Disruption of functional organization within the primary motor cortex in children with autism

Mary Beth Nebel[1,2], Suresh E Joel[1,2], John Muschelli[1,3], Anita D Barber[1,2], Brian S Caffo[3], James J Pekar[1,2], and Stewart H Mostofsky[1,2]

[1]Kennedy Krieger Institute, Baltimore, Maryland, United States, [2]Johns Hopkins School of Medicine, Baltimore, Maryland, United States, [3]Johns Hopkins School of Public Health, Baltimore, Maryland, United States

Title: Disruption of functional organization within the primary motor cortex in children with autism

Introduction: Clinical observation and empirical studies suggest that children with autism spectrum disorder (ASD) exhibit impairments in motor abilities that may reflect abnormal connectivity within networks underlying motor control and learning. Recently, several groups have used patterns of correlations in spontaneous BOLD activity, referred to as resting-state functional connectivity (FC), to localize functionally relevant subdivisions of anatomically defined regions [1]. Motivated by the utility of these methods in establishing functional organization, this study had two aims: (1) to parcellate a key area of the motor network, the precentral gyrus (M1), in neurotypical adults and typically developing (TD) children; (2) to apply this approach to children with ASD to determine if M1 functional organization differs in children with ASD compared to TD children.

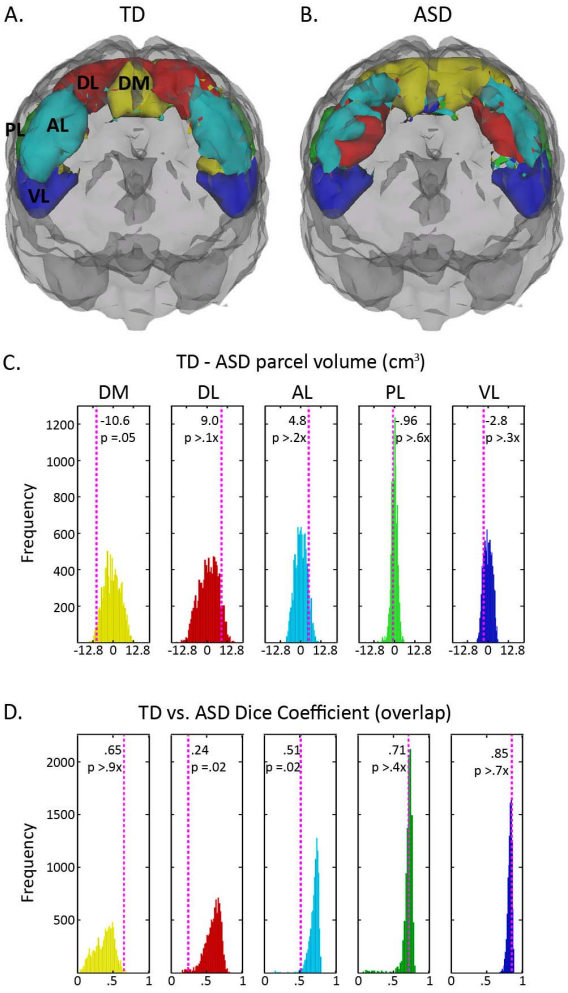

Fig.1. M1 parcels for **(A)** TD and **(B)** ASD children. The histograms illustrate the distribution of differences in **(C)** volume and **(D)** overlap when group labels were randomly assigned. The color of each histogram reflects the color of the corresponding parcel in **(A)** & **(B)**. The dashed, vertical lines indicate the observed differences in **(C)** volume and **(D)** overlap between TD and ASD parcels. In **(C)**, a negative value indicates that the TD parcel was smaller than the ASD parcel. In **(D)**, a dice coefficient closer to 1 indicates greater overlap.

Methods: Resting state fMRI and anatomical images were collected from 32 children with ASD (8-12 years old) and 33 TD children balanced for age, gender, handedness and perceptual reasoning. Scan-rescan reliability imaging data from twenty healthy adult volunteers with no history of neurological conditions were also used for parameter estimation [2]. Functional images were adjusted to account for slice acquisition order and participant motion, coregistered with each participant's anatomical image, and normalized to MNI space using unified segmentation (SPM5). Motion parameters, global mean signal and nuisance covariates from white matter and CSF were extracted using CompCor [3]. Data were then temporally filtered using a 0.01-0.1 Hz pass-band.

The M1 ROI was selected from the "Type II Eve Atlas" [4] and transformed to MNI space using unified segmentation (SPM5). For every M1 voxel (down-sampled to 4-mm resolution), an FC map with all voxels outside of M1 was computed using Pearson's correlation and converted to Z-scores using the Fisher transform. Similarity of FC maps for every pair of M1 voxels was computed using η^2 [1], and spectral clustering was performed on the resulting η^2 matrix. Adjacency matrices were constructed for each participant and averaged to generate a consensus matrix for each group; the elements of the consensus matrix corresponded to the proportion of times a given pair of voxels was assigned to the same parcel across participants. Spectral clustering was reapplied to the group consensus matrices, and the labels of the clustering solutions were matched by maximizing the average overlap of similarly-labeled parcels between groups.

To estimate the optimal number of functional parcels (k) in which to divide M1, we assessed the similarity of cluster solutions generated for adult scan-rescan data using Dice's coefficient for a range of k (2-11). We defined the optimal k to be the non-trivial (i.e., k>2) clustering solution that demonstrated the highest scan-rescan Dice's coefficient (overlap).

TD and ASD parcels were compared by spatial overlap and volume. The significance of the observed relations between these spatial patterns and diagnosis was assessed by permutation testing: diagnosis labels were randomly assigned, consensus matrices were recalculated and second-level spectral clustering was reapplied 10,000 times.

Results and Discussion: A gross dorsomedial to ventrolateral organization emerged within M1 in both groups which was left-right symmetric (Figs 1A and 1B). However, the dorsomedial-most (DM) parcel was significantly larger in ASDs than in TDs (10.6 cm^3, p = .05 [Fig 1C]) and encompassed much of the space occupied by the adjacent dorsolateral (DL) parcel in TDs. The displacement of the DL parcel in ASD caused additional functional segregation differences between groups in the region of M1 closest to the hand knob; group overlaps for the DL and anterior lateral parcels were significantly worse than predicted by permutation (.24, p=.02; .51, p=.02, respectively [Fig 1D]). Given the organization of the motor homunculus, these differences in M1 parcel size and segregation may have interesting developmental implications. The enlarged ASD parcel was located in a region of M1 that is normally reserved for lower limb control but also included areas normally recruited by the upper limbs, suggesting that developmental segregation of upper and lower limb control may be delayed in ASD.

Conclusion: We generated functionally relevant partitions in M1 based solely on patterns of connectivity between individual M1 voxels and all voxels outside of M1, and we devised a simple method for matching these partitions across groups of participants and testing group differences. In so doing, we identified differences in the functional segregation of M1 in children with ASD compared to TD children, suggesting that the functional subnetworks of the motor control system may be altered in autism.

References: 1. Cohen et al. (2008) *NeuroImage,* 41(1):45-57. 2. Landman et al. (2011) *NeuroImage,* 54(4):2854-66. 3. Behzahdi et al. (2007) *NeuroImage* 37:90. 4. Oishi et al. (2009) *Neuroimage* 46:486-499.

Funding: This work was supported by the Autism Speaks Foundation and grants from the National Institute of Biomedical Imaging and Bioengineering (R01EB012547), the National Institute of Neurological Disorders and Stroke (R01NS060910 and R01NS048527), the National Institute of Mental Health (R01MH078160 and R01MH085328), and the National Center for Research Resources (P41 RR015241).