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The effects of gastrointestinal symptoms on structural grey matter volume in youth

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Abstract

Previous neuroimaging studies have examined the association between changes in brain structure and gastrointestinal symptoms (GIS), seen in disorders such as Irritable Bowel Syndrome and Irritable Bowel Disease. Studies in adults have found changes in white and grey matter volume (GMV) in patients with various gastrointestinal disorders. However, it is unclear whether GIS-related structural changes in the brain are limited to adults or could be present throughout the lifespan. Given that gastrointestinal disorders are typically diagnosed between 4 and 18 years old, we investigated GIS-induced morphological changes in pre-adolescents (8–10), adolescents (12–16 years) and young adults (17–21 years). Using a voxel-based morphometry (VBM) analysis, we compared regional grey matter volume (GMV) between participants with GIS and controls, using structural brain images from the Philadelphia Neurodevelopmental Cohort (PNC) database. A total of 211 participants (107 participants with GISs and 104 control participants) who had undergone structural magnetic resonance imaging were analysed. VBM analysis was used to objectively analyse GMV across the whole brain and compare between participants with GIS and controls. Participants experiencing GIS showed smaller GMV in regions within the limbic system/basal ganglia (bilateral caudate, bilateral ventral hippocampus, bilateral amygdala and bilateral superior orbital frontal cortex), and larger GMV in regions within the pain-matrix (thalamus, bilateral putamen, right mid-frontal gyrus) compared to controls. These differences were most prominent in the adolescent and young adult groups compared to pre-adolescents. In conclusion, the structural differences found in participants with GIS support the need for further research into the neurophysiological impact of these symptoms.

KEYWORDS

adolescence, fMRI, gastrointestinal disorders, gut-brain axis, neuroimaging, voxel-based morphometry

1 | INTRODUCTION

Gastrointestinal disorders are defined as disturbances of the gut-brain axis that occur without organic pathology (Drossman & Hasler, 2016) and may occur following an enteric infection that is associated with persistent immune activation (Rani, Ali, & Lee, 2016). Common disorders include irritable bowel syndrome (IBS) and irritable bowel disease (IBD). IBS is a disorder of the brain-gut axis involving specific symptoms such as recurrent abdominal pain and altered bowel movements that are not related to structural or biochemical abnormalities (Bhatt et al., 2019). IBD, on the other hand, occurs as a result of the activation of the mucosal immune system and the disruption of the epithelial barrier by the intestinal microbiota which might be influenced by genetic factors. IBD includes ulcerative colitis (UC) and Crohn's disease (CD) (Collins, Piche, & Rampal, 2001; Piche et al., 2010; Vivinus-Nébot et al., 2014). Gastrointestinal disorders and their corresponding symptoms are highly prevalent in the general population and in children, in particular. For example, IBS consists of well-known gastrointestinal symptoms (GIS) and affects 9%–23% of the general population (Oświęcimska, Szymlak, Roczniak, Girczys-Połedniok, & Kwiecień, 2017; Saha, 2014). It is most prevalent in children between the ages of 4 and 18 (Korterink, Diederen, Benninga, & Tab bers, 2015; Oświęcimska et al., 2017). Moreover, up to 17% of adolescents in middle- and high-school fit the criteria for IBS diagnosis as they experience multiple symptoms (Hyams, Burke, Davis, Rzepski, & Andrulonis, 1996). While the causes of gastrointestinal disorders remain elusive, they may be associated with chronic inflammation (Baumgart & Carding, 2007; Ng et al., 2017) and immune activation (Rani et al., 2016), altered gut microbiota and psychological disorders, like anxiety and depression (García Rodríguez, Ruigómez, Wallander, Johansson, & Olbe, 2000; Graff, Walker, & Bernstein, 2009; Mikocka-Walus et al., 2007; Rani et al., 2016).

