Structural Neural Phenotype of Autism: Preliminary Evidence from a Diffusion Tensor Imaging Study Using Tract-Based Spatial Statistics

ORIGINAL RESEARCH

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BACKGROUND AND PURPOSE: There is mounting evidence suggesting widespread aberrations in neural connectivity as the underlying neurobiology of autism. Using DTI to assess white matter abnormalities, this study implemented a voxelwise analysis and tract-labeling strategy to test for a structural neural phenotype in autism.

MATERIALS AND METHODS: Subjects included 15 boys with autism and 8 controls, group-matched on age, cognitive functioning, sex, and handedness. DTI data were obtained by using a 3T scanner. FSL, including TBSS, was used to process and analyze DTI data where FA was chosen as the primary measure of fiber tract integrity. Affected voxels were labeled by using an integrated white matter tractography atlas. Post hoc correlation analyses were performed between FA of each affected fiber tract and scores on the Social Responsiveness Scale.

RESULTS: The autism group exhibited bilateral reductions in FA involving numerous association, commissural, and projection tracts, with the most severely affected being the forceps minor. The most affected association tracts were the inferior fronto-occipital fasciculus and superior longitudinal fasciculus. There were no areas of increased FA in the autism group. All post hoc correlation analyses became nonsignificant after controlling for multiple comparisons.

CONCLUSIONS: This study provides preliminary evidence of reduced FA along many long-range fiber tracts in autism, suggesting aberrant long-range corticocortical connectivity. Although the spatial distribution of these findings suggests widespread abnormalities, there are major differences in the degree to which different tracts are affected, suggesting a more specific neural phenotype in autism.

ABBREVIATIONS: AMY = amygdala; ASD = autism spectrum disorders; ATR = anterior thalamic radiation; BCC = body of corpus callosum; CNG = cingulum; CST = corticospinal tract; DAS = Differential Abilities Scale; DTI = diffusion tensor imaging; FA = fractional anisotropy; FDT = FMRIB Diffusion Toolbox; FFA = fusiform face area; FMAJ = forceps major; FMIN = forceps minor; fMRI = functional MR imaging; FMRIB = Oxford Centre for Functional Magnetic Resonance Imaging of the Brain; FSL = FMRIB Software Library; GRAPPA = generalized autocalibrating partially parallel acquisition; IFOF = inferior fronto-occipital fasciculus; ILF = inferior longitudinal fasciculus; JHU = Johns Hopkins University; MNI = Montreal Neurologic Institute; SLF = superior longitudinal fasciculus; SRS = Social Responsiveness Scale; SSC = somatosensory cortex; STS = superior temporal sulcus; TBSS = Tract-Based Spatial Statistics; TDC = typically developing control; TPJ = temporal parietal junction; UNF = uncinate fasciculus; VMPC = ventromedial prefrontal cortex

Advances in anatomic and functional imaging techniques studying brain-behavior relationships and the application of these technologies to the study of ASD have resulted in substantial evidence correlating both core and secondary symptoms to abnormalities in brain connectivity.[1-3] Over the past decade, there has been mounting evidence from structural MR imaging, fMRI, and DTI suggesting that the brain phenotype in ASD includes deficiencies of long-range connections such as association and commissural fibers connecting different lobes and hemispheres, respectively. However, the neuroimaging literature remains inconsistent, possibly owing to diagnostic heterogeneity, intersubject variability across sites, scanning protocols, and image processing and analysis methods. Because of the disjointed nature of the current body of evidence, the identification of an autism-specific neural phenotype remains elusive despite a rapidly growing body of research literature.

