Brain imaging correlates of peripheral nerve stimulation

Ausaf A. Bari, Nader Pouratian

Department of Neurosurgery, David Geffen School of Medicine at UCLA, Los Angeles, California

E-mails: *Ausaf A. Bari - ausafb@gmail.com; Nader Pouratian - npouratian@mednet.ucla.edu

*Corresponding author

Received: 22 August 12 Accepted: 04 September 12 Published: 31 October 12

This article may be cited as:
Bari AA, Pouratian N. Brain imaging correlates of peripheral nerve stimulation. Surg Neurol Int 2012;3:S260-8.
Available FREE in open access from: http://www.surgicalneurologyint.com/text.asp?2012/3/5/260/103016

Abstract

Direct peripheral nerve stimulation is an effective treatment for a number of disorders including epilepsy, depression, neuropathic pain, cluster headache, and urological dysfunction. The efficacy of this stimulation is ultimately due to modulation of activity in the central nervous system. However, the exact brain regions involved in each disorder and how they are modulated by peripheral nerve stimulation is not fully understood. The use of functional neuroimaging such as SPECT, PET and fMRI in patients undergoing peripheral nerve stimulation can help us to understand these mechanisms. We review the literature for functional neuroimaging performed in patients implanted with peripheral nerve stimulators for the above-mentioned disorders. These studies suggest that brain activity in response to peripheral nerve stimulation is a complex interaction between the stimulation parameters, disease type and severity, chronicity of stimulation, as well as nonspecific effects. From this information we may be able to understand which brain structures are involved in the mechanism of peripheral nerve stimulation as well as define the neural substrates underlying these disorders.

Key Words: Functional magnetic resonance imaging, occipital nerve, peripheral nerve, positron-emission tomography, sacral nerve, single-photon emission computed tomography, stimulation, trigeminal nerve, vagus nerve

INTRODUCTION

Direct peripheral nerve stimulation using implanted electrodes has been used to treat a number of different conditions including complex regional pain syndrome (CRPS), diabetic neuropathy, occipital neuralgia, low back pain, nerve injury pain, migraines, incontinence, depression and epilepsy. The rationale for peripheral stimulation was initially based on the gate control theory of pain in which a non-noxious stimulus competes with or interferes with the transmission of pain-related sensory input. However, accumulating evidence suggests that peripheral stimulation may also alter pain perception via central mechanisms of neuromodulation. Stimulation of the peripheral nerves ultimately leads to modulation of activity in neurons in the central nervous system that integrate this information and lead to the potential therapeutic effect. In order to better understand the brain regions involved in this integration, one must correlate peripheral nerve stimulation with changes in brain activity. In order to better understand the central mechanisms underlying the response to peripheral nerve stimulation, we review the literature for imaging correlates of central neuronal activity in response to direct peripheral nerve stimulation. We focus our review on human studies in which peripheral nerves were stimulated directly with permanently implanted electrical stimulators with...
concurrent functional brain imaging. A comprehensive PubMed search was conducted using the keywords “nerve”, “stimulation”, “electrode”, “fMRI”, “PET” “SPECT”, “MRI”, as well as a review of references within the manuscripts identified from the primary search. In order to ensure direct applicability to management of these disorders in humans, we excluded animal studies. Moreover, because the literature suggests that transcutaneous and direct peripheral nerve stimulation do not correlate with respect to efficacy (e.g., responses to transcutaneous stimulation does not predict response to direct nerve stimulation), for the purposes of this review, studies in which peripheral nerves were stimulated indirectly or transcutaneously were omitted.

To date, only four distinct peripheral nerve stimulation paradigms have been investigated with concurrent functional brain imaging. These are vagus nerve stimulation (VNS) for epilepsy and depression, occipital nerve stimulation for headaches and occipital neuralgia, trigeminal nerve stimulation for neuropathic trigeminal pain, and sacral nerve stimulation for urinary and fecal incontinence or detrusor hyperactivity. We will review the literature relating to the use of functional imaging to study the central mechanisms involved in the peripheral stimulation of these nerves.