Adolescence is a critical period of development as it results in physiological changes as well as social and cognitive maturation (Sisk & Foster, 2004). During this transitional period to adulthood, adolescents experience a variety of psychosocial stressors. The presence of certain stressors can increase the prevalence of psychiatric illnesses during this period (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003). The influx of gonadal steroid hormones during this period induces rapid physiological changes as well as significant brain reorganization and remodelling (Levitt, 2003; Sisk & Foster, 2004; Sisk & Zehr, 2005). Regional grey matter (GMV) and white matter (WMV) volumes as well as cortical thickness also changes during puberty and adolescence (Bramen et al., 2008 ; Herting et al., 2014; Neufang et al., 2009; Peper et al., 2009). GMV development follows an inverted U-shaped trajectory, increasing during childhood, peaking during puberty and steadily declining into adulthood (Giedd et al., 1994, 1999; Giorgio et al., 2010; Neufeld, Luczynski, Oriach, Dinan, & Cryan, 2016; Pfefferbaum et al., 1994; Reiss, Abrams, Singer, Ross, & Denckla, 1996; Sowell, Thompson, Tessner, & Toga, 2001; Sowell et al., 2003). Conversely, WMV follows a linear trend, increasing throughout childhood and adolescence and remaining constant in adulthood (Barnea- Goraly et al., 2005; Giedd et al., 1999; Neufeld et al., 2016). These neural changes indicate that pre-adolescence and adolescence are periods of increased brain plasticity compared to the adult brain. The pre-adolescent and adolescent brains also have greater sensitivity to environmental factors (Hensch, 2004). Exposure to stress and inflammation during adolescence can alter brain functioning in an enduring manner (Burnett, Sebastian, Kadosh, & Blakemore, 2011; Holder & Blaustein, 2014; Neufeld et al., 2016; Spear, 2013). Therefore, any stressor, including one originating in the gut may have a significant impact on brain structure. Due to the complexity of each metric of brain development, GMV was the only measure assessed in this manuscript. Future reports will address other aspects of brain development and brain-gut health.

The central nervous system (the brain) and the enteric nervous system (the gut) form the gut-brain axis and communicate bidirectionally to control physiological functions and overall homeostatic state (Kano, Dupont, Aziz, & Fukudo, 2018; Mayer, 2011). The gut-brain axis provides direct connections between brain regions belonging to the limbic circuit/basal ganglia (i.e. amygdala, thalamus) and the intrinsic neural network of the GI tract (Agostini et al., 2011; Wood, Alpers, & Andrews, 1999). Alterations in the functioning of the gut-brain axis can lead to the development of gut-brain disorders and their corresponding symptoms such as GIS (Mayer, 2011; Mayer, Tillisch, & Gupta, 2015; Rhee, Pothoulakis, & Mayer, 2009). Additionally, the gut-brain axis appears to impact emotional behaviour (Tillisch et al., 2013). For example, individuals experiencing GIDs tend to have increased anxiety (Naliboff & Rhudy, 2009). Additionally, studies have found that alterations of the GMV in regions of the emotional arousal circuit such as the ventral striatum, medial thalamus/midbrain, medial prefrontal cortex, pregenual anterior cingulate cortex (ACC) and orbital frontal cortex are related to anxiety and depression (Seminowicz et al., 2010).

Recent MRI studies suggest that GIS related to gastrointestinal disorders are linked to changes in GMV. For example, male and female patients with Crohn's disease (CD) have decreased GMV in the frontal cortex and the anterior mid-cingulate cortex compared to healthy controls (Agostini et al., 2013). Moreover, girls, aged 7–17 years old, diagnosed with IBS display less GMV in the thalamus, caudate nucleus, nucleus accumbens, anterior mid-cingulate (aMCC) and dorsolateral prefrontal cortex compared to healthy controls (Bhatt et al., 2019). Women with IBS

TABLE 1 Participants scanned

	Experimental			Control		
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
	$N = 31$	$N = 49$	$N = 26$	$N = 30$	$N = 50$	$N = 24$
Females	16	25	18	14	25	16
Males	15	24	8	16	25	8
Age (years)	10.10 ± 0.86	14.46 ± 1.40	18.91 ± 1.17	10.10 ± 0.90	14.58 ± 1.42	19.08 ± 1.16
BMI	18.92 ± 0.23	21.57 ± 0.24	24.23 ± 0.15	19.86 ± 0.17	24.11 ± 0.19	24.03 ± 0.15

also display reduced GMV in the bilateral superior frontal gyrus, bilateral insula, bilateral amygdala, bilateral hippocampus, bilateral middle orbital frontal gyrus, left cingulate, left gyrus rectus, left post-central gyrus, brainstem and left putamen compared to healthy controls (Labus et al., 2014). There is a sex difference in the prevalence of gastrointestinal disorders such as IBS where women are twice more likely to develop the disorder than men (Oświęcimska et al., 2017; Saha, 2014). Due to the higher prevalence of gastrointestinal disorders in women, male-specific studies are limited. However, some sex differences have been reported where male IBS patients display greater, pain-associated activation in the insula compared to females (Labus et al., 2013). Conversely, female IBS patients have greater pain-related activation in the ACC compared to males (Naliboff et al., 2003).

