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Brief Report - Basic Science

Resting-State Functional Connectivity of the Cerebellum Differs Between Persons With Inflammatory Bowel Disease and Healthy Controls in Relation to Executive Function

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Lay Summary

Persons with inflammatory bowel disease exhibit a weaker relationship between executive function and functional connectivity of cerebellar regions (VIIa Crus I and VIIa Crus II) to cortical areas involved in visual processing compared to healthy counterparts with comparable performance.

Key Words: inflammatory bowel disease, functional magnetic resonance imaging, executive functioning, functional connectivity, cerebellum

Introduction

Persons with inflammatory bowel disease (IBD) experience cognitive deficits, including impaired executive functioning (EF), more often than in the general population.[1] The neural mechanisms underlying impaired EF in IBD are not known. Studies in cognitive neuroscience have established the role of the cerebellum in EF, with right hemisphere lateralized regions VI, VIIa Crus I, and VIIa Crus II implicated in EF specifically.[2] Previous work has shown differences between people with IBD and a healthy control group in the way the cerebellum functions in relation to the rest of the brain using resting-state functional connectivity (FC) analysis.[3] Resting-state FC is a measure of the temporal synchrony of functional magnetic resonance signal between anatomically separated brain regions during wakeful rest.[4] Here, we hypothesize that there will be a difference between IBD and HC in their relationship between cerebellar resting-state FC and scores on a separately performed EF task. Establishing if EF is associated with different resting-state FC of cerebellar regions for persons with IBD will expand our understanding of brain–gut axis dysregulation in IBD and support future investigation of EF impairment as a comorbidity of the disease.

Methods

Participants

Participants with IBD were recruited through a parent longitudinal study in immune-mediated inflammatory disease (IMID study).[5] Healthy controls (HC) were recruited through an IMID substudy.[6] The IMID study and substudy were approved by the University of Manitoba Health Research Ethics Board. All participants signed an informed consent form. Eighty-four participants with confirmed diagnoses of IBD and 100 HC were recruited. Participants with incomplete MRI data were not considered further, resulting in a sample of 72 participants with IBD and 90 HC.

Measures

Date of birth and gender were recorded for all participants. For participants with IBD, disease-modifying medication use, disease duration, IBD subtype, disease severity, and disease phenotyping were recorded. Executive function was measured using a test in the Delis–Kaplan Executive Function System.[7] Specifically, this study used the inhibition and rule-switching task of the color-word interference test as a measure of EF, where scores reflect the participant's number of errors and time to completion and, therefore, higher scores indicate worse performance.

Image Acquisition

Whole-brain anatomical and resting-state functional images were acquired on a 3T Siemens TIM Trio MRI system with a Siemens 32-channel receive-only head coil (Siemens Healthcare). The complete imaging parameters for the HC group are described in a separate protocol paper[6] and identical parameters were used for the IBD group.

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Data Analysis

Participant demographics and clinical presentation

Descriptive statistics were calculated for age, gender, and EF scores for all participants and, for the IBD group, disease-modifying medication use, IBD type, disease duration, activity, and phenotype. To assess differences between the IBD and HC groups, independent samples *t*-tests were run for age and EF scores and a chi-square test for gender.

Image analysis

Functional and anatomical data were preprocessed using default settings in a CONN toolbox preprocessing pipeline (CONN toolbox v18.b).[8] Functional and anatomical data were normalized into standard Montreal Neurological Institute space, segmented into gray matter, white matter, and cerebrospinal fluid (CSF) tissue classes, and resampled to 2-mm isotropic voxels. Functional data preprocessing included removal of initial 10 scans, realignment, potential outlier scan identification, and smoothing using an 8-mm Gaussian kernel. Functional data were denoised using the default pipeline, including the regression of potential confounding effects of signal from white matter and CSF time series, motion parameters, and any identified outlier scans, followed by bandpass filtering (0.008-0.09 Hz). First-level connectivity matrices were estimated characterizing the FC between each pair of regions among 132 Harvard-Oxford atlas regions of interest (ROIs). A second-level analysis assessed the FC of 3 a priori selected cerebellar ROIs (right VI, VIIa Crus I, and VIIa Crus II) simultaneously with all other brain ROIs. Between-group analyses were performed using a general linear model to determine whether the IBD and HC groups differed in FC for any of the cerebellar VI, VIIa Crus I, and VIIa Crus II with ROIs spanning the rest of the brain, while controlling for age. The *F*-test results were thresholded using a combination of a $P < .05$ connection-level threshold and a false discovery rate (FDR)-corrected $P < 0.05$ cluster-level threshold. Planned contrast analyses assessed the main effect of each of the 3 cerebellar ROIs separately while controlling for age with the *T*-tests thresholded at $P < .05$ FDR-corrected. Post hoc analyses were also run without controlling for age to determine whether age had a significant impact on the FC results.

