Cyclic Vomiting Syndrome is characterized by altered functional brain connectivity of the insular cortex: a cross-comparison with migraine and healthy adults

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Abstract
Cyclic Vomiting Syndrome (CVS) has been linked to episodic migraine, yet little is known about the precise brain-based mechanisms underpinning CVS, and whether these associated conditions share similar pathophysiology. We investigated the functional integrity of salience (SLN) and sensorimotor (SMN) intrinsic connectivity networks in CVS, migraine and healthy controls using brain functional Magnetic Resonance Imaging. CVS, relative to both migraine and controls, showed increased SLN connectivity to middle/posterior insula, a key brain region for nausea and viscerosensory processing. In contrast, this same region showed diminished SMN connectivity in both CVS and migraine. These results highlight both unique and potentially shared pathophysiology between these conditions, and suggest a potential target for therapeutics in future studies.

KEYWORDS
brain imaging, Cyclic Vomiting Syndrome, functional Magnetic Resonance, imaging, migraine

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1 | INTRODUCTION

Cyclic Vomiting Syndrome (CVS) has been compared to episodic migraine because of similarity in their dynamic progression of symptoms during ictal events or "attacks." While migraine is characterized by neuropathic/visceral symptoms, CVS symptoms are more purely visceral and localized to the gut. Ultimately, little is known about the brain mechanisms underpinning CVS or whether these two anecdotally linked disorders actually share any similarity in pathophysiology.

CVS is an episodic disorder characterized by recurrent episodes of nausea and vomiting with interictal symptom-free periods. While several theories have linked the disorder to predisposing factors such as migraine, psychological or infectious stress, gastric dysrhythmias, food allergies, and mitochondrial dysfunction, aberrant neural physiology for viscerceptive brain circuitry may support a common pathophysiological pathway for all these factors. Our previous research, using functional Magnetic Resonance Imaging (fMRI) has linked the anterior and middle insula cortex with nausea perception. In fact, the middle and/or posterior insula, which has been referred to as the primary visceral sensory cortex, may be a key region for visceral sensory and nausea-associated autonomic processing in CVS. Functional brain connectivity, a tool that has revealed disruptions in various chronic gastroenterological, neurological, and psychiatric disorders, has highlighted altered intrinsic information flow at the network level in migraine, and cross-comparison to CVS patients may help differentiate these two linked disorders in terms of neural pathophysiology.

The aim of our study was to investigate the functional integrity of two brain networks that encompass insula cortex, i.e. Sensorimotor (SMN) and Salience (SLN) Networks, in CVS. While primary (S1) and secondary (S2) somatosensory regions included in the SMN play a key role in bottom-up somatosensory processing, the SLN is thought to appraise the relative importance (i.e. salience) of internal and sensory stimuli, both visceral and somatic. Moreover, both of these networks are central to pain processing in the brain. For instance, a previous study found that evoked deep-tissue somatic pain involved reduced functional connectivity of the somatotopy-targeted S1 area to SMN, but increased connectivity to SLN. We hypothesized that (i) CVS is characterized by altered connectivity between these brain networks and viscerosensory processing brain areas, and (ii) similarities and differences in brain connectivity between CVS and migraine patients will highlight both the shared and unique pathophysiology underlying CVS.

2 | MATERIALS AND METHODS

We enrolled 13 patients diagnosed with CVS (12 women; age 29.7±12.0, mean±SD), 14 patients diagnosed with episodic migraine (13 women; age 35.8±13.4), and 12 healthy controls (HC, 11 women, age 25.8±3.6). All participants were right-handed. Written informed consent was obtained from all participants, and the protocol was approved by the Human Research Committee of Partners Healthcare and Massachusetts General Hospital.

Key Points

- Cyclic Vomiting Syndrome (CVS) and Episodic Migraine have been suggested to share pathophysiology, but no studies have yet compared these conditions.
- CVS, compared to migraine and healthy controls, displayed increased connectivity between the salience brain network and the mid/posterior insula, a brain region important for viscerosensory processing. Both CVS and migraine displayed diminished insular connectivity with the sensorimotor network.
- We identify both CVS-unique and potentially shared pathophysiology between CVS and episodic migraine, highlighting the middle/posterior insula as a potential target for therapeutics in future studies.