**Neuroimaging of central neuromodulation**

The main functional imaging modalities that have been used to study the central effects of peripheral nerve stimulation are single-photon emission computed tomography (SPECT), positron-emission tomography (PET) and functional magnetic resonance imaging (fMRI). SPECT uses a gamma-emitting radioligand with a 6-9 mm spatial resolution, 1-minute single acquisition time and a 2-hour inter-acquisition interval. PET uses a positron emitting ligand with a 4-5-mm spatial resolution, ten second acquisition time and 20-30-minute interacquisition interval. Finally, fMRI is based on the changes in concentration of oxyhemoglobin and has the smallest spatial resolution at 1-2 mm, a 2-3 second single acquisition time and 2-3 second interacquisition interval. Thus, fMRI has the advantage of being able to measure changes on a smaller spatial and temporal scale without the need to administer radio-labeled compounds. On the other hand, PET and SPECT imaging may be helpful for assessing changes on a longer time scale and can take into account ligand-receptor interactions.

**Vagus nerve stimulation**

The largest body of data involving central neuroimaging in response to peripheral nerve stimulation is in the field of VNS for epilepsy. Although VNS has been shown to empirically reduce seizure frequency in patients, the central mechanisms underlying this effect remain elusive.

The vagus nerve carries several different fiber categories including general somatic afferent (GSA), special somatic afferent (SSA), general visceral afferent (GVA), and general visceral efferent (GVE). The major afferents from the vagus nerve have their cell bodies in the nodose ganglion and are composed of GVA fibers that synapse on the nucleus of the solitary tract, medial reticular formation, the dorsal motor nucleus of the vagus, area postrema, and the nucleus cuneatus. Ninety-five percent of these vagus afferents project to the nucleus of the solitary tract (NTS).

The NTS in turns projects to the medial reticular formation, hypothalamus, thalamus (via the parabrachial nucleus), amygdala, hippocampus, and the dorsal raphe. Tract-tracer studies in monkeys demonstrate projections from the NTS to the VPM nucleus of the thalamus. These anatomical studies suggest a major role for the NTS and thalamus in the mechanism of action of VNS.

Both the NTS and the thalamus, based on their connectivity, are well-positioned to modulate seizure activity. In addition, the thalamus directly influences activity in limbic structures as thalamic stimulation in rats produces long-term potentiation in the amygdala and entorhinal cortex. Electrical stimulation of the NTS has been shown to prevent epileptogenesis in an amygdaloid kindling model in cats. Clinical studies also support the role of the thalamus in seizure control. The SANTE group found that bilateral stimulation of the anterior nucleus of the thalamus reduces seizures. Thus, the anatomical and empiric clinical evidence suggests a major role of structures such as the thalamus and mesial limbic regions downstream to the NTS in the mechanism of action of VNS.

**Thalamic modulation by vagus nerve stimulation in epilepsy**

*Positron-emission tomography imaging correlates of vagus nerve stimulation for epilepsy*  
Functional neuroimaging in patients implanted with VNS supports a major role of the thalamus and limbic structures in the mechanism of action of VNS for refractory epilepsy. For example, Garnett et al. used H315O-PET to study a series of five patients with VNS for epilepsy. They found increased rCBF in the ipsilateral anterior thalamus and the cingulate gyrus. However, this study was confounded by the occurrence of seizures during the scanning period in two out of five subjects.

These results were extended by Ko et al. in their PET study of three patients with VNS for intractable partial seizures (60 s on time, 2 mA, and 30 Hz). The duration of VNS prior to PET imaging was 2, 6 and 7 months. They found increased rCBF in the right middle temporal gyrus and right thalamus, left posterior cerebellum and left putamen in all three patients. The patient with the most clinical improvement had the highest increase in rCBF in the left posterior cerebellum and right thalamus while the other two patients showed smaller increases in rCBF in these areas.
regions.\(^{18}\) Both of these studies were limited in the small number of subjects studied. This may also account for the discrepancy in thalamic laterality between the two studies.