Results

Participant Demographics and Clinical Presentation

Participants with IBD were significantly older than the HC (Table 1). EF scores were significantly worse in the IBD group; however, this difference was no longer significant after correcting for age. Gender did not differ significantly

Table 1. Participant demographics and clinical presentation.

	IBD ($n = 72$)	HC ($n = 90$)	*P*-value
Age	54 ± 14 (22-77)	38 ± 16 (18-81)	$P < .001$
Gender, women	49 (68%)	62 (69%)	$P = .91$
Executive function	60.3 ± 15.97 (32-108)	53.4 ± 10.80 (38-92)	$P < .001$
Medications			
5-ASA oral	19		
5-ASA rectal	4		
Thiopurines	18		
Methotrexate	3		
Antibodies to TNF	23		
Prednisone	1		
Steroid enemas	0		
Ustekinumab	6		
Vedolizumab	3		
None	25		
IBD disease duration	26.2 ± 13.2 (6-57)		
IBD type	49 CD; 23 UC		
CD active/inactive	16/30		
CD phenotype:			
Location	20 L1; 5 L2; 24 L3; 1 L4		
Behavior	17 B1; 17 B2; 18 B3; 5 P		
UC active/inactive	10/11		
UC phenotype	2 E1; 11 E2; 9 E3		

Age, EF, and disease duration are reported in mean ± standard deviation (range). Gender, medication use, IBD type, disease activity, and disease phenotype are reported in number of participants.
Persons may have been on more than 1 disease-modifying medication; therefore, medication use totals do not equal $n = 72$. Data are missing for 3 CD Harvey–Bradshaw scores, 2 UC Powell–Tuck scores, and 1 UC phenotype.
Abbreviations: IBD = inflammatory bowel disease, HC = healthy controls, CD = Crohn's disease, UC = ulcerative colitis, L1 = ileum, L2 = colon, L3 = small bowel/colon, L4 = upper GI which can accompany any of the L1, L2, or L3, B1 = inflammatory, B2 = fibrostenosing, B3 = fistula, P = perianal disease, E1 = ulcerative proctitis, E2 = left sided colitis, E3 = extensive UC/pancolitis.

