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SPECIAL REPORTS AND REVIEWS

Brain-Gut Axis in Health and Disease

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Because it is common to experience gastrointestinal (GI) symptoms such as diarrhea, dyspepsia, and abdominal discomfort in response to alterations in emotional state, clinicians have long appreciated that the brain modulates gut function.[1] This association, however, began to be explored critically only in the 19th and the early 20th century by Beaumont,[2] Pavlov,[3] and Cannon[4] and later by Wolf and Wolff,[5] who showed not only that external sensory events eliciting strong emotional reactions can alter the function of the alimentary canal but also that different emotional states produced different patterns of GI motor function.

Because the experimental design of these early studies was not always as rigorous as would be expected today and the methodology used is now considered archaic, their validity has been questioned. Nevertheless, a close relationship between emotional state and GI function is repeatedly reported by patients with functional bowel disorders.[6,7] Furthermore, studies in healthy volunteers have also shown alterations in GI function when they are subjected to experimental stressors.[8]

More tangible evidence for the brain's influence on GI function comes from reports of alterations in gut function after lesions of the central nervous system (CNS). For instance, brain stem can produce alterations in small bowel motility,[9] and dysphagia can occur in stroke patients.[10] Spinal cord transection can lead to gastric distention with delay of postprandial gastric emptying of liquids and ileus.[11] Bilateral resection of sacral nerves during removal of sacral tumors can lead to disruption of anal function leading to incontinence,[12] and bilateral truncal vagotomy is well known to result in postprandial bloating, abdominal pain, and diarrhea.[13]

Despite unequivocal evidence of the brain's influence on gut function, our ability to study human brain gut interactions in vivo has been restricted until recently by the lack of noninvasive neurophysiological techniques. However, with recent advances in neuroscience, functional brain imaging techniques have become available that not only allow objective assessment of sensorimotor pathways between the brain and the periphery but also provide information about the functional neuroanatomy of the brain, enabling the acquisition of real-time images of brain function. These techniques have found diverse applications. For instance, psychologists are now able to study brain physiology during the performance of complex mental tasks involving memory and cognition,[14,15] and psychiatrists have gained insight into devastating mental illnesses such as schizophrenia.[16] Neurophysiologists are studying the brain's processing of somatosensory, visual, and auditory information,[17,18] and neurosurgeons are able to identify the homunculus in patients before stereotactic surgery, thereby avoiding damage to functionally important areas.[19] The availability of functional brain imaging techniques has also opened up an exciting new area of GI research and allowed gastroenterologists to explore the CNS control of human gut function in health and disease.

The aim of this review is to introduce the readers to the basic principles, advantages, and limitations of functional brain imaging techniques and to bring them up to date with studies of the human brain-gut axis in health and disease.

Review of the Anatomy and Physiology of the Brain-Gut Axis

Gut function is modulated by both extrinsic and intrinsic neural pathways.[20–22] The intrinsic innervation is provided by neurons of the myenteric and the submucous plexi, and the extrinsic innervation is provided by

Abbreviations used in this paper: CEP, cortical evoked potential; CPG, central pattern generator; DMN, dorsal motor nucleus; DRG, dorsal root ganglia; EMG, electromyography; ENS, enteric nervous system; fMRI, functional magnetic resonance imaging; GI, gastrointestinal; IBS, irritable bowel syndrome; MEG, magnetoencephalography; MRI, magnetic resonance imaging; NA, nucleus ambiguus; NTS, nucleus of solitary tract; PBN, parabrachial nuclei; PET, positron emission tomography; SQUID, superconducting quantum interference device; TCMS, transcranial magnetic stimulation; WDRMN, wide dynamic range mechanonociceptors.

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the splanchnic "sympathetic" and vagal-sacral "parasympathetic" nerves (Figure 1). The proximal esophagus[22,23] and the external anal sphincter[22,24] are composed of striated muscle with sparse intrinsic innervation so that motor function in these regions is regulated almost entirely by extrinsic control. The rest of the GI tract, in contrast, is composed of smooth muscle, controlled largely by the intrinsic plexi that receive modulatory influence from the extrinsic innervation.

Intrinsic Innervation

The enteric nervous system (ENS) is an integrative system of neurons with structural complexity and functional heterogeneity similar to those of the brain and the spinal cord. The principal role of the ENS is to control and coordinate GI functions such as motility, secretion, mucosal transport, and blood flow that are necessary for normal digestive processes.[25–28] The ENS performs these functions via motor neurons located within its ganglia, which form the final common pathway to the effector cells of the GI tract. Although specialized "command" motor neurons that form intrinsic neural circuits for the control of GI motility receive some inputs from the CNS via parasympathetic and sympathetic pathways, the function of most motor neurons is predominantly coordinated by sensory neurons and interneurons located within the ENS.

Extrinsic Innervation

Vagal (parasympathetic) innervation. The vagus nerve conveys information between the viscera and the brain stem. It contains both afferent and efferent nerves and, in humans, innervates the entire gut except the distal third of the colon.[22,29]

Vagal afferent pathways. Of the fibers within the vagal trunks, 70%–90% are unmyelinated afferent neurons with cell bodies located in the nodose ganglia[22,29–31] lying just below the jugular foramen. The nodose ganglia display a crude viscerotopic organization corresponding to the rostrocaudal organization of the alimentary canal, sensory neurons projecting to the soft palate and pharynx being located superiorly, whereas those projecting to the lower GI tract are located more inferiorly.[32] Vagal afferent fibers from the nodose ganglia terminate in the brain stem within the medial division of the nucleus of solitary tract (NTS), where they also display rostrocaudal viscerotopic organization within distinct subnuclei[32,33] (Figure 2).

Vagal afferents have a low threshold of response[34,35] to mechanical stimulation and are saturated at levels of stimulation well within the physiological range. They are therefore believed to mediate nonnoxious physiological sensations such as satiety and nausea. Recently, however, a role for vagal afferents in the modulation of nociception has been established. Experimental studies suggest that vagal afferents acting via the brain stem exert both inhibitory and excitatory influences on spinal nociceptive transmission.[36,37] Loss of such influences may be responsible for the altered sensation experienced by patients after vagotomy.

Vagal motor pathways. The vagal motor nuclei comprise the nucleus ambiguus (NA) and the dorsal motor nucleus (DMN).[20,22,32,33] The NA is located in the ventrolateral medulla and has rostrocaudally aligned subdivisions. Within the NA, the striated musculature of upper GI tract has a distinct pattern of representation so

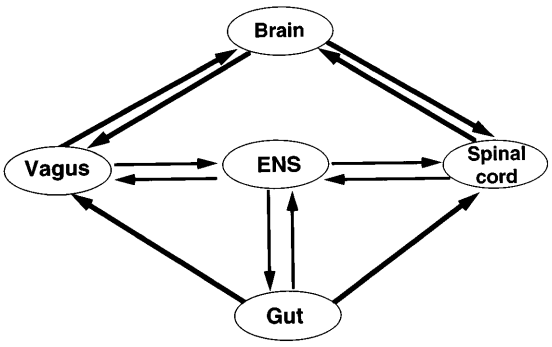


Figure 1. Schematic representation of the intrinsic and extrinsic innervation of the smooth muscle region of the gut shows dual extrinsic innervation via vagal and spinal pathways.

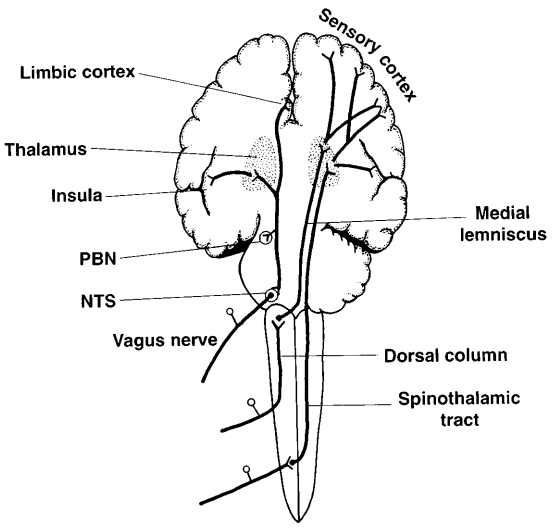


Figure 2. The bulbar and suprabulbar projections of vagal and spinal afferent pathways. Vagal afferents terminate in the NTS from where projections ascend via the PBN to the thalamus, limbic, and the insular cortices. Spinal afferents ascend in the spinothalamic tract and the dorsal columns. The spinothalamic tracts ascend to the thalamus, and the dorsal columns ascend to the nucleus gracilus and cuneatus in the rostral medulla, from where they project to the thalamus via the medial lemniscus. From the thalamus, projections ascend to the primary somatosensory and insular cortices.

that different populations of neurons project to the pharynx, larynx, and the upper esophagus.[32,33,38] Dendrites from the subdivisions of the NA project into the surrounding reticular formation where they form networks for coordinating complex motor events such as swallowing.[33,38]

The DMN is the source of efferents to the smooth muscle region of the gut that synapse with the neurons of the myenteric plexus.[20,22,33] Within the DMN, motoneurons innervating specific abdominal viscera show topographic organization.[33,39] The DMN motoneurons also show extensive dendritic arborizations allowing coordination of efferent activity throughout the rostrocaudal extent of the nucleus.[33] Dendrites from the DMN that innervate specific viscera also terminate within the NTS, where they overlap with their respective primary sensory neurons leading to organ-specific monosynaptic interaction between the two structures.[33]

Vagovagal reflexes. GI function is modulated by a number of vagally mediated reflexes including gastrogastric, enterogastric, hepatopancreatic, and gastrocolic reflexes.[20,22,40] The circuitry for these reflexes is organized in the medulla, where vagal afferents are integrated with vagal efferents. The functional specificity and heterogeneity of vagovagal reflexes is due to the structural organization within the NTS and DMN, which are not compartmentalized into distinct anatomic units but are composed of relatively unspecialized neurons, topographically organized into partially overlapping zones corresponding to different nerve branches. The NTS and DMN are effectively fused together and, because of the orthogonal organization of the sensory and motor neurons, have an architectural organization of a lattice.[40] This organization may be responsible for the specificity of GI reflexes because each intersecting node of this lattice could organize a specific reflex. The heterogeneity of these reflexes is probably due to the fact that each nerve branch within this lattice is capable of carrying multiple modalities of information, so that the intersection of the lattice that represents the gastrogastric reflex would mediate chemical, mechanical, and secretory responses.

