

The Effects of Age and Sex on Symptom Severity and Brain Volumes of Irritable Bowel Syndrome Patients

By Anna Chia

Anglo-Chinese School (Independent), 121 Dover Rd, Singapore 139650, Singapore; annachia1906@gmail.com
Mentor: Barbara Biney

ABSTRACT: Irritable Bowel Syndrome is a common functional bowel disease that affects a large proportion of the general population. Often associated with changes in bowel habits and the manifestation of abdominal pain, IBS greatly impacts a patient's quality of life. This research paper analyzes a dataset to understand the relationship between sex, age, IBS symptom severity, and patient brain volumes. It was found that there were statistically significant differences in volumes of the left lateral orbitofrontal gyrus between the sexes. Female IBS patients in the dataset had comparable symptom severity to male IBS patients, and generally smaller brain volumes in individual brain regions. Older IBS patients were observed to have smaller brain volumes, but greater symptom severities. These results are contrary to the current consensus of IBS symptom severity in various populations.

KEYWORDS: Biomedical and Health Sciences, Pathophysiology, Neuroscience, Physiology, Neurobiology.

■ Introduction

Irritable Bowel Syndrome (IBS), a functional bowel disease (FBD), is a very common disorder, affecting 9–23% of the global population.¹ IBS is often defined as pain associated with a change in bowel habits. FBD refers to a gut disorder that does not show any structural or biochemical abnormalities, and according to the Rome criteria, is defined as symptoms stemming from the middle and lower gastrointestinal tract and symptoms appearing at least three days a month in the last three months.^{2,3} Symptoms of IBS often include abdominal pain, either diarrhea or constipation, and bloating.⁴ IBS has been associated with impaired quality of life and increased prevalence of mental disorders like depression.⁵

All forms of IBS, such as IBS with symptoms of constipation (IBS-C), diarrhea (IBS-D), or a mix of both (IBS-M), have been reported to manifest moderate to severe pain that interferes with daily life.⁶ A meta-analysis by Tillisch, Mayer, and Labus noted that IBS participants showed greater brain activity in regions associated with visceral afferent processing and regions associated with emotional arousal.⁷ IBS patients were also detailed to have reduced activation and decreased gray matter density in various areas of the brain, leading to impairment of the body's pain inhibitory system and possibly contributing to the pain levels of IBS.⁸

Recent studies also found associations between pain in IBS and brain morphology – research by Labus *et al.* observed that greater severity in IBS symptoms, such as heightened abdominal pain, was associated with lower brain region volumes.⁹

This study aimed to explore the correlation between sex and age and the pain severity of IBS. In addition, this paper aimed to investigate any correlation between sex or age and regional brain volume. It was hypothesized that females and younger age group individuals (18–29) would experience more severe IBS pain symptoms. It was also hypothesized that individuals

experiencing greater pain symptoms would have lower brain volumes in regions associated with visceral sensation, emotional arousal, and attention.

■ Methodology

Source of Data:

The dataset (April 2011 NI IBS Pain) was obtained from the Statistics Online Computational Resource website by the University of Michigan.¹⁰ This dataset originated from a brain imaging study of IBS patients and normal control participants.¹¹ The overall severity of gastrointestinal symptoms (BSQ Overall, on a scale of 0 to 20), severity of the abdominal pain experienced (BSQ abdominal pain, on a scale of 0 to 20) and general symptom severity (BSQ severity, on a scale of 1 to 5) were determined using the Bowel Symptom Questionnaire, where increasing scores indicate increasing severity.¹² The proneness of the participants to anxiety was determined using the State-Trait Anxiety Inventory, where a higher score also indicated greater anxiety.¹³ Neuroimaging data were also used to obtain volumes of regions of interest in the brain, reported in mm³.¹⁰

Statistical Analysis:

Statistical analysis was conducted using RStudio (Version 2024.12.0+467). Participants with incomplete data were not included in the statistical analysis. Histograms for each variable's data were generated to identify outliers, which were then excluded from the analysis. Normality of the data was determined using a Shapiro-Wilk test, where a p-value of greater than 0.05 indicated a normal distribution.

An Independent Samples T-test was used to compare the data values between male and female participants if both data sets were normally distributed. The Independent Samples T-test is designed to compare the means of two normally

distributed populations, which is also equivalent to the medians of these populations.^{14,15} If one or both sets of data were not normally distributed, a Mann-Whitney U test was used instead. The Mann-Whitney U test is an alternative to the T-test that can compare groups that are not normally distributed by testing if one group tends to have higher values than the other group.¹⁶

For comparison across different age groups (18-29, 30-39, 40-49, and >50), a Kruskal-Wallis H test was performed. The Kruskal-Wallis H test is the non-parametric equivalent of the one-way ANOVA and can compare the medians of three or more groups of non-normally distributed data.¹⁷ If the p-values, as calculated in the statistical tests, were less than 0.05, differences between groups were considered statistically significant.

