Patterns of excitability in human esophageal sensorimotor cortex to painful and nonpainful visceral stimulation

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Central Nervous System Plasticity describes the ability of neuronal systems to alter function in response to both physiological and pathophysiological input (5). Although the precise role of neuroplasticity in modeling and remodeling neuronal function remains to be determined, a number of studies (5–7, 12, 15, 17–20) have now begun to shed light on the mechanisms responsible. These studies have demonstrated that neuroplasticity may be either beneficial, as in recovery from disability after cerebral injury (4), or maladaptive, such as in the development of pain syndromes, e.g., phantom limb pain after amputation (7). The latter forms part of an increasing body of evidence that now links cortical plasticity to somatic pain behavior (5–7). In comparison, the relationship between cortical plasticity and the development of visceral pain remains poorly understood. A greater knowledge of this physiological mechanism is therefore of fundamental importance to develop more targeted therapies for improving the management of conditions in which visceral pain is a major feature.

In previous studies (9–12) with transcranial magnetic stimulation (TMS), we have described the normal pattern of projections of swallowing musculature in the human sensorimotor cortex. Pharyngeal and esophageal sensorimotor cortex are organized bilaterally but display interhemispheric asymmetry independent of handedness (10, 11). We (12) have also demonstrated that the organization of the healthy human swallowing sensorimotor cortex can be altered in a sustained manner after sensory stimulation: a 10-Hz train of electrical stimuli to the pharynx for 10 min resulted in increased excitability of the pharyngeal corticobulbar projection for 30 min. Sensory input thus plays a crucial role in the modulation of swallowing sensorimotor cortex, and it is possible that alterations in sensory input might also induce neuroplastic cortical changes in areas linked to visceral perception.

Because maladaptive cortical plasticity has been implicated in the development of chronic functional pain syndromes, we wondered whether pain might also alter esophageal sensorimotor cortex excitability, establishing a physiological relationship between brain function and visceral pain. The aim of this study was therefore to test the hypothesis that the corticobulbar projection to the esophagus can be altered in a specific and sustained manner by painful esophageal stimulation.

METHODS

Electrophysiological Techniques

Subjects (n = 8) were healthy adult volunteers (6 male, 2 female, age range 24–36 yr, mean age 31 yr). No subjects...
reported swallowing problems, and all gave informed written consent before the study, which was previously approved by the Salford and Trafford Health Authority Ethics Committee.

**Focal transcranial stimulation.** Focal transcranial stimulation of the cerebral cortex was performed using a magnetic stimulator (Magstim 200, Magstim, Whitland, Dyfed, Wales) connected to a 70-mm outer diameter figure-eight coil, placed over the regions of interest on the scalp. With this configuration, the maximal magnetic field generated by the stimulator was 2.2 T.

**Electromyographic responses.** We detected electromyographic (EMG) responses from the upper esophagus using a pair of bipolar platinum ring electrodes, built into an intraluminal catheter of 3-mm diameter (Gaeltec, Dunvegan, Scotland). A single solid-state strain gauge transducer (Gaeltec) was also incorporated into the catheter, between the electrode pair. The latter enabled the esophageal electrodes to be maintained in position and allowed motility patterns to be monitored during the course of the study, giving an online assessment of any abnormal peristaltic activity. The thenar muscles of the contralateral (left) hand were also studied for assessment of any abnormal peristaltic activity. The thenar gland) with an interelectrode distance of 1 cm, one pair being positioned over each thenar eminence in the orientation of the first metacarpal. Each electrode pair was connected to a preamplifier (CED 1902, Cambridge Electronic Design, Cambridge, England) with filter settings of 2–5 kHz. Response signals were then collected through a laboratory interface (CED 1401 Plus) at a sampling rate of 4–8 kHz.

**Mechanical stimulation of esophagus.** We performed mechanical stimulation of the esophagus using a technique previously developed and described in detail by our laboratory (8). In summary, a 2-cm-long silicone balloon (Medasil Surgical, Leeds, UK) was sited 6 cm from the tip of a 4-mm-diameter polyvinyl catheter (Cook UK, Letchworth, UK) and connected to a specially constructed pump (Medical Physics Department, Hope Hospital) capable of rapidly and repeatedly distending the balloon at a frequency of 1 Hz. The maximum flow rate produced by the pump was 200 ml/s, and the rise time to maximum balloon inflation was fixed to 165 ms for any given volume. The balloon volume was controlled by altering the pump pressure (pressure range = 0–25 psi) and was allowed to deflate immediately after inflation. In vitro, the pump was capable of delivering a maximum balloon volume of 30 ml.

