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NEURAL CORRELATES OF ELECTROINTESTINOGRAPHY: INSULAR ACTIVITY MODULATED BY SIGNALS RECORDED FROM THE ABDOMINAL SURFACE

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Abstract—Although the neural correlates that underlie abdominal pain have been investigated, so-called brain processes involved in modulating ''gut feelings'' remain unclear. In the current study, we used electrointestinography (EIG) to measure intestinal activity of healthy humans at rest. EIG measured myoelectrical activity of intestinal smooth muscles from the abdominal surface and was simultaneously conducted along with brain activity measurement using functional magnetic resonance imaging (fMRI). Correlations between the frequency powers of EIG and fMRI signals during 30 min of rest were then examined to elucidate gut–brain interactions. Neural activity correlating with 0.14- to 0.21-Hz EIG (suggested to reflect intestinal activity) was observed in the right anterior and middle insula. Moreover, this EIG frequency band correlated with anxiety scores along with resting-state functional connectivity between the insula and dorsal anterior cingulate cortex. These findings suggest that the insular cortex could be the core region involved in central visceral processes associated with subjective feelings.

Key words: autonomic, fMRI, gut, resting-state functional connectivity, viscera.

INTRODUCTION

Maintenance of gastrointestinal homeostasis requires gut–brain interactions (Mayer, 2011). These interactions have been extensively investigated using invasive gastrointestinal stimulations. For example, enhanced insular activity can be induced by distending stimulation of digestive organs, including the esophagus (Aziz et al., 2000), stomach (Wang et al., 2008), descending colon (Hamaguchi et al., 2013), and rectum (Hobday et al., 2001). In contrast, neural responses to intestinal activity during resting and steady states remain less understood.

Previous rodent studies report that the insular cortex is involved in autonomic, viscerosensory, and visceromotor processes (Cechetto and Saper, 1987; Bagaev and Aleksandrov, 2006). Electrogastrography of the abdominal surface of humans watching disgusting scenes has shown an association between subjective disgust and anterior insular activity (Harrison et al., 2010). Meta-analyses of neuroimaging studies (Kelly et al., 2012; Chang et al., 2013) suggest that the posterior to middle insula is involved in sensory and motor visceral processes and in interoception, while the anterior insula is associated with cognitive and affective functions. Moreover, a central autonomic network including the insular and cingulate cortices (Beissner et al., 2013) has been detected. Visceral inputs to the insula are involved in autonomic integration, subjective feelings, and self-awareness (Craig, 2009; Critchley and Harrison, 2013). However, neural responses to usual intestinal activity have been less investigated.

Electrointestinography (EIG) is a technique for non-invasive measurement of myoelectrical activity elicited from intestinal smooth muscles that are mainly controlled by the parasympathetic nerve. Ablation and elimination studies have reported that EIG activity around 0.1 Hz reflects myoelectric activity of the colon, that 0.13–0.2 Hz reflects small intestinal activity, and that slower waves of 0.05 Hz reflects normal activity of the stomach (Riezzo et al., 2013).

In this study, functional magnetic resonance imaging (fMRI) was used to determine the neural correlates of EIG activity during 30 min of rest in order to elucidate the network associated with the resting gut–brain axis.

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Abbreviations: ACC, anterior cingulate cortex; EIG, electrointestinography; EPI, echo planar imaging; FA, flip angle; fMRI, functional magnetic resonance imaging; FWE, family-wise error; FWHM, full-width half-maximum; HF, high frequency; LF, low frequency; MF, middle frequency; MNI, Montreal Neurological Institute; MPRAGE, magnetization-prepared rapid acquisition gradient echo; rsFC, resting-state functional connectivity; TE, echo time; TI, inversion time; TR, repetition time; VLF, very low frequency.

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Additionally, since a previous study has suggested a link between intestinal activity and anxiety (Foster and McVey Neufeld, 2013), correlations between EIG activity and anxiety scores were examined. We hypothesized that the insula and cingulate cortices would be involved in visceral processing and anxiety (Paulus and Stein, 2006; Coen et al., 2009; Berman et al., 2012; Larsson et al., 2012).

EXPERIMENTAL PROCEDURES

Subjects

The study participants comprised of 18 healthy adults (10 men and 8 women) aged 20–39 years. The participants who reported present or history of gastrointestinal and neurological/psychiatric disease were excluded. Mean body mass index was 21.45 ± 2.62 (± standard deviation). Participants fasted for at least 8 h before the experiment and were instructed to refrain from taking medications within 48 h of the study. Written informed consent was obtained from each participant, the experiment was conducted in accordance with the Declaration of Helsinki, and all procedures were approved by the RIKEN Research Ethics Committee.

