

Sex-Specific Differences in Brainstem Microstructure in Chronic Visceral Pain

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Background

- Sex differences in sensorimotor, salience and emotional-arousal brain networks have been demonstrated in irritable bowel syndrome (IBS).^{1, 2}
- These brain networks are involved in the processing and response to visceral afferent signaling (Figure 1) and are heavily involved in descending modulation via brainstem-spinal pathways in the form of descending pain modulation and autonomic nervous system activity (Figure 2).^{2,3}
- There are reciprocal connections with several closely adjacent, interconnected nuclei that play important roles in bidirectional brain gut interactions including the noradrenergic locus coeruleus complex (LCC), the serotonergic dorsal and raphe nuclei (DRN) and the parabrachial nucleus (PBN).
- Sex-related changes in the neural organization of brainstem nuclei that are critical for processing visceral afferent signaling and descending pain modulation have not been studied in IBS.

1. Gupta et al *J Neurosci Res*. 2017.
2. Mayer et al *NRGH*, 2015.
3. Mayer, Naliboff, Craig *Gastro* 2006

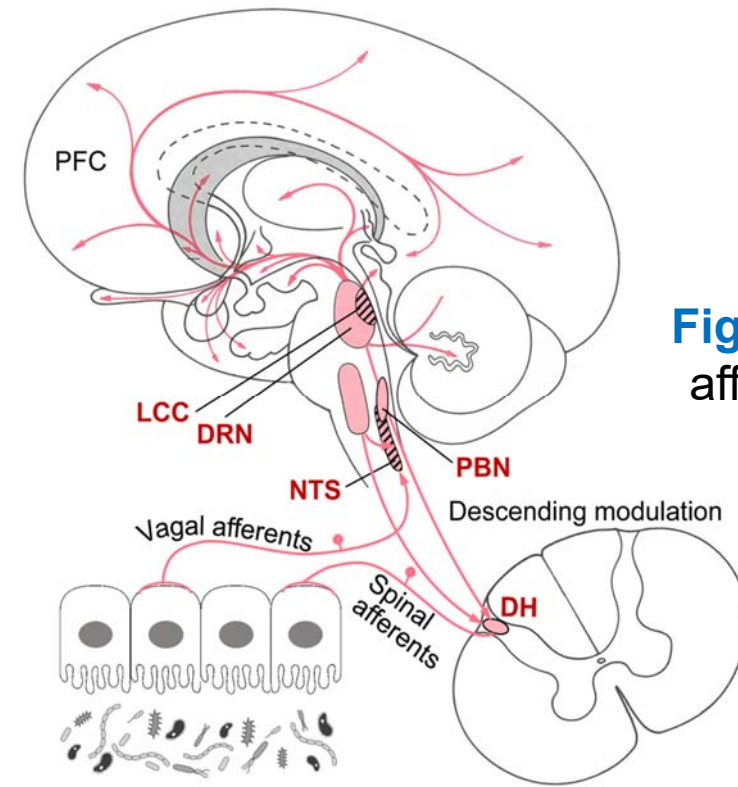


Figure 1. Visceral afferent signaling

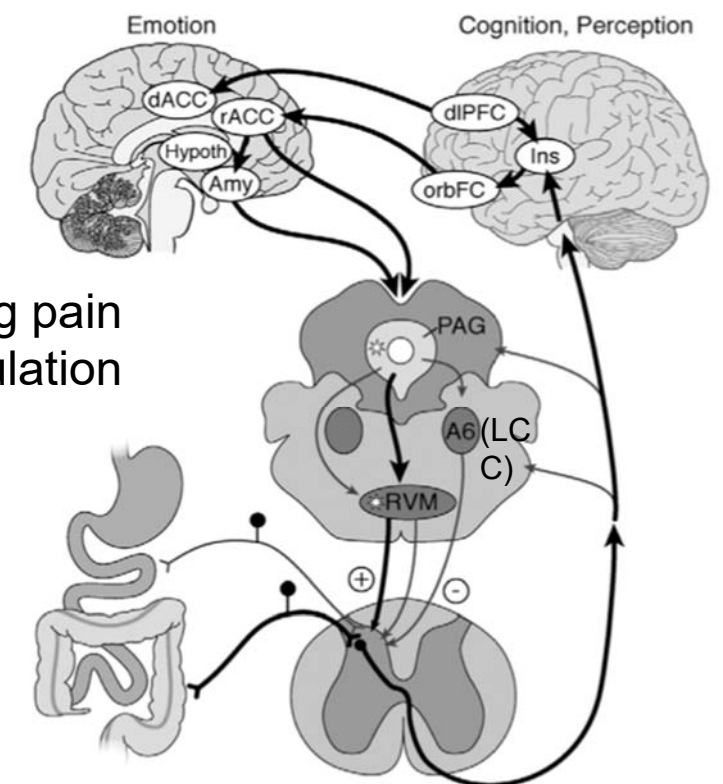


Figure 2. Descending pain modulation

Methods

- High resolution T1 and diffusion tensor images were obtained in 107 female and 45 male nonobese IBS subjects on a 3T Siemens Trio.
- DTIs were collected in 64 equidistant diffusion-sensitizing directions with $b=1000\text{s/mm}^2$, along with a single $b=0\text{s/mm}^2$ image, with echo time (TE)/repetition time (TR)=88ms/9500ms; matrix size=128×128; field of view (FOV)=256mm; and a slice thickness=2mm, with no interslice gap. All subject DTI data was resampled to 1 mm isotropic resolution for analyses in standard space.
- Fractional Anisotropy (FA) and mean diffusivity (MD) images for each participant were registered to the Johns Hopkins University DTI atlas (ICBM-DTI-81 1mm FA atlas) using the FLIRT and FNIRT commands in FSL.^{4,5}
- Region of interest based on the Harvard Ascending Arousal Network (AAN) Atlas⁶: locus coeruleus (LC), dorsal (DRN) and median raphe (MR) nuclei, parabrachial complex (PBC), and the periaqueductal gray (PAG)
- The general linear model was applied to test differences in the FA and mean diffusivity (MD) in ROIs controlling for age and BMI.
- A cluster threshold was applied from permutation tests by estimating data's smoothness through command 3dFWHMx in AFNI, and then estimating the cluster extent thresholds at a level of significance, $p < 0.05$, through command 3dClustSim in AFNI.

4. Mori et al, 2005, 5. Wakana et al, NeuroImage 2007. 6. Edlow et al, J Neuropath Exper Neurol. 2012. 7. Ellingson et al, Pain, 2013