Importantly, CVS patients were enrolled prior to significant neuromodulatory pharmacotherapy (e.g. benzodiazepines, anticonvulsants, and opioids). While this affected enrollment and sample size, maintaining this strict criterion was important to limit potential false positive group differences related to drug-induced alterations in neurovascular coupling. Inclusion criteria for CVS were age 18–80, diagnosis of CVS by Rome III criteria, and English proficiency. Inclusion criterion for HC was age 18–64. Exclusion criteria for CVS and HC were pregnancy (or planned pregnancy), acute illness, chronic illness such as kidney failure, congestive heart failure, diabetes, those awaiting organ transplantation, use of prescription benzodiazepines within the previous 7 days, use of prescription opioids, use of cannabinoids within the previous 7 days, and any nausea/vomiting episode within 48 hours prior to experimental session. CVS patients were also required to avoid alcohol for at least 24 hours prior to testing, and not to drink coffee (or caffeinated beverages) or smoke in the morning of the day of testing. Inclusion criteria for episodic migraine patients were age 18–60, diagnosis of migraine based on classification by the International Headache Society (Headache Classification Committee of the International Headache Society, 2004), and 2–15 uncomplicated migraine episodes per month. Exclusion criteria included other neurological or major psychiatric disorders. Similar to CVS and HC, none of the enrolled migraine patients were using prescription benzodiazepines, opioids, or cannabinoids.

All CVS (140.5±189.6 days since previous episode, mean±SD) and migraine (6.1±5.8 days since previous episode) patients were in an interictal state at the time of MRI scanning. A Shapiro–Wilk test for normality did not indicate that interictal index data was non-normally distributed for either patient group (CVS: 0.94, P=.58; Migraine: 0.93, P=.29).

Functional integrity of SLN and SMN was assessed using intrinsic network analysis of resting state fMRI data. Heart rate and respiration were monitored and used for physiological noise correction of the fMRI data. The data were corrected for motion artifacts, spatially smoothed (FWHM=5 mm), and high-pass filtered...
(f>0.008). A dual regression Independent Components Analysis was performed to identify SLN (Fig. S2) and SMN (Fig. S3) networks, based on canonical template matching. To investigate whether SLN connectivity differed between CVS and HC, we performed a whole-brain mixed effects analysis (FSL-FLAME1+2, cluster corrected for multiple comparisons at FWE corrected P<.05), followed up by cross group region-of-interest (ROI) analyses (see Data S1 for additional details).

3 | RESULTS

The whole-brain analysis revealed that, compared to HC, CVS demonstrated increased SLN connectivity to a cluster encompassing posterior/middle insula (p/mINS), secondary somatosensory cortex, and superior temporal sulcus (Fig. 1A). A follow-up ROI analysis of this cluster evaluated connectivity relative to migraine, and found a significant Analysis of Variance (ANOVA) group effect for SLN connectivity (F(2, 36)=12.7, P<.001), with a direct contrast showing increased SLN connectivity for CVS compared to migraine (95% confidence interval (CI) 0.55–1.18, P=0.012) (Fig. 1B). Next, an ROI analysis was performed to evaluate if this region (p/mINS) also showed altered SMN connectivity. There was again a significant ANOVA group effect (F(2, 36)=5.3, P=0.01), with group-wise contrasts displaying reduced SMN connectivity to this p/mINS cluster for CVS relative to HC (CI −0.94 to −0.191, P=0.004), but not migraine (CI −0.46 to 0.26, P=0.57) (Fig. 1C). In fact, similar to CVS, migraine showed reduced SMN connectivity relative to HC (CI −0.83 to −0.097, P=0.015).

Interestingly, five CVS patients reported migraine diagnoses, reflecting the noted comorbidity of these disorders. To investigate whether such comorbidity influenced the results, we performed the above ROI analyses controlling for migraine diagnosis. Including this confound regressor in the model did not influence ANOVA significance (SLN: F(3, 35)=8.28, P=0.001; SMN: F(3, 35)=3.46, P=0.027). Similarly, as 8 of the migraine patients also reported some recurring nausea during episodes, we performed the above ROI analyses controlling for nausea report. Including this confound regressor also did not influence ANOVA significance (SLN: F(3, 35)=8.52, P=0.001; SMN: F(3, 35)=3.44, P=0.027) (see Data S1 methods for more detail). These findings strengthen the conclusion that increased SLN connectivity with p/mINS is unique to CVS, while reduced SMN connectivity to this region may characterize pathophysiology underlying both CVS and migraine.