Henry et al. studied the effects of long vs. short-term VNS on brain activation patterns using \(^{11}\)C-O-PET in ten subjects with refractory partial epilepsy. The subjects were also divided into high and low (“active control”) stimulation groups. Stimulation parameters for the low-stimulation group were pulse width of 130-μs at 1 Hz in trains of 30 s, average current of 0.85 mA, with 180 minutes between trains. High-stimulation parameters were 30 Hz in trains of 30 s, pulse width of 500 μs, average current of 0.5 mA, with 5 minutes between trains. Subjects were imaged after short-term (20 h after starting VNS) and long-term (12 weeks of VNS) stimulation. Both acute and long-term VNS led to increased rCBF in the bilateral thalamus, hypothalamus, inferior cerebellar hemispheres, and right postcentral gyrus. Interestingly, acute VNS lead to cortical rCBF changes with decreases in bilateral hippocampi, amygdala, and cingulate gyri and increases in the bilateral insula but these did not persist after chronic VNS. This pattern was similar across low- and high-stimulation groups although the volume of change was higher in the high-stimulation group.\(^{16}\) Thus, VNS may lead to temporary changes in certain brain regions that lead to more long-lasting changes in the thalamus.

**Single-photon emission computed tomography, correlates of vagus nerve stimulation for Epilepsy**

Surprisingly, studies using SPECT to investigate central neuromodulatory mechanisms of VNS are not, at first glance, consistent with the reported PET literature. Ring and colleagues used \(^{99}\)mTc-HMPAO SPECT to study seven patients with VNS for epilepsy. Patients had been implanted with VNS for at least 6 months prior to imaging (30 Hz, pulse width 500 μs, 0.5-2.0 mA, 7 s on, and 12 s off). Unlike the PET studies, they found decreased activity in the bilateral medial thalamus.\(^{38}\) Likewise, Barnes et al. used \(^{99}\)mTc-HMPAO SPECT to study the acute effects of VNS on patients previously not exposed to VNS. Like Ring and colleagues, they found decreased rCBF relative to baseline in several regions including the thalamus (ipsilateral pre- and postcentral gyri, ipsilateral amygdala, contralateral posterior thalamus, contralateral putamen, contralateral parahippocampal gyrus, ipsilateral precuneus, contralateral medial frontal gyrus, and contralateral anterior cingulate). Interestingly, they did not find any areas of increased rCBF. Overall, this study corroborated the inhibitory effect of left VNS stimulation on the thalamus, amygdala and parahippocampal gyrus as seen in the previous SPECT study.\(^{22}\) While the precise reason for the discrepant results between PET and SPECT studies is not clear, one can hypothesize that these modality-specific differences may be due to the longer time course sampled by SPECT relative to PET.

Similar results were reported by Vonck and colleagues using \(^{99}\)mTc-ethyl cysteinate SPECT in 12 patients with refractory epilepsy (30 Hz, pulse width 500 μs, 0-3 mA, 30 s on and 600 s off). This study also found decreased thalamic activity with acute hypoperfusion in the left thalamus.\(^{48,46}\) The authors expanded on these results to study both acute and long-term VNS effects using the same stimulation parameters in a group of 23 patients with refractory epilepsy. Again, in the acute setting, they found decreased rCBF in the left thalamus, right parahippocampal gyrus, and right hippocampus. Acute stimulation in the chronic state (an average of 5.7 months after VNS placement) resulted in left thalamic activation. However, when compared to the pre-VNS baseline, chronic stimulation resulted in hypoperfusion of the bilateral thalamus. In addition, this study looked at the correlation between perfusion and therapeutic response and found a significant correlation between acute hypoperfusion of the right amygdala and clinical response to VNS.\(^{47}\)

The same group published another expanded SPECT study in a group of 27 patients that were studied after acute VNS and 12 “chronic” VNS patients that were studied after six months of stimulation. Acute VNS lead to decreased rCBF in the left thalamus, bilateral parahippocampal gyrus, and right hippocampus. When compared to the initial baseline, baseline imaging after chronic VNS showed decreased rCBF in the left thalamus with no changes observed in any other region. When chronic activation was compared to chronic baseline, there was increased rCBF in the left thalamus with no changes in other brain regions.\(^{49}\) This study underlines the complex time course of VNS induced changes with active VNS leading to an apparent sensitization of activation in the thalamus and an overall decrease in the baseline thalamic activity over time. Metabolic changes within the thalamus and limbic system are due to an interaction between the effects of acute stimulation superimposed on chronic changes due to plasticity within this network. This overall decrease in baseline thalamic metabolic activity with time may underlie the observation that VNS becomes more efficacious with time.