Since the widespread use of MR imaging in psychiatric re-

search, many studies examining the neurobiology of autism have been published. Early volumetric MR imaging studies first established the existence of larger brains in ASD,[4] and later research attributed this to increased white matter,[5] the substance of neural fiber tracts. Later work, again using volumetric MR imaging techniques, suggested a pattern of short-range overconnectivity[6] and long-range underconnectivity.[7] With the application of fMRI in autism-related research came many studies using this technique to demonstrate a pattern of activation consistent with impairments in long-range connectivity.[8-11] Finally, there are now many DTI studies that have consistently demonstrated abnormalities in FA in the brains of ASD participants.[12-17] Because FA is a widely accepted measure of the structural integrity of white matter,[18] these studies have collectively demonstrated a pattern of findings consistent with neural disconnectivity in ASD. However, given the significant heterogeneity in methodologies and participants in these studies, it is difficult to identify a common underlying pattern of neuropathology across all studies. Greater confidence in the disconnectivity hypothesis could be gained if an autism-specific neural phenotype was identified from data collected and analyzed by using more standardized methods.

FSL is an image processing and analysis suite that is widely used, freely available, and well documented (www.fmrib.ox. ac.uk/fsl). FSL includes several tools for processing and analyzing DTI data by using a standard processing and analysis pipeline that includes FDT and TBSS, discussed further in the Image Processing and Analysis section).[19] At the time of this writing, it has been used in at least 4 DTI studies identifying white matter abnormalities in ASD.[17,20-22] Although an encouraging trend, generalization of abnormalities cannot yet be established with such few studies; therefore, more studies sharing these procedures are needed. The current investigation responds to this need by implementing FSL with its recommended processing and analysis pipeline while also implementing a voxelwise, atlas-based tract-labeling approach not used in previously published studies. The latter provides more precise and quantitative characterization of potentially affected fiber tracts that is essential for the assessment of an autism-specific neural phenotype.

The specific hypotheses posed in the present study are motivated by 2 recently published DTI studies, both using an entirely different group of participants and processing and analysis procedures, demonstrating impairments in the inferior fronto-occipital fasciculus (among other association tracts) and the corpus callosum.[17,23] The inferior fronto-occipital fasciculus is unique in that it connects all 4 major lobes of the brain,[24] potentially serving an important role in linking all the components in what is commonly called the "social brain" (Fig 1). Therefore, it is hypothesized that the neural phenotype in ASD consists of widespread impairments in long-range connections with higher aberrations seen in the inferior fronto-occipital fasciculus. This would be supported by DTI data demonstrating widespread reductions in FA with abnormalities skewed toward the aforementioned tract. In addition, reductions in FA also are expected in fibers of the corpus callosum, a structure consistently reported as abnormal in ASD.[25]
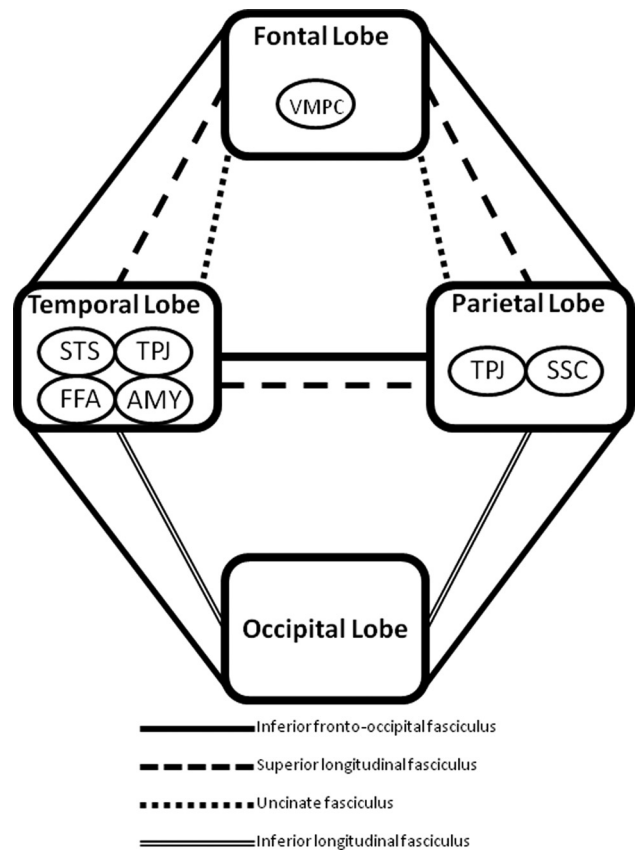

Fig 1. Schematic diagram of the 4 major cerebral lobes, association tracts, and brain regions involved in social information processing.