While the current literature reports an association between GISs and structural changes in the adult brain, the effects of GISs on GMV in the pre-adolescent and adolescent developing brain remain poorly understood. The objective of this study was to examine GMV in participants, aged between 8 and 21 years, with GIS and in control participants. Due to the limited literature present on pre-adolescents and adolescents, our study is motivated in examining these age groups. In this novel study, all participants underwent multimodal neuroimaging as part of the Philadelphia Neurodevelopmental Cohort (PNC) (Satterthwaite et al., 2014), a large scale NIMH funded initiative to understand how brain maturation mediates cognitive development and vulnerability to psychiatric illness. Participants of the PNC who self-reported to experiencing GI and digestive problems within the last 6 months of the study were split by age (i.e. 8–11 years pre- adolescent, 12–16 years adolescent and 17–21 years young adult) and compared to those who had not experienced GI problems at all, their age and sex matched control counterparts. It was hypothesized that participants who experience GI and digestive problems would display noticeable deficits in regional GMV compared to their control counterparts. We also hypothesized that due to the increased brain plasticity that occurs during the pre-adolescence and adolescence periods, participants in these groups will display more prominent GIS-induced structural changes in the brain compared to the young adult participants.

2 | MATERIALS AND METHODS

2.1 | Participants

This study acquired MR images from the Philadelphia Neurodevelopmental Cohort (PNC) dataset (https://www.med.upenn.edu/bbl/philadelphianeurodevelopmentalcohort.html). The PNC is an ongoing collaborative study between the Brain Behavior Laboratory at the University of Pennsylvania and the Center for Applied Genomics and the Children's Hospital of Philadelphia. The study sample size consists of 31 pre-adolescent (8–10 years), 50 adolescent (11–16 years) and 26 young adult (17–21 years) participants who reported experiencing GI and/ or digestive problems as well as problems within the last 6 months (Calkins et al., 2014, 2015). These participants were compared against age-matched counterparts: 30 pre-adolescents (8–10 years), 50 adolescents (11–16 years) and 24 young adults (17–21 years) who had not experienced GI or other digestive problems as a control (Table 1). The questions asked were "Do you or did you have any of the following problems?—Gastrointestinal—digestive system, gut (Has Problem?)" and "Is it (gastrointestinal problems) current (within the last 6 months)?". Participants above 18 years of age provided informed consent. For participants under 18 years of age, informed consent was provided by parents. Of the participants who were eligible for inclusion in the present analysis (i.e. those that have experienced GI and/ or digestive problems within the last 6 months and age-matched controls), participants were excluded if they had a history that suggests a potential abnormality of brain development. Participants were excluded if they had a history of inpatient psychiatric hospitalization, a history of a medical disorder that could affect brain structure (e.g. sickle cell, HIV, current or past malignancy or epilepsy), were taking medications with potentially psychotropic effects or had incidentally encountered an abnormality in brain structure. (Institutional review boards at the University of

Pennsylvania and the Children's Hospital of Philadelphia approved the protocol.)

2.2 | Structural magnetic resonance imaging

Structural MRI data were acquired using a 3T Siemens TIM Trio whole body scanner (Siemens AG, Siemens Medical Solutions, Erlangen, Germany) with a 32-channel head coil in the hospital of the University of Pennsylvania. A high-resolution brain anatomic image was obtained for each participant with a T1-weighted MPRAGE sequence (TR/TE 1810/3.5 ms, flip angle (FA) 9°, field of view (FOV) 180 × 240 mm, voxel size = 1×1 × 1 mm, slice thickness = 1 mm, 160 sagittal slices, band-width 130 Hz). Image quality assessment was performed using visual inspection.

2.3 | Structural voxel-based morphometry analysis

T1 structural imaging data were analysed using Matlab (R2017b) (Mathworks Inc., Sherborn, MA, USA) and SPM 12 with the DARTEL algorithm (http://www.fil.ion.ucl.ac.uk/spm). Before the preprocessing, T1-weighted images were aligned with the anterior and posterior commissures line on the transverse plane. Then default step-by-step preprocessing procedures were applied as suggested by the DARTEL toolbox. (1) The T1 structure images were first field bias-corrected to correct non-uniform fields. (2) The new segment function implemented in SPM12 was applied (Ashburner & Friston, 2005). Using the tissue probability maps based on the international Consortium of Brain Mapping (ICBM), the images were segmented to grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF). (3) The average study-specific GM and WM templates were subsequently computed and created. (4) After an initial affine registration of the GM DARTEL templates to the tissue probability maps in Montreal Neurological Institute (MNI), non-linear warping of individual GM images was performed to the DARTEL GM template and an individual flow field for each participant was created. (5) The individual GM images were normalized into the MNI space with a 1.5 × 1.5 × 1.5 mm3 voxel size with the normalized images modulated to ensure the relative volumes of GM were preserved following the spatial normalization procedure. (6) The modulated, normalized GM images were then smoothed with an 8-mm FWHM Gaussian kernel.