Results

This section presents the results of the data analysis. Table 1 shows the characteristics of the dataset used.

Table 1: Characteristics of the dataset used.

Characteristics	IBS (n=87)
Sex	
Male	18
Female	69
Median Age, (Std)	30 (10.2)
Age groups	
18-29	41
30-39	20
40-49	21
>50	5

Comparison of Median Brain Volumes between Sex:

As shown in Figure 1, it was found that males have a significantly larger brain volume in the left lateral orbitofrontal gyrus than females (p-value of 0.0337 (<0.05)). While it was observed that males generally showed slightly larger volumes in individual brain regions, no other brain regions showed statistically significant differences in brain volumes. Other results can be found in Figures 2, 3, 4, and Tables 2, 3, and 4.

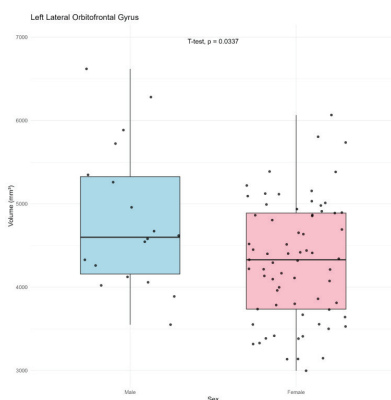


Figure 1: A box-and-whisker plot showing the difference in brain volume of the left lateral orbitofrontal gyrus between male and female IBS participants. Males were observed to have a larger brain volume than females in this brain region. The difference between these volumes was statistically significant.

Table 2: Table summarizing median brain volumes of regions in the frontal lobe for male and female IBS participants. The male IBS patients were generally observed to have greater brain volumes of regions in the frontal lobe. However, statistical tests for these comparisons suggest that the differences are not statistically significant, except for the left lateral orbitofrontal gyrus (p-value = 0.0337 (<0.05)).

Frontal lobe			
Brain Region	Median Male Brain volume (mm ³)	Median Female Brain volume (mm ³)	P-value
Left superior frontal gyrus	53827	51219	0.276
Right superior frontal gyrus	55871.5	53459	0.986
Left middle frontal gyrus	54586	53154	0.305
Right middle frontal gyrus	53519.5	51336	0.0773
Left inferior frontal gyrus	18714.5	17643	0.955
Right inferior frontal gyrus	24717.5	22941	0.0595
Left middle orbitofrontal gyrus	8556	8307	0.691
Right middle orbitofrontal gyrus	8959	9186	0.855
Left lateral orbitofrontal gyrus	4599.5	4329	0.0337 *
Right lateral orbitofrontal gyrus	4227.5	3840	0.0923
Left gyrus rectus	1970	1992	0.580
Right gyrus rectus	2426.5	2552	0.792

* indicates that the p-value is less than 0.05

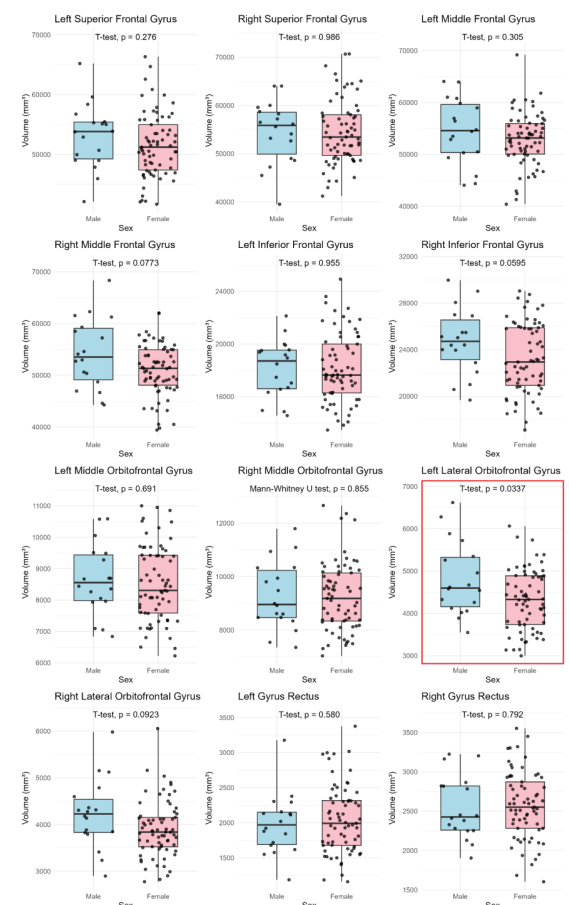


Figure 2: Box-and-whisker plots showing median brain volumes of regions in the frontal lobe of male and female IBS participants. The male IBS patients were generally observed to have greater brain volumes of regions in the frontal lobe. However, statistical tests for these comparisons suggest that differences are not statistically significant, except for the left lateral orbitofrontal gyrus (p-value = 0.0337 (<0.05)). The significant finding is highlighted with a red box above.