Materials and Methods

Subjects

Study participants included 15 children and adolescents with ASD (mean age, 10.9 ± 3.7 years; range, 4.9–17.0 years) and 8 TDC participants (mean age, 11.5 ± 2.6 years; range, 8.9–16.7 years), matched on age, sex, handedness, and race. Female participants were very limited in number and were excluded from the analysis because the sample size was insufficient to accommodate the structural variability associated with sex. Those included in the ASD group had confirmed *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*[26] diagnoses and absence of medical and neurologic disease that might be associated with ASD. Diagnosis of ASD was based on parental information, clinical history, and expert evaluation. In addition, 2 standard research diagnostic instruments were used: Autism Diagnostic Interview-Revised[27] and Autism Diagnostic Observation Schedule.[28] The TDC group consisted of healthy volunteers recruited from the same community as participants with ASD. A semistructured clinical interview was conducted with TDC participants, their parents, or both to rule out any history of neurologic problems, neurologic insult resulting in loss of consciousness, psychiatric disorders, and history of ASD in first- or second-degree relatives. The DAS[29] was administered to study participants to assess the wider range of cognitive functioning inherent in ASD subjects. Additional psychological measurements were collected for all participants, including the SRS.[30] The study was approved by the University Human Investigations Committee. Informed consent was obtained from the parent(s) or guardian(s) of all participants, as well as each participant's verbal assent.

Image Acquisition

MR imaging was performed by using a 3T Magnetom Tim Trio system (Siemens, Erlangen, Germany). Diffusion-weighted data were collected with an 8-channel head coil, using parallel imaging to gain better signal intensity at air-tissue interfaces. Diffusion imaging parameters include: diffusion directions = 30, B0 = 5, TR = 6200 ms, TE = 85 ms, FOV = 240 mm^2, section thickness = 2.5 mm (isotropic), GRAPPA on, number of sections = 55, averages = 3, and total scan time = 11 minutes. With a standard single-channel head coil, whole-brain T1-weighted MR imaging was performed by using a sagittal 1-mm^3 magnetization-prepared rapid acquisition of gradient echo sequence. The pulse sequence parameters were as follows: TR = 2530 ms, TE = 3.66 ms, TI = 1100 ms, flip angle = 7°, NEX = 1, number of sections = 176, bandwidth = 181 Hz/pixel, matrix = 256 × 256, FOV = 256 mm^2, GRAPPA off, and scan time = 8 minutes. All imaging was performed in the same session.

Image Processing and Analysis

Data preprocessing and local diffusion modeling were conducted using FSL.[31] First, all volumes were inspected by an experienced rater for severe motion and other artifacts. Diffusion-weighted images were then corrected for eddy current distortion and simple head motion. Next, the 3 runs (per subject) of diffusion-weighted data were averaged to improve signal intensity–to-noise ratio. The program was then used to generate a mask to separate brain from nonbrain areas. The binary brain mask, averaged diffusion-weighted data, b-values, and vector information were then input into FDT, which fits a diffusion tensor model at each voxel. The result of this process was a FA map for each subject. Given the preliminary nature of this investigation and the aim to eloquently identify a neural phenotype, FA was chosen as the sole measure of the structural integrity of axonal fiber tracts.

Voxelwise analysis of multisubject diffusion data was conducted using TBSS that provide a satisfactory solution to the challenge of aligning FA images from different groups for subsequent voxelwise analysis that differs from standard registration algorithms.[19] With the use of an optimized nonlinear registration followed by projection onto an alignment-invariant tract representation, TBSS allows for valid conclusions to be drawn from analysis of multisubject diffusion imaging studies. The procedure as implemented in the current study consists of the following steps: 1) conversion of FA data into appropriate format, 2) application of nonlinear registration so all FA images are in MNI space, 3) creation of mean FA image, 4) skeletonization of mean FA image by using an FA threshold of 0.3,[20] 5) projection of all subjects' FA data onto the mean FA skeleton, and 6) submission of the 4D-projected FA data for statistical testing. Voxel-wise analysis was performed on multisubject diffusion data. Areas of significant difference were computed and displayed as 1 P value image, where $P < 0.05$, corrected for multiple comparisons across space via threshold-free cluster enhancement.[32] Using the T1-weighted MR imaging data, intracranial volume was calculated by using FreeSurfer image analysis suite (Martinos Center for Biomedical Imaging, Charlestown, Massachusetts) that consists of automated tools for reconstruction of the brain from MR imaging data.[33]

