Brain-Gut-Microbiome Differences between Women with Subtypes of Irritable Bowel Syndrome

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Irritable Bowel Syndrome (IBS) is a common female-predominant disorder of gut-brain interaction

The constipation-predominant subtype of IBS (IBS-C) is almost twice as prevalent in women (40%) compared to men (21%) with IBS.

The Brain-Gut-Microbiome (BGM) has been implicated in the pathophysiology of IBS.

Some studies suggest that individuals with IBS subtypes may have distinct alterations in brain connectivity, while others have revealed different gut microbiomes, but no study to date has used a systems biology approach to elucidate BGM alterations in IBS subtypes.

In an effort to explore the underlying mechanisms and physiology of IBS subtypes, we use a systems biology approach.

Methods

Cross-sectional study

Fecal samples and resting state fMRI imaging were obtained from 138 premenopausal women

36 IBS-C (constipation-predominant), 28 IBS-D (diarrhea-predominant), 35 IBS-M (mixed, alternating, and unspecific bowel habits), and 39 HCs (healthy controls). Differences were explored between IBS-C, IBS-D, and HC. IBS-M were excluded in our analyses

Partial Least Squares Discriminant Analysis (PLS-DA) explored group differences

Brain regions and fecal metabolites with PLS-DA VIP>1.0 assessed by Student’s t-test

Partial correlation analysis between significantly changed metabolites and neuroimaging data

Controlled for age, BMI, and diet, FDR correction with q<.05 as significant (to correct for multiple comparisons)
Results

**Figure 1.** sPLS-DA Analysis of Brain Connectivity among IBS-C, IBS-D, and HC

- IBS-C, IBS-D, and HCs can be distinguished from each other by their alterations in functional links on MRI (“brain connectivity”) with an accuracy of 75%.
- IBS-C had greater functional connectivity within the sensorimotor, default mode, and emotional regulation networks compared to IBS-D and HCs.
- IBS-D had greater functional connectivity within the central executive network and the occipital cortex compared to IBS-C and HCs.
In a separate, integrated analysis, IBS-D showed tryptophan-related metabolites that positively correlated with activity in sensory network regions on MRI (N-acetyltryptophan: $r=0.38$, $p=0.04$).

Fecal metabolites differentiate IBS-C, IBS-D and HCs with an accuracy of 78%
Conclusions

This study is the first to integrate neuroimaging and microbiome data to characterize subtypes of IBS.

IBS-C showed greater alterations in regions involved in the processing and perception of sensory signals and emotional arousal, while IBS-D showed greater alterations in those involved in decision-making and problem-solving.

These brain patterns may enhance centrally-mediated visceral perception in IBS-C and IBS-D.

Distinct fecal metabolite patterns in IBS subtypes, including the relationship between tryptophan-related metabolites and sensorimotor connectivity, may highlight the role of serotonin in the pathophysiology of IBS subtypes in premenopausal women.

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