For the group-level analyses, two sample *t*-tests were employed to explore the overall group differences in regional GMV between GI and control groups, followed by similar analyses conducted in the three age groups respectively (i.e. pre-pubertal; pubertal; young adults). Age, gender and total intracranial volume (TIV) were included in the models as covariates of no interest.

The whole-brain results were derived at the threshold of uncorrected $p < .005$ at the voxel-wise level, and only the clusters survived after family-wise-error (FWE) correction $p < .05$ at the cluster level were reported. All reported voxels consisted of 20 or more contiguous voxels.

3 | RESULTS

3.1 | Overall regional GMV differences between GIS and the non-symptomatic control group

GMV was significantly decreased in the GIS group compared to controls in several brain regions within the limbic system, including bilateral caudate, bilateral ventral hippocampus, bilateral amygdala and bilateral superior orbital frontal cortex (OFC) (Figure 1a, Table 2). However, GMV was significantly greater in the GIS group compared to controls in the thalamus, bilateral putamen, right mid-frontal gyrus and the supplementary motor area (SMA) (Figure 1b, Table 2).

3.2 | Regional GMV difference in the pre-adolescent group

The differences in regional GMV between GIS and the control groups in three age groups (i.e. pre-adolescent; adolescent; young adult) was then explored. Although, in the pre-adolescent group, there were regions showing GMV differences between control and GIS groups, none survived the applied threshold of cluster-level FWE multiple comparison correction ($p < .05$). Nevertheless, there was a similar pattern of overall differences in GMV between controls and the GIS group in the pre-adolescent group as in the other groups. These results are reported in Table R1 in the Supporting Information for reference.

3.3 | Regional GMV difference in the adolescent group

In the adolescent group, significant GMV differences were observed between the GIS group and controls in a number of regions. Specifically, compared to the controls, the GIS group showed decreased GMV in the rectus/OFC area, medial frontal gyrus and the right caudate (Figure 2a, Table 2). Additionally, the GIS group showed bilateral increase in GMV in the dorsal hippocampus and the pallidum/putamen compared to the control group. (Figure 2b, Table 2).

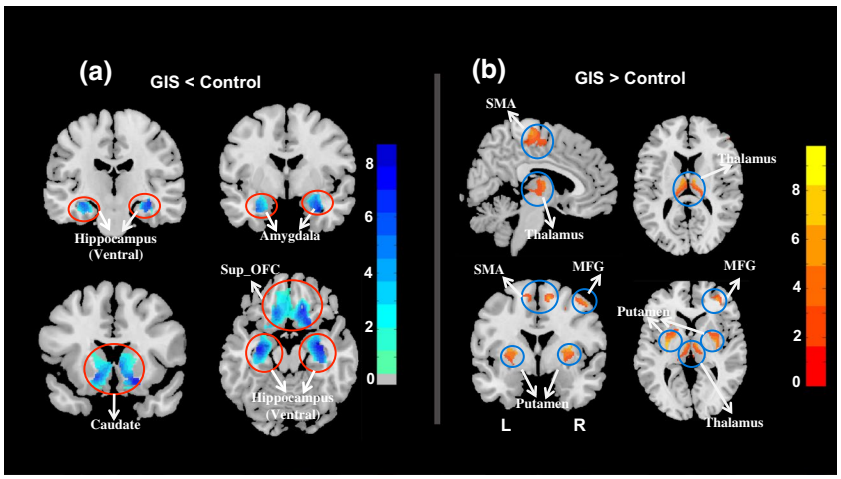

FIGURE 1 Overall GMV differences between GIS groups and the Non-symptomatic control group across all ages. (a) Decreased GMV in the GIS group compared to the control group, including the bilateral hippocampus (ventral part), the bilateral amygdala, the bilateral caudate and the bilateral superior orbital frontal. (b) Increased GMV in the GIS group compared to the control group, including the supplementary motor area (SMA), middle frontal gyrus (MFG), bilateral putamen and the thalamus. All the clusters were derived at the threshold of uncorrected $p < .005$ at the whole-brain level and FWE corrected $p < .05$ at the cluster level and the activation cluster size >20 voxels

3.4 | Regional GMV difference in the young adult group

In the young adults, the GIS group also showed significant decreased regional GMV compared to the control group in the left precuneus, left lingual gyrus, bilateral ventral hippocampus, right amygdala, right anterior insula and OFC areas (Figure 3a, Table 2). Comparatively, the GIS group showed a regional increase of GMV in the bilateral posterior insula, bilateral dorsal hippocampus/parahippocampus and thalamus compared to the control group (Figure 3b, Table 2).

