Corticospinal Tract Anatomy and Functional Connectivity of Primary Motor Cortex in Autism

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Objective: Growing evidence indicates that autism spectrum disorder (ASD) stems from abnormal structural and functional connectivity of neural networks. Although diagnostic symptoms are sociocommunicative, motor-related functions (beyond repetitive mannerisms) are also impaired. However, evidence on connectivity at the level of basic motor execution is limited, which we address here.

Method: We compared right-handed children and adolescents (aged 7–18 years) with ASD (n = 44) to matched typically developing participants (TD, n = 36) using magnetic resonance imaging (MRI). Diffusion-weighted imaging and probabilistic tractography measured microstructure of the corticospinal tract (CST). Intrinsic functional connectivity MRI examined whole-brain voxelwise correlations, both with identical precentral gyrus (PCG) seeds.

Results: In the group with ASD, radial and mean diffusivity were increased bilaterally in the CST, particularly in superior segments, and a leftward asymmetry of CST volume detected in the TD group was reversed. Functionally, overconnectivity was found for both left and right PCG with prefrontal, parietal, medial occipital, and cingulate cortices. The group with ASD also showed significantly reduced asymmetry of functional connectivity for both left and right PCG seeds. Finally, in the group with ASD, significant correlations were found for functional overconnectivity of the right PCG seed with anisotropy and mean diffusivity in the right CST.

Conclusion: The findings, implicating both functional and anatomical connectivity of the primary motor cortex, suggest that network anomalies in ASD go well beyond sociocommunicative domains, affecting basic motor execution. They also suggest that even in right-handed adolescents with ASD, typical left hemisphere dominance is reduced, both anatomically and functionally, with an unusual degree of right hemisphere motor participation.

Key Words: autism spectrum disorder, diffusion tensor imaging, probabilistic tractography, functional connectivity MRI, primary motor cortex

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Although autism spectrum disorders (ASD) are diagnosed based on socio-communicative impairments and restricted or repetitive behaviors,[1] there is increasing evidence that ASD is associated with abnormal motor-related functions beyond repetitive motor mannerisms, including hypotonia,[2] abnormalities of gait,[3,4] and dyspraxia or apraxia.[2] Delays in motor development[5] and impairments of gross and fine motor function[6] have also been reported, which may be present as early as infancy[5,7] and may persist into adulthood.[8]

In a typically developing (TD) brain, voluntary movements are controlled by primary motor cortex (M1) and its outputs through the corticospinal tract (CST), with indirect modulation through the basal ganglia and cerebellar circuits. Motor abnormalities in ASD are often interpreted as implicating the basal ganglia and/or cerebellum,[3,4] whereas evidence related to the motor control system itself remains limited. In 8- to 12-year-olds with ASD, increased white matter volume in the motor/premotor area (precentral gyrus) was found to be predictive of poorer motor function, a reversal of the correlation seen in typically developing children.[9] The authors suggested that this effect primarily reflected local (rather than long-distance) connections. In the present study, we examined connectivity of the motor control system in ASD, including anatomical organization of its output pathway along the CST and functional connectivity of primary motor cortex, using diffusion tensor imaging (DTI) and intrinsic functional connectivity (iFC) magnetic resonance imaging (MRI).

Studies using DTI indicate atypical trajectories for white matter maturation.[10] Toddlers with ASD show increased fractional anisotropy (FA),[11,12] whereas school-aged children and adolescents show reduced FA, increased mean diffusivity (MD), and radial diffusivity (RD). This suggests an early acceleration of maturation followed by a plateau, further supported by longitudinal findings[13] and similar to what is seen in volumetric studies of gray matter.[14-16] Abnormalities have been reported in frontal,[17,18] temporal,[17,18] and parietal white matter,[19] cerebellar peduncles,[20] and large association tracts.[17,21-23] Although none of these studies has systematically examined CST, a few authors have reported limited findings within the tract. Shukla *et al.*[24] and Jou *et al.*[21] reported reduced FA and increased

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MD in segments of the white matter "skeleton" corresponding to CST. One region-of-interest study found decreased FA in the posterior limb of the internal capsule bilaterally and in the right inferior CST (cerebral peduncle),[20] whereas another found increased MD but no effects on FA.[25]

Complementing the investigation of anatomical connectivity through DTI, functional connectivity MRI (fcMRI) assesses functional coordination between spatially distributed brain regions.[26,27] Intrinsic functional connectivity (iFC)—inferred from interregional cross-correlations of the blood oxygen level-dependent (BOLD) signal—can be detected at rest, in the absence of an overt task.[28] Importantly, iFC patterns correspond to brain networks recruited during specific cognitive processes[29,30] and likely reflect functional networks associated with functional specialization.[31,32] The iFC patterns are largely consistent with anatomical connectivity[33,34] and are highly reliable across individuals.[27,33,35]

A growing number of fcMRI studies point to widespread abnormalities in interregional connections in ASD,[26,36,37] including decreased connectivity within a motor system (M1, thalamus, and cerebellum[38]), partially replicated by a study showing reduced iFC between (pre)motor cortex and thalamus.[39] Another study suggested reduced differentiation within M1 between upper and lower limb regions in ASD.[40]

The present study provides a comprehensive and multimodal investigation of anatomical and functional connectivity of the motor control system in children and adolescents with ASD compared to TD children. We used DTI and probabilistic tractography to examine the major output pathway of M1, the CST, and iFC to examine the functional connectivity of M1.

