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Differential role of temporoparietal junction and medial prefrontal cortex in causal inference in autism: An independent component analysis

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HIGHLIGHTS

- This fMRI study examined Theory of Mind (ToM) and brain in adults with autism.
- Stimuli required participants to make intentional and physical causal attribution.
- We used independent component analysis to examine brain responses.
- We found reduced brain response in autism in right temporoparietal junction.
- TPJ response to ToM was more robust than medial prefrontal cortex response.

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ABSTRACT

Neuroimaging studies have consistently identified a network of brain regions responsible for making inferences of others' mental states. This network includes the medial prefrontal cortex (MPFC), posterior superior temporal sulcus (pSTS) at the temporoparietal junction (TPJ), and temporal poles. Although TPJ and MPFC are key nodes of the Theory of Mind (ToM) network, their relative functional roles are still debated. This study sought to examine the contribution of these regions in causal attribution and to explore the nature of the ToM network in people with autism spectrum disorders (ASD). Participants watched a series of comic strip vignettes in the MRI scanner, and identified the most logical ending to each vignette, which sometimes required intentional causal attribution. Independent component analysis was done to isolate temporally correlated brain networks. The functional networks for intentional causality included the TPJ and MPFC, with an increased contribution of TPJ. There was also a significant group difference in the TPJ, with reduced response in participants with ASD. These results suggest an increased role of TPJ in intentional causality. In addition, the reduced response in ASD in TPJ may reflect their difficulties in social cognition.

1. Introduction

The mindblindness account attributes deficits in Theory of Mind (ToM) as key to the social and communication impairments in ASD [1]. Having a ToM involves recognizing others as intentional agents with beliefs or goals. Previous neuroimaging studies have consistently identified a network of brain regions responsible for inferring others' mental states, including the medial prefrontal cortex (MPFC), posterior superior temporal sulcus (pSTS) at the temporoparietal junction (TPJ), and temporal poles [2–4].

Although these regions have shown consistent activation in ToM tasks, their specific role in mentalizing is a topic of debate. One argument is that the MPFC is directly involved in inferring mental states, while the TPJ supports it by gathering important cues of intentionality and causality [5]. Another proposal suggests the TPJ has dual roles of attributing mental states to others as well as integrating those attributions to explain and predict behavior [3,6]. These findings imply the sensitivity of TPJ to intentionality. However, TPJ functional specialization does not reach full development until late childhood or early adolescence [7], which may explain why some individuals with ASD display delayed development of basic mentalizing ability [8]. Specific to ASD, previous studies have

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reported diminished activation in the MPFC and TPJ, as well as weaker connectivity between them [9–11].

Some of the discrepancy regarding the specific roles of the nodes of the ToM network may be due in part to the inconsistency of the type of tasks used, as well as, to the specific regions of interest (ROI) examined in different studies. With new neuroimaging multivariate methods, such as the application of independent component analysis (ICA), we now can identify functionally relevant neural networks elicited by cognitive tasks. The benefit of this approach is that ICA has the advantage of being data-driven without the need of a seed voxel or temporal filtering [12]. As such, ICA uses algorithmic constraints so that each voxel in a component that has the same time course can be considered a functionally connected network without being limited to a priori ROIs. Since ICA methods do not impose prior constraints on the shape of the HRF, it might detect responses that would not have been revealed by a General Linear Model (GLM) analysis. In addition, ICA can be correlated to the time-course of the fMRI task in order to determine which functional networks are being elicited by the specific task. Indeed, studies have used ICA successfully in identifying functional networks in healthy individuals during performance of a task [12–15]. However, to our knowledge, this is the first study to assess task related brain responses using ICA in ASD. Previous neuroimaging studies in ASD using ICA have thus far focused solely on the resting state network (e.g., [16,17]. While there is considerable overlap between the resting state network and the ToM network, further deduction of the differential roles of individual nodes of the ToM network can be conducted using ICA with ToM task-related data.