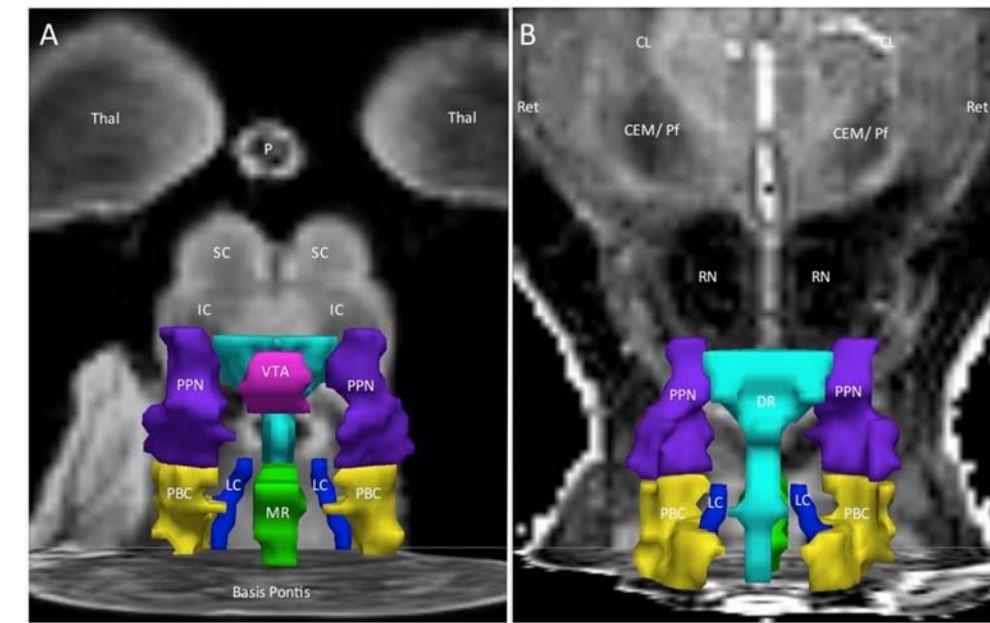


Figure 3. 3-D Regions of interest from AAN. A. Dorsal B. Ventral

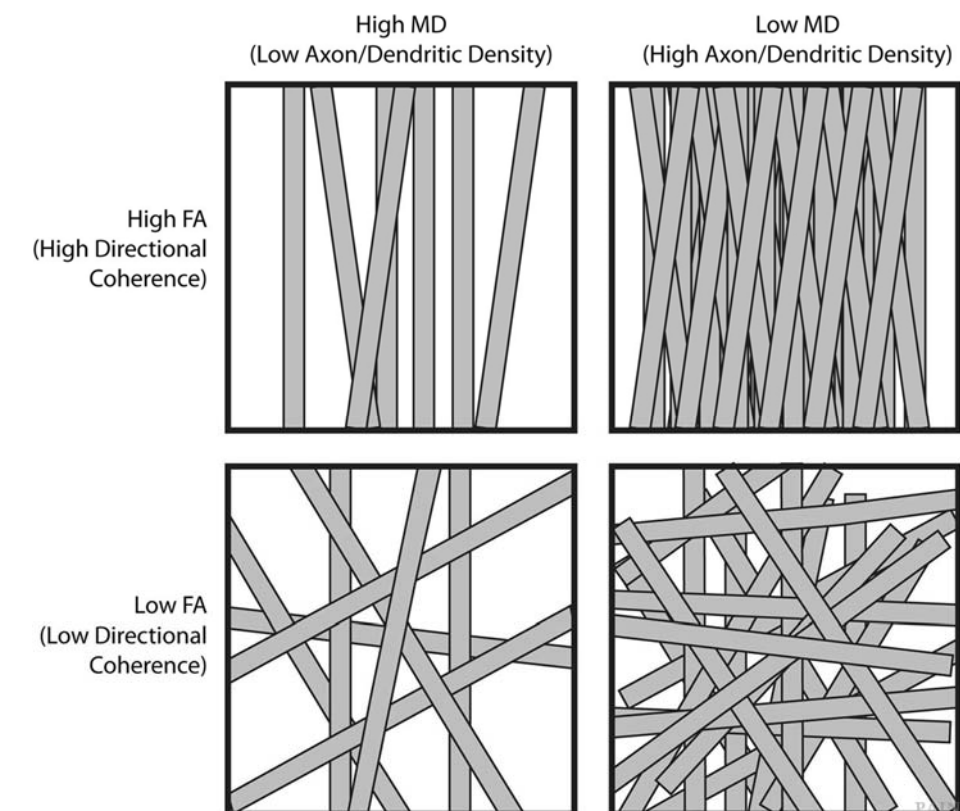


Figure 4. Microstructural interpretation of FA and MD⁷

Results