EIG measurement

Bipolar EIGs were recorded using seven pairs of MRI-compatible ceramic-mounted silver/silver-chloride electrodes from the abdominal skin surface with a reference electrode on the right sacrum (Fig. 1, left). The umbilicus served as the base and seven points were marked on the abdominal surface according to individual girth. The seven points were (1) 5% right, (2) 5% left, (3) 5% inferior, (4) 10% right–5% inferior, (5) 10% right–5% superior, (6) 10% left–5% superior, and (7) 10% left–5% inferior to the umbilicus. Positive electrodes were placed 2.5 cm superior to each point and negative electrodes were placed 2.5 cm inferior to each point along the bowel peristalsis direction except for points four and five, which had positive electrodes placed 2.5 cm inferior to them and negative electrodes placed 2.5 cm superior to them since they were located over the ascending colon.

EIG signals were amplified using an MRI-compatible, shielded, nonmagnetic, battery-operated constant current amplifier (BrainAmp ExG MR; Brain Products, Germany), and amplifier output occurred via twin-fiber optic channels to a laptop. EIG signals were sampled and digitized at 100 Hz and were recorded on the laptop.

One session lasted for a total of 10 min and three sessions were conducted in total with 2-min inter-session intervals. For each session, EIG data were recorded for 11 min with 10 min being recorded during the fMRI, and 0.5 min being recorded for a pre- and post-session.

Analysis of EIG data. EIG data were analyzed in Matlab using purpose-written routines according to the following frequency bands: very low frequency (VLF), 0.0083–0.05 Hz; low frequency (LF), 0.06–0.13 Hz; middle frequency (MF), 0.14–0.21 Hz, and high frequency (HF) 0.22–0.29 Hz. The 11-min EIG time series of a session was downsampled to 2 Hz and filtered (low cut = 0.0083 Hz, high cut = 0.3 Hz). Then, the pre-sessions of 0.5 min and post-sessions of 0.5 min were discarded from the EIG data. Power spectral analyses (frequency domain) using discrete fast Fourier transforms were applied to EIG data averaged across the seven pairs of electrodes, with a single fast Fourier transform being applied to a minute epoch; a total of 30 epochs were analyzed for each subject.

Anxiety scores

The State-Trait Anxiety Inventory (STAI, Japanese version) (Spielberger et al.) was used immediately after

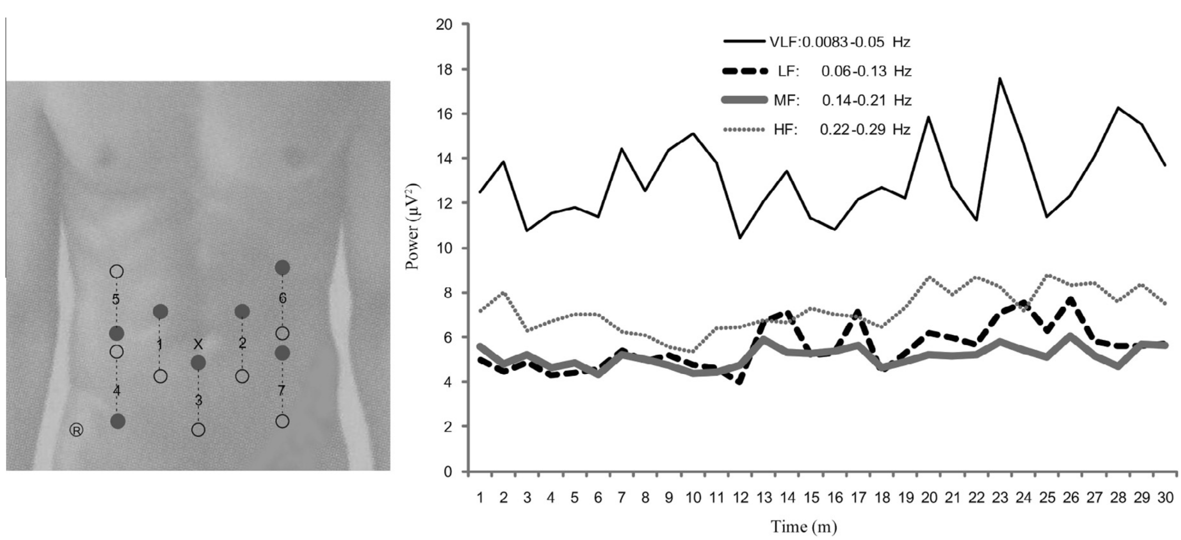

Fig. 1. Electrode placements and mean electrical power changes of four frequency bands. Filled and unfilled circles display cathodes and anodes, respectively (left panel). Dotted lines show seven pairs of cathode/anode electrodes. X shows umbilicus and R shows the reference electrode. Signals from electrodes (Electrointestinography, EIG) were recorded during 30 min of rest in the MRI scanner. In the right panel, the grand mean of EIG signals from seven electrodes of all participants (n = 18) is shown. EIG signals were categorized into four frequency bands of 0.0083–0.05 Hz (VLF), 0.06–0.13 Hz (LF), 0.14–0.21 Hz (MF), and 0.22–0.29 Hz (HF). EIG powers per minute of each frequency band were calculated.