**Functional magnetic resonance imaging correlates of vagus nerve stimulation for epilepsy**

In contrast to PET and SPECT, fMRI can track the effects of VNS with much higher temporal resolution. Using fMRI, Narayanan et al. studied five patients that were newly implanted with VNS for treatment resistant epilepsy (30 Hz and 0.5-2.0 mA, 30 s on and 30 s off). They found acute activations of bilateral thalamus and other regions (bilateral insular cortex, ipsilateral basal ganglia, ipsilateral postcentral gyrus, contralateral superior temporal gyrus, and the ipsilateral more than contralateral inferomedial occipital gyri). However, the most robust activation was in the bilateral thalamus and insular cortex.\(^{35}\)
Liu et al. extended these results in a study of five patients with treatment resistant epilepsy who had been implanted with VNS from 1 to 11 months (30 Hz, pulse width 250 μs). They showed BOLD activation in response to VNS stimulation in the frontal and occipital lobes of all five patients, the middle temporal lobe and cingulate gyrus in three of the five patients, the insula and thalamus in two patients, and the cerebellum in four patients. Of the five patients in this study, only patients that showed clinical improvement in seizure occurrence had thalamic activation.[22] This was corroborated by the PET study by Henry et al. which showed increased thalamic blood flow in patients with clinical improvement.[16] The authors state that these findings are consistent with the connectivity of the vagus nerve with the parabrachial nucleus which, in turn, is connected with basal forebrain regions, ventral posterior thalamus and insula.[22]

**Importance of thalamic inhibition and integration of imaging**

While the majority of PET and fMRI studies show activation in the thalamus and other limbic structures, SPECT studies show a general trend toward thalamic and limbic inhibition. As discussed by Barnes, these differences may be partly attributable to differences in time course between imaging modalities with fMRI and PET tracking changes over a time window of seconds, while SPECT has a time window of minutes.[54] Taken together, these studies suggest that while acute VNS leads to thalamic activation, chronic stimulation may lead to a decrease in baseline thalamic activity over time. Interestingly, a study by Sucholeiki et al. using fMRI performed 6-7 months after chronic VNS (30 Hz, pulse width 500 μs) found no thalamic activation but robust activation in the left superior temporal gyrus, the bilateral inferior frontal gyri, bilateral medial superior frontal gyri, and the bilateral posterior middle frontal gyri.[45] This supports the findings of overall decreased thalamic activity after chronic VNS. As the thalamus supplies excitatory glutamatergic input to the cortex, it is not surprising that chronic thalamic deactivation and decreased limbic activity are associated with VNS efficacy particularly over time. Indeed, studies in rats show that seizure onset in the hippocampus is linked to the onset of neuronal activity in the midline thalamus and lidocaine infusion in the midline thalamus decreases afterdischarge duration in the hippocampus.[4] Taken together, these studies support the hypothesis that the thalamus may serve a gating structure for the secondary generalization of limbic seizures to the rest of the cortex.[45]

Although the majority of functional imaging studies of VNS stimulation have used PET, SPECT or fMRI, for completeness we mention a single case report of a patient with a VNS for epilepsy that was imaged using DWI MRI. This patient had known baseline bilateral hippocampal atrophy and had been implanted with a VNS (1.25 mA, 25 Hz, 250 μs, 30 s on and 5 min off). One year after initial onset of her seizures, the patient presented with status epilepticus that was successfully terminated with IV lorazepam. The patient was imaged with DWI within 24 hours of seizure termination with the VNS turned off. DWI revealed ipsilateral right temporal, bilateral posterior-lateral thalamic, and bilateral diffuse midbrain hyperintensities that resolved completely on repeat imaging 6 weeks later. Thus, DWI also supports the involvement of thalamic, limbic and midbrain regions in VNS, although the study was confounded by the presence of status epilepticus.[44]