Higher CNS control of vagal nuclei. The brain stem vagal nuclei provide the circuitry for the basic reflex control of GI function, but they are also modulated by higher brain regions.[20,22,31,41,42] The NTS acts as a relay for the vast amount of information arriving to it from abdominal viscera and, in turn, sends out a large ramifying fiber network to higher centers while also receiving information from these centers. There are four levels of output from the NTS.[41–44] The first is a direct projection to the autonomic motor nuclei involving both the parasympathetic and the sympathetic preganglionic neurons in the DMN/NA and the interomediolateral cell column of the spinal cord, respectively. These projections provide an anatomic substrate for short autonomic reflex loops. Second, the NTS sends relays to the motor components of ingestion found in the trigeminal, facial, hypoglossal nuclei and also the NA. Third, visceral information is relayed to more rostral regions of the brain stem such as the parabrachial nuclei (PBN), which in turn is connected to higher brain centers. Fourth, long projections terminate in the thalamus, hypothalamus, and limbic and insular cortical regions that mediate autonomic, neuroendocrine, and behavioral functions (Figure 2).

Vagal motor nuclei have numerous reciprocal connections with other brain regions such as area postrema, the PBN, hypothalamus, amygdala, and the orbitofrontal, insular, and infralimbic-anterior cingulate cortex.[20,41–43] These connections integrate sensory input arriving from the NTS with the descending influences from the higher brain centers and provide the circuitry for visceral reflex loops; allow integration of GI, cardiovascular, and respiratory activities that occurs in autonomic reflexes such as vomiting; and also provide the conduit through which various emotions and environmental influences modulate gut function.

Sacral (parasympathetic) innervation of the GI tract. Projections from preganglionic neurons located in the intermediate grey matter of the cord segments S1–S5 innervate the distal colon, rectum, and internal anal sphincters via pelvic ganglia from where postganglionic pelvic nerve fibers innervate the enteric ganglia.[20,22,45,46] Interneurons in the sacral autonomic nuclei receive projections from the colon via the pelvic nerve afferents, whose cell bodies lie in dorsal root ganglia (DRG) and then send projections to the preganglionic neurons to form the spinal reflex that regulates colonic motility and defecation. Supraspinal sites such as the cerebral cortex, pons, and medullary reticular formation also send projections to the sacral cord and exert a modulatory influence on colonic function.[20,47]

Spinal pathways innervating the GI tract. Although in the past both afferent and efferent spinal innervation of the GI tract were referred to as "sympathetic,"[48] it is now usual to refer to visceral afferents running in the spinal cord as "spinal visceral afferents" and to restrict the term "sympathetic innervation" to the spinal efferent innervation.[29]

Spinal visceral afferent nerves. Spinal visceral afferents constitute 5%–10% of all afferent fibers in the thoracic and lumber dorsal nerve roots.[20,22,29,49–51] Most

visceral afferents pass via prevertebral and paravertebral ganglia en route to the spinal cord. Collaterals to the prevertebral ganglia from visceral afferents participate in the mediation of local autonomic reflexes. Spinal afferents have cell bodies in the DRG at the cervical, thoracic, and upper lumbar spine. These afferents are predominantly unmyelinated C and A δ fibers and show sensitivity to both mechanical and chemical stimuli. Spinal mechanoreceptive afferents are present predominantly in the muscular layer, serosal layer, and the mesentery of the gut.[29] Innervation of different viscera shows considerable segmental overlap in the spinal cord, which probably explains the poor viscerotopic localization of sensation in the GI tract. The convergence of visceral and spinal afferents in the dorsal horn of the spinal cord is thought to be the basis for the referral of visceral sensation to somatic structures.[50,52,53]

Visceral afferent information is transmitted proximally along the spinal cord via a number of tracts of which the spinothalamic tracts and the dorsal columns are the most important[20,29,49,52,53] (Figure 2). The lateral spinothalamic neurons mediate the sensory-discriminative aspects of pain, whereas the medial spinothalamic neurons mediate the motivational-affective aspects of pain.[49,54,55] In contrast to conventional wisdom that the dorsal columns do not mediate visceral afferent information, recent evidence from human studies now suggests that is not so, because posterior midline myelotomy that interrupts the dorsal columns alleviates pelvic visceral pain in patients with colon cancer.[56] Additional visceral afferent information is also carried in the spinoreticular, spinomesencephalic, and spinosolitary tracts,[49,52,57] which project to the thalamus via relays in the brain stem (e.g., the NTS) and in the midbrain.[58] These pathways are responsible for the integration of somatic and visceral input from wide areas of the body, and they also allow afferent information encoded within vagal afferents to modulate afferent information encoded within spinal afferents.[36,37] From the thalamus, sensory information passes to the insular cortex, the primary somatosensory cortex, and the prelimbic, limbic, and infralimbic areas of the medial prefrontal cortex.[58,59]

Although spinal afferents are usually only thought of as pathways for transmission of nociceptive information to the CNS,[29,49,51,54,55] the majority of afferents have stimulus response functions that cover both physiological and nociceptive ranges of stimulation.[29,35,60,61] This suggests that the quality of visceral sensation must depend on the intensity of discharge within the spinal visceral afferent fibers. There are several extensive review articles on the role of visceral afferents in the mediation of GI sensation in health and disease.[36,37,49,51,62,63]

Sympathetic efferent pathways. The GI tract receives efferent neural input from the cervical, thoracic, and lumbar segments of the spinal cord.[20,22] The preganglionic (cholinergic) neurons have cell bodies in the intermediate gray region of the thoracolumbar spinal cord and terminate in the spinal ganglia. The postganglionic (noradrenergic) neurons to the stomach, small intestine, and proximal large intestine are located in the celiac-superior mesenteric ganglion, the remainder of the large intestine is innervated by the inferior mesenteric ganglion, and the rectum is innervated by the pelvic ganglion. Postganglionic neurons project to the ganglia of the myenteric plexus and inhibit GI function via inhibition of the release of acetylcholine from submucous and myenteric neurons.[20,22,64]

Modulation of sympathetic neuron function. Sympathetic neurons of the prevertebral ganglia also receive synaptic input from enteric neural and spinal visceral afferents, which mediate peripheral regulatory reflexes such as the intestino-intestinal inhibitory reflex.[64,65] Furthermore, stimulation of the hypothalamus increases colonic motility, whereas stimulation of the medial forebrain bundle and anterior sigmoid, orbital, and cingulate gyri of the cerebral cortex inhibits colonic motility.[20,66] These supraspinal influences on colonic function are likely to be mediated via descending modulation of spinal preganglionic neurons.

Innervation of the striated muscle regions of the GI tract. Both swallowing and defecation are under conscious control, suggesting strong CNS influence on the striated musculature involved in these acts.[22]

Neural control of swallowing. Swallowing is a complex sensorimotor event requiring the coordinated contraction of muscles both in the buccopharynx and the esophagus.[22,67,68] The neural control of swallowing requires integration at the brainstem swallowing center of peripheral afferent inputs with inputs from the cortical swallowing centers (Figure 3).[20,67–71] Numerous studies have confirmed that once swallowing is initiated by stimulation of either an afferent pathway or voluntarily, the entire motor sequence of peristalsis proceeds even in the absence of peripheral feedback from an accompanying bolus. This suggests that the neural control of swallowing is governed by a central pattern generator (CPG), which organizes the sequential excitation of motor neurons controlling swallowing muscles.[67–71] In mammals, the swallowing center is located bilaterally in the medulla and the pons and consists of three functional components: an afferent component, and efferent component, and a complex organizing system of interneurons forming the CPG.

The afferent component comprises fibers within the

trigeminal nerve, glossopharyngeal nerve, and vagus nerve, especially its superior laryngeal branch.[67–70] The efferent component comprises the cranial motor nuclei of the Vth, VIIth, Xth, and XIIth nerves. Interneurons of the CPG are located in two main regions: the dorsal region, which includes the NTS and the adjacent reticular formation; and a ventral region, corresponding to the lateral reticular formation above the NA. Within each of these regions, activity of neurons corresponding to the different areas of the swallowing tract can be identified. Interneurons of the dorsal group receive synaptic connections from both peripheral afferents and the swallowing cortical area and trigger and organize the swallowing motor sequence, whereas interneurons of the ventral group distribute the sequential swallowing excitation generated within the dorsal group to the various pools of motor neurons involved in swallowing.

Neural control of defecation. The external anal sphincter is composed of striated muscle and is responsible for maintaining anal canal continence in situations of increased intrarectal and intra-abdominal pressure.[20,22,24] The motor neurons that innervate the external anal sphincter originate in Onuf's nucleus, located in the ventral horn of S1 and S2 segments, and project in the pudendal nerve.[20,72,73] These motor neurons receive input from pudendal nerve afferents, interneurons, and supraspinal sites. Relaxation of sphincteric tone during defecation and the existence of voluntary control over defecation indicates the extent to which the motor cortex (area 4a) is capable of modulating anorectal function.[73] Sensory pathways mediate feedback information from the external anal sphincter to the nucleus gracilis in the lower medulla[74] and to the cortex.[75]

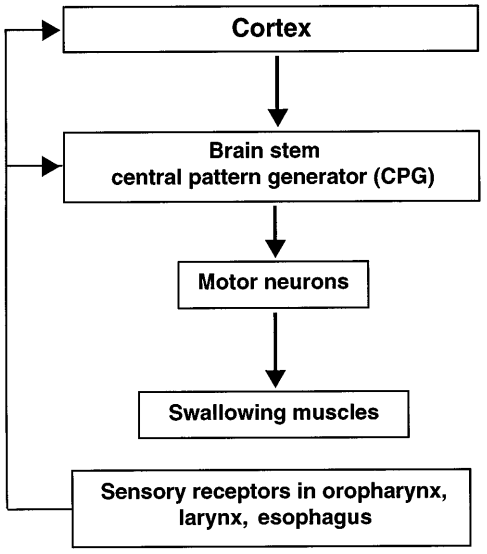


Figure 3. Schematic representation summarizing the CNS control of swallowing. The brain stem CPG neurons integrate information from both the cortex and swallowing tract and program the swallowing motor sequence, which is then executed via the motorneurons to the swallowing muscles.