4 | DISCUSSION

The results from this study elucidate alterations in brain physiology that may underpin CVS, and identifies features that are different from, and shared with, episodic migraine. While CVS was characterized by increased connectivity between a salience processing network and p/mINS, this viscerosensory region demonstrated diminished connectivity to a somatosensory processing network. Previous studies of episodic migraine have shown disruption of somatosensory and viscerosensory cortex morphometry16,17 and intrinsic connectivity,16,18 and disrupted posterior insular habituation responses to repeated sensory stimuli.19 Furthermore, a recent meta-analysis of functional neuroimaging studies of Irritable Bowel Syndrome (IBS) found m/pINS to be consistently hyper-activated in response to visceral stimulation using rectal distension in IBS patients.20 Other idiopathic chronic disorders such as fibromyalgia have also been characterized by altered intrinsic somatosensory connectivity,21 suggesting that chronic

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**FIGURE 1** Altered functional connectivity of middle/posterior insula (m/pINS) with salience (SLN) and somatosensory (SMN) processing brain networks in Cyclic Vomiting Syndrome (CVS), episodic migraine (MIG), and healthy controls (HC). (A) A whole-brain voxelwise analysis found that CVS, relative to HC, showed increased resting SLN functional connectivity to m/pINS. (B) A follow-up region of interest (ROI) analysis found that CVS also showed increased m/pINS connectivity with SLN compared to interictal MIG. (C) A ROI analysis also indicated similarity between CVS and MIG, in that both showed diminished m/pINS connectivity to SMN, relative to HC. Error bars represent standard errors of the mean. *P<.05; **P<.01
suffering from somato-visceral symptomatology can alter intrinsic brain physiology.

In CVS, but not migraine patients, reductions in m/pINS connectivity to SMN was accompanied by increased m/pINS connectivity to SLN, compared to healthy individuals. This may signify increased vigilance of viscerosensory signals in CVS patients, which bears similarity with the recent finding that sustained deep-tissue pain stimulation is characterized by a SMN-to-SLN shift in connectivity in healthy individuals.15

The mid/posterior insula has also been proposed as a primary viscerosensory-processing region, supported by neuroimaging studies of experimentally induced nausea.6,7 and the observation that direct electrocortical stimulation of central and posterior portions of the insula elicits visceroceptive sensations such as nausea, stomach "buzzing", etc.7 Thus, this brain region may be a potential target for therapeutics. For instance, pregabalin has been shown to modulate posterior insular glutamate levels and functional connectivity in chronic pain patients.22

Several limitations should be noted. Firstly, as cross-sectional fMRI studies limit inferences about causality, future studies should address the degree to which disrupted m/pINS connectivity is a consequence or a cause of these disorders. Secondly, as all patients were interictal at the time of testing, the results cannot inform us of brain mechanisms involved during CVS attacks. However, fMRI during ongoing CVS episodes would be practically and ethically challenging, due to patient discomfort and the risk of vomiting while scanning in a supine position. It is nevertheless striking that consistent disruptions of the SLN and SMN networks can be observed even between episodes, consistent with findings of altered intrinsic connectivity in interictal episodic migraine.18 Although we did not find evidence for limbic (e.g. amygdala, hypothalamus) or brainstem circuitry as having differential connectivity to SLN or SMN, it is possible that limbic/brainstem circuitry may be more involved during actual episodes rather than during an interictal state.

In sum, while CVS has been linked to episodic migraine, little is known about the precise brain-based mechanisms underpinning CVS, and whether these associated conditions share similar pathophysiology. In our study, a direct comparison between CVS and migraine identified both similarities and differences in functional network integrity, indicating that while disruption of somatosensory processing (i.e. SMN connectivity) in the mid/posterior insula is shared between CVS and migraine, increased SLN connectivity to this viscerosensory region may be unique to CVS, proposing a target for future therapeutics.

DISCLOSURES

No conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

VN, BK study concept and design; RGG, JL, RLL, JK, AHT, SC, LD acquisition of data; DME, VN, BK analysis and interpretation of data; DME, VN drafting of the manuscript; DME, RGG, JL, NH, BK, VN critical revision of the manuscript for important intellectual content; DME, VN statistical analysis; BK, VN obtained funding; BK, VN technical, or material support; BK, VN study supervision.

REFERENCES


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