Figure 7. Whole brain FA Female compared Male IBS

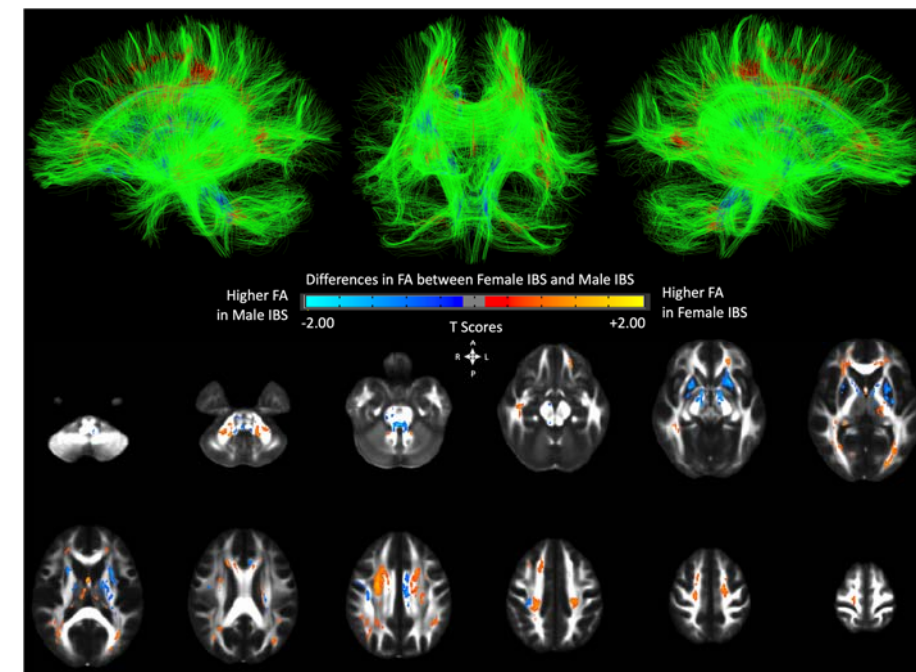


Figure 8. Whole brain MD Female compared Male IBS

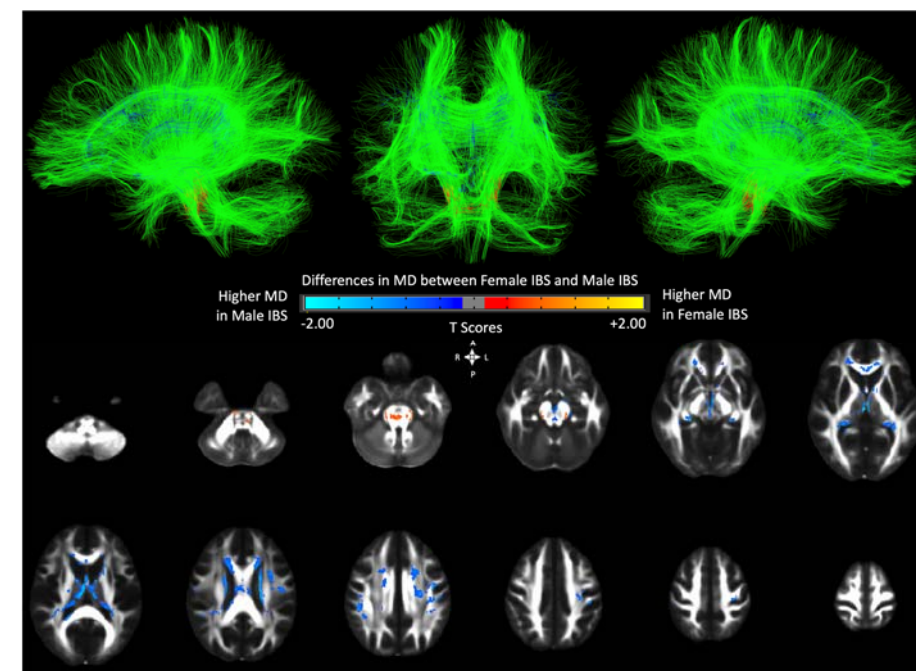