Table 3: Table of median brain volumes of regions in the limbic lobe of male and female IBS participants. Data analysis showed that female IBS participants had higher median brain volumes as compared to males in this region, except for in the right cingulate gyrus and the right hippocampus, but statistical analysis of these comparisons yielded p-values greater than 0.05.

Limbic Lobe					
Brain Region	Median Male Brain volume (mm ³)	Median Female Brain volume (mm ³)	P-value		
Left cingulate gyrus	10618	10866	0.741		
Right cingulate gyrus	11479	10798	0.399		
Left hippocampus	3450.5	3616	0.876		
Right hippocampus	4105	3917	0.431		

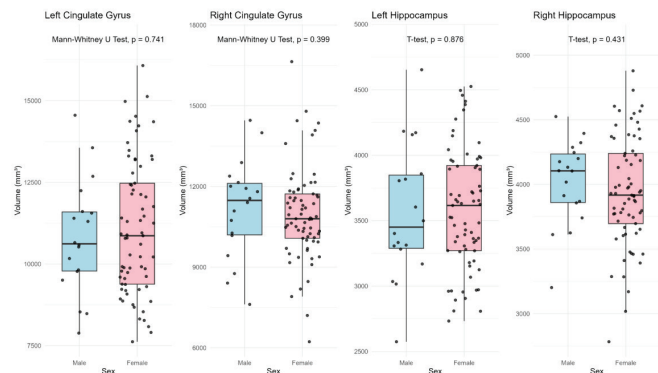


Figure 3: Box-and-whisker plots showing median brain volumes of regions in the limbic lobe of male and female IBS participants. Analysis shows that females had higher median brain volumes as compared to males in this region, except for in the right cingulate gyrus and the right hippocampus. These differences were not statistically significant.

Table 4: Table of median brain volumes of regions in the insular cortex, dorsal striatum (caudate and putamen), and brainstem of male and female IBS participants. Males displayed greater median brain volumes in most of these regions, though statistical analysis produced p-values greater than 0.05, suggesting that these differences had little statistical significance.

Insular cortex, dorsal striatum (caudate and putamen) and brainstem			
Brain Region	Median Male Brain volume (mm ³)	Median Female Brain volume (mm ³)	P-value
Left insular cortex	7920.5	7813	0.667
Right insular cortex	5136.5	5013	0.656
Left caudate	1565.5	1753	0.428
Right caudate	2037	2110	0.324
Left putamen	2802	2662	0.460
Right putamen	4037.5	3814	0.702
Brainstem	25931	26500	0.795

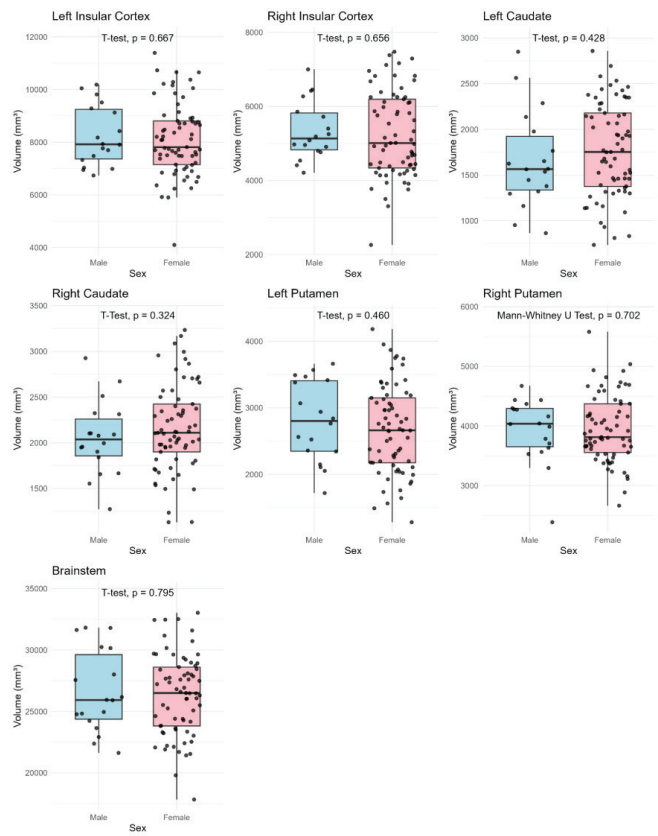


Figure 4: Box-and-whisker plots showing median brain volumes in the insular cortex, dorsal striatum (caudate and putamen), and brainstem of male and female IBS participants. Males displayed greater median brain volumes than females in most of these regions, apart from the caudate and the brainstem. Statistical analysis showed p-values greater than 0.05, suggesting that the differences had little statistical significance.

