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Motion sickness increases functional connectivity between visual motion and nausea-associated brain regions

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ABSTRACT

The brain networks supporting nausea not yet understood. We previously found that while visual stimulation activated primary (V1) and extrastriate visual cortices (MT+/V5, coding for visual motion), increasing nausea was associated with increasing sustained activation in several brain areas, with significant co-activation for anterior insula (aIns) and mid-cingulate (MCC) cortices. Here, we hypothesized that motion sickness also alters functional connectivity between visual motion and previously identified nausea-processing brain regions. Subjects prone to motion sickness and controls completed a motion sickness provocation task during fMRI/ECG acquisition. We studied changes in connectivity between visual processing areas activated by the stimulus (MT+/V5, V1), right aIns and MCC when comparing rest (BASELINE) to peak nausea state (NAUSEA). Compared to BASELINE, NAUSEA reduced connectivity between right and left V1 and increased connectivity between right MT+/V5 and aIns and between left MT+/V5 and MCC. Additionally, the change in MT+/V5 to insula connectivity was significantly associated with a change in sympathovagal balance, assessed by heart rate variability analysis. No state-related connectivity changes were noted for the control group. Increased connectivity between a visual motion processing region and nausea/salience brain regions may reflect increased transfer of visual/vestibular mismatch information to brain regions supporting nausea perception and autonomic processing. We conclude that vection-induced nausea increases connectivity between nausea-processing regions and those activated by the nauseogenic stimulus. This enhanced low-frequency coupling may support continual, slowly evolving nausea perception and shifts toward sympathetic dominance. Disengaging this coupling may be a target for biobehavioral interventions aimed at reducing motion sickness severity.

1. Introduction

Nausea is a universal human experience. It is a perceptual state that evolves slowly over time and the brain networks supporting this state are not well understood. Non-invasive investigations of human brain connectivity, using functional connectivity MRI (fcMRI), have been applied to evaluate both trait and state spatiotemporal dynamics (Geerligs et al., 2015), and are sensitive to networks typically characterized by low frequency signal fluctuations (Baria et al., 2011). Hence, this method is well suited to evaluate the neural networks underlying slowly progressing perceptual states such as motion sickness induced nausea.

Recent neuroimaging studies have investigated brain activation in response to nausea. Our previous fMRI study employing a visual stimulus found that while phasic activation in fear conditioning and noradrenergic brainstem regions precipitates transition to strong nausea, sustained activation following this transition occurs in a broader interoceptive, limbic, somatosensory, and cognitive network. This most likely reflects the multiple dimensions of nausea perception (Napadow et al., 2013a). Specifically, while the stimulus activated vision and visual motion processing brain areas (primary visual, V1, and middle temporal area, MT+/V5, respectively), increasing nausea was associated with activation in brain areas such as insula and anterior cingulate cortex. These

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latter regions are classical targets for interoceptive afference (Craig, 2002; Wiens, 2005; Critchley et al., 2004) as well as autonomic processing (Beissner et al., 2013), which in turn is strongly modulated by motion sickness and nausea (LaCount et al., 2011; Muth, 2006; Sclocco et al., 2016). Interestingly, a further fMRI study found that these areas differ from those implicated in vection alone (Kovacs et al., 2008), suggesting that visually induced illusions of self-motion may be supported by a different circuitry than that supporting a perceptual state in which vection is accompanied by a nausea percept. Functional connectivity response to visual motion stimulation (but not nausea) shows reduced functional connectivity between MT+/V5 and several other striate and extra-striate visual processing areas (Hampson et al., 2004) in comparison to a resting state. Recently, Miyazaki et al. (Miyazaki et al., 2015) found that a brief (6 min) visual stimulation that was accompanied by mild motion sickness resulted in desynchronization between left and right MT+ areas for the high frequency (>0.1 Hz) component of the BOLD fMRI signal. Few other studies exist that have evaluated functional brain connectivity response to motion sickness-induced nausea following sustained stimulation.

In this study, we evaluate brain connectivity response to nausea induced by vection. We focus our analysis on key brain regions robustly activated by our vection-inducing visual stimulation, as well as on brain regions shown to activate with increasing nausea perception (Napadow et al., 2013a). Specifically, we investigate how nausea alters functional connectivity between primary visual (V1), middle temporal (MT+/V5), anterior insula, and anterior cingulate cortices.