**Cerebellar and nonlimbic modulation by vagus nerve stimulation in epilepsy**

In addition to thalamic and limbic involvement, a number of the studies have also reported that VNS leads to changes in the cerebellum and nonlimbic cortices.[18,2,35,22] These studies report increased activation of the cerebellum or non-limbic cortical regions except for the SPECT study by Barnes which showed a decrease in rCBF in the putamen.[2] Combined EEG and fMRI studies have shown that interictal epileptic discharges are associated with activation of widespread cortical, subcortical and white matter regions including the cerebellum.[12] The cerebellar cortex via Purkinje neurons provides inhibitory input to the deep cerebellar output nuclei which send excitatory ascending projections to the red nucleus and thalamus.[17] Thus, the cerebellum has direct access to the previously mentioned thalamo-cortical network that has been shown to be involved in seizure modulation. Maiti et al. showed that electrical stimulation of the cerebellar cortex shortened or terminated electrically induced afterdischarges, whereas stimulation of deep cerebellar nuclei had the opposite effect.[27] This supports the view that deep cerebellar nuclei are in a position to potentiate seizure activity while inhibitory influence from upstream inhibitory Purkinje neurons may inhibit epileptogenesis. However, based on the above review of neuroimaging in patients with VNS, it is unclear whether the cerebellar activation was in the cerebellar cortex or deep nuclei. This may be due to the lack of spatial resolution of the imaging modalities employed. In conclusion, the role of the cerebellum in VNS for refractory epilepsy is unclear and additional studies with greater spatial resolution are needed.

**Vagus nerve stimulation-mediated central neuromodulation in depression**

In addition to epilepsy, VNS is efficacious in some patients with treatment-resistant depression.[23] A wide network of brain regions has been implicated in the pathogenesis of depression including the prefrontal cortex, cingulate cortex, amygdala, hippocampus, thalamus and basal forebrain.[56] The efficacy of VNS in refractory depression is not surprising given that
vagus afferents, via the nucleus of the solitary tract (NTS) and parabrachial nucleus, show connectivity with many of these regions. In addition, in a study showing the efficacy of deep brain stimulation of the subgenual cingulate gyrus for treatment-resistant depression, PET imaging showed that the antidepressant effect of DBS was associated with a decrease in rCBF in the subgenual cingulate, hypothalamus, anterior insula, medial frontal cortex (BA10), dorsolateral prefrontal cortex (BA9/46), dorsal anterior and posterior cingulate gyrus (BA24/31), premotor cortex (BA6), and parietal regions (BA40).

The neuroimaging data from patients with VNS for treatment-resistant depression (TRD), as reviewed below, show changes in similar regions. For example, the first imaging study of VNS for TRD utilized fMRI in patients chronically implanted with VNS and showed increases in BOLD signal in the orbitofrontal cortex, bilateral parieto-occipital cortex, ipsilateral temporal cortex, hypothalamus and ipsilateral amygdale.[8] Although subsequent studies have shown a decrease in limbic activation over time, this study was potentially confounded by a small sample size and by the fact that the patients were on various antidepressant medications.

Zobel et al. used [9] Tc-HMPAO SPECT (30 Hz, pulse width 500 μs, 30 s on, 5 min off) to measure rCBF at four weeks after the onset of VNS compared to a prestimulation baseline. They showed only one area of increased rCBF, the left dorsolateral prefrontal cortex (Brodman area 46). On the other hand, using SPM analysis, decreased rCBF was found in the left medial frontal gyrus (BA 9), left area subcentralis (BA 43), left inferior and right medial temporal gyrus (BA 20, BA 39), left caudate head, and limbic system (bilateral amygdala, left parahippocampal gyrus, right posterior cingulate gyrus). Compared to the SPM analysis, ROI analysis showed decreased rCBF in the amygdala bilaterally, left subgenual cingulate, left hippocampus, bilateral ventral anterior cingulum, left dorsal anterior cingulum, right DLPFC, right thalamus, left caudate nucleus, and brainstem.[3] The decrease in signal in the subgenual cingulate, in particular, is concordant with early results from DBS in this region.[28]

In another study of the acute effects of VNS for treatment resistant major depression, Conway et al. used H[15]O-PET to study four patients within three weeks of VNS placement (0.5 or 1.0 mA, 20 Hz, and a pulse width of 130 or 500 μs with 30 s on and 5 min off times). Compared to the off state, acute VNS resulted in increased rCBF in the bilateral orbitofrontal, anterior cingulate, superior frontal, and inferior frontal regions and unilaterally in the right fusiform gyrus, left cerebellar body, left inferior putamen, and right anterior insula. Decreases in rCBF were seen in the bilateral temporal cortex, unilateral left precentral and left postcentral gyri, left precuneus, and right superior and inferior parietal lobules.[10] At first, these results showing limbic activation seemed contradictory to the previous studies. However, when the same group expanded their study to include more patients, they found decreases in rCBF in the bilateral lateral orbitofrontal cortices and left inferior temporal lobe. Increases in rCBF were still found in the right dorsal anterior cingulate, left posterior limb of the internal capsule/medial putamen, right superior temporal gyrus, and left cerebellar body.[9] The authors suggest that the lateral orbitofrontal cortex integrates visceral and other modalities and is involved in decision-making and cognitive control. In addition, this orbitofrontal network has been shown to be interconnected to a distinct medial network which includes the subgenual cingulate and medial prefrontal cortex which have been shown to have increased metabolism in depression.[9] The unexpected increase in rCBF in the dorsal anterior cingulate may be due to the fact that the cingulate may be subdivided into rostral and caudal regions that have been shown to play separate roles in pain modulation and may also play different roles in modulation of depression.[50]