Female IBS patients also had a greater median brain volume than males, as seen in Figure 5 and Table 5, observing a larger median total brain volume, gray matter volume, and white matter volume. However, further statistical analysis showed no statistically significant difference when comparing these volumes between sexes.

Table 5: Table summarizing median overall brain volumes for male and female IBS participants. Female IBS participants are observed to have larger median total brain volumes, gray matter volumes, and white matter volumes. However, the Mann-Whitney U Test yielded p-values greater than 0.05, indicating that the differences from these comparisons had little statistical significance.

Brain Region	Median Male Brain volume (mm ³)	Median Female Brain volume (mm ³)	P-value
Total Brain	1143998.5	1226341	0.214
Gray Matter	528439.5	564193	0.0829
White Matter	489131	529262	0.278

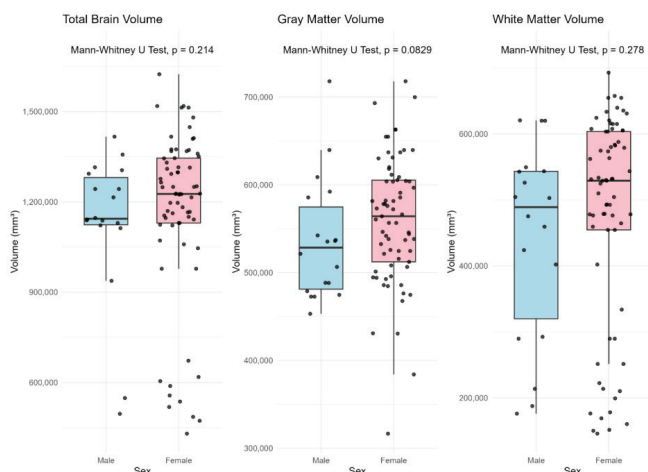


Figure 5: Box-and-whisker plots of median overall brain volumes of male and female IBS participants. Female IBS participants are observed to have larger median total brain volumes, gray matter volumes, and white matter volumes. However, the Mann-Whitney U Test yielded p-values greater than 0.05, indicating that the differences from these comparisons were statistically insignificant.

Comparison of IBS Symptom Severity between Sex:

Comparing symptom severity between sexes in Figure 6 and Table 6, women scored slightly higher on the BSQ questionnaire, and both male and female participants with IBS had similar median scores on the State-Trait Anxiety Inventory. Further statistical analysis reveals that these scores were not statistically significant, suggesting that male and female IBS patients experience comparable IBS symptom severities.

Table 6: Table summarizing IBS symptom severity data for male and female IBS participants. Analysis of the dataset showed that female participants with IBS had higher BSQ Overall and BSQ abdominal pain scores, while both male and female participants shared similar median scores for BSQ severity and for the State-Trait Anxiety Inventory. However, statistical tests indicate that the differences in these comparisons of these scores were not statistically significant.

Symptom Measurement	Male Score	Female Score	P-value
BSQ Overall	10	12	0.693
BSQ abdominal pain	10	11	0.372
BSQ severity	3	3	0.752
Trait Anxiety (Raw)	34	34	0.892
Trait Anxiety	48.5	48	0.904

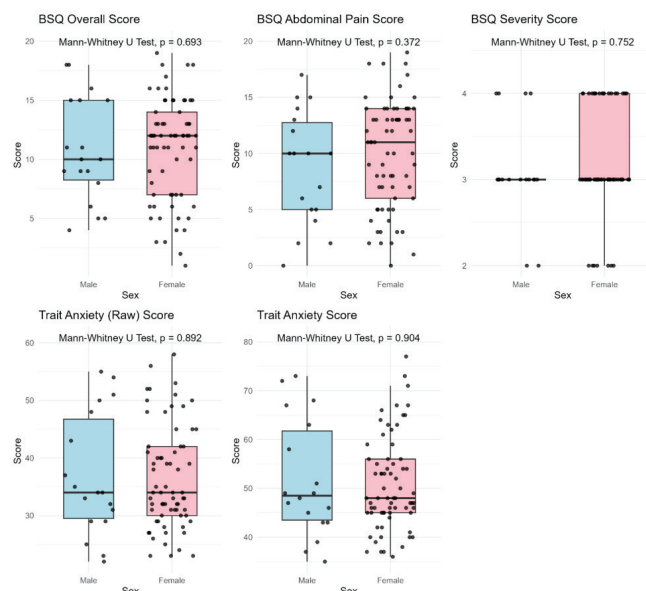


Figure 6: Box-and-whisker plots showing IBS symptom severity data of male and female IBS participants. Analysis of the dataset showed that female participants with IBS had higher BSQ Overall and BSQ abdominal pain scores, while both male and female participants shared similar median scores for BSQ severity and for the State-Trait Anxiety Inventory. However, statistical tests indicate that the differences in these comparisons of these scores were not statistically significant.