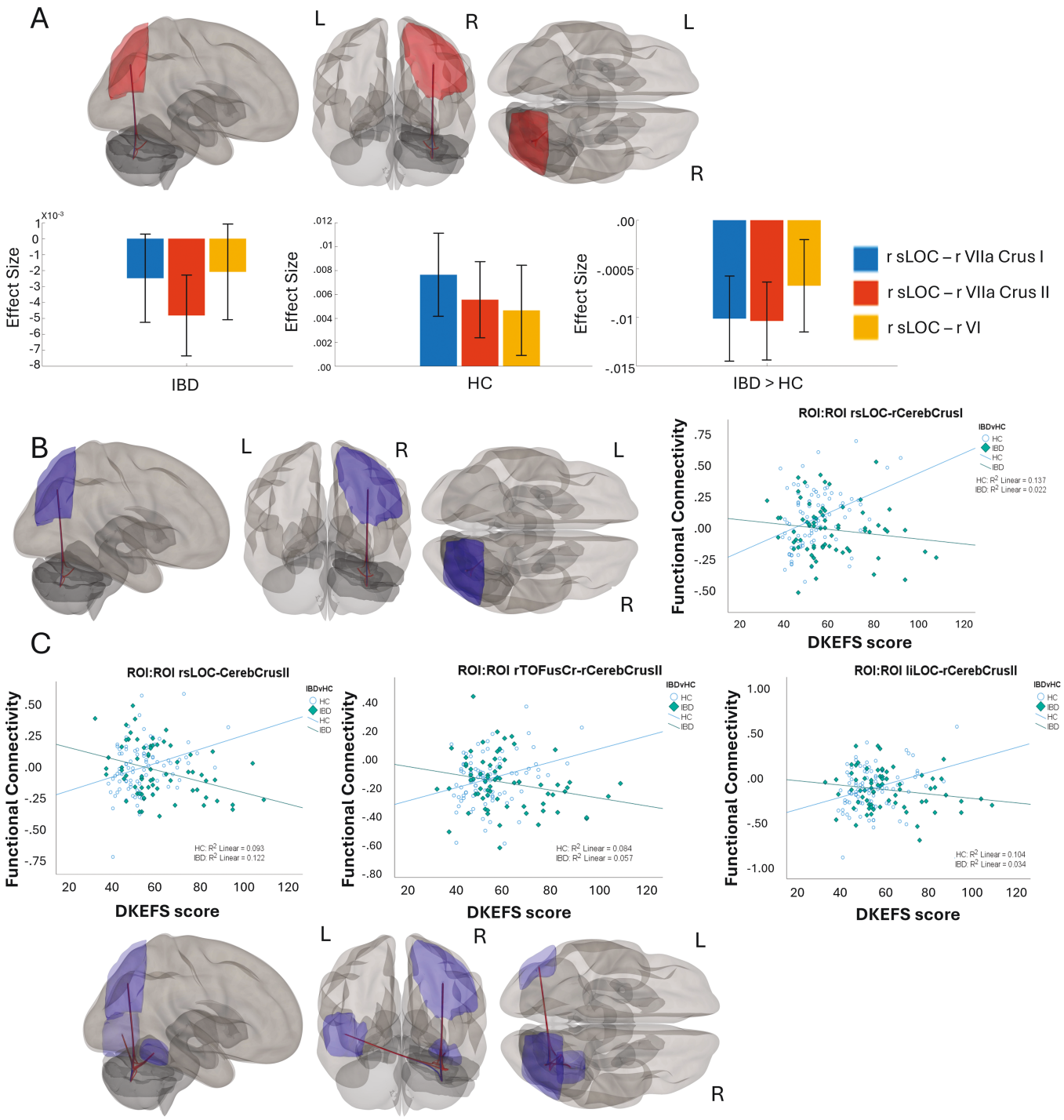

Figure 1. Cerebellar functional connectivity differences between IBD and HC relative to executive function. A) Glass brain (displayed from left to right in sagittal, coronal, and axial views) showing the IBD and HC groups differences for the relationship between functional connectivity and executive function for the right superior lateral occipital cortex with functional connectivity lines from the 3 cerebellar ROIs. Bar graphs of effect size and 90% CI for each connection for the IBD group, HC group, and the IBD > HC contrast are shown below. The between-group difference for cerebellar CrusI and the sLOC is driven by the stronger relationship between FC and EF in the HC group where increasing FC is associated with poorer EF, whereas the IBD group has a weaker, and opposite, relationship between FC and EF, as demonstrated by the bar graphs in (A) and the scatterplot in (B). B) Glass brain (displayed from left to right in sagittal, coronal, and axial views) showing that the relationship between executive function and the cerebellar VIIa Crus I functional connectivity was weaker in the IBD group for its connection with the right superior lateral occipital cortex. The scatterplot of relationship between functional connectivity and executive function for this connection is displayed to the right. C) Glass brain (displayed from left to right in sagittal, coronal, and axial views) showing that the relationship between executive function and functional connectivity was weaker for the IBD group for connections between the cerebellar VIIa Crus II and the right superior lateral occipital cortex, right temporal occipital fusiform, and left inferior lateral occipital cortex. Scatterplots of the relationship between functional connectivity and executive function scores for these 3 connections are shown. ROI = region of interest; L = left; R = right; r sLOC = right superior lateral occipital cortex; IBD = inflammatory bowel disease; HC = healthy controls; r ToFusCr = right temporal occipital fusiform; l iLOC = left inferior lateral occipital cortex.

between groups. Disease-modifying medication use among participants with IBD, IBD type, disease duration, and phenotype are reported in Table 1.

Imaging

A significant difference was observed between the IBD and HC groups for the relationship between EF and FC for the right superior lateral occipital cortex (sLOC; $F(3,153) = 8.38$, p-FDR = 0.004) (Figure 1). Planned contrast analyses revealed that the relationship between FC and EF was weaker for the IBD group for connections involving VIIa Crus I and VIIa Crus II. The relationship between EF and the VIIa Crus I FC was weaker in the IBD group for its connection with the right sLOC ($T = 3.83$, p-FDR = 0.024). The relationship between EF and FC was weaker for the IBD group for connections between the VIIa Crus II and the right sLOC ($T = 4.28$, p-FDR = 0.004), the right temporal occipital fusiform ($T = 3.44$, p-FDR = 0.035), and the left inferior lateral occipital cortex (iLOC; $T = 3.42$, p-FDR = 0.035). The same connections were observed without controlling for age. No significant connections involving cerebellar lobule VI were found.