Affected white matter structures were identified by using the JHU White Matter Tractography Atlas,[34] which is fully integrated into the FSL software package. This atlas was not only useful for identification of potentially affected fiber tracts (ie, those tracts onto which the voxels of significant difference were mapped via the tractography atlas) but also for more precise characterization of potential pathology by quantifying af-

Table 1: Subject characteristics

	ASD Group, n = 15		TDC Group, n = 8		t Test, df = 21	
	Mean	SD	Mean	SD	t	P
Age	10.87	3.75	11.46	2.62	0.394	.698
Intracranial volume, ml^3	1433.6	202.6	1497.7	236.4	0.682	.502
DAS	94.87	25.57	110.25	7.59	1.647	.114

fected voxels based on their tract labels. The MNI coordinates of all affected voxels were captured and intersected with the JHU White Matter Tractography Atlas. These voxels were assigned to atlas labels numbered from 0 (no label) to 1–21, with the latter group consisting of association, commissural, and projection tracts. For all participants individually, affected voxels were grouped by label with their corresponding FA, and counts were generated for each fiber tract. The following summary statistics were computed for each fiber tract: mean FA, SD, and effect size (Cohen d). Finally, exploratory Pearson correlation analyses were performed between mean FA data of the most severely affected fiber tracts and SRS scores, by using the Statistical Package for the Social Sciences 17.0 (SPSS, Chicago, Illinois). Bonferroni correction was used to control for multiple comparisons.

Results

There were no significant group differences in age, intracranial volume, and cognitive functioning (Table 1). The main results of this study are summarized in Table 2 and Fig 2. The ASD group had significant bilateral reductions in FA involving numerous association, commissural, and projection tracts. Affected association tracts include inferior fronto-occipital fasciculus, superior longitudinal fasciculus, inferior longitudinal fasciculus, uncinate fasciculus, and cingulum. Commissural fibers include both forceps major and minor of the corpus callosum. Projection tracts included the anterior thalamic radiation and corticospinal tract. As evident from Table 2, all white matter structures were not equally affected, and the variability was substantial. The fiber tracts with the greatest number of affected voxels were the forceps minor, right inferior fronto-occipital fasciculus, and left inferior fronto-occipital fasciculus. Notably, there were no voxels where FA was significantly increased in the ASD group. Exploratory Pearson correlation analyses did not yield any significant relationships between mean FA within affected fibers and clinical measures (SRS) after adjusting for multiple comparisons.

Discussion

The central question addressed in the present study was whether an autism-specific neural phenotype can be identified from DTI data collected and analyzed by using more standardized methods (ie, FSL/TBSS). It was hypothesized that the brain phenotype in ASD is characterized by a generalized pattern of impaired long-range connectivity with pathology skewed toward fiber tracts with probable connections to the modules of the social brain, particularly the inferior fronto-occipital fasciculus (Fig 1). This hypothesis was supported by DTI data presented in this preliminary study, where numerous long-range tracts (association, commissural, and projection) in both hemispheres were affected as evidenced by reductions in FA, a well-established measure of fiber tract integrity.[18] Al-