Clinical Investigation of the Human Brain-Gut Axis

It is evident from the information given above that the GI tract is intricately connected to the CNS by pathways that are continuously sampling and modulating gut function. However, relatively little is known of the role played by these pathways in humans, and consequently the relation between the CNS and the development of GI dysfunction is incompletely understood. Recently, a number of noninvasive techniques have become available to assess brain-gut interactions, allowing progress to be made.

Studies of Gut to Brain Pathways

Gut to brain pathways have been studied using cortical evoked potentials (CEPs), magnetoencephalography (MEG), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). The literature relating to these studies is summarized.

CEPs: basic principles and methodology. CEPs are the electrical manifestation of the brain's response to an external stimulus[17,76] and are recorded using surface scalp electrodes placed in relation to fixed anatomic landmarks as recommended by the International Federation of Societies for Electroencephalography and Clinical Neurophysiology, known as the International 10–20 System.[77] CEPs are always measured as the potential difference between two recording sites.[17,76] The most commonly used recording strategy is known as the referential montage, in which potential differences for each electrode position are determined with respect to a single relatively electrically inactive common reference electrode, usually placed on the ear lobes.

Because the stimulus-specific CEP response always occurs at a fixed time interval, whereas other brain activity does not, signal averagers can be used to extract the desired signal from the background activity. When repetitive stimuli are applied and the cortical electrical activity is averaged, the cortical response specific to the stimulus becomes recognizable independently of background brain activity (Figure 4). CEPs consist of a series of positive and negative potentials, the spatiotemporal distribution of each representing a specific step in the cortical processing of the information from the stimulus.

The nomenclature for describing the CEP waveform is as follows. First the components are numbered in sequence by polarity; for example, the first negative potential is labeled N1, the second negative potential is

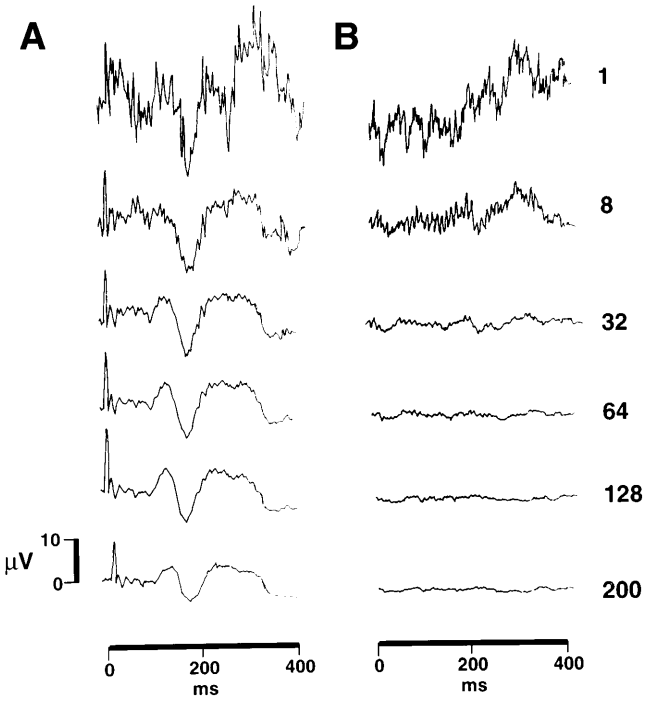


Figure 4. The beneficial effect of averaging on the quality of CEP (*A*) to repeated esophageal electrical stimulation and (*B*) sham stimulation. The quality of esophageal CEP improves with increasing number of stimuli averaged. The amplitude of the response after 200 stimuli is lower than that at 128 stimuli, suggesting adaptation of the response.

N2, and the positive potentials are numbered in a similar way (P1 and P2). Additionally, the components are labeled according to their mean latency in normal subjects, for example, a positive wave occurring at 100 milliseconds is termed as P100.[76,78]

Topographic mapping of CEP. To generate topographic maps, the evoked potentials recorded from each of the multiple electrode positions are analyzed. By coding the amplitudes of the evoked potentials, two-dimensional topographic maps of the cortical electrical activity that highlight areas of maximal and minimal electrical activity can be obtained. From the spatial distribution of the "hot spots" for each potential, the location of the neuronal sources generating each potential can be estimated.[79,80]

Because standard topographic maps do not provide information about the precise position, orientation, or strength of the neuronal source, dipole analysis methods have been developed.[17,81] In dipole analysis, the head is assumed to be a spherical conductor consisting of four concentric shells representing the brain, cerebrospinal fluid, skull, and the scalp, each of which is of different but homogenous electrical conductivity. Currents associated with neuronal activity of a focal population are mathematically modeled as though they are generated by a dipole source. The position, orientation, and the strength of the dipole that best accounts for the pattern of potentials on the scalp is then mathematically computed.

Advantages of CEP. The equipment necessary for CEP recording is relatively inexpensive and is available in most clinical neurophysiology departments. CEPs are useful in determining the integrity of afferent conduction to the cortex and in other areas of clinical research; for example, in visual science, abnormalities in sensory conduction can be detected even when clinical features of disease are equivocal. CEPs are also useful for monitoring disease progression and response to therapy[17,76] in neurological conditions such as demyelinating diseases. CEPs provide excellent temporal resolution of cortical events on a millisecond by millisecond basis.

Limitations of CEP. The quality of CEPs is influenced by many environmental, technical, and psychological variables.[76] For instance, failure to eliminate repetitive environmental background sound may contaminate signals recorded after stimulation of other sensory modalities. Inaccurate placement of scalp electrodes may lead to inaccurate identification of dipole location. Inappropriate filtering of the amplified signal may distort waveform amplitudes and latencies. The morphology, latencies, and amplitudes of CEP wave forms can also be easily altered by psychological variables such as inattention and drowsiness; therefore, consistent and reproducible results may be difficult to obtain.

During topographic mapping, the attenuation and distortion of signal by the skull impairs the location of the intracranial source, which limits its spatial resolution. Furthermore, with CEP, the number of neuronal sources activated is difficult to determine because multiple distinct sources may be activated simultaneously and the spatiotemporal distribution of CEP may represent the summation effect of these potentials.[17]

CEPs evoked by gut stimulation. CEP recording is now being used by a number of research groups to study the conduction and processing of GI sensation by the brain. So far, CEP has been evoked by either electrical or mechanical stimulation of the gut.

Esophageal CEP. CEP to electrical stimulation of the esophagus was first described by Frieling et al. in 1989,[82] and several other groups subsequently repeated these experiments.[83–86] The stimulation intensity is usually adjusted to produce either a definite but nonpainful sensation[82,83] or pain,[84–86] and a stimulus duration of between 0.1 and 0.2 milliseconds is used. Stimulation frequencies have ranged from 0.1 to 1 Hz, and the number of stimuli has varied between 16 and 50.

The characteristics of the CEPs derived from these studies vary with the stimulation parameters. Frequent stimulation (0.5–1 Hz) is associated with smaller ampli-

tude responses than infrequent stimuli (0.1 and 0.2 Hz),[82] while CEP amplitudes are directly and latencies are inversely proportional to the intensity of the stimulus.[82–86] The amplitudes also seem to be related to the number of stimuli because after 25 stimuli, the response is attenuated.[83]

Latencies of early potentials recorded from the proximal and the distal esophagus vary between studies. In most studies, the latencies of the early potentials are shorter after stimulation of proximal than stimulation of distal esophagus[82,83]; however, in a study by Frobert et al.,[85] CEP latencies evoked by stimulation of the proximal esophagus were longer than those obtained by stimulation of the distal esophagus. The main difference between this study and others is that painful stimuli were applied, and it could be argued that spinal afferents were activated in this study, whereas vagal afferents were activated in previous studies. However, even this explanation does not fully explain the discrepancy between the studies, because spinal afferents from different esophageal regions show a considerable overlap in the spinal cord[87]; therefore, the latencies of CEPs evoked by stimulation of these regions would be expected to be similar. Also, the case for the transmission of nonpainful sensation only via vagal afferents is far from proven. Given the complexity of esophageal innervation, the comparison of CEP latencies evoked by stimulation of different esophageal regions should be interpreted with caution.

CEP to mechanical stimulation of the esophagus was first reported by Castell et al. in 1990.[88] Since then other groups have also shown that CEP to esophageal distention by a rapidly inflated balloon can be reliably recorded,[89–96] although there is a larger variation in latencies, amplitudes, and morphology of the responses compared with those evoked by electrical stimulation.

With electrical stimulation, the peak stimulus intensity is reached rapidly and excellent synchronization between the stimulus and the afferent neural discharge is provided. During mechanical stimulation, however, the interval between the onset of balloon inflation and the onset of afferent discharge from esophageal distention is longer and will vary with different rates of distention leading to poorer synchronization. Because the balloon volumes required to induce a sensory response will also vary between individuals, interindividual differences in the time to onset of the afferent discharge will also occur, leading to a wider intersubject variation in CEP latencies.

