despite this limitation, however, our data revealed significant volume differences across the two hemispheres between nonverbal children with autism and typically developing children, while any systematic errors associated with our DTI sequence should be evident across all individuals.

This is a preliminary study that examined structural abnormalities in the arcuate fasciculus specifically in completely nonverbal children with autism. Future studies on this understudied population could test a larger sample of children; use higher resolution and isotropic scanning parameters if possible, considering that these children may not be sedated during scanning sessions; and examine the structure of other language-related tracts, such as the uncinate fasciculus and the extreme capsule fiber tract. Finally, it would be interesting to examine whether the atypical asymmetry observed in the nonverbal children is also present in other family members. Identifying brain abnormalities in these children will help with the development and refinement of effective treatment programs.

Acknowledgments

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Conflicts of interest

The authors declare no conflicts of interest.

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