Comparison of Median Brain Volumes between Age Groups:

Analysis of the brain volume data in Figure 7 and Table 7 showed that participants in the 30-39 age group were seen to have the greatest median total brain volume, while participants in the >50 age group had the greatest median gray matter volume. Participants in the 18-29 age group also had the greatest median white matter volume. In contrast, participants in the 40-49 age group had the lowest median total brain volume and white matter volume, and participants over 50 had the lowest median gray matter volume. These differences, however, were not statistically significant.

Table 7: Table summarizing median overall brain volumes for IBS participants of different age groups. Participants from the 40-49 age group and the >50 age group were found to have the lowest median total brain volumes, white matter volumes, and gray matter volumes. On the other hand, participants aged 30-39, >50, and 18-29 were determined to have the greatest median total brain volume, gray matter volume, and white matter volume, respectively. The results of the Kruskal-Wallis H tests indicate that these differences were not statistically significant.

Brain Region	Median Brain Volume for each age group (mm ³)				P-value
	18-29	30-39	40-49	>50	
Total Brain	1226341	1237565.5	1196812	1214995	0.707
Gray Matter	545699	569724	524661	603971	0.0614
White Matter	530256	501885.5	526213	459476	0.879

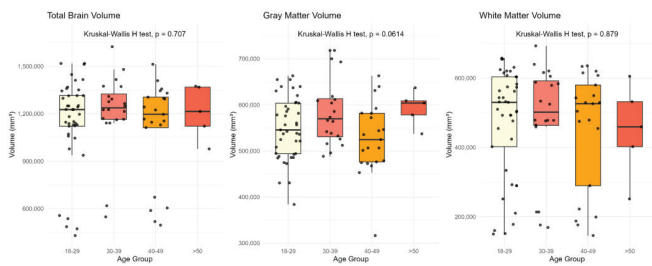


Figure 7: Box-and-whisker plots of median overall brain volumes for IBS participants of different age groups. Participants from the 40-49 age group and the >50 age group were found to have the lowest median total brain volumes, white matter volumes, and gray matter volumes. On the other hand, participants aged 30-39, >50, and 18-29 were determined to have the greatest median total brain volume, gray matter volume, and white matter volume, respectively. The results of the Kruskal-Wallis H tests indicate that these differences were not statistically significant.

In reference to the individual regions of interest in Figures 8, 9, 10, and Tables 8, 9, 10, individuals aged 18-29 and 30-39 typically had the greatest median brain volumes. Similarly, participants in the 40-49 and >50 age groups often showed the smallest median brain volumes. Further statistical analysis showed that the differences between these values were not statistically significant.

Table 8: Table summarizing median brain volumes of regions in the frontal lobe for IBS participants of different age groups. IBS patients aged between 40 and 49 and aged over 50 often showed the lowest median volumes in the frontal lobe, while participants in the 30-39 age group exhibited the highest median volumes in most regions. Further analysis of the dataset suggested that the differences between median volumes in each comparison had little statistical significance.

Frontal Lobe					
Brain Region	Median Brain Volume for each age group (mm ³)				P-value
	18-29	30-39	40-49	>50	
Left superior frontal gyrus	51514	54215.5	50542	52215	0.535
Right superior frontal gyrus	53210	56464.5	54094	53803	0.482
Left middle frontal gyrus	53900	53455	51160	53778	0.149
Right middle frontal gyrus	51499	52244.5	49685	52398	0.649
Left inferior frontal gyrus	17632	18540.5	17151	19132	0.275
Right inferior frontal gyrus	23292	24764	22084	22816	0.450
Left middle orbitofrontal gyrus	8634	8403.5	8307	8161	0.858
Right middle orbitofrontal gyrus	8995	9268.5	9257	8422	0.554
Left lateral orbitofrontal gyrus	4329	4476.5	4294	5123	0.387
Right lateral orbitofrontal gyrus	3840	3941.5	3886	3506	0.784
Left gyrus rectus	1921	2245	2114	1717	0.358
Right gyrus rectus	2541	2582	2552	2451	0.824