Study of various methods of esophageal distention used to record CEP suggests that a slow stimulation frequency of $\leq$0.2 Hz results in best quality responses.[88–95] A threshold intensity above sensory threshold is required to produce a response, and the amplitudes are proportional to the stimulus intensity. The latencies and amplitudes are also influenced by age, latencies becoming longer and amplitudes smaller with increasing age.[91]

Pathways involved in mediating esophageal CEP. Investigators have attempted to identify the pathways that mediate CEP. Tougas et al.[83] compared the CEPs induced by direct electrical stimulation of the cervical vagus nerve (using vagal nerve implants in patients with epilepsy) with those recorded after direct electrical stimulation of the esophagus. They found that the morphology of CEP recorded after vagal stimulation resembled that after esophageal stimulation, leading these investigators to conclude that both were mediated by vagal afferents. However, the recent demonstration of similarity of CEP evoked by stimulation of the esophagus and the chest wall has cast some doubt on this interpretation.[84]

More recently, DeVault et al.[96] compared sensation scores and CEP to esophageal distention in patients with spinal cord injury at cervical segments C6 or C7 with those in healthy volunteers. The results show that although the sensory threshold was higher in patients than in healthy volunteers, the pain threshold was similar in the two groups. The qualitative sensory experience and CEP to painful distention of the midesophagus were also similar in the two groups. These results could suggest that CEP is mediated via vagal pathways; however, because the patients experienced pain at thresholds similar to those of the volunteers and because the role of the vagus nerve in mediating pain is not conclusive, it is equally likely that either these patients had incomplete spinal lesions or that spinal innervation to the midesophagus occurs from segments rostral to C6/C7, as has been suggested by animal studies.[87]

Speculation about the afferent pathways activated by esophageal stimulation requires caution because of the nature of the stimulus and the complexity of esophageal innervation. Animal studies suggest that esophageal electrical stimulation can activate afferents mediating different sensory modalities in the muscular layers.[97] Esophageal vagal afferents have a low threshold of activation and are maximally activated by stimuli such as mucosal stroking, which are well within the nonnoxious range.[29,34,35] It would therefore be expected that if CEP is vagally mediated, they would be evoked by stimuli even below the sensory threshold. This is not the case, however, and perception is generally necessary to evoke CEPs.[82–95] There is also a progressive increase in CEP magnitude with increasing perception scores. This suggests that they are mediated via the wide dynamic range mechanonociceptors (WDRMNs), which are activated by stimulation intensities ranging from nonnoxious to the noxious and are present in spinal not vagal afferents.[35,60,61]

On the basis of the above arguments it seems likely that spinal afferents are involved in mediating CEP evoked by esophageal stimulation, but this does not mean that vagal afferents are not also activated. In fact, animal studies suggest that both are probably activated simultaneously[35,60] and that, when stimulation occurs at intensities close to the sensory threshold, a large proportion of vagal afferents together with some spinal afferents contribute to the CEP. As the intensity increases, however, the vagal afferent discharge will become saturated while the discharge from the spinal WDRMNs will continue to increase; when pain is perceived, the high-threshold mechanonociceptors that are also known to exist in the esophagus and that travel via the spinal cord will also then contribute to the CEP.

Topographic mapping of esophageal CEP. Studies of the spatiotemporal distribution of esophageal CEP have provided some information about the cortical areas activated by esophageal stimulation. Weusten et al.[92] identified bilateral neural generators probably in the dorsal peri-insular cortex or the ventral insular cortex after esophageal stimulation. Because the insular cortex is a major visceral sensorimotor area that receives projections from both vagal and spinal afferents,[59,98] they concluded that esophageal afferent information may be transmitted via either pathway.

More detailed spatiotemporal dipole modeling of esophageal CEP[93] confirms that the cortical generators of esophageal CEP are probably located bilaterally within the insular cortex; in addition, the cingulate cortex, which is known to subserve visceromotor functions, is also activated.

Aziz et al.[94] have also shown that multiple cortical sources are activated in sequence. The spatiotemporal distribution of these potentials suggests that the primary somatosensory cortex or the insular cortex are the first to receive the afferent volley; thereafter, secondary processing occurs in the orbitofrontal and cingulate cortices. The early negative potentials evoked by stimulation of the proximal and distal esophagus showed viscerotopic distribution (Figure 5).

CEP in esophageal disease. Smout et al.[95] studied CEP evoked by esophageal distention in patients with noncardiac chest pain and found that the degree of distention required to produce esophageal sensation was lower than in healthy volunteers. The patients also had lower CEP amplitudes, although when these were adjusted for the lower balloon volumes, they were comparable to those in healthy volunteers. It therefore seems that esophageal afferent pathways to the cortex are normal in patients with noncardiac chest pain and that the increased perception of esophageal distention is likely caused by abnormal central processing of the afferent information.

In a more recent study,[99] comparison was made of CEP evoked by esophageal and sternal skin electrical stimulation in patients with noncardiac chest pain and age- and sex-matched healthy volunteers. Despite similar esophageal and skin sensory and pain thresholds, the amplitudes of the CEP responses were smaller in patients than controls. However, the latencies of all esophageal CEP components and the early sternal skin CEP components were similar in both groups, suggesting that conduction of visceral and somatic afferent signals to the brain is normal in these patients but that aberrant CNS processing of the information occurs.

Although these two studies represent important steps toward understanding the pathophysiology of noncardiac chest pain, the results need to be interpreted with caution. Both studies rely on the differences in the amplitudes of esophageal CEP between a control and a patient group. However, the amplitude of long latency potentials such as those of esophageal CEP are particularly vulnerable to psychological variables such as attention to the stimulus.[76] Patients with noncardiac chest pain are well known to have a variety of psychological abnormalities such as anxiety, depression, and somatization disorders.[100] It is therefore difficult to control for their psychological state and attention to the stimulus during the study, and this may have an important impact on the amplitude of the CEP response.

Rathmann et al.[101] studied CEP evoked by esophageal electrical stimulation in diabetic patients with esophageal and gastric motor dysfunction and compared them with those of healthy controls. The diabetics had higher perception thresholds than controls and no CEP could be recorded in the majority, suggesting the presence of an afferent neuropathy.

Anorectal CEP. CEP to electrical and mechanical stimulation of the rectum have also been studied, the first report being that of Meunier et al.[102] after endorectal electrical stimulation in 3 healthy volunteers. Since then numerous reports of CEP to either electrical or mechanical stimulation have been published.[103–110]

Loening-Baucke et al.[104,105] studied factors influencing the quality and reproducibility of CEP to electrical stimulation of the rectum. Their results show that rectal stimulation evokes two distinct responses. Multiphasic CEP with short-onset latencies (26 ± 2 milliseconds) were recorded in some subjects, whereas triphasic responses with longer mean onset latencies (55 ± 3 milliseconds) were recorded in others (Figure 6). Both early- and late-onset responses could be recorded in some subjects. A stimulation frequency of 0.6 Hz seemed to be

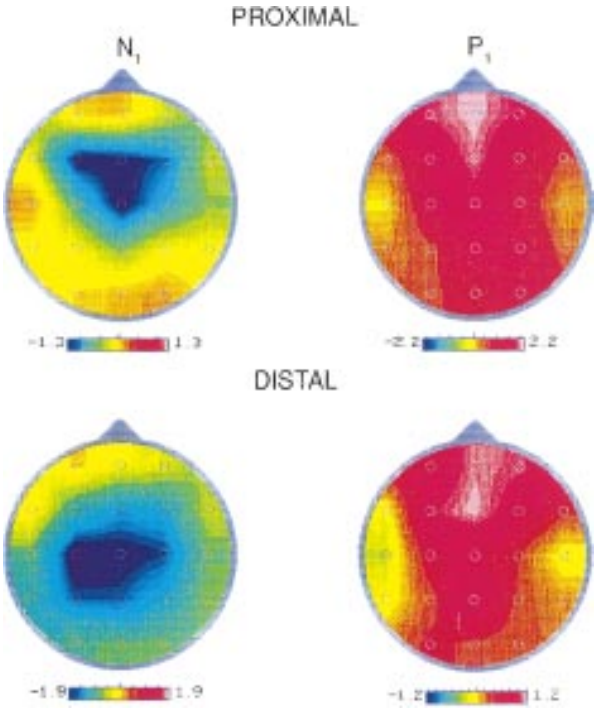


Figure 5. Two-dimensional topographic representation of the N1 & P1 potentials evoked by proximal and distal esophageal distention. The N1 potential for the proximal esophagus is represented more anteriorly than that for the distal esophagus, but the scalp topography of the two P1 potentials is similar. (Adapted with permission.[94])

best for eliciting the CEP; frequencies of 3 Hz resulted in attenuation of the early responses and abolished the late responses. Averaging >50 stimuli reduced the amplitude of the late responses, whereas the early responses remained unaltered even with averages of 50–1000 stimuli. Factors such as age and height were not related to the CEP latencies.