Table 2: Characteristics of affected long-range fiber tract by type

| | | Analysis Using Tract-Based Spatial Statistics | | |
| | | Mean FA ± SD | | |
Affected Long-Range Fiber Tract	Voxels	ASD	TDC	Cohen d
Association fiber tracts				
Left cingulum	447	0.45451 ± 0.03748	0.52135 ± 0.03437	1.86
Right cingulum	384	0.39698 ± 0.03405	0.46118 ± 0.03644	1.82
Left inferior fronto-occipital fasciculus	1800	0.42609 ± 0.02737	0.47815 ± 0.01963	2.19
Right inferior fronto-occipital fasciculus	2613	0.40417 ± 0.02381	0.45627 ± 0.02336	2.21
Left inferior longitudinal fasciculus	600	0.40164 ± 0.02973	0.45423 ± 0.02529	1.90
Right inferior longitudinal fasciculus	516	0.35894 ± 0.02004	0.40471 ± 0.01826	2.39
Left superior longitudinal fasciculus	1139	0.39142 ± 0.02292	0.44631 ± 0.03429	1.88
Right superior longitudinal fasciculus	1239	0.38618 ± 0.02924	0.43763 ± 0.02567	1.87
Left uncinate fasciculus	629	0.38364 ± 0.02023	0.42668 ± 0.01602	2.36
Right uncinate fasciculus	692	0.40255 ± 0.02456	0.45125 ± 0.01872	2.23
Projection fiber tracts				
Left anterior thalamic radiation	1249	0.44658 ± 0.02330	0.49437 ± 0.01814	2.29
Right anterior thalamic radiation	1676	0.44793 ± 0.02493	0.49573 ± 0.01988	2.12
Left corticospinal tract	781	0.57413 ± 0.03155	0.61171 ± 0.02482	1.32
Right corticospinal tract	701	0.52393 ± 0.03138	0.56246 ± 0.01939	1.48
Commissural fiber tracts				
Forceps major	716	0.50708 ± 0.03044	0.55487 ± 0.02163	1.81
Forceps minor	2878	0.51958 ± 0.02770	0.57127 ± 0.01877	2.18

though it is evident from Table 2 that all major long-range fiber tracts are affected, not all tracts were equally impaired. The fiber tract with the greatest number of affected voxels was the forceps minor. This was followed by the right and left inferior fronto-occipital fasciculi, respectively. Abnormalities in the corpus callosum may be a nonspecific manifestation of generalized deficits in long-range connectivity because abnormalities also have been reported in other neuropsychiatric disorders such as schizophrenia,[35] Alzheimer disease,[36] and bipolar disorder.[37] However, significant findings in the inferior fronto-occipital fasciculus may reflect ASD-specific atypicalities given its connections to all major cerebral lobes, thus potentially connecting all major modules in the social brain network (Fig 1). This does not imply that aberration of a single fiber tract can explain the diversity of clinical manifestations that characterize ASD. Although numerous tracts may be implicated, the pattern by which all tracts are affected may be revealing, raising the question of whether a unique disconnectivity "fingerprint" may be ascribed to ASD.

Why the inferior fronto-occipital fasciculus may play an important role in the neurobiology of ASD is evident after considering its spatial extent and what it known about the areas of the brain involved in social information processing. Postmortem studies show that the inferior fronto-occipital fasciculus has direct connections to the fusiform gyrus and provides connections between all major lobes of the human brain: frontal, temporal, parietal, and occipital.[24] This broad neuroanatomic extent is a unique quality of the inferior fronto-occipital fasciculus and fits well with broad spatial distribution of brain structures involved in social cognition (Fig 1), including but not limited to, the fusiform gyrus (temporal lobe), amygdala (temporal lobe), superior temporal sulcus (temporal lobe), ventromedial prefrontal cortex (frontal lobe), temporoparietal junction (temporal and parietal lobes), and somatosensory cortices (parietal lobe). More striking, however, is the recent report demonstrating the important role of the inferior fronto-occipital fasciculus in correctly rec-

ognizing emotion in faces. In a large group of patients with focal brain lesions ($n = 103$), damage associated with the right inferior fronto-occipital fasciculus significantly predicted overall facial emotion recognition impairment with specific deficits recognizing sadness, anger, and fear.[38] The inability to properly identify and recognize facial emotions is a well-known impairment in ASD.[39] Moreover, previously published DTI studies lend support to abnormalities of the inferior fronto-occipital fasciculus in ASD.[15,17,21,23,40,41] In the present study, the right inferior fronto-occipital fasciculus was the most severely affected association tract, which suggests a potential mechanism for known impairments in facial emotion recognition in ASD.

