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Executive Dysfunction in Autism Spectrum Disorder Is Associated With a Failure to Modulate Frontoparietal-insular Hub Architecture

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ABSTRACT

BACKGROUND: Comorbid executive dysfunction in autism spectrum disorder (ASD) is a barrier to adaptive functioning, despite remittance of core social-communication symptoms. Network models of ASD address core symptoms but not comorbid executive dysfunction. Following recent demonstrations in healthy adults that, with increasing executive demands, hubs embedded within frontoparietal-insular control networks interact with a more diverse set of networks, we hypothesized that the capability of hubs to do so is perturbed in ASD and predicts executive behavior.

METHODS: Seventy-five 7- to 13-year-old children with ASD (n = 35) and age- and IQ-matched typically developing control subjects (n = 40) completed both a resting-state and a selective attention task functional magnetic resonance imaging session. We assessed changes in the participation coefficient, a graph theory metric indexing hubness, of 264 brain regions comprising 12 functional networks between the two sessions. Parent reported executive impairment in everyday life was measured using the Behavior Rating Inventory of Executive Function.

RESULTS: The participation coefficient of the frontoparietal-insular cortex, including core nodes of the frontoparietal control and salience networks, significantly increased in typically developing children but not in children with ASD during the task relative to rest. Change in frontoparietal-insular participation coefficient predicted Behavior Rating Inventory of Executive Function scores indexing the ability to attend to task-oriented output, plan and organize, and sustain working memory.

CONCLUSIONS: Our results suggest that executive impairments in ASD emerge from a failure of frontoparietal-insular control regions to function as adaptive and integrative hubs in the brain's functional network architecture. Our results also demonstrate the utility of examining dynamic network function for elucidating potential biomarkers for disorders with comorbid executive dysfunction.

Keywords: Autism, fMRI, Frontoparietal, Graph theory, Hubs, Networks

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Functional network–level investigations of autism spectrum disorder (ASD) pathophysiology have focused primarily on social cognition, despite pervasive impairment in another domain, executive function (EF), the goal-oriented control of cognition. Comorbid EF impairment is observed in 41% to 78% of cases (1), increases with age (2,3), and persists despite amelioration of ASD symptoms (4). This impairment in ASD spans component processes of EF (e.g., inhibition, shifting, working memory, planning/organization) (5), moderates defining ASD symptoms (6), and predicts worse adaptive functioning (7,8) as well as quality of life (3). Current hypotheses of ASD, which posit pathophysiology of network-level dysfunction, target core social-communicative symptoms (9), but leave open our understanding of comorbid executive dysfunction.

EF is supported by frontoparietal and salience/cingulo-opercular functional networks anchored in the prefrontal cortex (PFC), collectively termed control networks (10). A long-standing theory posits that PFC enables adaptive goal-oriented behaviors by integrating information from distributed cortical regions (11). Indeed, functional connectivity (FC) of PFC control regions increases with a diverse array of brain regions (i.e., those belonging to other networks) during tasks evoking EF processes (12,13). Select nodes within control networks, often identified as hubs, are posited to enable these widespread interactions by integrating information from multiple brain networks (14,15). Dysfunction of control network hubs is a candidate mechanism for EF impairment in ASD, as pervasive EF deficits could result from an inability of hubs to interact widely with other networks or serve as convergence

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zones (16) when it is necessary to adapt to new behavioral demands.

While a growing body of work has established disruption of large-scale functional networks in ASD (16–18), the integrity of integrative processing within the PFC remains unexamined. Findings from studies using task (17,18) and task-free (i.e., resting-state) experimental designs (19–23) reveal atypical FC in children and adults with ASD, including both weaker and stronger FC relative to typically developing (TD) control subjects (24). Contrasting task states requiring EF relative to rest, atypical FC changes were observed between a subset of brain network nodes (25) and among voxelwise long-distance connections (26) in children with ASD. While this evidence suggests a possible maladaptive response of brain networks to task demands in ASD, whether hubs within PFC are instrumental in that response is not known. Here we tested the hypothesis that EF impairment in ASD results from the frontoparietal control network failing to adaptively integrate information from throughout the brain.