4 | DISCUSSION

This study examined the link between GISs and changes in brain morphology in boys and girls aged between 8 and 21 years old who participated in the PNC. While controlling for age and gender, we initially conducted an analysis of GMV at the whole-brain level using the VBM approach. We found that participants, regardless of their age, experiencing GIS displayed alterations of the GMV in limbic brain regions as well as in the pain-matrix compared to control participants.

The limbic system is an important regulator of GI function, as it controls human emotions, visceral pain as well as visceral sensation (Blankstein, Chen, Diamant, & Davis, 2010; Coss-Adame & Rao, 2014; Liu et al., 2019; Seminowicz et al., 2010). Morphological changes were also observed in areas of the "pain matrix" (Bao et al., 2012, 2017; Labus et al., 2014; Seminowicz et al., 2010; Srinath, Young, & Szigethy, 2014) that are generally involved in pain processing and pain modulation (Iannetti, Salomons, Moayedi, Mouraux, & Davis, 2013), such as the thalamus, amygdala, middle frontal gyrus and basal ganglia (caudate and putamen) (Bao et al., 2015; Labus et al., 2014; Seminowicz et al., 2010). Compared to the control group, the GIS group showed both increased GMV (i.e. the thalamus and putamen) and decreased GMV (i.e. the amygdala, middle frontal gyrus and the caudate) in the pain-matrix. It is reasonable to expect both increases and decreases of GMV in the pain-matrix because the different regions that make up the pain-matrix are associated with more than just pain processing. The regions in the pain-matrix are involved in different networks like the emotional arousal network, the salience network and the sensorimotor network, which are involved in chronic visceral pain (Mayer et al., 2015). The thalamus is part of the sensorimotor network which is involved in processing somatic and visceral sensation. The amygdala is a part of the emotional arousal network which is involved in fear-related responses (Tillisch, Labus, & Naliboff, 2018).

VBM studies have found that a decrease in GMV could be linked to a decrease in cell size, decrease in spine density, neural or glial cell apoptosis, dendritic atrophy or change in blood flow or intestinal flow (Agnostini et al., 2013; Good et al., 2001). In a majority of gastrointestinal disorders, duration, pain and inflammation may play a role in GMV changes (Agostini et al., 2013, 2015; May, 2008). Chronic abdominal pain is associated with inflammatory activity which sends input to the pain-matrix and the corresponding brain regions that are involved in nociception. The overstimulation of cytokines may lead to neural loss and excitotoxicity (Agnostini et al., 2015; May, 2008). Additionally, intestinal inflammatory signals may influence the brain due to the bidirectional communication that is established by the gut-brain

