Graph curvature as a method for discerning robustness in brain networks in autism spectrum disorder

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Introduction

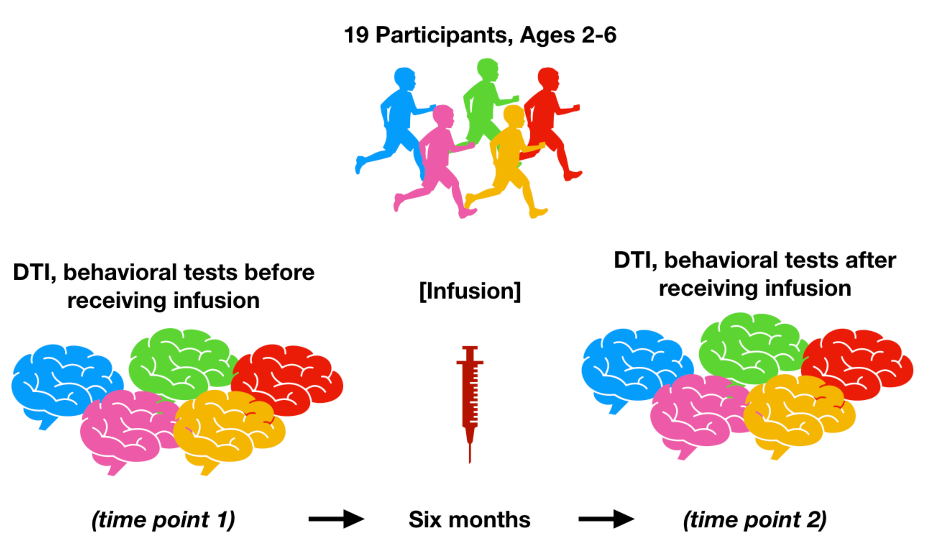
- Altered immune responses in ASD have been linked to brain overgrowth and altered white matter connectivity.
- Immune modulating therapeutic interventions have the potential of impacting neurodevelopment and clinical outcomes in ASD.
- We have previously reported white matter changes that are associated with significant improvement following treatment with a single infusion of autologous cord blood.
- Curvature, as a measure of network robustness, represents a novel putative biomarker using a systems-level approach that accounts for the interrelatedness of the entire brain network.

The current study employed an approach that takes into account all the connections into the brain region and pairs of brain regions to assess the robustness of such brain networks and connections.

Participants and Clinical Methods

Demographics	N=19
Sex (M/F)	17/2
Age in Months Mean (std. dev)	54 (13)
Nonverbal IQ Mean (std. dev)	62 (20.3)
ADOS Severity Mean (std. dev)	8 (1.4)

25 children who were between 24 and 72 months, met criteria for a clinical DSM-5 diagnosis of ASD, and had a banked autologous umbilical cord blood unit of adequate size and quality took part in the trial. Of these children, 19 had MRI data at baseline and 6 months post-treatment.



Clinical Outcomes

- Vineland Adaptive Behavior Scales (VABS) Socialization Score
- Expressive One Word Picture Vocabulary Test (EOWPVT) Raw Score
- Clinical Global Impression-Improvement (CGI-I) Score

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Network curvature identified both key hubs, namely the dlPFC and the insula, and white matter pathways that were not identified by traditional DTI analysis methods, yet demonstrated significant change following treatment in this trial.

These results support network curvature (robustness) as a novel method for the identification of patterns of white matter connectivity that are not identified by common measures of DTI, but yet are related to treatment outcomes in ASD.

Network Curvature Definition

$$k(x,y) := 1 - \frac{W_1(\mu_x, \mu_y)}{d(x,y)}$$

$k(x,y)$	Curvature
$W_1(,)$	Wasserstein distance
$d(x,y)$	Geodesic distance
x, y	Node x, Node y
μ	Probability distribution around a node

