Possible sources of functional connectivity and under-connectivity in adolescents with autism spectrum disorders

T. B. Jones[1], L. Kenworthy[1,2], L. K. Case[1], S. C. Milleville[1], P. A. Bandettini[1], A. Martin[1], and R. M. Birn[1]

[1]National Institute of Mental Health, National Institutes of Health, Bethesda, MD, United States, [2]Center for Autism Spectrum Disorders, Childrens National Medical Center, Washington, DC, United States

Introduction:

Relative to typically developing individuals (TD), adolescents with Autism Spectrum Disorders (ASD) show weaker correlations of BOLD fMRI time series between spatially remote regions of the brain, supporting a model of underconnectivity in autism [1]. These weak correlations could arise from a number of possible mechanisms – differences in 1) neuronal activation to different task types; 2) trial-to-trial variability in performance; 3) non-neuronal fluctuations, such as cardiac pulsation, respiration, subject motion, or scanner artifacts; and 4) task-unrelated, or "spontaneous," neuronal fluctuations. The purpose of the present study is to determine which of these factors contributes to the weak or decreased correlations between brain regions in ASD.

We investigate functional connectivity (FC) during overt fluency tasks designed to probe language and executive function deficits typical of ASD. These tasks have been shown to yield robust activations in regions associated with language and executive functions including the left fusiform gyrus (LFUS) and left inferior frontal gyrus (LIFG) [2]. In order to elucidate potential sources that might underlie group difference in connectivity, we performed several seed-ROI functional connectivity analyses. For these analyses, task-related and task-unrelated effects were sequentially removed. In addition, we investigated whether any observed decreases in functional connectivity were a result of an overall decrease in signal or an increase in noise in ASD individuals.

Methods:

Participation included 18 ASD (age: 15.3 +/- 1.6 yrs) and 18 TD (age 16.3 +/- 2.1 yrs) subjects (all male). Scans were performed on a 3T MRI scanner. (TR/TE = 2000ms/30ms, resolution: 3.8 x 3.8 x 5 mm^3, 115 time points per run). The tasks involved 10s blocks of overt word generation for 3 fluency conditions: letter (phonemic), category (semantic), and control (over-learned category). These three task types were each presented twice in randomized order during 8 different runs and were separated by 10s periods of fixation. This blocked design (10s task/10s rest) minimizes the impact of task-induced motion during general linear model analysis [3]. BOLD response amplitudes were obtained by multiple regression analysis and submitted to a Group (ASD, TD) by Condition (Letter, Category) ANOVA. Three subregions of both the LFUS and LIFG (6 total regions) showing differences in task-activation between conditions were used as seed regions of interest (ROIs). Average time series from these ROIs were correlated with all voxels in the brain. Common pre-processing steps included motion correction, time-shift correction, and percent signal scaling. Motion detrending was performed in methods 2, 3 and 4 described below.

Method one (M1) used the signal time series from the blocked-design task-activation data. The resulting "connectivity maps" are similar to a task-related regression analysis. Method two (M2) consisted of regressing out the task, but treating all task types as being the same. This results in a signal analogous to continuous task switching without rest intervals. Method three (M3) consisted of regressing out individual task responses, effectively removing task-related fluctuations. Method four (M4) additionally regresses out the global signal in an effort to control for global vascular effects such as respiration [4, 5].

Correlation coefficients were converted to Fisher-Z scores, averaged within groups, and submitted to two-tailed t-tests to determine significant differences between groups. Individual subject FC maps for each seed ROI time course were calculated for every subject and submitted to group (ASD, TD) voxel-by-voxel two-tailed t-tests after conversion to Fisher-Z scores. These maps indicate the spatial extent of differences in connectivity. To test the influence of trial-to-trial task variability on connectivity, we integrated the ROI time courses from M3 across task blocks and correlated this integrated signal with behavioral performance (number of words produced). The standard deviations of the ROI timecourses from M3 were also calculated to determine if decreased connectivity in ASD subjects was a result of increased noise levels.

