Increased variability across time accounts for reduced connectivity within the default mode network in autism: a dynamic fcMRI study

Maryam Falahpour[1], Wesley K. Thompson[2], Angela E. Abbott[3], Mark E. Mulvey[3], Michael Datko[3], Ralph-Axel Müller[3], and Thomas T. Liu[1]
[1]*Center for Functional MRI, University of California San Diego, La Jolla, CA, United States,* [2]*Department of Psychiatry, University of California San Diego, La Jolla, CA, United States,* [3]*Brain Development Imaging Lab, Department of Psychology, San Diego State University, CA, United States*

Purpose: fMRI resting state studies of people with autism spectrum disorder (ASD) have revealed altered functional connectivity (FC) in the default mode network (DMN), as compared to typically developed (TD) subjects [1-5]. As there is a growing understanding that functional connectivity can vary across time [6], we hypothesized that the group differences in FC might reflect differences in the temporal variability of the FC measures. To test our hypothesis, we examined the relation between FC and the temporal variability in FC between the two major nodes of the DMN, the posterior cingulate cortex (PCC) and the medial prefrontal cortex (mPFC) [2, 3, 7].

Methods: We selected 356 (213 TD, 143 ASD) low motion participants from the Autism Brain Imaging Database Exchange (ABIDE; http://fcon_1000.projects.nitrc.org/indi/abide/) [7]. Resting state data were time-shift and motion corrected, co-registered to the anatomical image and resampled to 3mm^3 isotropic voxels. Nuisance regressors removed from data included: 1) linear and quadratic trends, 2) six motion parameters and their first derivatives 3) mean WM and CSF signals and their first derivatives. Then each functional volume was spatially smoothed to 6mm FWHM, and transferred to standard space (MNI). Average ROI time series for PCC and mPFC were extracted using masks defined as 6mm-radius spheres using the coordinates described in Van Dijk et al [8]. Data were also lowpass filtered to f<0.1 Hz. To minimize the effects of motion in the BOLD signal, only data points with root sum of the squares of the derivatives of all motion parameters, and frame-wise displacement (FD) [9] less than 0.25mm were retained. Additionally, the 5 time points after each motion event [9] and BOLD signal outliers were also censored from the time series. Sliding window correlation was performed between the ROI time series with a window length of 30 seconds and time shift of 10 seconds. In each window if more than 6 seconds of data were censored, the window was excluded. Participants with fewer than 22 usable windows were excluded. For all remaining subjects, 22 windows were selected to form the sliding window correlation time series. For each subject, "FC" was calculated as the static correlation between the ROI time series, and "Std FC" was calculated as the standard deviation of the sliding window correlation time series. From the remaining sample, 85 participants per group (170 total), who passed all the aforementioned critera for censoring and were matched on age, sex, nonverbal IQ, handedness, motion and eye status at scan, were included for further analysis. ***Mediation analysis***: Mediation analysis evaluates the effect of a third variable (mediator) on the relation between the other two variables [10]. There are three linear models for the causal steps mediation statistical analysis, 1)$Y = d1 + cX + e1$, 2)$Y = d2 + c'X + bM + e2$, and 3)$M = d3 + aX + e3$, where Y is the dependent variable, X is the independent variable, M is the mediator, *d1, d2* and *d3* are intercepts, and *e1, e2* and *e3* are residuals [10]. Here we used the grouping factor (e.g. ASD or TD) as the independent variable (X), Std FC as the mediator (M), and static FC as the dependent variable (Y). Using this analysis we investigated whether adding the mediator (Std FC) in the model (equation 2) would significantly change the relation between the dependent and independent variable, i.e. the difference in FC between the two groups.

Results and Discussion: As compared to TD subjects, ASD subjects exhibited significantly lower FC (t(168)= -3.04, p=0.003) and significantly higher Std FC (t(168)=2.49, p=0.014). As shown in the left panel of Figure 1, FC showed a significant negative correlation with Std FC for both the ASD (r=-0.46, p=9×10^{-6}) and TD (r=-0.54, p=8×10^{-8}) groups. The red and blue horizontal lines show the FC group means for ASD and TD, respectively, and the vertical lines indicate the Std FC group means. There was a significant mediated effect ($c - c'$) (p=0.016), which indicates that the group difference in FC can largely be accounted for by the mediating variable (Std FC). This result suggests that the previously reported underconnectivity between PCC and mPFC in the ASD subjects may be in part due to higher temporal variability in functional connectivity in the ASD population.

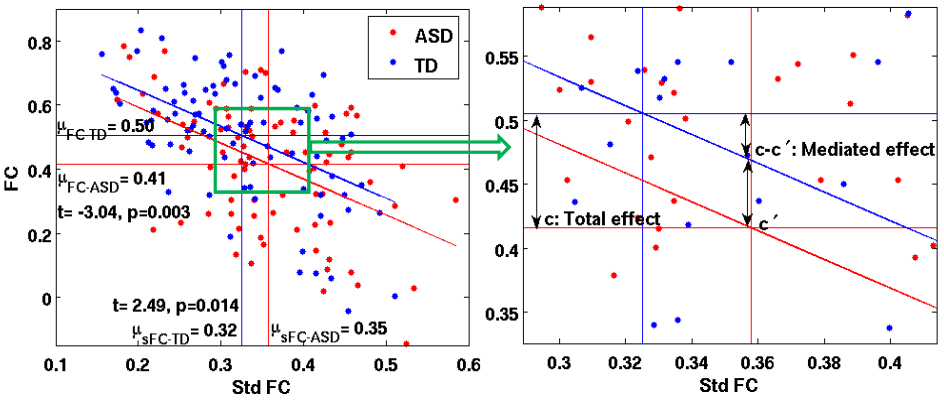

Figure 1. Left: Relation between static FC and Std FC between PCC and mPFC across subjects. Right: Zoomed-in view to show the total effect (c = difference in mean FC), and the mediated effect ($c - c'$).

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