Scatterplots provide visualization of the differences for each connection (Figure 1). For the HC group, worse EF performance is associated with increased FC between the ROIs, whereas for the IBD group, this relationship was negative or nonsignificant.

Discussion

Research on the neural correlates of EF differences in IBD is scarce. The present study is one of few to examine how EF relates to resting-state FC in IBD and the first to apply an a priori focus on the cerebellar FC changes relative to EF in IBD. Cerebellar regions VIIa Crus I and VIIa Crus II exhibited differences in the association between EF and FC for persons with IBD compared to HC. Scatterplots revealed a consistent interaction across all of the ROI pairings for which the relationship between FC and EF was significantly different between groups. Worse EF performance (higher score) was associated with greater FC in HC, but not in IBD. While correcting for the between-group age difference revealed comparable EF performance, correcting for age in the FC analyses did not add or remove any of the significant relationships identified without controlling for age. Persons with IBD therefore exhibit a divergent relationship between EF and FC compared to HC, even in the context of comparable EF performance.

Notably, although all brain regions were included in the analysis, the cortical regions with which cerebellar VIIa FC differentially related to EF for IBD all involve the occipital cortex. Altered FC of the occipital cortex in IBD has been reported in our previous work and that of others but not in relation to EF. A visual event-related potential study in multiple sclerosis (MS), which is another immune-mediated inflammatory disease, demonstrated that interhemispheric connectivity of the LOC is related to EF dysfunction in MS but not in HC.[9] Work by others demonstrated increased FC between the cognitive cerebellum (a single ROI that included cerebellar VI, VII, IX, X) and the occipital cortex in MS as compared to HC.[10] They further demonstrated that the FC between the cognitive cerebellar ROI and occipital cortex was positively correlated with cognitive function, independent of structural damage. Their results, indicating that higher FC was associated with greater cognitive performance in MS, are contrary to our results indicating that higher FC was associated with poorer cognitive performance in IBD. In our study, however, the IBD and HC groups did not differ in EF performance. The differences in cerebellar VIIa FC with visual processing regions may represent compensatory mechanisms maintaining EF in the IBD group. Conversely, altered cerebellar VIIa FC may precede the development of EF deficits. Longitudinal studies of both EF and FC in IBD would provide clarity.

The present study provides further support for an association between EF and cerebellar FC, in addition to highlighting the role of cerebellar VIIa in distinguishing FC differences between persons with IBD and HC. Limitations of the current study include the participant sample heterogeneity and the use of various disease-modifying medications within the IBD group. Nonetheless, this study provides valuable insight into the role of the cerebellum and the potential neural underpinnings of cognition in IBD.

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Author Contributions

C.N.B. and J.K. shared responsibility for study conception/design; J.K. performed data analysis in consultation with T.A.M., R.P., and R.A.M.; J.K. and T.A.M. drafted the manuscript; C.N.B., R.P., and R.A.M. provided critical revision; all authors reviewed and approved of the final manuscript being submitted.

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Conflicts of Interest

C.N.B. is supported by the Bingham Chair in Gastroenterology. C.N.B. has served on advisory Boards for AbbVie Canada, Amgen Canada, Bristol Myers Squibb Canada, Eli Lilly Canada, JAMP Pharmaceuticals, Janssen Canada, Pendopharm Canada, Sandoz Canada, Takeda Canada, and Pfizer Canada; Educational grants from Abbvie Canada, Boston Scientific, Bristol Myers Squibb Canada, Ferring Canada, Pfizer Canada, Takeda Canada, Janssen Canada, Organon Canada, Eli Lilly Canada, and Amgen Canada. Speaker's panel for Abbvie Canada, Janssen Canada, Pfizer Canada, and Takeda Canada. Received research funding from Abbvie Canada, Amgen Canada, Sandoz Canada, Takeda Canada, and Pfizer Canada. R.A.M. receives research funding from: CIHR, MS Canada, Crohn's and Colitis Canada, National Multiple Sclerosis Society, CMSC, US Department of Defense, the Arthritis Society, and Pfizer Foundation. She is supported by the Gillian's Hope Chair in Multiple Sclerosis. She is a co-investigator on a study funded by Roche Canada and Biogen Idec. J.K., T.A.M., and R.P. have nothing to declare.

Data Availability

The authors do not have permission to share data.

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