Rapid distention of the rectum by a balloon is also able to evoke CEP.[108,109] As with electrical stimulation, CEP with either short- or long-onset latencies are evoked. Shorter onset latency responses are more likely to occur at low inflation volumes (10 mL), whereas longer onset latency responses are more likely to occur at higher inflation volumes (20 mL). The latencies of the early- and late-onset responses were not influenced by sex or height of the subjects. It is likely that the early-onset responses

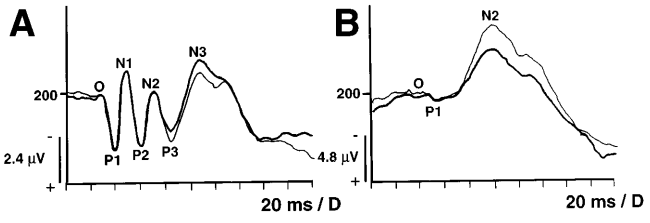


Figure 6. (*A*) Early-onset and (*B*) late-onset cortical potentials evoked by rectal stimulation. (Reprinted with permission.[104])

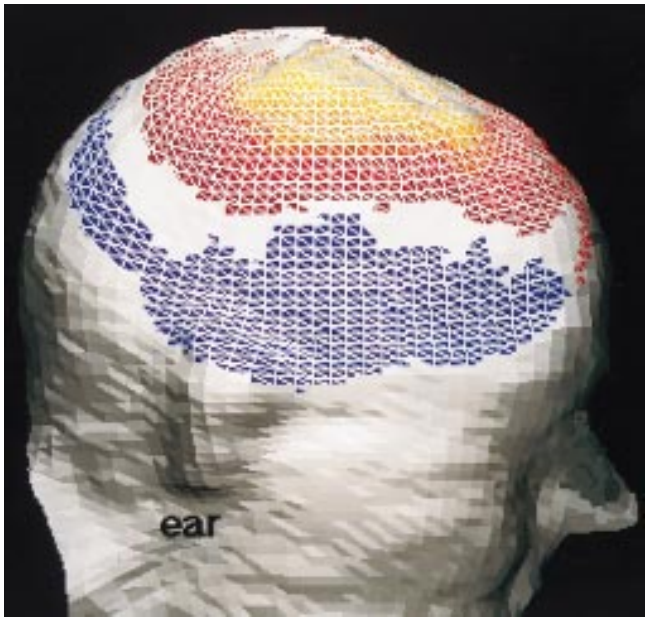


Figure 7. Topographic distribution of the magnetic field pattern evoked by esophageal distention. The areas shown in *red* and *yellow* represent scalp sites where magnetic field exits from the head, and the *blue* areas represent the sites where the magnetic field reenters the head. Once the sites of exit and reentry of the magnetic field into the head are known, inverse solution algorithms can be used to estimate the location of the source emitting the magnetic field. Courtesy of P. Furlong.

are mediated via somatic nerves (pudendal nerve) and the late-onset responses are mediated via visceral nerves (pelvic nerve).

CEP in anorectal disease. Speakman et al.[110] studied CEP after electrical stimulation of the rectum in

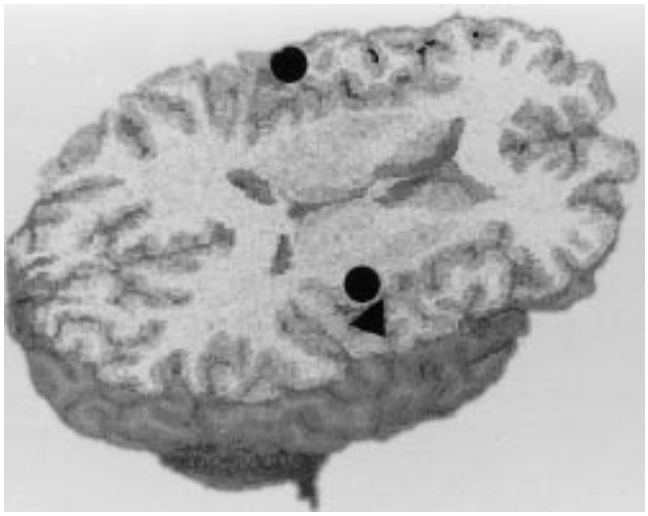


Figure 8. MRI scan showing the estimated location of the neuronal source of the magnetic fields emitted during distention of the proximal and distal esophagus in a subject. The proximal esophagus (▼) is represented unilaterally, but the distal esophagus (●) shows bilateral representation in the insular/secondary somatosensory cortex. Courtesy of P. Furlong.

patients with severe constipation and neurogenic fecal incontinence. Because they were unable to record reproducible CEP in most patients, they suggested that the technique was of limited use. This failure to record CEP may have been due to the stimulation parameters used, because at a stimulus frequency of 3 Hz and filter settings of 20 Hz to 2 kHz, other investigators have also shown poor-quality responses. In another study, Loening-Baucke et al.[109] studied anorectal CEP in children with constipation and encopresis and found significantly prolonged latencies of the early-onset potentials, suggesting a defect in afferent pathway conduction.

MEG

MEG is a technique that measures the time-varying magnetic fields generated by current flow within neurons of the brain.[18,111,112] Because neuromagnetic signals emitted by the brain are small, only a few picotesla (10^{-15}) in amplitude, extremely sensitive detectors are required.

Basic principles and methodology.

When a time-varying magnetic field passes perpendicular to the plane of a wire loop, it induces a small electrical current within the wire.[18,111,112] Superconducting wire loops made of special material such as niobium are extremely sensitive to small changes in magnetic flux such as those associated with neuronal activity. In magnetometers, superconducting wire loops are coupled to a superconducting quantum interference device (SQUID), which produces a voltage output proportional to the current flowing in the loops. The use of an array of SQUIDs covering the entire head enables spatiotemporal mapping of cortical sources to be estimated.

The magnetic signals generated by a stimulus are averaged to extract the time-locked signal from the background noise. By mathematically modeling the topographic distribution of the magnetic field pattern on the scalp (Figure 7), the three-dimensional location of the neurons generating the signal can be inferred using mathematical models.[18] Once the location of the active neurons is deduced, this information can be coregistered with magnetic resonance imaging (MRI) scans to estimate their anatomic location.

Advantages of MEG.

The main advantage of studying magnetic rather than electrical fields is that they are much less distorted by the conductivity of intervening tissues, and therefore mathematical analysis of the spatial pattern of the field is more accurate. Using MEG, the anatomic location of the cortical neurons generating magnetic fields can be estimated to within 1–5 mm[18,111,112] and cortical events can be followed on a millisecond to millisecond basis. Furthermore, unlike CEP in which neuronal source strength is difficult to predict accurately because of the interindividual variability in the conductivity of intervening tissues, with MEG, neuronal strength can be predicted objectively in each subject and used to estimate the spatial extent of corresponding cortical activity. In contrast to the lengthy preparation of subjects required for CEP, no preparation is necessary for MEG, making it less time consuming and more comfortable for the subjects.

Limitations of MEG.

The main limitation of MEG at present is that the equipment is expensive (currently 1–2 million dollars), which restricts availability. It is also important to recognize that only those cortical sources that generate magnetic fields oriented in a plane tangential to the skull surface are detectable, so that some sources may be missed.[18,111,112] In addition, magnetic fields generated by subcortical neurons are not readily detectable because, unlike cortical neurons, which are arranged in columns, many of the subcortical neurons are arranged in a spherically symmetric manner so that the magnetic fields emitted are mutually cancelled.

Clinical studies using MEG.

Although in theory both afferent and efferent pathways are accessible for study, so far MEG has only been used to assess esophageal afferent pathways.[113,114] Using stimulation characteristics similar to those used in the study of CEP, Furlong et al.[113] have shown that the cortical representation of the proximal esophagus is lateralized to either the right or left hemisphere but that of the distal esophagus is bilateral (Figure 8). Furthermore, the trunk area of the primary somatosensory cortex is more consistently activated after proximal than distal esophageal stimulation. Multiple cortical sources were also simultaneously activated in the insular cortex and caudal aspect of primary somatosensory and secondary somatosensory cortices after both proximal and distal esophageal stimulation. Activation of the anterior cingulate cortex was also occasionally observed. In another recent MEG study,[114] activation of the secondary somatosensory cortex was observed most consistently after electrical stimulation of the distal esophagus.

Vagal afferent projections to the primary somatosensory cortex have not been described; hence, its activation seen in MEG studies implicates the involvement of spinal afferents in the transmission of nonpainful esophageal sensation. The insula is an important sensory motor area for visceral function and receives projections from both vagal and spinal afferents. It has connections with other areas of the limbic cortex and also with subcortical sites and therefore plays a role in coordinating the autonomic response to visceral sensation.

PET

PET is an exciting research tool for imaging brain function that has now found clinical application in the GI tract.

Basic principles and methodology. The detection and location of the source of positron-emitting radioisotopes in the brain is now an established method for studying the functional neuroanatomy of the human brain.[115–118] Selection of appropriately radiolabeled compounds allows the study of biochemical and physiological processes involved in cerebral metabolism. After intravenous injection, compounds accumulate in the brain areas with altered neuronal metabolism or blood flow. Positron-emitting isotopes decay rapidly on arrival in the brain and emit a positron that combines with an electron. This combination leads to the release of two photons that travel in opposite directions with sufficient energy to be detected outside the head by sensitive detectors. With the use of computerized reconstruction of the source of these emissions, tomographic images can be produced that represent the spatial distribution of the radioisotopes in the brain. The PET data can also be coregistered with MRI data to provide spatial correlation of structure and function. To measure regional cerebral blood flow to the brain, labeled water ($H_2{}^{15}O$) is commonly used, whereas ^{18}Fl-labeled fluorodeoxyglucose is used for studying glucose metabolism.

Advantages of PET. PET has a high spatial resolution, and sources of brain activity can be identified with an accuracy of approximately 2–8 mm.[115,116] Furthermore, unlike in MEG and CEP, subcortical brain sources can also be identified. PET can also be used to determine the size of an area of metabolic change even when structural change is not noticeable with MRI. PET studies can therefore provide an indication of the extent of disease, and serial measurements may also provide a measure of the effectiveness of therapy. Another main advantage is that ligands (radiolabeled chemicals that are either receptor agonists or anatagonists) can be used to study brain neurotransmission in health and disease.[115,116]

Limitations of PET. The main limitation of PET is that because radioactive compounds are required, repeat studies are restricted. PET scanning is also expensive (the average cost of PET facility together with a cyclotron is approximately 5 million dollars)[115] and requires sophisticated facilities for generation of radioisotopes and for data analysis, and its availability is restricted to specialized centers. The temporal resolution of PET (40 seconds) is less than that of MEG (1 millisecond), so that it cannot be used to determine the sequential pattern of the brain's processing of a signal.[115,116] Because of the relatively poor temporal resolution, it is difficult to differentiate between neighboring areas of activation because the activity of these areas is integrated during approximately 40 seconds.[116,117]

Studies of esophageal sensation using PET. The cortical loci that process human esophageal sensation have been identified.[119] Nonpainful stimulation elicited bilateral activation along the central sulcus, insular cortex, and frontal/parietal operculum. Painful stimulation produced more intense activation of the same areas, with additional activation of the basal areas of the right anterior insular cortex and the anterior cingulate gyri (Figure 9). Multiple areas of decreased activation were also observed; prominent among these was the right prefrontal cortex, which was inhibited during both nonpainful and painful stimulation.