Another severely affected association tract was the superior longitudinal fasciculus, which was the second most severely affected association tract in the current study. In the left hemisphere, this fiber tract connects the Broca and Wernicke areas.[42] It is well known that damage to this pathway can cause a relatively rare language disorder called conduction aphasia.[43] Given that language and communication abnormalities are core deficits in ASD, an abnormality in the left superior longitudinal fasciculus comes as no surprise. In fact, this finding is consistent with an influential fMRI study that found impaired functional connectivity between language areas by using a sentence comprehension task in individuals with ASD.[10] Moreover, several DTI studies also have revealed abnormalities of the left superior longitudinal fasciculus in ASD.[17,20,23,41,44] Although the important role the left superior longitudinal fasciculus has in language processing has been known since the 19th century, the importance of this structure in the right hemisphere is emerging. Abnormalities of the right superior longitudinal fasciculus also have important implications for ASD due to its connection to the superior temporal sulcus,[42] a region well known for its role in processing biologic motion, which is abnormal in ASD.[45] Moreover, several DTI studies have revealed abnormalities of the right superior longitudinal fasciculus.[17,20-22,46] Finally, similar to the inferior fronto-oc-
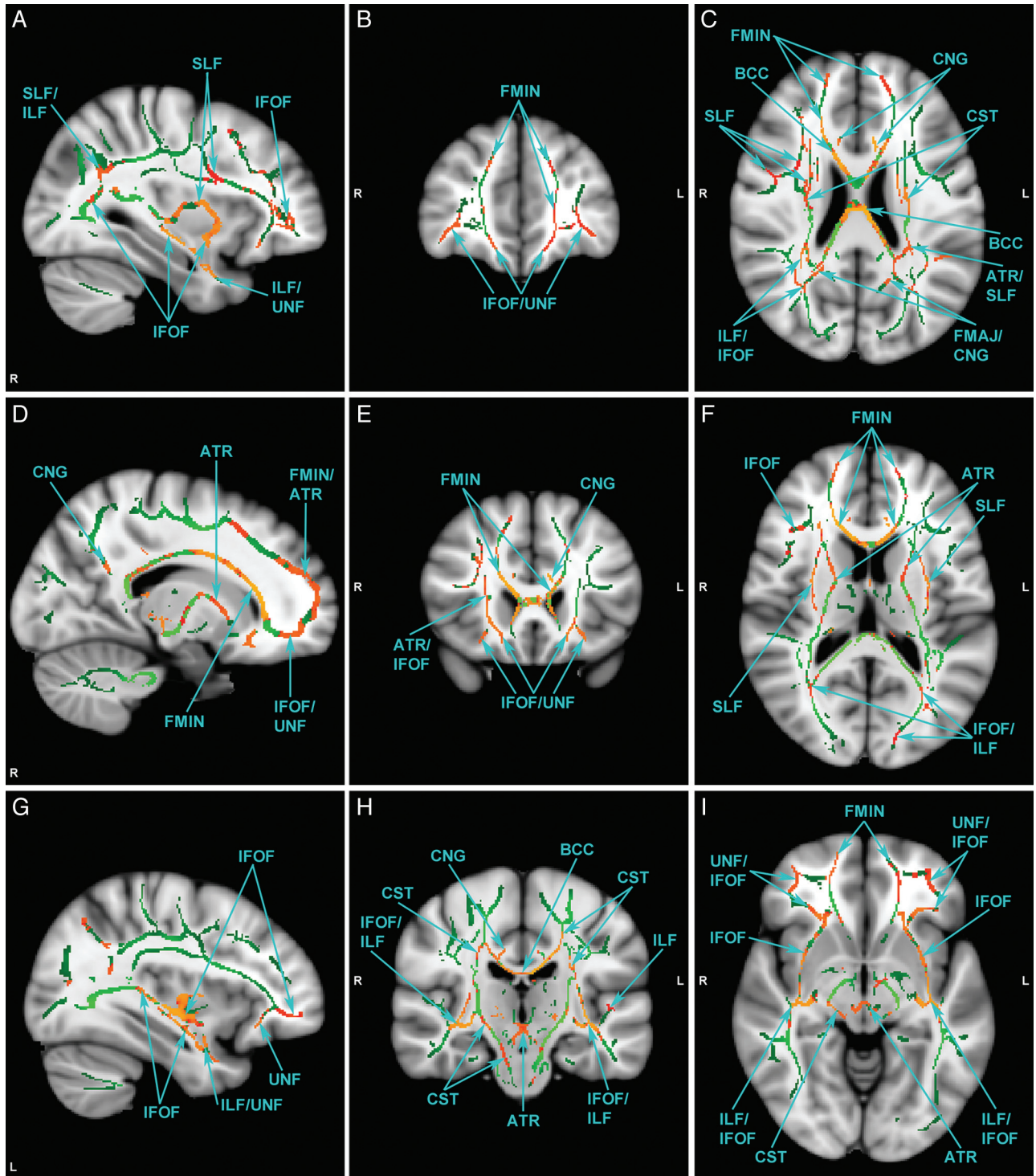
Fig 2. Selected views of affected fiber tracts with reduced FA, illustrated on MNI template brain. Identified in green are those voxels in the group-wise comparison where FA is not significantly different. Identified in red-orange are those voxels where FA is significantly lower in the autism group. Orange indicates higher statistical significance. There are no voxels where FA is significantly higher in the autism group. MNI coordinates for each view are as follows: $x = 57$ (*A*), $y = 167$ (*B*), $z = 95$ (*C*), $x = 73$ (*D*), $y = 149$ (*E*), $z = 86$ (*F*), $x = 124$ (*G*), $y = 106$ (*H*), and $z = 66$ (*I*). L = left; R = right.