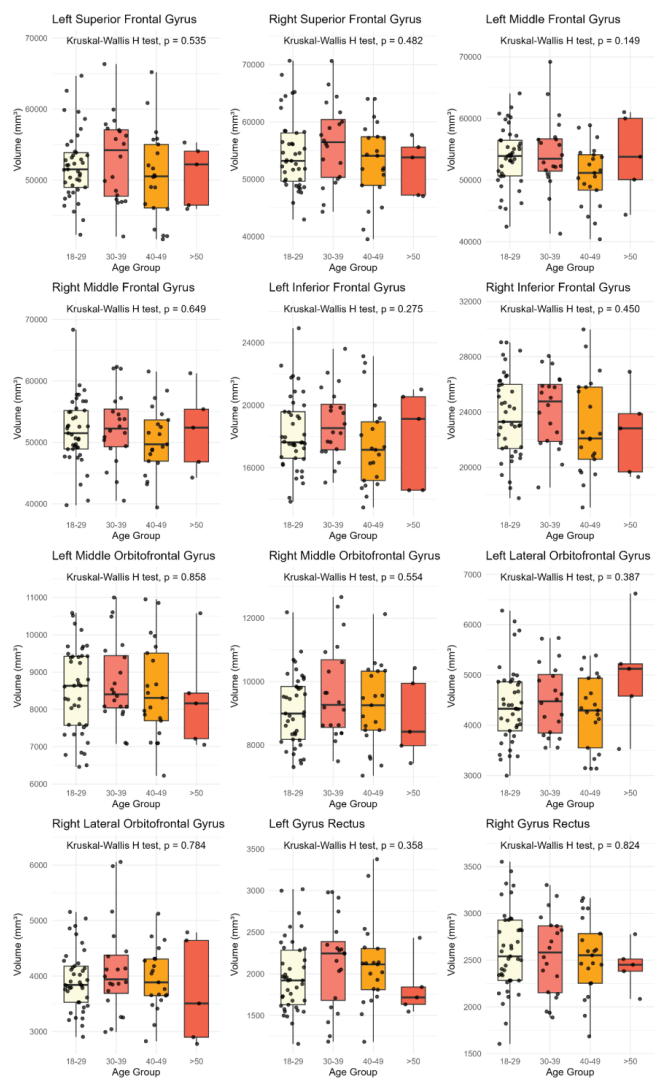


Figure 8: Box-and-whisker plots of median brain volumes of regions in the frontal lobe for IBS participants of different age groups. IBS patients aged between 40 and 49 and aged over 50 often showed the lowest median volumes in the frontal lobe, while participants in the 30-39 age group exhibited the highest median volumes in most regions. Further analysis of the dataset suggested that the differences between median volumes in each comparison had little statistical significance.

Table 9: Table summarizing median brain volumes of regions in the limbic lobe for IBS participants of different age groups. Participants from the 30-39 age group generally demonstrated the highest median brain volumes in this region, while the >50 and 18-29 age groups expressed the lowest median brain volumes. The Kruskal-Wallis H test showed little statistically significant difference within these comparisons.

Limbic Lobe					
Brain Region	Median Brain Volume for each age group (mm ³)				P-value
	18-29	30-39	40-49	>50	
Left cingulate gyrus	10222	11583	10954	9219	0.325
Right cingulate gyrus	10737	11645.5	10773	11679	0.321
Left hippocampus	3339	3680	3728	3410	0.251
Right hippocampus	3914	4130	3913	3667	0.632

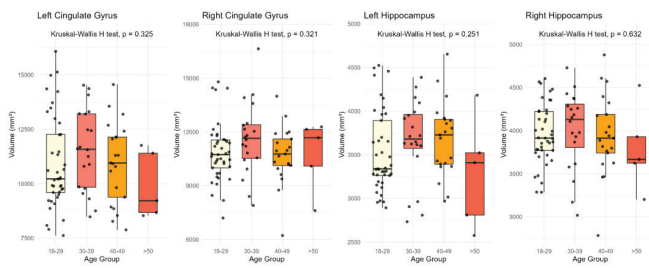


Figure 9: Box-and-whisker plots of median brain volumes of regions in the limbic lobe for IBS participants of different age groups. Participants from the 30-39 age group generally demonstrated the highest median brain volumes in this region, while the >50 and 18-29 age groups expressed the lowest median brain volumes. The Kruskal-Wallis H test showed little statistically significant difference within these comparisons.

Table 10: Table summarizing median brain volumes of regions in the insular cortex, dorsal striatum (caudate and putamen), and brainstem for IBS participants of different age groups. For most of these brain regions, participants in the 30-39 age group showed the greatest median brain volume, and participants over 50 years old generally showed the lowest median brain volumes. The p-values of these differences exceed 0.05, suggesting that the differences are not statistically significant.