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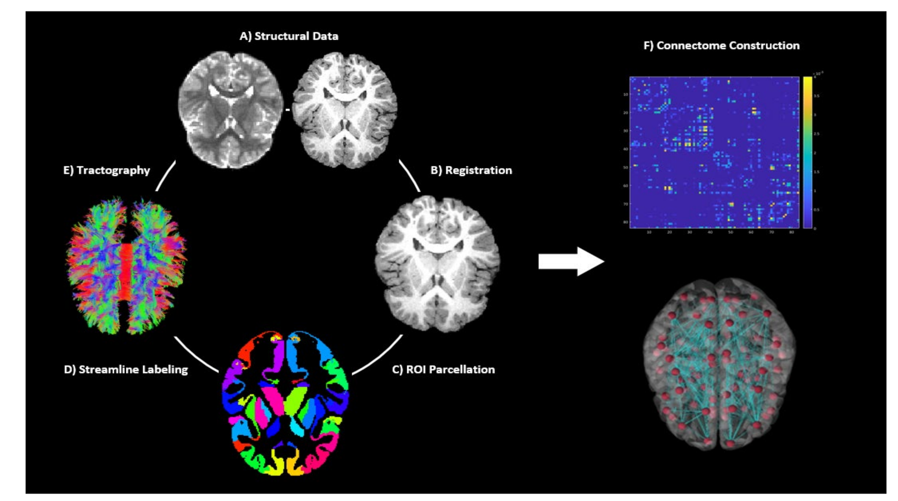
Brain Imaging Methods

25 direction Diffusion Tensor Imaging (DTI)



(A) Left; diffusion image, Right; T1 (B) T1 registered in diffusion space (C) warp parcellated dilated UNC Pediatric Atlas to diffusion image space using ANTS (D) Parcellated regions of interest (ROIs) used to label tractography results (E) DTI and deterministic tractography using the Connectome Mapper (F) Visualization of connectome for a representative subject.

Results

Curvature analysis identified two regions for which increased robustness of their connections with the rest of brain was associated with clinical outcomes: the left dorsolateral prefrontal cortex (dlPFC) and the left insula.

	Region Pairs	VABS	EOW	CGI
a	R. Paracentral - R. Amygdala	-0.53	-0.50	0.55
b	R. Superior Temporal - R. Accumbens	-0.77	-0.67	0.51
c	R. Caudate - R. Amygdala	-0.55	-0.54	0.58
d	L. Pars Orbitalis - L. Entorhinal	0.56	0.60	-0.49
e	L. Pars Triangularis - L. Temporal Pole	0.66	0.50	-0.46
f	L. Paracentral - L. Inferior Temporal	-0.52	-0.60	0.59
g	L. Pericalcarine - L. Lingual	-0.60	-0.49	0.57
h	L. Temporal Pole - L. Pallidum	0.46	0.51	-0.57

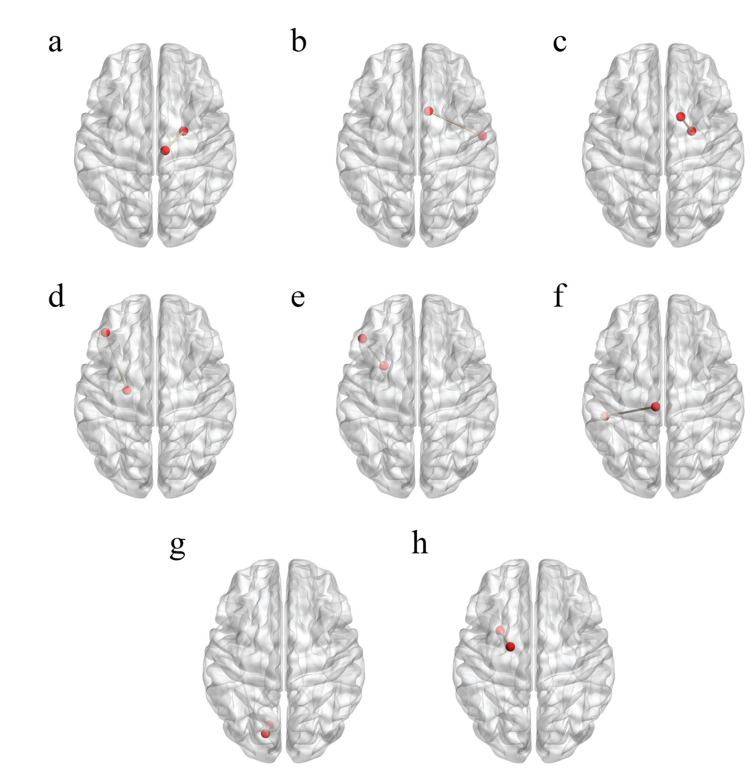


Figure: Axial projection of pairs where the change in curvature correlated significantly with clinical outcomes

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