We examined changes in hubness across the entire brain between two cognitive states in children with ASD and their TD peers. In the brain, hubness can be quantified using participation coefficient (PC), a graph theoretical measure capturing the diversity of a brain region's FC with all other networks (27). Often hubs are thought of as individual nodes, however, groups of nodes comprising functional networks, such as the frontoparietal network (28), can collectively carry out an integrative function. For this reason, we examined network-level PC by averaging the PC of all nodes within a given network in addition to examining the PC of individual nodes.

We manipulated EF demands across two cognitive states: resting state, signifying an absence of EF demands, and a selective attention task requiring monitoring a target shape in the context of distractors, signifying the presence of EF demands. Contrasting the resting state and task state allows examining adaptation to EF demands, which may manifest as changing FC patterns between hub regions and the rest of the brain (28). Specifically, we predicted that the PC of control networks, both at the network level and the nodes contained within, would increase in the task state in TD but would increase less so in children with ASD. Further, we predicted that these changes in PC would predict EF abilities. We examined EF manifested in stable behavioral characteristics (termed trait level) instead of a performance measure because EF impairments are multidimensional in ASD and EF tasks generally only capture a single dimension of EF (29). Furthermore, the performance of children with ASD in structured settings may not be ecologically representative of their ability to engage and disengage behavior in a goal-oriented manner in daily life (30). For these reasons, we utilized the Behavior Rating Inventory of Executive Function (BRIEF) (31), a commonly used parent-report questionnaire used in clinical settings that is also sensitive to normal EF variability.

METHODS AND MATERIALS

Participant Demographics

Seventy-five participants 7 to 13 years old (35 with a diagnosis of ASD and 40 TD children) participated in the study after complying with consenting guidelines of the Georgetown University and Children's National Medical Center Institutional Review Boards. A final sample of 23 children with ASD was retained after applying strict criteria for head motion to both resting-state and task functional magnetic resonance imaging (fMRI) data (see criteria below). A group of 23 TD children matched for age, IQ, and head motion were selected. Children with ASD were recruited through the Center for ASD at Children's National Medical Center, and TD children were recruited from the Washington, DC, area. This sample partially overlaps with (26). See Table 1 for demographic information.

Exclusion criteria included 1) full-scale IQ below 80 as measured by the Wechsler Intelligence Scale for Children or Wechsler Abbreviated Scale of Intelligence, 2) other neurological diagnosis (e.g., epilepsy) based on parent report, 3) psychiatric diagnosis based on Child and Adolescent Symptom Inventory-4R (32) for control children, and 4) contraindications for MRI. Five children with ASD were prescribed stimulant medication, which was withheld for at least 24 hours before fMRI data acquisition; no other children were medicated.

ASD classification followed diagnosis by author LK and staff based on DSM-IV-TR criteria and was confirmed with the Autism Diagnostic Interview-Revised (33) and the Autism Diagnostic Observation Schedule, Module 3 (34) following the criteria established by the National Institute of Child Health and Human Development/National Institute of Deafness and Other Communication Disorders Collaborative Programs for Excellence in Autism. These criteria require that the child meet the Autism Diagnostic Interview-Revised cutoff for autism in the social domain and at least one other domain (communication and/or repetitive behaviors and restricted interests), or meet Autism Diagnostic Observation Schedule, Module 3 cutoff for the combined social and communication score.

Table 1. Participant Demographics

	Age (years)	Full-Scale IQ	BRIEF-MI	BRIEF-BRI	ADOS-Social	ADOS-Communication	ADOS-Restricted/Repetitive Interests	ADI-Social	ADI-Restricted/Repetitive Interests	ADI-Communication
TD	11.33 ± 0.33	119.59 ± 2.76	46.75 ± 1.81	44.30 ± 1.22	—	—	—	—	—	—
ASD	11.18 ± 0.34	120.43 ± 2.87	66.09 ± 2.61	63.77 ± 2.86	7.14 ± 3.52 (2–14)	3.14 ± 1.59 (1–7)	1.74 ± 1.67 (0–5)	20.85 ± 4.87 (13–28)	4.80 ± 1.91 (1–9)	15.95 ± 4.60 (7–24)

Values are mean ± SD (range).

ADI, Autism Diagnostic Interview; ADOS, Autism Diagnostic Observation Schedule, Module 3; ASD, autism spectrum disorder; BRI, Behavioral Regulation Index; BRIEF, Behavior Rating Inventory of Executive Function; MI, Metacognition Index; TD, typically developing.