Results and Discussion:

Decreased connectivity between LFUS and LIFG was observed in ASD subjects even after removing task-related responses (Table 1, Figure 1). Seed regions in the fusiform were significantly correlated with distinct regions of the brain, including the LIFG. Individual subjects showed correlations between behavioral performance and the M3 signal in the range of [-0.6, 0.7], but no significant group differences were found in any pre-processing method. Additionally, no significant difference was found between the standard deviations of the ASD and TD ROI time courses. These findings suggest that the decrease in connectivity is at least partially due to decreased amplitude or coherence in task-unrelated fluctuations.

Regressing out the global signal significantly reduced the correlation between brain regions (Table 1). This global brain signal, however, was significantly correlated with the task-modulation. Furthermore, spatial maps showed the highest correlation with the global signal in functionally active regions, not just with large vessels and gray matter. Therefore, removing this global signal may eliminate correlated spontaneous neuronal fluctuations that drive the measure of FC.

Conclusion:

Functional connectivity analysis can be effectively implemented during overt speech with an appropriate paradigm design. Significant differences in the functional connectivity in ASD compared to TD subjects were observed even after regressing out task-related effects, subject motion, and global signal changes. This finding suggests that the disruption in functional connectivity in ASD is partially due to differences in task-unrelated neuronal fluctuations. Furthermore, regressing out the global signal should be performed with caution, since this signal may contain interesting task-unrelated neuronal fluctuations that are correlated between regions of the brain.

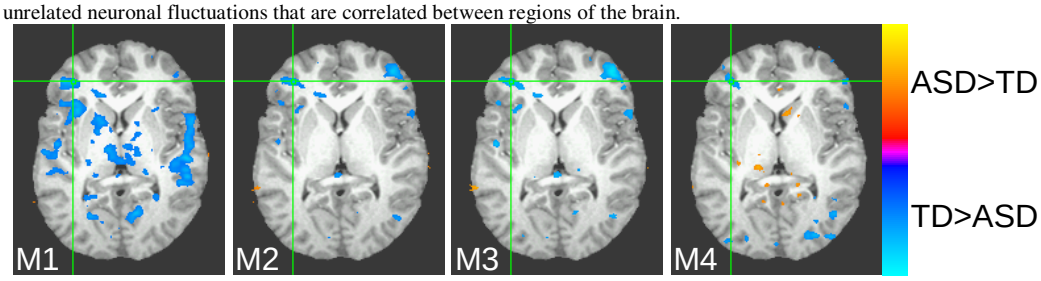

Figure1: T-statistic maps of voxel-by-voxel LFUS2 seed FC differences between groups (ASD, TD) for all pre-processing methods. LIFG focus point, threshold of $p < 0.01$.

M1		LIFG1	LIFG2	LIFG3
LFUS1	ASD	0.395	0.508	0.337
	TD	0.599	0.679	0.576
LFUS2	ASD	0.540	0.716	0.529
	TD	0.689	0.816	0.689
LFUS3	ASD	0.387	0.554	0.382
	TD	0.517	0.609	0.505

M2		LIFG1	LIFG2	LIFG3
LFUS1	ASD	0.369	0.516	0.385
	TD	0.506	0.610	0.538
LFUS2	ASD	0.471	0.689	0.500
	TD	0.595	0.763	0.656
LFUS3	ASD	0.303	0.503	0.349
	TD	0.430	0.545	0.485

M3		LIFG1	LIFG2	LIFG3
LFUS1	ASD	0.381	0.532	0.396
	TD	0.541	0.622	0.548
LFUS2	ASD	0.461	0.684	0.488
	TD	0.581	0.752	0.642
LFUS3	ASD	0.321	0.521	0.362
	TD	0.433	0.551	0.489

M4		LIFG1	LIFG2	LIFG3
LFUS1	ASD	-0.024	-0.048	-0.063
	TD	0.056	0.048	0.020
LFUS2	ASD	0.051	0.221	0.036
	TD	0.117	0.288	0.137
LFUS3	ASD	0.074	0.247	0.111
	TD	0.147	0.270	0.205

Table 1: Group average correlation coefficients for LFUS/LIFG interactions for all pre-processing methods. Highlighted cells show significant differences ($p < 0.05$) between groups.

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