Insular cortex, dorsal striatum (caudate and putamen) and brainstem					
Brain Region	Median Brain Volume for each age group (mm ³)				P-value
	18-29	30-39	40-49	>50	
Left insular cortex	7696	8221.5	8205	7135	0.513
Right insular cortex	4962	5546	5018	4679	0.546
Left caudate	1679	1730.5	1753	1625	0.991
Right caudate	2091	2198.5	2124	1805	0.297
Left putamen	2683	2708.5	2835	2149	0.468
Right putamen	3956	4125	3802	3530	0.259
Brainstem	26305	26548.5	25915	24827	0.999

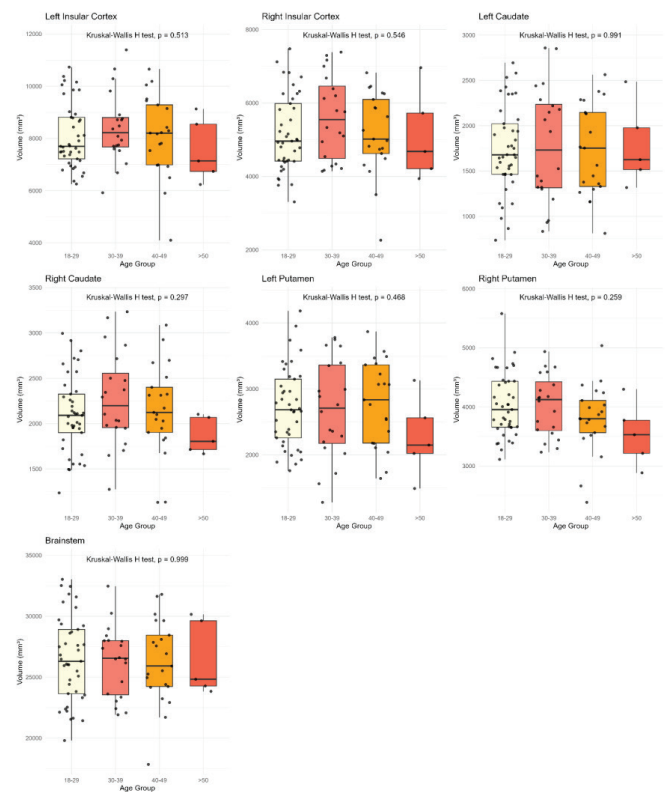


Figure 10: Box-and-whisker plots of median brain volumes of regions in the insular cortex, dorsal striatum (caudate and putamen), and brainstem for IBS participants of different age groups. For most of these brain regions, participants in the 30-39 age group showed the greatest median brain volume, and participants over 50 years old generally showed the lowest median brain volumes. The p-values of these differences exceed 0.05, suggesting that the differences are not statistically significant.

Comparison of IBS Symptom Severity between Age Groups:

In regard to age and symptom severity in Figure 11 and Table 11, participants in the age group of 40-49 showed higher median scores on the BSQ questionnaire, while participants in the age groups 18-29 and >50 showed lower median scores for BSQ overall and BSQ abdominal pain, respectively. Participants aged >50 years old showed the highest median scores on the State-Trait Anxiety Inventory. Comparisons of the symptom measurements yielded p-values that suggested little statistical difference.

Table 11: Table summarizing IBS symptom severity data for IBS participants from different age groups. Participants aged 40-49 displayed higher median scores on most parts of the BSQ questionnaire, while participants from the >50 age group showed the highest scores on the State-Trait Anxiety Inventory. These comparisons of the symptom measurements yielded few statistically significant differences.

Symptom Measurement	Median scores for each age group				P-value
	18-29	30-39	40-49	>50	
BSQ Overall	11	12	13	12	0.112
BSQ abdominal pain	8	12	13	5	0.0672
BSQ severity	3	3	3	3	0.950
Trait Anxiety (Raw)	34	39	32	53	0.124
Trait Anxiety	48	53	47	72	0.0794

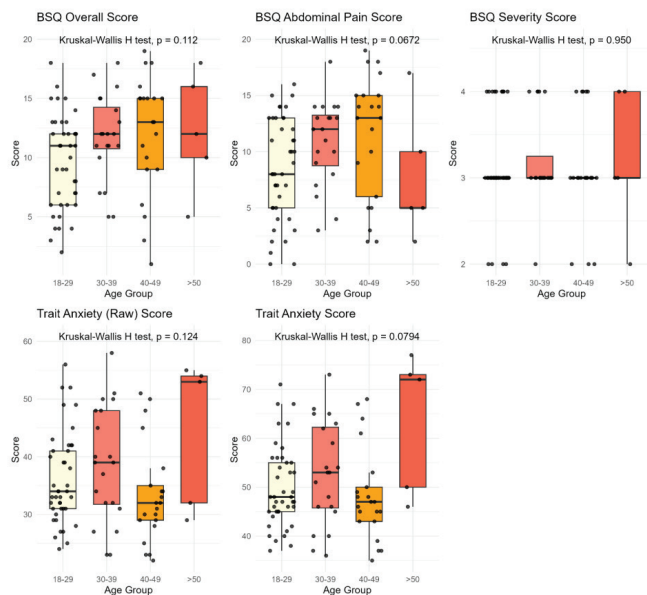


Figure 11: Box-and-whisker plots showing the different median IBS symptom severity scores for IBS participants of different age groups. Participants aged 40-49 displayed higher median scores on most parts of the BSQ questionnaire, while participants from the >50 age group showed the highest scores on the State-Trait Anxiety Inventory. The differences in symptom measurements were not statistically significant.