**Experimental Protocol**

For each study, the volunteer sat comfortably in a chair. The esophageal EMG catheter was then inserted transorally or transorally depending on subject preference, and the esophagus was manometrically mapped to determine the upper esophageal sphincter (UES). The catheter was then adjusted so that the electrodes were 3 cm below the UES, and resting baseline motility and raw EMG activity were recorded. With the subject at rest, the cranial vertex was marked on the scalp, and the optimal sites for magnetic stimulation were determined for both the esophagus and contralateral thenar muscles by discharging the figure-eight coil over multiple frontocentral scalp positions on the right hemisphere, using suprathreshold stimulus intensities. In this way, the sites evoking the largest EMG responses for the esophagus and the thenar muscles were then identified and marked on the scalp. Next, a series of cortical stimulations were performed over these positions, commencing at a subthreshold intensity and increasing by 5% stimulus-output steps until a threshold intensity was found that evoked esophageal EMG responses >20 μV and thenar EMG responses >100 μV in at least 5 of 10 consecutive trials. Repeated stimulations at each of these sites were then carried out at intensities of 95%, 100%, 105%, 110%, 115%, and 120% threshold, in a randomized order. Ten stimuli were delivered at each intensity for each muscle, with an interval of 5 s between each stimulation.

![Fig. 1. The cortically evoked esophageal electromyographic (EMG) responses in 1 individual are shown, at suprathreshold (110%) intensity, before and after nonpainful and painful stimulation. Ten responses are superimposed for each time point. The cortical stimulus (arrow) was applied at 0 ms. Nonpainful stimulation decreases the esophageal response amplitudes. In contrast, painful stimulation increases the esophageal response amplitudes.](image-url)
After completing this baseline stimulus-response procedure, we inserted the esophageal balloon catheter and adjusted it by inspecting manometric responses until the center of the balloon was 6 cm below the UES. At this point, an initial pain-volume thresholding procedure was performed (using 1-Hz inflations) in an ascending step-wise manner to determine the maximum tolerated volume of balloon distension. This was conducted three times, each measure taking ~30 s, with the mean value defined at the maximum tolerated intensity. Esophageal distension was then performed for 10 min at either a nonpainful intensity (defined as 25% of the balloon volume at the maximum tolerated intensity) or a painful intensity (100% of the maximum tolerated volume). All subjects received both levels of esophageal stimulation, in random order on two separate days, with preesophageal stimulation thresholding being performed on each occasion.

Each individual rated the distension of the esophagus on a visual analog scale of sensory perception, with one end representing no perceived stimulus and the other representing pain.

After esophageal distension, the balloon catheter was removed and cortical stimulation was then repeated immediately after, at 30 min after, and at 60 min after the visceral stimulus. At each interval, 10 stimuli were delivered in random order for each cortical intensity and each muscle, with 5 s between each stimulation. As performed previously, the upper esophagus was monitored at rest both with manometric and raw EMG recordings at 15-min intervals, to determine the presence of any abnormal peristaltic activity.

Data Analysis

The individual mean values of the cortically evoked EMG responses across all intensities for each interval after mechanical esophageal stimulation in both muscle groups were then compared using two-way ANOVA (Friedman test) to determine (1) the effect of time against prestimulation levels and 2) the conditional effects of pain vs. no pain. *P* = 0.05 was taken to indicate statistical significance.

The response amplitude was defined as the peak-to-peak difference in the EMG potential. The response latency was defined as the time taken between the cortical stimulus and the onset of the first deflection of the EMG potential from baseline. Raw motility and baseline EMG recording were finally analyzed offline by visual inspection of the traces by a suitably qualified individual, blinded to the condition received by the subject.

RESULTS

Balloon Volumes

Painful esophageal sensation was reached at a mean balloon volume of 11 ± 3 ml, and nonpainful esophageal sensation was reached at a mean volume of 4 ± 2 ml. At these volumes, subjective perception of the esophageal stimuli were rated as "painful" and "just perceived," respectively, on the visual analog scale of sensation.

Manometry and Resting EMG

The resting upper esophageal manometry recordings after stimulation were similar to those recorded before stimulation. No abnormal peristaltic activity was seen during the studies, either before or after stimulation. Similarly, no changes in the raw EMG recordings from the muscle were identified.

