Graded fMRI Response in Rat Rectal Distention Model

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Purpose

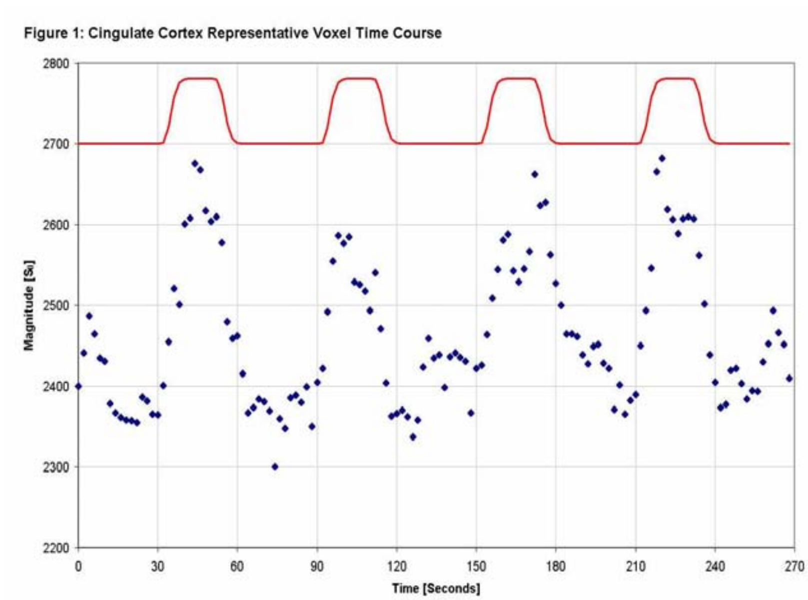
Irritable bowel syndrome (IBS) affects 10% to 20% of the general population and is one of the most common of disease diagnosed by Gastroenterologists. Functional gastrointestinal disorders are assumed to be caused by altered physiological function instead of a defined structural or biochemical cause. Therefore, diagnosis can be quite difficult and the disease is unidentifiable by standard clinical techniques such as standard radiography and blood chemistry panels. IBS symptoms result from what appears to be a disturbance in the interaction between the enteric nervous system (ENS), the autonomic nervous system (ANS), and the central nervous system (CNS) that alters regulation of bowel motility (motor function) or sensory function. Understanding how the CNS is involved with the perception and processing of visceral pain is a major goal of gastrointestinal research.[1] Recent fMRI studies using human models of IBS have been successful at identifying brain regions involved in visceral pain processing of the gut.[2] However, the inherent difficulties in using human subjects necessitate the development of an animal model for study of neural and neurosensory response in functional GI disorders. The development of an animal protocol that displays a graded response to different levels of visceral stimulation of the gut will be a major advance in the field. This work describes a rectal distention fMRI protocol for rodents with an infused anesthesia at 9.4 Tesla. A differential response to different levels of balloon inflation was observed.

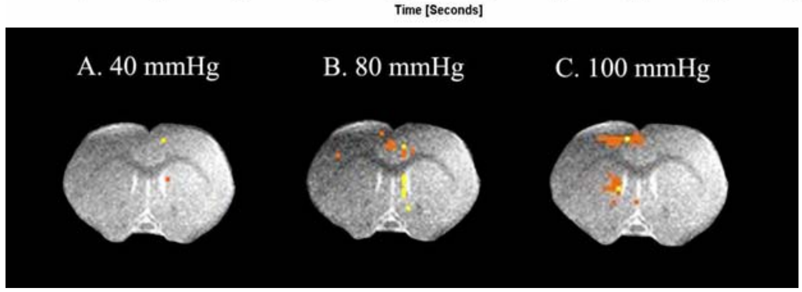
Materials and Methods

Three Sprague-Dawley male rats (n=3), 400-450 grams were used for studying visceral sensitivity to rectal distension utilizing fMRI. Prior to the procedure, the animals were fasted overnight to reduce the amount of stool in the GI tract and facilitate the insertion of a rectal balloon. A custom made disposable polyethylene balloon was used for this procedure. The rectal balloon was infinitely compliant with a maximal inflation diameter of 10 mm and length of 1.2 cm. The animals were initially anesthesitized with an induction of 1.5% to 2.5% of Isoflurane and then maintained at 1.0% to 1.5% for surgery. The right femoral vein was cannulated for controlled infusion. After achieving adequate level of anesthesia, the balloon was carefully inserted into the rectum and positioned at 2 cm for the anal verge. The catheter was taped to the base of the animal's tail to prevent displacement. The catheter was connected to a computer driven pressure transducer device (barostat B428C, Iowa University) which was placed outside of the scanner room. The Isoflurane was discontinued and an infusion of Medetomidine (100 µg/kg/min) was started and continued throughout the imaging session. Medetomidine infusion has been shown be as effective for BOLD fMRI experiments as the drug ά-Chloralose.[3,4] The rat was placed in newly developed MRI holder device, and placed into the bore of the Bruker Biospec 9.4T MRI scanner.[5] Ascending phasic air distensions were applied to the rat's lower gastrointestinal tract in an fMRI block design for 20 seconds on every 40 seconds off for a total of 4.5 min. This distension paradigm was repeated 8 times during each study. The pressure delivered to the balloon varied between 40mmHg and 100 mmHg. The signal from the pressure transducer was processed through a data acquisition module (DATAQ Instruments) and recorded on a personal computer. The animal's temperature, respiration, pulse, and blood oxygenation was monitored and recorded throughout the entire length of the experiment.

Results & Discussion

Animals were imaged using a single shot gradient echo EPI sequence with a TR of 2.0 secs, TE of 21 msec, FOV of 4cm, matrix size of 96x96, slice thickness of 1.5mm, flip angle of 90, with 17 slices. Anatomical images where obtained for each animal using a RARE sequence for the same image slices with a TR of 2.5 secs and an in-plane resolution of 256X256. During the experiments no significant change in heart rate was observed between different intensity levels of visceral stimulation. With each phasic rectal distension, the frequency of heart rate increased 5-10% from baseline. A 3dDeconvolve (F-statistics) was used to calculate the functional brain maps. The statistical maps were overlaid on the anatomical images using a P-Value of 0.001. The brain activation maps showed a dose dependant response with ascending rectal balloon pressures (Shown in images A, B, and C). The largest brain volume activated was observed with rectal distension of a 100mmHg. Figure 1 shows a representative time course map of an activated voxel in the cingulate cortex, which was observed to be the most commonly activated brain region. Some of these findings are in concordance with previously published work[6]. In this study, visceral stimulation of the lower GI tract induced graded neurosensory response. This line of work has demonstrated a stable animal model which may be useful for studying physiologic and pathophysiologic brain gut interactions. Further research needs to be performed to further optimize the animal model protocol.





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