These findings now allow us to conclude that, like somatic sensation,[118,120] the sensory-discriminative aspects of esophageal sensation are processed in the primary somatosensory cortex and the affective-motivational aspects of sensation are processed in the anterior cingulate cortex. Furthermore, inhibition of the medial prefrontal cortex, a region known to process the cognitive-evaluative aspects of sensation, may be indicative of the employment of a coping strategy by the subjects to endure the esophageal sensation.

Studies of the cerebral processing of rectal sensation using PET. PET has also been used to compare the brain loci activated by rectal stimuli in healthy volunteers and patients with irritable bowel syndrome (IBS).[121] In healthy subjects, perception during either actual or simulated delivery of painful stimuli was associated with activity of the anterior cingulate cortex. In patients with IBS, anterior cingulate cortex activation failed to occur (Figure 10) and, in contrast, the left prefrontal cortex was activated, suggesting that aberrant CNS processing occurred, possibly because of hypervigilance to painful stimuli.

Further studies in patients with IBS[122] also suggest that rectal hypersensitivity induced by repetitive distention of the sigmoid colon correlates closely with an increase in blood flow in the thalamus and that an aberrant thalamic response to pain may be responsible for the abnormal sensitization. In another study,[123] the autonomic response to painful rectal stimuli in patients with IBS was different from that of healthy subjects, again suggesting aberrant CNS processing of visceral sensation.

Although the above studies implicate aberrant brain processing of gut sensation in the etiology of IBS, correlation between abnormalities detected and the affective and cognitive experience of patients to the experimental pain remains to be confirmed. Patients with IBS have

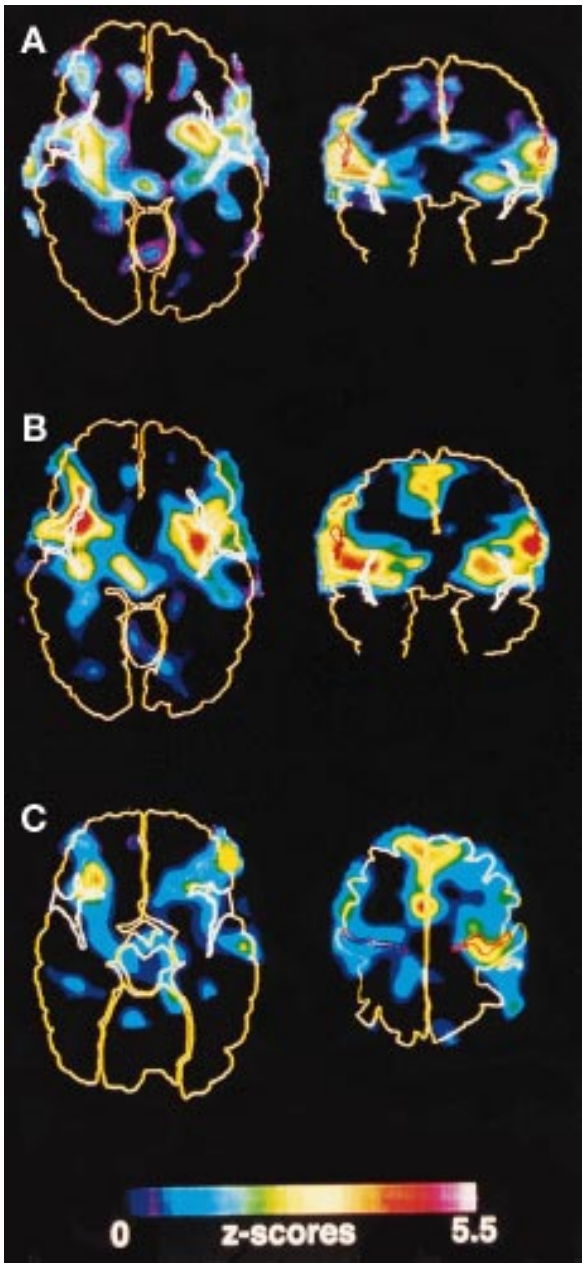


Figure 9. Images showing PET data superimposed onto group mean MRI scans shown in inferior views. (*A–C*) Cortical areas activated during definite sensation–no sensation, pain–no sensation, and pain–definite sensation contrasts, respectively. (*A*) *Left* and *right* scans show bilateral activation of the insular and the primary somatosensory cortices, respectively. (*B*) Activation of the insular and primary somatosensory cortex is of greater magnitude. In addition, activation of the anterior cingulate gyrus is also seen (*right*). (*C*) *Left* scan shows activation of the right anterior insular cortex, and the *right* scan shows activation of the anterior cingulate cortex. (Adapted and reprinted with permission.[119])

a variety of psychological symptoms,[6,7] and their subjective pain experience is likely to vary. Recent studies suggest that multidimensional verbal pain descriptors allow not only determination of the affective and cognitive response to pain[124] but also allow characterization of individual differences in the perception of the pain

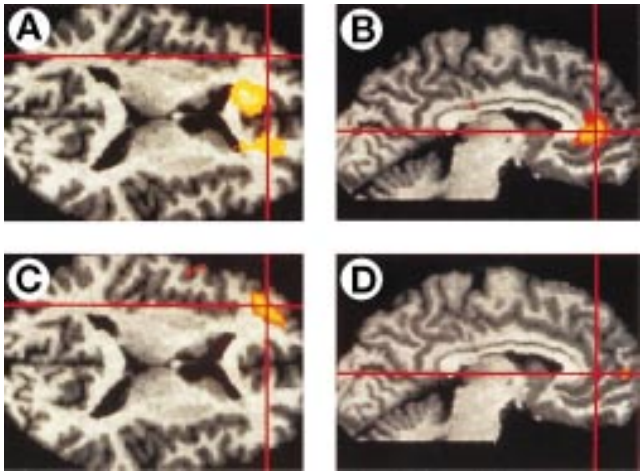


Figure 10. Group mean PET scans superimposed on MRI scans shown in (*A* and *C*) axial and (*B* and *D*) sagittal views in normal subjects and patients with IBS during anticipation of delivery of painful stimuli. (Reprinted with permission.[121])

experience to be determined. Studies aimed at characterizing the brain processing of gut sensation in relation to the subjective pain experience will therefore be useful to help our understanding of the abnormalities detected.

fMRI

Whereas MRI is a well-established technique for imaging brain structure, fMRI is a technique for correlating brain structure and function.

Basic principles and methodology

fMRI detects increases in oxygen concentration in areas of heightened neuronal activity.[116,125] PET studies have shown that an increase in neuronal activity is accompanied by an increase in blood flow and glucose utilization without a concomitant increase in oxygen consumption, because the brain resorts to anaerobic metabolism during spurts of neuronal activity. This increased blood flow without increase in oxygen consumption leads to an increase in oxygen concentration in the areas of neural activity and a decrease in the concentration of deoxyhemoglobin. The amount of oxygen carried by hemoglobin influences its magnetic properties; when hemoglobin is deoxygenated, it becomes paramagnetic and decreases its magnetic signal. In contrast, the presence of more oxyhemoglobin, which is diamagnetic, leads to an increase in signal. With appropriate signal processing, such subtle changes in hemoglobin concentration can be identified and associated with brain structures.

Advantages of fMRI

The major advantage of fMRI over PET is its safety, because radioisotopes are not required.[116,125] However, head and trunk exposure has been limited to 2 T by the U.S. Food and Drug Administration. The temporal resolution of fMRI (4–8 seconds) is also faster than that of PET, but it is still much

longer than that of CEP recording and MEG. Therefore, fMRI like PET is best suited for locating the site but not the sequence or duration of neuronal activity. The spatial resolution of fMRI is excellent (~2 mm), and because both anatomic and functional information is available simultaneously in each subject, paradigms for coregistration are not necessary.

Limitations of fMRI. The spatial resolution of fMRI depends on the brain structures being imaged. For instance, the presence of bony cavities and clusters of large blood vessels such as circle of Willis cause magnetic field irregularities and artifacts.[116] Furthermore, artifacts produced by changes in head position between data acquisition sequences reduce the spatial resolution.[116,126] There is some potential for false-positive or false-negative results because of the dependence of the technique on the orientation of vessels relative to the imaging planes; certain orientations are therefore more accessible for imaging than others.[116] This can be avoided by acquiring images in different orientations. It is also possible that changes in blood flow measured with fMRI reflect changes that occur in the large vessels draining an area rather than in the capillary bed itself.

Studies of the cerebral processing of esophageal sensation using fMRI. So far, only a few preliminary studies have been published on the cerebral processing of esophageal sensation using fMRI. Kern et al.[127] used fMRI to identify the cortical areas activated by proximal and distal esophageal distention. They found that the parieto-occipital and the midparietal cortices were activated by distention of the distal esophagus and the proximal esophagus, respectively. In another study,[128] activation of the insular and the premotor cortex occurred in response to esophageal distention. A comparison of the cortical areas activated in response to esophageal acid perfusion and distention has shown that acid perfusion induces cortical activation that is spatially and temporally distinct from that induced by distention.[129]

More recently, the pattern of cortical activation in response to esophageal distention of varying intensity, frequency, and duration has been studied.[130] Activity was observed most consistently in the presylvian area comprising the insular cortex, the frontal and the parietal operculum, and the secondary somatosensory cortex. Activation of the anterior cingulate cortex was also observed during high-intensity stimulation.

Studies of Brain to Gut Pathways

Brain-gut pathways can now be studied noninvasively in humans by using transcranial magnetic stimulation (TCMS).