2. Methods

2.1. Subjects

We recruited right-handed subjects [Edinburgh Inventory (Oldfield, 1971)] through public advertisement. All subjects underwent prescreening to determine propensity to motion sickness as evaluated through the Motion Sickness Susceptibility Questionnaire (MSSQ) (Golding, 1998). The MSSQ consists of two separate sections related to childhood experiences (below 12 years of age) of travel and motion sickness and to experiences of travel and motion sickness over the last 10 years. The MSSQ score has been shown to be a significant predictor of severity and tolerance of nausea and vomiting in response to controlled nauseogenic motion stimuli exposure, with an average MSSQ score of 24 ± 13.3 (mean ± SD) in a population of 106 healthy subjects not suffering from migraine (Golding, 1998). A complete medical history and physical examination was performed by a gastroenterologist. Two (2) subjects reported a history of migraines in the nausea group, while 1 subject reported a history of migraines in the control group (Fisher's Exact test, two-tailed: $p = 1$). Subjects with irritable bowel syndrome or upper gastrointestinal disorders were excluded from both groups. Upon clinical examination, subjects had no history of balance or vestibular disorders. Additional confirmation of susceptibility to motion sickness was obtained through subjective nausea intensity ratings from a mock MRI session which included a visual nauseogenic stimulus (see below). In the nausea group, we excluded subjects with an MSSQ score > 60 who reported low (<2 on an integer scale from 0 to 4) maximum nausea rating in response to the stimulus. All subjects with an MSSQ score > 60 and maximum nausea rating > 1 were allocated to the motion sickness (NAUSEA) group, and all subjects with an MSSQ score < 60 and maximum nausea rating < 2 were allocated to a control group. A cutoff of 60 in MSSQ score was chosen because it has been shown that subjects with MSSQ scores > 60 experienced moderate nausea to visual nauseogenic stimulation more reliably and more quickly than those with scores below this inflection point (Golding, 1998). This resulted in a nausea group of sixteen subjects (female, age: 27.5 ± 8.6 years, mean ± SD) and a control group of eight subjects (female, age: 25 ± 1.1 years, mean ± SD). All twenty-four subjects agreed to continue to the experimental MRI session. Subject who needed corrective vision were allowed to wear contact lenses. Given the increased risk of vomiting during the experimental session, for safety reasons all subjects were asked to refrain from food and water intake for 12 h and from cigarettes and alcohol for 24 h prior to fMRI. While alcohol and nicotine withdrawal can produce nausea in addicted individuals, the baseline nausea rating for all subjects was 0 (no nausea - see below), suggesting that subjects in our study did not experience withdrawal associated nausea. All experiments took place between 7 AM and 12 PM at the A.A. Martinos Center for Biomedical Imaging in Charlestown, MA. Written informed consent was obtained from all participants, and the protocol was approved by the Human Research Committee of Massachusetts General Hospital.

3. Experimental protocol

3.1. Scanner and screen configuration

Subjects were placed, supine, in a 1.5 T Siemens Avanto MRI scanner (Siemens Medical Systems) equipped with a specialized 23-channel head coil constructed at the Martinos Center for Biomedical Imaging (Wiggins et al., 2006) which provided an extra-wide field of view. This was necessary for unobstructed administration of visual stimuli during fMRI. We used video projection onto a screen which comprised a central section (30.48 cm wide, 40.64 cm high), and 2 side wings (10.16 cm wide, semicircular) inclined at 45° with respect to the central section. This screen was positioned approximately 10 cm in front of their eyes. Thus, assuming a single central visual focus, the field of view was 165.7°, covering both central and peripheral visual fields.

3.2. Stimulus design and nausea rating

Subjects were instructed to lie still and look directly at a crosshair which was projected onto the center of the screen for an initial baseline period of 5 min (Fig. 1). After baseline, the nauseogenic stimulus was projected as follows: alternating black and white stripes (black stripes 1.2 cm, 6.9° viewing angle; white stripes 1.85 cm, 10.6° viewing angle) with left-to-right circular motion at 62.5°/s. The horizontal translation induces vection, i.e. a false sensation of translation of the subject itself directed to their left. During and after the stimulus, all subjects rated the intensity of the nausea they were experiencing on a scale ranging from "0" to "4" (0 = no nausea, followed by 1 = mild/2 = moderate/3 = strong/4 = severe nausea) using a button box. Ratings were verbally instructed and practiced during the mock scanner session and performed without predetermined timings/cues. The stimulus was immediately terminated when a rating of 4 was reached (corresponding to the urge to vomit according to past experience) - see Fig. 1. The experimental procedure ended with a second 5-min period of crosshair fixation.

3.3. MRI and ECG data collection

Whole-brain blood oxygen level-dependent (BOLD) fMRI data were collected in a 1.5 T scanner using a gradient echo T_2^*-weighted pulse sequence (repetition time [TR] / echo time [TE] = 3 s/30 ms, slice thickness = 3.0 mm, interslice gap = 0.6 mm, matrix = 64 × 64, FOV = 200 mm, flip angle [FA] = 90°). The fMRI acquisition ran continuously throughout the experimental protocol, resulting in a maximum of 600 volumes, unless stimulation was interrupted as a consequence of severe nausea rating (see above). Prior to fMRI, we also acquired a high-resolution T_1-weighted structural image, using a standard MPRAGE sequence (TR/TE/TI = 2730/3.39/1000 ms, slice thickness = 1.33 mm, FOV = 156 mm, FA = 7°). Concurrently with MRI data acquisition, ECG signals were collected at a sampling frequency of 400 Hz using Chart Data Acquisition Software (ADInstruments) on a laptop equipped with a 16-channel Powerlab DAQ System (ADInstruments) using an MRI-compatible Patient Monitoring system (Model 3150, Invivo Research, Inc.)