■ Discussion

This study compared the volumes of various brain regions of interest and symptom measurement scores between sexes and different age groups of IBS participants. While analysis of the dataset showed a statistically significant difference in comparisons of the left lateral orbitofrontal gyrus between sex and a general trend of females and patients above 40 years old having smaller median brain volumes, statistically significant differences were generally not found for most comparisons.

Statistically significantly greater volumes of the left lateral orbitofrontal gyrus were observed in males compared to females. The left lateral orbitofrontal gyrus is typically involved in changing emotional behavior, and lower volumes in this region have been associated with higher abdominal pain, due to reduced brain volumes altering the processing of visceral sensations.^{18,19}

However, the lack of difference in symptom severity, despite the significant structural difference in the left lateral orbitofrontal gyrus and statistically insignificant structural differences in other brain regions, does not align with the anticipated inverse correlation between brain volume and pain. This may reflect a true lack of association between brain volumes and IBS pain severity or may be attributed to the limitations of this study. As such, this result should be interpreted cautiously.

The lack of significant differences in IBS symptom severity between sexes does not support this study's hypothesis and the general literature reporting that female IBS patients experience more severe abdominal pain during colorectal distention and significantly higher symptom scores.²⁰⁻²² The lack of significant differences in brain volumes also does not align with the literature, which shows significantly lower brain volumes in

regions associated with pain processing.¹² However, this study had a sample size of 87 participants, which is smaller than the larger sample size often used for scientific studies. This dataset also observed a sample imbalance, with 69 females and only 18 males. This imbalance may have affected the observed trends and reduced the statistical significance between the two groups.

Similarly, comparisons of symptom severity and brain volumes between different age groups yielded non-significant differences in median values. The lack of significant differences in symptom severity across ages is inconsistent with the general understanding of younger IBS patients experiencing significantly greater abdominal pain and visceral hypersensitivity.^{23,24} Once again, this lack of significant differences should be understood in consideration of the dataset's limited sample size and uneven sample distribution, with only 5 participants being above 50 years old.

The general statistically insignificant trend of younger patients having greater brain volumes, while patients older than 40 have the smallest brain volumes, aligns with prior studies that also reported statistically insignificant decreases in cortical thickness and gray matter in IBS patients as they aged.²⁵ However, as the differences between the groups did not reach statistical significance, which may be indicative of the limitations of the small and uneven sample size, the results cannot be directly correlated with existing literature.

Although most of the findings were non-significant, this data analysis can still contribute to broader literature. The lack of significant results reflects the limitations of the dataset's sample size and research design and highlights the importance of replication and larger-scale datasets in order to determine population trends. The results may also reflect a true lack of association between the volumes of most brain regions and IBS pain severity, and the trends observed may warrant further investigation with larger sample sizes. If future studies with larger sample sizes yield similar results, this may influence future counseling and patients' expectations of IBS symptoms and their severity. Women are currently expected to observe greater symptom severity, and many types of IBS medications, like Alosetron, cater towards female patients.^{26,27} Similarly, younger patients are also expected to experience stronger psychological and abdominal pain symptoms and are thus anticipated to require more support.^{28,29} As such, these exploratory results may help inform IBS diagnosis and treatment to promote more balanced care for both sexes and different age groups.

■ Conclusion

In conclusion, apart from volumes of the left lateral orbitofrontal gyrus between sexes, analysis of the data yielded mostly no statistically significant differences in IBS symptom severity and brain volumes between different sexes and age groups. Although the findings do not strongly support existing literature and hypotheses, these findings help to explore the relationship between brain volumes and IBS symptom severities, and the trends found can help guide the building of hypotheses in future, larger studies.

The study experienced a few limitations. The study had a limited sample size, and the uneven distribution between variable groups may have also affected the trends observed. Although the findings explore correlations between IBS symptoms and brain volumes, their causal relationship cannot be confirmed. Moreover, inherent limitations of the Bowel Symptom questionnaire and the State-Trait Anxiety Inventory were that they rely on a participant's self-reported symptom severity, which may also be influenced by a patient's own perception of their pain and how they communicate it.

Future studies investigating relationships between sex/age and IBS should focus more on identifying the causal link between the different variables and pain severity for IBS, and determine the mechanism causing such a relationship, which can help provide a greater understanding of how IBS works.

■ Acknowledgments

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■ Author

Anna Chia is currently attending Anglo-Chinese School (Independent) in Singapore. She is interested in pathophysiology and neuroscience. She aspires to pursue a career in the medical profession.