TABLE 2 Regional GMV differences between GIS versus non-symptomatic control

Hemisphere	Brain region	Cluster size	Coordinate			*t*-value	Cluster-level FWE correction *p*-value
			x	*y*	*z*		
Overall GIS < Control							
L	Caudate	30,313	−15	18	−11	6.91	<.001
R	Caudate		18	20	−12	8.62	
L	Hippocampus (ventral)		−30	−11	−15	8.09	
R	Hippocampus (ventral)		33	−11	−15	8.19	
L	Frontal_Sup_Orb		−13	27	−17	5.45	
R	Frontal_Sup_Orb		15	29	−15	7.4	
L	Amygdala		−32	−6	−24	6.7	
R	Amygdala		32	−5	−23	7.07	
Overall GIS > Control							
L	Thalamus	12,880	−8	−9	9	6.3	<.001
R	Thalamus		8	−8	8	6.74	
L	Putamen		−30	−9	9	8.41	
R	Putamen		32	2	14	7.42	
R	Frontal_Mid		33	47	2	7.18	
L	Supp_Motor_Area	2,742	−9	−20	68	8.04	.017
R	Supp_Motor_Area		11	−21	68	8.12	
GIS versus Control in pre-adolescent group							
No significant cluster							
GIS < Control in adolescent group							
L	Rectus	2,673	−15	29	−17	7.03	.03
R	Rectus		20	18	−14	8.26	
L	Frontal_Sup_Orb		−23	47	−11	8.02	
R	Frontal_Sup_Orb		15	29	−15	5.41	
L	Frontal_Inf_Orb		−36	36	−8	7.61	
R	Frontal_Inf_Orb		23	33	−11	4.97	
R	Caudate		5	18	2	6.91	
R	Middle Frontal gyrus		27	41	−9	5.38	
GIS > Control in adolescent group							
L	Hippocampus (dorsal)	10,052	−17	−12	−12	8.15	<.001
R	Hippocampus (dorsal)		18	−11	−11	7.85	
L	Pallidum/putamen		−11	2	−6	7.17	
R	Pallidum/putamen		11	2	−6	6.28	
GIS < Control in young adults							
L	Precuneus	3,933	−9	−50	14	5.41	.002
L	Lingual gyrus		−17	−68	−3	5.8	
L	Hippocampus (ventral)		−33	−38	−3	5.71	
R	Hippocampus (ventral)	4,120	38	−29	−11	6.13	.04
R	Amygdala		33	−2	−29	5.89	
R	ant.Insula		36	29	6	7.24	
L	Frontal_Sup_Medial	3,758	−12	54	11	6.46	<.001
L	Frontal_Sup_Orb		−15	66	−14	6.47	
L	Frontal_Mid_Orb		−41	56	−11	6.03	
R	Frontal_Mid_Orb		44	48	−17	5.89	

(Continues)

TABLE 2 (Continued)

Hemisphere	Brain region	Cluster size	Coordinate			*t*-value	Cluster-level FWE correction *p*-value
			x	*y*	*z*		
GIS > Control in young adults							
L	pos.Insula	3,946	−45	12	−8	4.07	.003
R	pos.Insula		47	15	−6	5.83	
L	Hippocampus (dorsal)		−17	−27	−14	4.58	
R	Hippocampus (dorsal)		15	−29	−9	4.72	
L	Thalamus		−3	−21	−3	4.53	

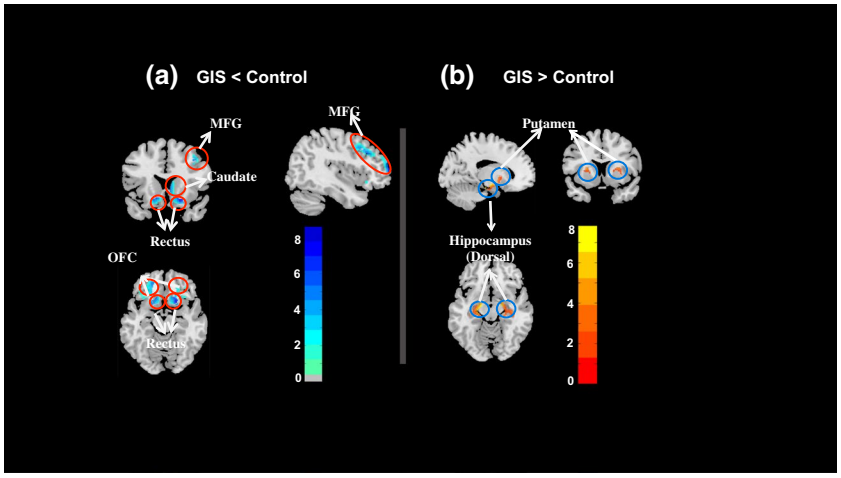

FIGURE 2 GMV differences between the adolescent GID group and Non-symptomatic controls. (a) Decreased GMV in the GIS group compared to the control group, including the MFG, the bilateral rectus, bilateral OFC and the right caudate. (b) Increased GMV in the GIS group compared to the control group, including the bilateral hippocampus (dorsal parts) and the bilateral putamen. All the clusters were derived at the threshold of uncorrected $p < .005$ at the whole-brain level and FWE corrected $p < .05$ at the cluster level and the activation cluster size >20 voxels

axis (Agnostini et al., 2015; Jones, Dilley, Drossman, & Crowell, 2006; Rapps, Oudenhove, Enck, & Aziz, 2008).

