



# Neural correlates of nausea: a functional MRI Study



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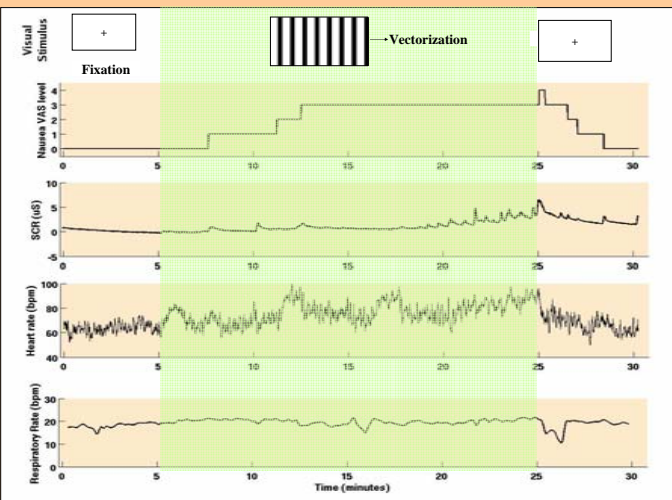
**Background:** Nausea, a common and unpleasant GI-associated sensation, has never been evaluated with functional MRI (fMRI). Similar to pain, nausea also elicits autonomic response and may be modulated by specific brain networks.

**Aim:** To interrogate the neural correlates of nausea using fMRI.

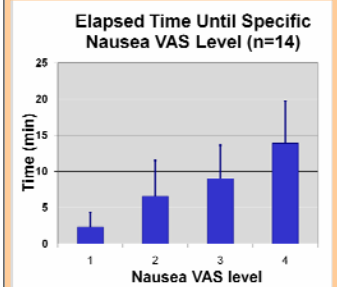
**Methods:** The nauseagenic stimulus was a standardized visual presentation of alternating black (1.2cm, 6.9° viewing angle) and white stripes (1.85cm, 10.6° viewing angle) with left-to-right linear motion 62.5°/sec. This stimulus was projected on to a 150° field of view screen positioned to fill the subject's full visual field. A specialized 23-channel head coil was used to allow unimpeded visual stimulation. BOLD T2\*-weighted fMRI was performed with a 1.5T Siemens Avanto with concurrent autonomic monitoring. Subjects were instructed not to perform compensatory breathing mechanisms (which could change blood CO<sub>2</sub> levels and affect fMRI signal). fMRI data were analyzed using a parametric approach driven by subject button-box response to estimate the brain correlates of nausea. Subjects were trained to recognize and rate VAS nausea levels on a scale of 1-4, with 4 corresponding to 75% of the worst nausea experienced. After a 5 minute baseline fixation, the stimulus was presented and continued until either (1) the subject rated a nausea intensity of 4 or (2) 20 minutes had expired. The stimulus was then terminated and subjects were presented with another 5 minutes of fixation. We first defined 1-minute ON blocks beginning at nausea level transitions (0 to 1, 1 to 2, and 2 to 3). Data at the single subject level were analyzed with a general linear model (GLM), which contained regressors for each of the transition blocks, as well as a regressor capturing the entire stripes presentation as a regressor of no interest. Data from the single subject level (transition block regressor parameter estimates and their variance) were transformed to MNI-space and passed up to a group level mixed-effects model which included a contrast coding for nauseagenic transition periods weighted by linearly increasing nausea intensity.

**Results:** 14 female subjects (mean age 30 yrs) completed both mock scan training and fMRI imaging sessions. The average time of visual stimulation was 13.6 ± 6 min. 10/14 subjects reached a level 4. No vomiting occurred during the study for any subject.

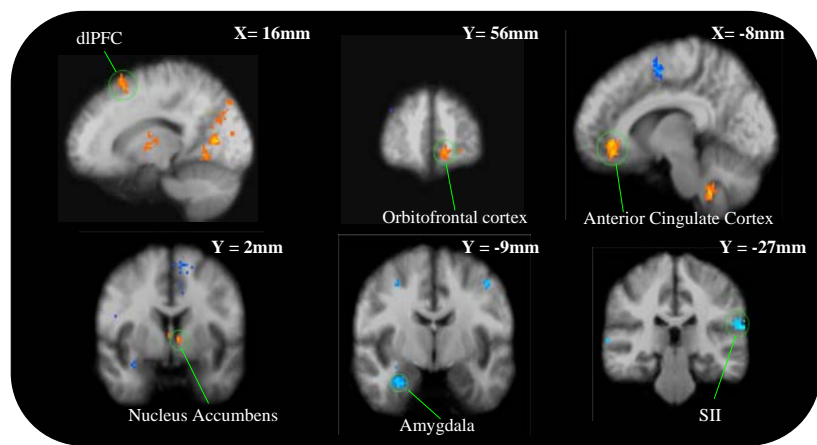
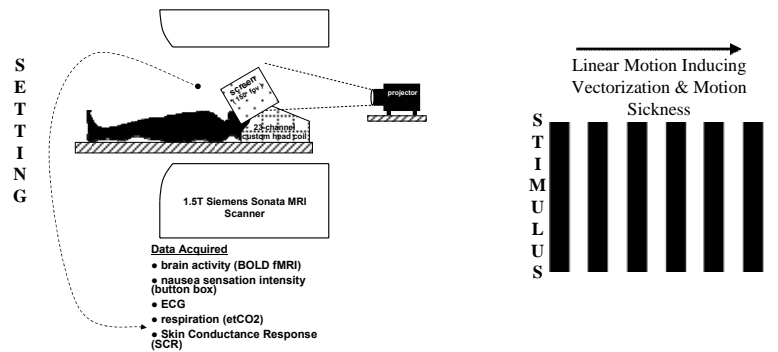
Nausea Level (Button Box), Skin Conductance Response (SCR), Heart Rate, and Respiratory Rate over Time during Nausea fMRI Trial (Single Subject)



For most subjects, increasing nausea was associated with an increase in skin conductance level, and heart rate. Subjects were instructed not to perform compensatory breathing mechanisms (which could change blood CO<sub>2</sub> levels and affect fMRI signal).



[BELOW] Increasing nausea level transitions were correlated with brain activation in the orbito-frontal, sub-genual anterior cingulate, and dorsolateral prefrontal cortices, as well as nucleus accumbens (NA) and caudate. Conversely increasing nausea was correlated with deactivation in the amygdala and SII – a potential compensatory mechanism.



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**Conclusions:** Nausea induces affective and autonomic dysregulation by modulating limbic (e.g. ACC) brain regions as well as reward circuitry (e.g. NA). Our novel fMRI paradigm was successful in characterizing the neural correlates of nausea for the first time in humans. This approach can serve as a model to evaluate the neurobiology of nausea with pathology, as well as the impacts of potential interventions.