cipital fasciculus, the superior longitudinal fasciculus also has a broad neuroanatomic extent, connecting the frontal, parietal, and temporal lobes.[42] As evident in Fig 1, this tract also may potentially serve an important role in linking all the components of brain structures involved in social cognition.

The widespread presence of potential pathology is evident from Table 2 where numerous white matter tracts seem to be affected. Thus, there are many more affected tracts other than the inferior fronto-occipital fasciculus and superior longitudinal fasciculus. Even though specific clinical manifestations are difficult to link to each affected tract, this neither contradicts the hypothesis that the neurobiology of ASD consists of impairments in long-range connections nor precludes the possible existence of an autism-specific neural phenotype. The im-
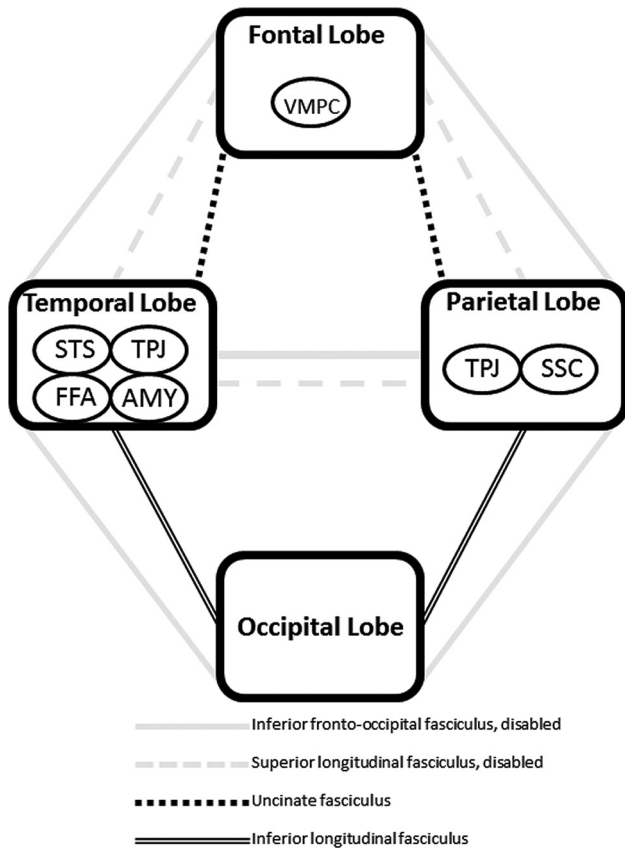
Fig 3. Schematic diagram illustrating how the inferior fronto-occipital and superior longitudinal fasciculi might account for the social disability that characterizes autism. Disability of major pathways connecting the modules of the social brain causes reliance on smaller tracts leading to inefficient corticocortical communication. Whether any social information processing is possible depends on how severely impaired the major pathways are and whether alternative pathways are available. Abbreviations indicate modules of social information processing.

