

## Altered Cerebral Effective Connectivity in Theory-of-Mind in Autism Spectrum Disorders

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### Introduction:

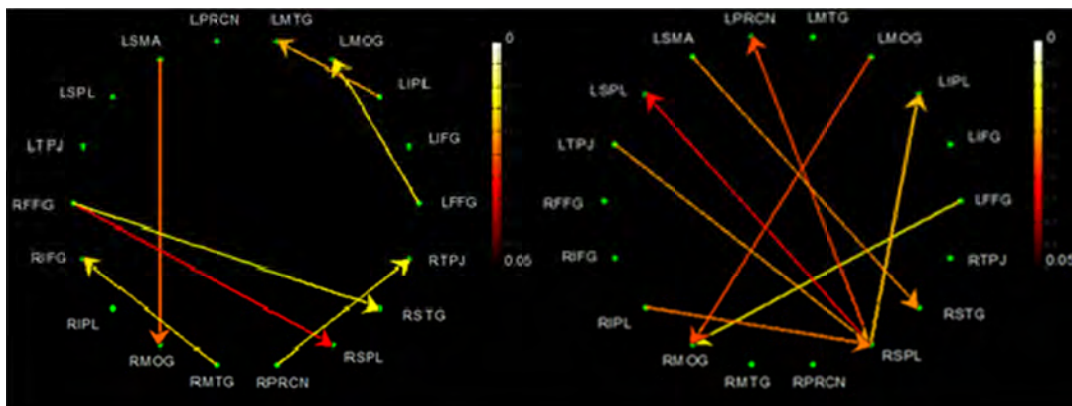
Recent theories of neurobiological functioning in autism have suggested interregional connection abnormalities as a hallmark of the pathobiology of autism [1,2]. Altered functional and anatomical connectivity have been reported widely in complex cognitive and social tasks in autism in the last few years. While disrupted cortical connectivity may be an explanatory model for autism, an important piece missing in these studies is about effective connectivity, the causal influence of a brain area on another. The current study focuses on addressing this in an fMRI study of Theory-of-Mind (ToM) in high-functioning adults with autism. Previous studies of ToM in autism have found altered functional connectivity among core brain areas. The long-term goal of the present study is to examine effective connectivity to derive a comprehensive picture of the nature of brain response in autism.

### Method:

Fifteen high-functioning adults with autism and 15 typically developing control participants viewed a series of comic strip vignettes in the fMRI scanner. After each strip, participants were asked to choose the most logical end to the story from three alternatives. In one experimental condition (physical causality), participants relied on laws of physics to arrive at their judgment and in the other (intentional causality) they relied on social rules or ToM. fMRI data were acquired on a Siemens 3T Allegra scanner with a TR of 1000ms. Mean time series were extracted from 18 different activated regions of interest (ROIs) for all participants. The extracted time series were normalized and the hemodynamic response de-convolved using a cubature Kalman filter [3] to get the underlying neuronal response, which were input into the multivariate autoregressive model (MVAR) [4,5] and connectivity matrices were obtained for each of the 15 autistic and control participants. After this, a t-test was performed on the connectivities to examine the paths which were significantly different between the groups ( $p < 0.05$  corrected). Using mediation analysis [6], the paths which significantly mediated the relationship between subject category (i.e. autistic or control) and 10 different behavioral measures, were obtained.

### Result:

Fig 1 shows the paths which were significantly stronger in controls than in Autistics and also significantly mediated the relationship between subject category (i.e. control or autistic) and behavioral scores. Of most interest are two specific results: a) In control participants, significantly more than in autistic participants, Autism Quotient (AQ) was mediated by the causal connections from right middle temporal gyrus (RMTG) to right inferior frontal gyrus (RIFG), from right ventral premotor (RPRCN) to right temporoparietal junction (RTPJ), and from right fusiform gyrus (RFFG) to right superior temporal gyrus (RSTG); and b) In control participants, significantly more than in autistic participants, the Mind in the Eye task (MIE) score was mediated by the causal connections from left FFG to right middle occipital gyrus (RMOG), from left TPJ to right superior parietal lobule (RSPL), and from RSPL to left PRCN.



**Fig.1** Paths significantly stronger in controls than autism and also mediating AQ (left) and MIE (right scores)

### Discussion:

The main findings of this study can be summarized as follows: 1) There was significantly weaker causal relation between key ToM areas (e.g., LIPL to LIFG, RMTG to RPRCN) in participants with autism relative to typical controls; 2) Mediation analysis involving several neuropsychological and diagnostic measures and causal connections in the brain revealed significant connectivity mediators. The findings mainly suggest reduced information flow from temporal and parietal regions to frontal regions in participants with

autism relative to controls. Information transfer from superior temporal and inferior parietal (associated with biological motion and ToM) to ventral premotor and inferior frontal areas (associated with simulation, and goal detection) may be vital in making intentional causal attributions. The present findings provide an important corollary to previous findings of functional connectivity impairments in this circuitry in autism. In addition, our findings of key neuropsychological measures like MIE and AQ scores being mediated by causal relations of temporal/parietal to frontal connections is interesting, especially when the mediating paths were weaker in participants with autism compared to controls. Overall, the findings from this study provide an important element in building a comprehensive account of brain connectivity in people with autism spectrum disorders.

### References:

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