Figure 5. Female compared Male IBS FA differences in Brainstem ROIs

Brainstem Nuclei	T	No. voxels
DR	-3.36	98
LC	-2.89	84
MR	-3.20	41
PBC	-2.89	45
PAG	2.49	63

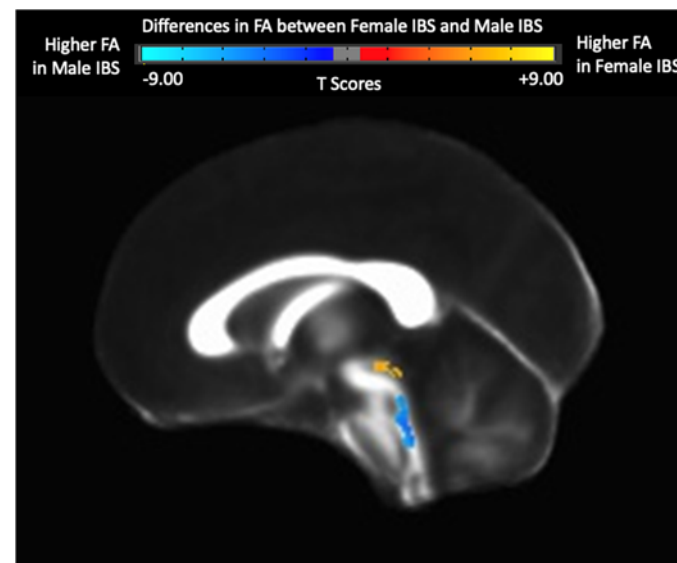
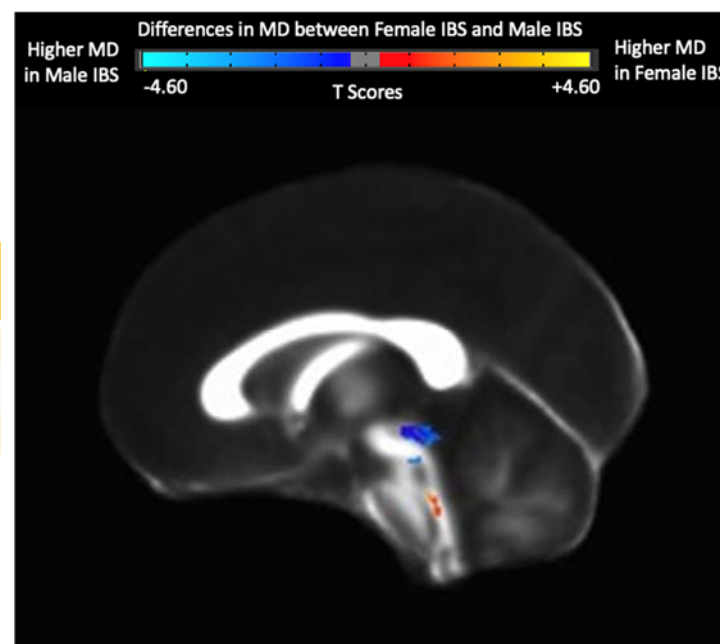