METHOD

Participants

All participants with ASD met *DSM-V* criteria for ASD.[1] Prospective participants with ASD were administered the Autism Diagnostic Observation Schedule (ADOS),[41] and parents were administered the Autism Diagnostic Interview–Revised (ADI-R)[42] with final diagnosis confirmed by an experienced clinical psychologist. Children with known neurological disorders other than ASD (e.g., Fragile X syndrome, epilepsy) were excluded. Prospective TD participants with personal or family history of autism, or personal history of other neurological or psychiatric conditions, were excluded. Additional assessments included the Wechsler Abbreviated Scale of Intelligence (WASI),[43] the Developmental Test of Visual–Motor Integration, 6th Edition (VMI),[44] and the Edinburgh Handedness Inventory.[45] The study was approved by the University of California–San Diego and San Diego State University institutional review boards, with written informed consent and assent provided by all participants and caregivers.

We scanned 108 children and adolescents, excluding 28 because of: non–right-hand preference (4 ASD, 6 TD), exclusionary finding on MRI or other measures (6 ASD, 1 TD), or incomplete or poor-quality data in multiple imaging modalities (8 ASD, 3 TD; additional exclusions for single modalities [DTI or iFC] described in Results; for quality criteria, see Analysis sections). The final sample included 44 participants with ASD (8 female) and 36 TD individuals (9 female) aged 7 to 18 years, all right-handed (Table 1) and matched for age and IQ.

MRI Data Acquisition

MRI data (GE Discovery MR750 3.0T, 8-channel head coil) included the following: T1-weighted anatomical scan (fast spoiled gradient echo; TR = 8.108; TE = 3.172 milliseconds; flip angle = 8°; resolution = 1 mm^3); diffusion weighted images (two-dimensional [2D] echo planar imaging [EPI]; 61 noncollinear diffusion directions at b = 1,000 s/mm^2, 1 at b = 0 s/mm^2; TR = 8500 milliseconds; TE = 84.9 milliseconds; flip angle = 90°; resolution = 1.875 × 1.875 × 2 mm^3);

TABLE 1 Participant Demographics

	ASD[a] (n = 44, 8 Female)		TD[b] (n = 36, 9 Female)		
Characteristic	**Mean ± SD**	**Range**	**Mean ± SD**	**Range**	***p***
Age, y	13.2 ± 2.9	7–18	12.8 ± 2.4	8–17	.50
Nonverbal IQ	104.5 ± 17.9	69–140	105.4 ± 11.8	83–129	.79
Verbal IQ	100.7 ± 20.4	56–147	106.1 ± 12.4	73–133	.17
Full Scale IQ	102.4 ± 18.7	66–141	106.5 ± 11.9	79–132	.26
SRS Total	79.7 ± 10.4	57–100	41.9 ± 5.0	35–52	<.001
ADOS Social	9.0 ± 3.5	4–21			
ADOS Communication	4.3 ± 2.5	0–13			
ADOS S+C	12.6 ± 4.9	1–22			
ADOS Repetitive Behavior	2.2 ± 1.6	0–6			
ADI Social	19.1 ± 5.9	6–28			
ADI Communication	15.2 ± 5.9	2–25			
ADI Repetitive Behavior	6.5 ± 2.3	3–12			
DTI Total Motion Index (TMI)	2.61 ± 4.71	−1.50–18.70	0.87 ± 2.53	−1.97–10.88	.07
iFC-MRI RMSD	0.10 ± 0.07	0.02–0.30	0.09 ± 0.07	0.02–0.30	.46

Note: ADI-R = Autism Diagnostic Interview–Revised; ADOS = Autism Diagnostic Observation Schedule; DTI = diffusion tensor imaging; iFC-MRI = intrinsic functional connectivity magnetic resonance imaging; RMSD = root mean square of displacement; S+C = Social+Communication subscale; SRS = Social Responsiveness Scale; TD = typically developing.

[a]*IQ scores unavailable for 2 participants; SRS unavailable for 1 participant; ADOS scores unavailable for 4 participants; ADI-R scores unavailable for 2 participants.*

[b]*SRS scores unavailable for 2 participants.*