TCMS. In the last 11 years TCMS has become widely available for stimulation of the cerebral cortex and the spinal cord.[131–133]

Basic principles and methodology. TCMS is based on the principle of electromagnetic induction first described by Michael Faraday,[134] who discovered in 1831 that in conducting tissues, a time-varying magnetic field induces an electric field and causes current to flow. In 1985, Barker et al.[131] used this principle to develop a magnetic stimulator that could be used for noninvasive stimulation of the human motor cortex and showed that discharging a time-varying magnetic pulse through a coil placed on the scalp induced an electrical current in the underlying motor cortex that led to contraction of somatic muscles.

Magnetic stimulators now available for clinical use consist of a high-current pulse generator and a stimulation coil. When the pulse generator discharges an electric current rapidly into the coil, a time-varying magnetic field is produced with strengths of up to 2 T.[131–133,135] The area of the brain activated depends on the configuration of the coil used.[135] A circular coil stimulates the underlying neural tissue diffusely, whereas two coils wound together into a figure of 8 coil creates a "hot spot" in the center and can be used for focal stimulation.

Topographic mapping using TCMS. Focal TCMS can be used to determine the topographic representation of muscle function on the human motor cortex.[136–139] Focal stimulation of multiple points on a 1–2-cm scalp grid is performed, and each stimulation point is assigned the amplitude value of the evoked electromyographic (EMG) response. These values are used to create a topographic map that is coregistered with MRI brain scans to determine the anatomic location of the muscle responses being studied.

Advantages of TCMS. Magnetic stimulation is painless and causes neither neuronal damage or seizures even at high-stimulation intensities when single-pulse stimuli are used.[133,140] TCMS is useful in assessing the integrity of both central and peripheral motor pathways and is able to provide diagnostic as well as prognostic information in a variety of neurological disorders such as cerebrovascular accidents, demyelinating disorders, motor neuron disease, and peripheral motor neuropathies.[132–133]

Limitations of TCMS. Despite its high safety profile, TCMS studies are best avoided in patients with a history of epilepsy[133,140] and in patients with intracranial metallic implants or cardiac pacemakers. The spatial resolution of TCMS mapping is inferior to other functional imaging techniques such as PET and fMRI, because of current spread via cortico-cortical connections.

Studies of swallowing using TCMS. TCMS of the motor cortex evokes two distinct EMG responses in the

oropharynx and the striated muscle region of the esophagus.[137,138,141,142] The first short-latency response (Figure 11) is likely to be mediated via a direct paucisynaptic pathway, whereas the second, longer latency response, is caused by either polysynaptic processing of corticofugal potentials or to a reflex response mediated via brain stem neurons. It is not yet certain whether the pathways mediating the early and the late responses pass via the CPG neurons or via a more direct pathway to the motor neurons[142–144]; however, it is speculated that they are mediated by pathways that pass either via the CPG or other closely related neurons[142] because, in animals, single-pulse cortical stimulation activates a pathway to the swallowing motor neurons via the CPG.[67,70] Furthermore, direct corticofugal pathways to the swallowing motor neurons have not been identified.[70,145,146] Although both responses are facilitated during swallowing,[142] swallowing itself is not induced by TCMS, probably because the initiation of swallowing by the brainstem usually requires spatial summation of synaptic potentials generated by repeated cortical stimuli.[67,70]

Cortical topography of swallowing muscles. The topographic representation of muscles involved in the oral, pharyngeal, and esophageal phases of swallowing has now been established in healthy subjects.[137,138] Swallowing muscles are bilaterally but asymmetrically represented on the human motor and premotor cortices, some subjects lateralizing to the right hemisphere and others to the left hemisphere irrespective of handedness or hereditary factors (Figure 12). Moreover, there is evidence of somatotopic organization of these muscles on the cortex (Figure 13), with the mylohyoid muscles being represented most laterally on the motor cortex and the inferior frontal gyri, whereas the pharynx and esophagus are represented more rostromedially on the motor cortex as well as the middle and superior frontal gyri, respectively, suggesting that the brainstem CPG neurons mediating the different phases of swallowing may be influenced by distinct cortical regions.

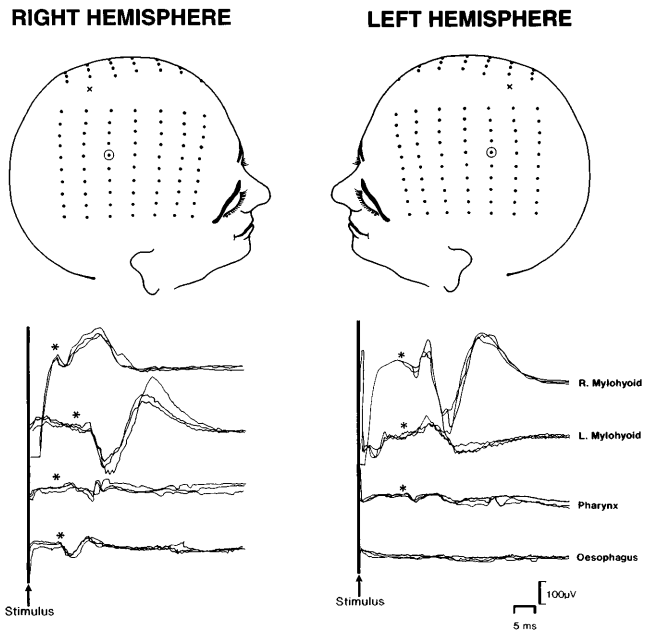
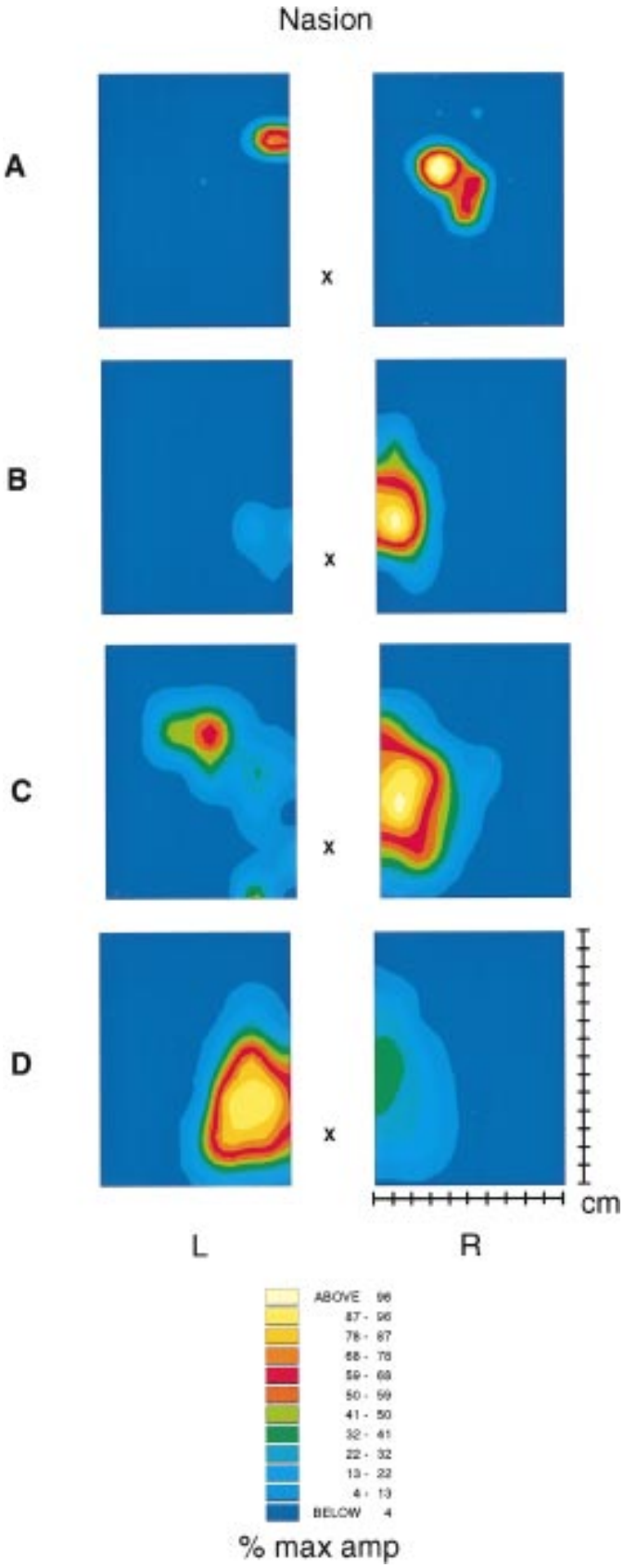


Figure 11. EMG responses of mylohyoid muscle, pharynx, and esophagus, evoked by focal stimulation of a single grid point on each side of the scalp. Symmetrical EMG responses are evoked in each mylohyoid muscle; however, the pharyngeal and esophageal responses are asymmetrical and are greater after stimulation of the right hemisphere. (Reprinted with permission.[138])

Afferent feedback modulation of swallowing motor pathways. Focal stimulation of the extracranial trigeminal and vagus nerves evokes EMG responses in swallowing muscles that are mediated reflexly via the brain stem.[141,142,147] When either trigeminal or vagus nerve stimulation is applied immediately preceding cortical stimulation, swallowing muscle responses are facilitated and their discharge is larger and occurs earlier than in the resting state.[142,147] This suggests that TCMS-induced stimulation of cranial nerve afferents provides sensory feedback modulation of the corticofugal pathway to the swallowing muscles. It is therefore now possible not only to study the corticofugal and brainstem-mediated reflex control of swallowing muscles in humans, but also to study the sensory feedback modulation of corticofugal pathways, thus making the assessment of neurogenic dysphagia feasible in intact humans.