Our results also indicate a decrease in GMV in the amygdala in participants who experience GIS compared to our non-symptomatic controls, hereby amplifying the role of the gut-brain axis in mental health. A major function of the amygdala is to process emotional stimuli (Agostini et al., 2011; Costafreda, Brammer, David, & Fu, 2008; Sergerie, Chochol, & Armony, 2008) in addition to being an essential structure of the gut-brain axis allowing for the link between emotions and gastrointestinal functions (Agostini et al., 2011; Van Oudenhove, Demyttenaere, Tack, & Aziz, 2004; Wilhelmsen, 2000; Wood et al., 1999). Agostini and colleagues (2011) found that in patients with UC in response to positive emotional stimuli there is a decrease in the BOLD signal in the amygdala while performing a positive versus rest contrast. This indicates that UC, a disorder that consists of various GIS, is associated with emotional dysfunction, in particular with a decrease in sensitivity to positive emotions of joy and well-being.

Our findings supported our hypothesis and showed that there are changes in GMV between participants suffering from GIS and healthy control participants at different age groups. However, the ages that displayed the greatest alterations were the adolescents and the young adults. Although our pre-adolescent group did not show any significant difference compared to their healthy controls (refer to supplementary section, Table S1), they did display non-significant alterations in similar regions, indicating that our results support our hypothesis, but in an age-dependent manner. We can speculate that the reason as to why the pre-adolescent participants did not show significance was because they were at different stages of the U-shaped trajectory in GMV development (Giedd et al., 1994, 1999; Giorgio et al., 2010; Pfefferbaum et al., 1994; Reiss et al., 1996; Sowell et al., 2001; Sowell et al., 2003; National Institutes of Health, 2012; Neufeld et al., 2016) thus resulting in a high within group variability.

Participants in the adolescent and young adult groups experiencing GIS displayed less GMV in the OFC compared to non-symptomatic controls. The OFC is a brain region that

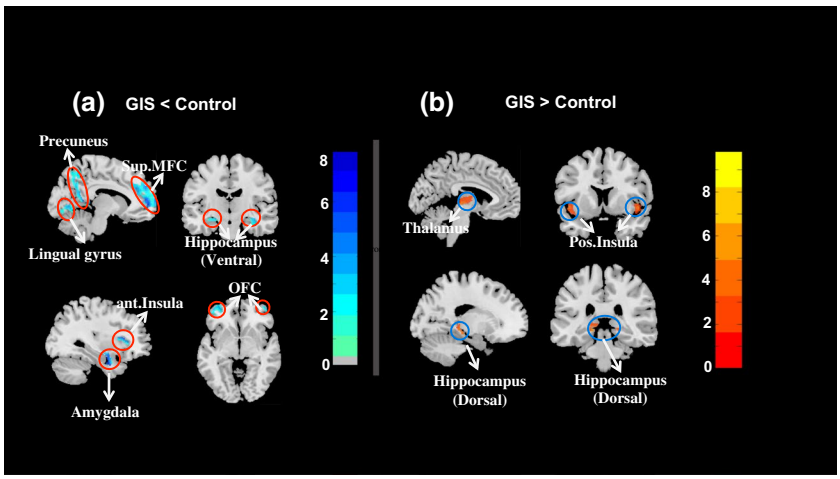

FIGURE 3 GMV differences between the young adult GIS group and the non-symptomatic control group. (a) Decreased GMV in GIS group compared to the control, including the left precuneus, left lingual gyrus, the bilateral hippocampus (ventral parts), the right amygdala, the right anterior insula, the left superior medial frontal cortex (Sup.MFC) and the OFC. (b) Increased GMV in the GIS group compared to the control group, including the thalamus, the bilateral hippocampus (dorsal parts) and the bilateral posterior insula. All the clusters were derived at the threshold of uncorrected $p < .005$ at the whole-brain level and FWE corrected $p < .05$ at the cluster level and the activation cluster size >20 voxels

is interconnected with the limbic system and a key player in the emotional arousal network where it processes emotional input and modulates visceral responses (Jin et al., 2019; Keszthelyi, Troost, & Masclee, 2012; Tillisch, Mayer, & Labus, 2011). The OFC receives visceral input from sensory areas while providing output to the hypothalamic and midbrain regions that are involved in the regulation of homeostatic functions (Hubbard et al., 2016; Ongur & Price, 2000; Price, 1999). Current brain imaging studies have shown in both paediatric and adult patients with IBS that the bilateral OFC is altered both functionally and structurally (Hubbard et al., 2016). Taken together, these findings suggest that changes in this important regulation area may be common across age for GISs.