Figure 6. Female compared Male IBS MD differences in Brainstem ROIs

Brainstem Nuclei	T	No. voxels
DR	-2.36	40
MR	2.81	26
PAG	-2.81	130



- Female compared to males were younger (26.7 y v 31.87) and reported shorter pain duration 8.7y v 12.9y).
- Females also had greater pain catastrophizing, visceral sensitivity, IBS symptom severity, somatic awareness, and widespread pain (p 's ≤ 0.05).
- Compared to males, female demonstrated significantly higher FA in the PAG, the primary control center for descending pain modulation, but lower FA in the noradrenergic LC, serotonergic raphe (DR, MR), and PBC, major viscerosensory relay center.
- Females had lower MD for DR and PAG but higher MD for the MR (cluster-level significance at 5% false discovery rate).
- Compared to males, females demonstrated significantly higher FA and lower MD in thalamus and along pathways passing through brainstem, such as corticospinal tracts, thalamic radiation and (superior) cerebellar peduncle. However, white matter tracts along corona radiata were found to show lower FA and higher MD in females (Figures 7 & 8)

Table 1. Brain-symptom correlation in Males

	Fractional Anisotropy						Mean Diffusivity					
	DR		MR		LCC		DR		MR		PAG	
	r	p	r	p	r	p	r	p	r	p	r	p
VSI	0.33	0.03	0.34	0.02								
Resilience (BRS)					0.43	0.004						
Depression (HAD)			0.38	0.01	-0.31	0.04					0.3	0.049
State Anxiety (HAD)									0.31	0.04		
Trait Anxiety					-0.37	0.02			0.33	0.03		
Widespread Pain (PHQ)			0.41	0.006								
Neuroticism							0.34	0.03	0.24	0.04		
Catastrophizing							0.37	0.01				

Table 2. Brain-symptom correlations in Females

	Mean Diffusivity					
	DR		MR		PAG	
	r	p	r	p	r	p
Resilience (BRS)	0.23	0.02				
State Anxiety (HAD)			-0.23	0.02		
Trait Anxiety (STAI)	-0.21	0.03				
Neuroticism	-0.25	0.01				
Perceived Stress (PSS)	-0.2	0.04			-0.22	0.03
Early Adverse Life Events (ETI)	-0.28	0.004				
Symptoms (Past Week 0-20)			-0.27	0.005		
IBS-SSS					-0.23	0.02

Conclusions

- There are sex differences in the neural organization of cortical and brainstem systems that are critical for viscerosensory processing and modulation and descending pain inhibition.
- Sex-specific associations between the brainstem region microstructure with symptom and psychosocial measures were observed.
- In IBS women brainstem nuclei microstructure was associated with IBS-specific symptoms whereas in IBS males the association was with widespread pain.
- The serotonergic dorsal raphe nucleus appears to contribute most to symptom presentation in women whereas the noradrenergic locus coeruleus has more influence in men.