In the present study, we used group ICA in order to differentiate key functional networks associated with ToM in a causal inference task. Specifically, we presented a pictorial causal inference task known to elicit robust activation of the ToM network [2,18,19]. The type of task chosen is critical, as it is unclear whether all previous ToM tasks used in neuroimaging studies were optimal in eliciting activity from all regions of the ToM network (see [11] for commentary on ToM task selection). Traditional ToM tasks, such as verbal stories or narratives are language-oriented and the performance of individuals with ASD might be confounded by linguistic constraints. The current study avoids this bias by using non-verbal social situations. This task depicted scenarios that required either a physical causal attribution or an intentional causal attribution to build a logical ending to the scene. We hypothesized that the ASD group will differ in their brain responses, from control participants only in intentional causal attribution. Based on the altered connectivity accounts of ASD [10,20], we expect individuals with ASD to show weaker connectivity between brain regions in the independent functional networks underlying intentional causal attribution, specific to the TPJ. We also predicted that the TPJ would play a decisive role in mentalizing, with the MPFC taking on the role of more auxiliary functions involved in ToM processes such as response selection and inhibitory control [21]. And lastly, based on the functional underconnectivity hypothesis of autism, we expect that the top component for ASD will show weaker connectivity between brain regions when compared with age-matched controls.

2. Materials and methods

2.1. Participants

Fifteen high-functioning young adults with ASD (all male, one left-handed) and twenty-one typical control participants (all male, right-handed) were included in this study. The participants with ASD had received a diagnosis based on the Autism Diagnostic Interview-Revised (ADI-R) [22] symptoms, Autism Diagnostic Observation Schedule (ADOS) [23], and clinical impressions. Six of the 15 participants with ASD had received a diagnosis of Asperger's Disorder. The ASD and control participants did not significantly differ in age (21.4 ± 3.9, ASD and 22.6 ± 4.2, Control: $t(34) = -0.728$, $p = 0.473$). The mean Wechsler Abbreviated Scale of Intelligence (WASI) full scale intelligence quotients for the two groups were not significantly different (105.2 ± 17.7, ASD and 113.3 ± 8.4, Control: $t(34) = -1.336$, $p = 0.194$). Participants were excluded on the basis of metal implanted in their bodies, history of kidney disease, seizure disorder, diabetes, hypertension, anemia, or sickle cell disease.

The control participants were screened through a parent-report (for participants younger than 18 years) or self-report (for participants older than 18 years) history questionnaire that asked if the participant had ever been diagnosed with Autism, Asperger's Disorder, PDD-NOS, Attention Deficit Hyperactivity Disorder, a Learning Disability, Mental Retardation, Cerebral Palsy, or Tourette's/Tic Disorder. All participants or their legal guardians gave written informed consent, approved by the UAB Institutional Review Board, to participate in the study and were compensated for their participation.

2.2. Experimental stimuli

The stimuli consisted of a series of black and white comic strip vignettes (adapted from [18]) depicting scenarios that demand either a physical causal attribution or an intentional causal attribution. The first part of the vignette was presented for 5 s and the participants' task was to choose a logical ending to the story from the three choices in the second panel presented for 6 s. The whole vignette remains on the screen for a total of 11 s. Participants were to indicate the answer by a button press. Participants viewed a total of 11 physical cartoons, and 11 character (intentional) cartoons (Supplemental Fig. 1) presented in an event-related design.

2.3. Data acquisition

Functional MRI data were collected on a Siemens 3.0 Tesla Allegra head-only scanner. A single-shot gradient-recalled echo-planar pulse sequence was used for rapid image acquisition (TR = 1000 ms, TE = 30 ms, flip angle = 60°). Seventeen adjacent oblique-axial slices were acquired in an interleaved sequence with 5 mm slice thickness, 1 mm gap, a 24 cm × 24 cm field of view, and a 64 × 64 matrix, resulting in an in-plane resolution of 3.75 mm × 3.75 mm × 5 mm.

2.4. fMRI data analyses: preprocessing

fMRI data were pre-processed and statistically analyzed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK). Images were motion-corrected using *INRIalign*, an algorithm unbiased by local signal changes [24]. After motion correction, a mean functional image was computed for each separate study and then matched to the EPI template provided within SPM8. Data were then spatially normalized to standard Montreal Neurological Institute (MNI) brain space and spatially smoothed using a three-dimensional Gaussian kernel of 8 mm full-width at half-maximum (FWHM).

2.5. fMRI data analyses: independent component analysis

After the data were preprocessed in SPM8, all 36 participants were included in a group independent component analysis (ICA) [13] using the fMRI Group ICA Toolbox (GIFT; http://icatb.sourceforge.net/, version 1.3e). A total of 34 independent components were estimated using dimensionality estimation performed using the minimum description length criteria, modified to account for spatial correlation [25]. The GIFT toolbox organizes the data into batch scripts, with the first script compressing the