Participants in the adolescent and young adult groups experiencing GIS also displayed an increase in GMV in the dorsal hippocampus compared to non-symptomatic controls. The hippocampus is also a limbic region and plays a major role in emotional processing (Blankstein et al., 2010; Seminowicz et al., 2010). The hippocampus also regulates immune responses through the hypothalamic-pituitary-adreanl (HPA) axis and neurohumoral pathways while playing a vital role in neural immune regulation (Bao et al., 2015; Lathe, 2001). Experimental colitis and intestinal dysbiosis studies have found them to be associated with abnormal mRNA or protein expression of brain-derived neurotrophic factor in the hippocampus along-side abnormal development of anxiety-like behaviour (Hassan et al., 2014; Bao et al., 2017). Additionally, the hippocampus may affect memory concerning emotional information as well as communication that occurs between other regions regarding mood regulation (Lie et al., 2019). Therefore, we can speculate that alterations of the GMV in the hippocampus may be implicated in mood disorders. In fact, studies conducted on CD patients have found that increased GMV in the hippocampus/parahippocampus is related to psychological distress (Boa et al., 2015; Oquendo et al., 2007). The increase in GMV of the hippocampus/parahippocampus has only been found in CD patients who are not experiencing pain. In CD patients experiencing pain, GMV was decreased (Bao et al., 2017). These findings suggest that the dysfunction of the CNS may be a contributing factor in the pathophysiologic mechanism that causes the symptoms experienced in gastrointestinal disorders (Liu et al., 2019).

Our young adults experiencing GIS also showed a decrease in GMV in the anterior insula and an increase in GMV in the posterior insula in comparison to the controls. The insula is known to be a vital region for the bidirectional gut-brain communication as it plays a role in processing and modulating visceral sensory, pain, emotion as well as maintaining homeostasis (Mayer, 2011; Mayer & Tillisch, 2011; Zeng et al., 2013). Brain imaging studies show that the insular cortex is a fundamental region involved in visceral pain. It involves the integration of the posterior insula that integrates somatic and visceral information, and the anterior insula, which translates this information into affect (Jin et al., 2019; Keszthelyi et al., 2012). Our results are consistent with previous findings as GMV increased in the posterior insula for the GIS participants (Seminowicz et al., 2010). The anterior insula performs various roles such as pain perception, emotional salience as well as visceral integration (Craig, 2009; Jin et al., 2019).

Despite the results, this study does have some limitations. This study used cross-sectional data, thus preventing the affirmation of a causal inference. Another limitation is the lack of knowledge of the particular GIS that each patient experienced.

The participants could have been a heterogeneous group that might have experienced multiple different symptoms. Additionally, boys and girls are affected differently while experiencing GISs. Although this study did not examine sex differences, it would be beneficial to explore them in future studies. Finally, the participants did not go through a standardized psychological assessment. There is often a comorbidity of GIS and psychological disorders; therefore, the addition of psychological testing would be beneficial for a future study.

Regardless of the limitations, this study highlights GIS-related differences to regional GMV in a younger population that has not been previously examined. The pre-adolescent and adolescent periods are critical periods of development, as the brain is rapidly changing and vulnerable to stressors. This study suggests the importance of early detection of gastrointestinal disorders through its symptomatology and highlights the need to advance our current understanding of the impact GISs have on the developing brain.

5 | CONCLUSIONS

This study suggests that the presence of GIS's, in youth, has an influence on brain structure. The study reports that the GIS alter GMV differently in adolescents and young adults. The current findings suggest that the duration of GIS may play a role in the development of morphological changes in the brain. Additional research on the pubertal population is needed in order to further explore the effects GISs have on the brain.

ETHICS APPROVAL STATEMENT

The Ethical Committee of University of Ottawa approved this database for this use in this study.

PATIENT CONSENT STATEMENT

Written informed consent was obtained from legal guardians; children provided written assent.

Permission to reproduce material from other sources: Data analyzed in this study can be accessed through the publically available dbGaP database (https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi? study_id=phs000607.v3.p2).

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The magnetic resonance imaging (MRI) protocol was comprised of scans designed to obtain information on brain structure, perfusion, structural connectivity, resting state functional connectivity, working memory function and emotion identification.

CONFLICT OF INTEREST

No conflict of interest was reported by the authors.

AUTHOR CONTRIBUTIONS

Atiqa F. Pirwani, Andra Smith, Georg Northoff and Nafissa Ismail designed this study. Atiqa F. Pirwani was also responsible for data analysis and manuscript preparation. Zhuo Fang contributed to data analysis and manuscript preparation. Bo Li aided in data organization. Nafissa Ismail, Andra Smith and Georg Northoff revised and edited the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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