portance of all fiber tracts can be appreciated given that, as a group, they join centers of language and communication, modules responsible for processing social information, or both (Fig 1); therefore, disruption in any fiber tract can theoretically cause disconnection. Moreover, the wide range of affected tracts remains consistent with the DTI literature on the neurobiology of ASD that, to date, consists of at least 25 published reports. Although a comprehensive review of this literature is beyond the scope of this discussion, many of the affected tracts listed in Table 2 have been reported previously as abnormal. Therefore, abnormal connectivity need not be limited to the inferior fronto-occipital fasciculus and superior longitudinal fasciculus. The possibility that other white matter structures are affected is expected, and this is consistent with the widely held belief that ASD are heterogeneous and distributed disorders.[47]

Although speculative, the brain phenotype in autism may be characterized by widespread fiber tract compromise with bias toward the inferior fronto-occipital fasciculus, superior longitudinal fasciculus, and corpus callosum. How the inferior fronto-occipital and superior longitudinal fasciculi might account for the social disability that characterizes autism is shown schematically in Fig 3. With the disability of major pathways connecting the modules of the social brain (ie, inferior fronto-occipital and superior longitudinal fasciculi that

connect frontal, temporal, and parietal lobes), there is possible reliance on smaller tracts that may lead to inefficient corticocortical communication. However, the aberrations present in all fiber tracts exacerbate the problem. Whether social information processing is possible may depend on how severely impaired the major pathways are and whether alternative pathways are available. The overall pattern of tract deficits may not only dictate the expression of autism but also its severity and heterogeneity.

Findings reported in this study must be interpreted in the context of several methodologic limitations. This is a preliminary study, and the sample size and age range reflect this fact; however, these impose limitations on the generalization of findings. This is further complicated by the relatively heterogeneous nature of the ASD group. In addition, the control group imposed limitations due to absence of developmentally delayed children without ASD. In the absence of such a comparison group, it remains unclear whether these findings are specific to ASD. Finally, there are several limitations in the voxelwise, atlas-based tract-labeling approach. The JHU White Matter Tractography Atlas provides a probability value and was constructed by using a different age group of subjects and registration procedure. Thus, this approach does not account for multiple fiber tracts within a single voxel. The differences in the registration procedure and subject sample may potentially induce errors. However, this would not be expected to bias the results given that the same procedure is used in both autism and control groups. Most important is that the autism subjects, who have aberrant long-range connections, also may have different fiber connections. Therefore, using the tractography atlas constructed from neurotypical subjects may potentially also introduce tract errors.

Conclusions

This study provides evidence of reduced FA along numerous long-range fiber tracts in ASD, supporting the existence of reduced long-range connectivity. The most severely affected association tracts include the inferior fronto-occipital fasciculus and superior longitudinal fasciculus, both of which have important implications in language and social information processing. The distribution of these findings points to a widespread abnormality in long-range connections that may not only contribute to both core and associated symptoms but also the well-known heterogeneity of this spectrum of disorders. Most importantly, however, is the widely different degree to which individual tracts are affected, raising the question of whether a unique disconnectivity fingerprint may be ascribed to ASD. Although speculative, this neural phenotype may consist of widespread fiber tract compromise with bias toward the inferior fronto-occipital fasciculus, superior longitudinal fasciculus, and corpus callosum. However, additional work is clearly needed before any conclusions can be made regarding an autism-specific brain phenotype. These future studies should implement a standardized image collection, processing, and analysis protocol and include large samples of individuals with autism subjects matched with developmentally delayed individuals without autism. A customized tractography atlas should be implemented for voxel labeling to reduce the probability of tract errors.

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