Esophageal Corticobulbar Projection

TMS evoked consistent biphasic esophageal EMG responses, the best site for stimulation being 4 ± 2 cm anterior and 6 ± 2 cm lateral to the vertex over the right hemisphere. The mean threshold intensity was 1.4 ± 0.2 T. Figures 1 and 2 show the results in detail.

Nonpainful distension. Compared with prestimulation levels, nonpainful distension resulted in a decrease in the cortically evoked response amplitudes immediately and at 30 min (72 ± 8 vs. 88 ± 12 μV, *P < 0.03), before returning to prestimulation levels by 60 min (Figs. 1 and 2). This was observed across each of the cortical stimulation intensities applied. Response latencies remained unchanged across each time interval (Table 1).

Painful distension. In contrast, painful distension resulted in an increase in the esophageal responses immediately and at 30 min (141 ± 12 vs. 101 ± 9 μV, *P < 0.05).

![Fig. 2. Histographic plots of the group mean cortically evoked esophageal EMG response amplitudes across all cortical stimulation intensities, before and after nonpainful (A) and painful esophageal stimulation (B). Pooled data are illustrated, being representative of the effects of each cortical intensity across subjects. The esophageal responses are reduced immediately and at 30 min after 10 min of nonpainful esophageal stimulation, whereas esophageal responses are enlarged immediately and at 30 min after 10 min of painful esophageal stimulation. Pre-stim, prestimulation. Values are means ± SE. *P < 0.05.](image-url)
CORTICAL PLASTICITY AND VISCERAL PAIN

Table 1. Latencies of cortically evoked responses

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<thead>
<tr>
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<th>Esophagus, ms</th>
<th>Thenar, ms</th>
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<tr>
<td></td>
<td>Painful</td>
<td>Nonpainful</td>
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<tr>
<td>Prestimulation</td>
<td>9 ± 0.4</td>
<td>8.5 ± 0.4</td>
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<tr>
<td>Immediate</td>
<td>9 ± 0.5</td>
<td>9.5 ± 0.5</td>
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<tr>
<td>30 min</td>
<td>8.5 ± 0.6</td>
<td>9 ± 0.5</td>
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<tr>
<td>60 min</td>
<td>8 ± 0.7</td>
<td>9.5 ± 0.5</td>
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Values are means ± SE.

P < 0.01) after stimulation, returning to prestimulation levels by 60 min (Figs. 1 and 2). As with nonpainful stimulation, the effect was observed across each cortical intensity. Response latencies, however, remained unchanged (Table 1).

Nonpainful vs. painful distension. Comparison of the nonpainful and painful conditions demonstrated a significant interaction in terms of effect, with the immediate and 30-min response amplitudes yielding inverse patterns of excitability (P > 0.001).

Thenar Corticospinal Projection

TMS evoked consistent biphasic thenar EMG responses, the best site for stimulation being 5 ± 2 cm anterior and 4 ± 2 cm lateral to the vertex over the right hemisphere. Mean threshold TMS intensity was 0.8 ± 0.1 T.

Neither nonpainful nor painful esophageal distension had any effect on the cortically evoked thenar responses compared with preconditioning levels (Fig. 3). Response latencies remained unchanged across each time interval for each condition (Table 1).

DISCUSSION

Our study has demonstrated that short-term painful stimulation of the human esophagus can drive long-term changes in the excitability of the esophageal corticobulbar projection, signifying a physiological association between visceral pain and plasticity. The ability of visceral stimuli to alter cortical excitability in a sustained manner merits further discussion. For example, Why should nociceptive input from the esophagus have an effect on the esophageal sensorimotor projection? To answer this question, one must consider the neurophysiology of swallowing and particularly the role of sensation. It is now well established (3) that sensory input from the esophagus projects to both the brain stem and cortex via both vagal and spinal pathways. A number of functional imaging studies (2, 4, 8, 14) of the cerebral loci processing human esophageal sensation have demonstrated strong activations within the primary sensory and motor cortex. It is likely therefore that afferent input from the esophagus projects either directly or indirectly to sensorimotor cortex and that these inputs have an influence on the excitability of these neurons and/or interneurons. In support of this effect, we (12) have already showed that pharyngeal stimulation could inhibit the esophageal corticobulbar projection, implying that input from remote swallowing fields can directly influence cortical excitability. Moreover, this effect does not appear to be specific to swallowing. Numerous reports (19, 20) of sensory denervation or deafferentation of peripheral muscles have demonstrated dramatic changes in the sensorimotor maps of muscles affected by that distribution, both at the level of the denervation and more proximally, clearly indicating that sensory input plays an important role in regulating sensorimotor function.

