Evidence of Oesophageal Stimulus Intensity Dependant Response in the Human Anterior Cingulate and Primary Somatosensory Cortex

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Synopsis

Studies investigating the neural correlates of non-painful and painful oesophageal stimulation have produced variable results. Furthermore, regions involved in the encoding of stimulation intensity are not fully understood. Using a standardised method for establishing quantifiable intensities of oesophageal stimulation, the neural correlates of four levels of oesophageal stimulation were investigated. Stimulation resulted in a complex pattern of cerebral activation that was similar across different levels of stimulation intensity. The anterior cingulate gyrus (ACG) and primary somatosensory cortex (SI), both showed evidence of stimulus dependent response, which may be a result of encoding of intensity and unpleasantness or levels of attention.

Introduction

Although the functional correlates of non-painful and painful visceral stimulation have previously been investigated (1), the results have been variable. Furthermore, despite the fact that functional Magnetic Resonance Imaging (fMRI) can be used to objectively quantify perception of visceral sensation, regions involved in the encoding of stimulation intensity are not fully understood. By using a standardised method for determining varying intensities of oesophageal stimulation, the neural correlates of four levels of stimulation and the regions involved in encoding of intensity can be investigated.

Aims: The purpose of this study was to determine the neural correlates of four intensities of oesophageal stimulation as well as investigating regions involved in the encoding of stimulation intensity, using fMRI.

Methods

Subjects: 7 healthy volunteers (5 male, mean age 22 years, +7 months) participated in the study. All subjects gave informed, written consent prior to intubation and scanning. The study was approved by our local ethics committee for research.

Oesophageal stimulation: a standard manometry catheter with a silicone balloon attached was passed trans-nasally into the lower oesophagus (35cm from the nostril). The catheter was attached to a pump that inflated the balloon with air at regular intervals. The experiment examined four conditions. During each condition one of four balloon distension intensities, obtained by dividing the difference between sensory (the point at which volunteers first perceived a sensation) and pain thresholds (100%) into 4 levels at 25% increments (i.e. 25%, 50%, 75%, and 100%), was used to stimulate the distal oesophagus. A modified block design was employed for each intensity, where each “active” and “rest” phase was repeated five times. Behavioural data measuring the subjective perception of the stimulus (0 = non-painful, 5 = discomfort, 10 = extreme pain) was acquired after each active epoch, using visual analogue scales (VAS).

fMRI acquisition: Functional Magnetic Resonance Imaging was performed using a GE Neuro-optimised 1.5 Tesla system (General Electric, Milwaukee WI, USA), based at the Maudsley Hospital, London. Sixteen 7mm slices (0.7 mm gap) parallel to the bicomissural plane were acquired, with a repetition time (TR) of 3 seconds and an echo time (TE) of 40ms, flip angle 90°. A total of 122 T2* weighted images per slice, depicting BOLD contrast (Ogawa et al. 1990) were collected over a six minute and six second period of continuous acquisition during which, subjects received localised phasic distensions to the oesophagus. This procedure was performed on four occasions to collect data for four levels of intensity of oesophageal distension.

Image Analysis: Spatially realigned BOLD responses were modelled as the weighted sum of the input function convolved with two Poisson functions. A goodness of fit statistic was computed and a voxel-wise inference was carried out non-parametrically. At the group level, individual statistic maps were transformed into standard stereotactic space and median activation images constructed.

Results

Mean VAS scores increased progressively with increasing stimulation intensities ($\chi^2 = 10.9$, df 3, $P=0.001$), (mean VAS $\pm$SEM): 25% = $3.2\pm0.80$, 50% = $3.6\pm0.91$, 75% = $5.6\pm0.79$, 100% = $7.3\pm0.48$). In response to 100% and 75% stimulation intensity, activation was seen in the anterior cingulate gyrus (ACG) (BA 24, 32), bilateral insula, supplementary motor area (SMA), thalamus, bilateral primary and secondary sensory cortices (SI&SII) and dorso-lateral prefrontal cortex (DLPFC). 50% and 25% intensity (non-painful) stimuli activated the same regions to a lesser extent, with the exception of the thalamus, and SI, and additional activation in the inferior frontal gyrus. A trend analysis revealed a significant trend ($p<0.05$) in intensity of cerebral activation in the anterior cingulate gyrus (BA24), and primary somatosensory cortex (bilateral), which increased with rising stimulation levels.

Discussion

Visceral stimulation results in a complex pattern of cerebral activation that is similar across varying levels of stimulation intensity. Additional activation of the thalamus at 100% and 75% intensity reflects previous studies that suggest a role for this region in mediating attentional aspects of pain (2). The ACG and SI, both show evidence of a stimulus dependent response, which has previously been reported in studies involving somatic stimulation (3). This type of response supports the view that these regions may be involved in the encoding of stimulus intensity, unpleasantness of the stimulus, or levels of attention devoted toward the stimulus (3, 4, 5).

References