Studies of dysphagia after unilateral hemispheric stroke. Although the cortical control of swallowing is bilateral,[71] dysphagia occurs in 30%–40% patients after unilateral cortical stroke,[10,148] but usually recovers rapidly. TCMS has been used to study dysphagia after unilateral cortical stroke.[138,149,150] Stimulation of the unaffected hemisphere evoked smaller pharyngeal responses in dysphagic than in nondysphagic patients. In contrast, responses to stimulation of the affected hemisphere were similarly impaired in both groups. This suggests that swallowing function was lateralized to the affected hemisphere in dysphagic patients; the development of dysphagia after stroke therefore depends on whether or not the dominant swallowing center is damaged.

To follow recovery of swallowing after stroke, Hamdy et al. have studied dysphagic and nondysphagic patients.[138,149,150] At presentation, both groups showed similarly reduced pharyngeal responses on the affected hemisphere, whereas a larger area of response was obtained in the nondysphagic patients on the unaffected hemisphere. At 3 months, the dysphagic patients, who had recovered normal swallowing function, had an increase in the size of pharyngeal representation on the



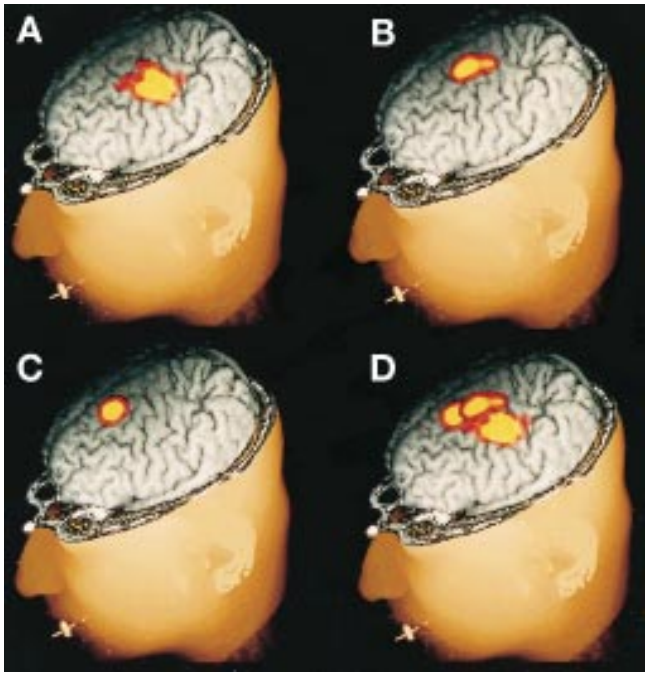


Figure 13. Three-dimensional MRI scans showing cortical representation of swallowing muscles studied using TCMS. (*A*) The mylohyoid muscle is represented on the motor cortex, and the (*B*) pharynx and (*C*) esophagus are represented on the motor and the premotor cortex. (*D*) Somatotopic representation of the three muscle groups. Courtesy of K. Singh.

unaffected hemisphere, whereas the affected hemisphere remained unchanged. The nondysphagic patients showed no change in the pharyngeal topography. This suggests that contralateral hemisphere reorganization underlies the improvement in swallowing seen after stroke (Figure 14).

Studies of the anorectum. Although direct electrical stimulation of the spinal cord and the pudendal nerves has been used to study the sensory and motor control of anal function in both health and disease, its cortical control remained unexplored until Ertekin et al.[151] and later Herdman et al.[152] used magnetoelectric stimulation of the cortex to evoke reproducible EMG responses in the external anal sphincter. In another study, Turnbull et al.[153] used TCMS to determine the topographic representation of the external anal sphincter and the pelvic floor muscles on the cortex; they showed bilateral representation of each group on the medial aspect of the primary

Figure 12. Two-dimensional scalp topographic maps showing cortical representation of the esophageal muscles on both the left (L) and (R) hemisphere in a (*A*) right-handed and (*B*) left-handed subject and (*C* and *D*) 2 right-handed monozygotic twins. In subjects *A–C,* the esophagus has a larger representation on the right hemisphere, and in subject *C* the representation is larger on the left hemisphere. x, vertex. (Reprinted with permission.[138])

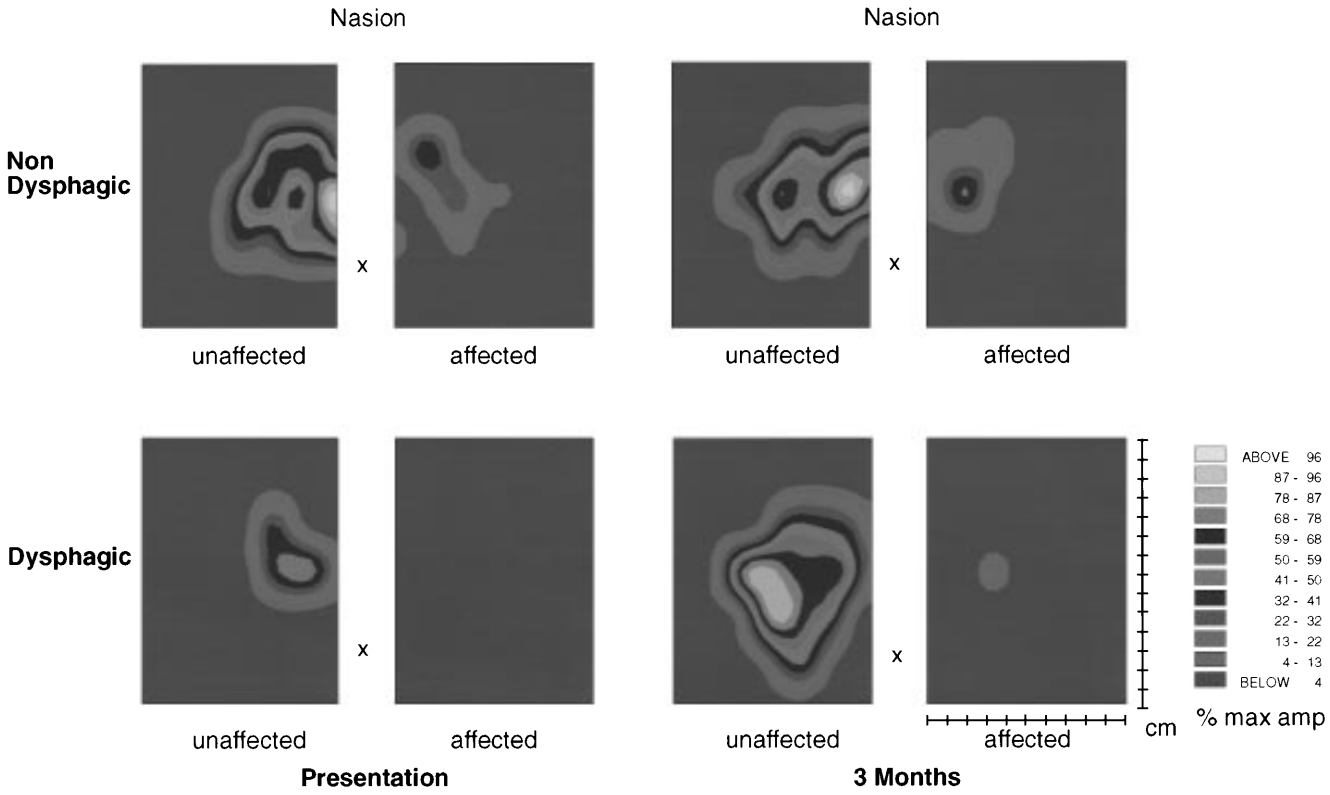


Figure 14. Two-dimensional scalp topographic maps of the pharyngeal muscles obtained by TCMS of the unaffected and affected hemispheres in a dysphagic and a nondysphagic patient after unilateral right hemispheric stroke. At presentation, the pharyngeal representation in the nondysphagic patient is greater on the unaffected hemisphere. In the dysphagic patient, stimulation of the unaffected hemisphere evoked small-amplitude responses. At 3 months, the pharyngeal representation in the dysphagic patient who had now recovered swallowing function had enlarged on the unaffected hemisphere to equal that in a nondysphagic patient. (Reprinted with permission.[138])

motor cortex and observed asymmetric representation in some subjects.

Herdmann et al.[154] studied the effect of TCMS on the pressure changes evoked in the external anal sphincter either at rest or during voluntary contraction (facilitation). The results showed that despite a wide range of pressure amplitudes observed in the two states, the contraction times of the external anal sphincter remain unchanged, suggesting that the external anal sphincter like other somatic muscles displays the principle of isochronism, i.e., strong muscle contractions are achieved in the same time as weaker contractions so that muscles are optimally adapted for use in different motor tasks. The increase in external anal sphincter pressure at constant time intervals may help to maintain continence in situations when a rapid increase in intra-abdominal pressure occurs.

Future Directions for GI Research Using Functional Brain Imaging

So far, functional brain imaging techniques have only been used to study the proximal and the distal gut, because these regions are most readily accessible and receive a relatively strong modulatory influence from the brain. Nevertheless, appropriate stimulation of other gut organs also generates sensation,[155] which makes it likely that these gut regions also receive cortical representation identifiable by the use of functional brain imaging techniques. It is possible therefore that future studies of the cortical representation of different gut organs may help to identify the gut sensory homunculus on the brain, to complement the somatic sensory homunculus. Identification of the visceral motor homunculus is likely to be more difficult, however, because motor activity of smooth muscle regions of the gut is autonomous, thereby precluding a major cortical influence.

For the future, the challenge is to discriminate those patients who have gut hypersensitivity due to sensitization of the primary visceral afferents and/or the spinal cord from those who have aberrant brain processing of sensation, because such a distinction may have therapeutic implications. This may now be possible with the use of spinal monitoring and brain imaging techniques.

Conclusion

Gastroenterologists are now provided with major opportunities to explore the CNS control of gut function using a series of new, powerful techniques. However, the availability of this new technology cannot alone advance knowledge, which will only occur if the technology is used appropriately to answer carefully considered biological questions, because they contain many technical traps for the unwary clinician. For advance to come, gastroenterologists will need to work in close collaboration with clinical neurophysiologists, neuroradiologists, and physicists.

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