In considering the mechanisms underlying this effect of visceral pain on cortical function, other studies (18) have suggested that “plasticity-inducing inputs” on sensorimotor cortical excitability produced by a variety of methods may be related to phenomena such as long-term potentiation (LTP) and depression (LTD). LTP and LTD appear to be evoked by fast (>1 Hz) and slow stimulation frequencies (<1 Hz), respectively. In the present study, we used a fast frequency (1 Hz) to accentuate the effects on corticobulbar excitability; this may thus have been expected to promote mainly LTP and an associated increase in response magnitude. However, contrary to a rise in excitation with increasing stimulus strength, we observed a bidirectional effect between the painful and nonpainful stimuli. Such findings, given the constant frequency used, must pre-
sumably relate to the perception of sensory input and its influence on the excitability that we measured. Previous studies (17) have reported that painful stimuli may induce changes in both sensory and motor cortices. The mechanism underlying these changes has yet to be established, although it is conceivable that pain itself may be driving inherent excitatory changes in the sensorimotor neural network. Whatever the mechanism, the bidirectional effect does implicate a pain-linked central nervous system threshold that favors excitation over inhibition, which may relate to the release of specific neurotransmitters. While our study does not provide a functional explanation for the pain effect on the corticobulbar projection, it might be speculated that increased excitability in the upper esophagus may be a defense mechanism to reduce oropharyngeal contents entering the lower esophagus. Perhaps future studies looking more specifically at the interaction between pain and swallowing may help to answer this question.

An additional issue that arises is the level at which the change in neural excitability occurs. For example, while our recordings were made to cortical stimulation, it is possible that the changes observed following esophageal distension may have resulted from alterations in excitability “downstream” of the cortex, i.e., subcortical regions, brain stem, and/or the vagal motoneuron. However, we argue that most of the effect is likely to be cortical for two reasons. First, the esophageal response amplitudes were increased or decreased after painful and nonpainful stimulation, respectively, without a concurrent shift in latency. This finding is compatible with an alteration in cortical excitability rather than a sustained excitation of more caudal brain regions such as the brain stem central pattern generator (CPG) or bulbar motoneurons. The reason for this statement is that in a resting subject the latency of the response includes time taken for excitatory input to depolarize quiescent motoneurons in the bulbar sensorimotor nuclei. If the excitability of these neurons is raised, then the time taken to reach the firing threshold is reduced and the latency of the response falls (16). Because we found no reduction in latency after painful esophageal stimulation (when responses and excitability were increased), it is reasonable to presume that brain stem excitability remained constant and to attribute the larger response to a greater or longer-lasting input from a more excitible sensorimotor cortex. This idea is consistent with the time course of events in the brain stem CPG, following a reflexively or cortically induced swallow in most animal species, where interneuronal synaptic activity during the swallow lasts on the order of 8–10 s (13). Since it is likely that a similar time course of CPG swallow activity exists for humans, then any changes in esophageal pathway excitability occurring beyond this period, e.g., at 30 min, cannot be attributed to synaptic processing within the CPG.

Second, we found no evidence for any changes in muscle activity either manometrically or by observing the resting raw EMG in the poststimulation period. Indeed, in our (12) previous studies of swallowing sensorimotor cortex reorganization to pharyngeal stimulation, we noted that brain stem reflexes, evoked to direct vagal and trigeminal nerve stimulation were unaffected, implying that the muscle itself is not the source of the increase in excitability. These latter data support the notion that lower-level circuitry in the bulbar vagal complex are not being excited or inhibited in this long-term manner, making cortical processes more likely.

As a final point, our finding of a link between visceral pain and cortical plasticity has potential implications for designing new therapies in the management of functional visceral pain syndromes, e.g., noncardiac chest pain (1). Specifically, it is possible to speculate that if cortical plasticity plays a causal role in visceral pain, then approaches that block the development of these changes may be of benefit. In relation to this concept, it has been demonstrated (20) that GABA-ergic agents (e.g., benzodiazepines) have an inhibitory effect on cortical plasticity. In addition, there is some evidence (19) that slow-frequency repetitive cortical stimulation is also inhibitory. Consequently, the utilization of approaches to “downregulate” plasticity may prove to be useful in blocking unwanted plasticity and altering patient symptoms.

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S. Hamdy is a Medical Research Council Clinician Scientist.

REFERENCES