The efficacy of VNS for TRD has been known to increase with time. Thus it is important to evaluate the changes that occur with chronic VNS. Nahas et al. performed a 3-month, double-blind, placebo-controlled serial-interleaved VNS/fMRI study with an open 20-month follow-up (7 s trains of VNS at 20 Hz, pulse width 500 ms). VNS resulted in decreased BOLD signal in the right medial prefrontal cortex, anterior cingulate, left anterior temporal pole, and right somatosensory cortex and an increased signal in the right superior temporal gyrus. In the placebo (sham stimulation) group, there was an increase in BOLD signal in the right orbitofrontal cortex and no significant decreases. Unlike previous studies, this group used multiple regression modeling to study the effect of duration of exposure to VNS, level of depression, and changes in VNS output current. They found that duration of VNS exposure accounted for most of the medial prefrontal/limbic deactivations including deactivation of the right insula over time while initial exposure to VNS lead to limbic activation. These deactivations were particularly pronounced after 30 weeks of exposure to VNS, which is around the time when the most pronounced clinical improvements are observed. This finding is similar to initial thalamic activations followed by chronic thalamic deactivation seen in VNS for epilepsy. Finally, higher VNS output current was associated with increased activity in the right somatosensory area which may correlate with a heightened awareness of pain in patients with depression necessitating lower levels of stimulation compared to patients with epilepsy.[51]

Similarly, Pardo et al., using PET to analyze changes in metabolism after chronic (greater than one year) VNS
therapy, found decreased rCBF in the ventromedial prefrontal cortex (VMPFC), a region that extends from the subgenual cingulate to the frontal pole. The authors point out that decreased VMPC is unique to VNS for TRD since the majority of neuroimaging studies in patients with VNS for epilepsy do not show changes in the VMPFC. This latter finding suggests that different disease states may alter the susceptibility of different brain regions to peripheral nerve stimulation.

In a follow-up study, Lomarev et al. sought to investigate the effect of varying frequencies of VNS stimulation in patients with treatment resistant depression. Six patients were studied 8-19 months following the date of their VNS implant (7 s at 5 Hz and 20 Hz). At the higher frequency of stimulation of 20 Hz, VNS led to increased BOLD signal in the orbitofrontal cortex, frontal pole, hypothalamus, left pallidum, and to a lesser extent, the thalamus. On the other hand, low frequency stimulation at 5 Hz, did not result in significant activation. In addition, the authors studied the longer-term effects of stimulation by having subjects listen to a tone during a stimulator “off” period. Their result was the first to suggest that higher frequency stimulation at 20 Hz results in lingering activation even while the VNS was turned off. This may also elucidate why VNS for epilepsy often leads to increased rCBF in the orbitofrontal cortex compared to a decrease seen in TRD patients since VNS for TRD is often programmed at a lower stimulation frequency. This suggests that stimulation frequency is another factor that may determine the regional pattern of brain activation.

Mu et al. extended these results to measure the effect of varying the pulse width in nine patients implanted with VNS for treatment resistant depression. They varied the pulse width between 130, 250 and 500 μs using a frequency of 20 Hz and found a significant effect of pulse width on BOLD activation with 130 μs producing the least activation. There was a trend toward increasing activation of the lateral orbitofrontal cortex, prefrontal cortex, insula and striatum with increasing pulse width. Interestingly, the lowest pulse width produced greater deactivation in the thalamus and cingulate relative to the higher pulse widths.

Taken together these studies support the inhibition of a wide network of limbic structures in the mechanism of action of VNS for TRD. The central components of this network are the orbitofrontal cortex and ventromedial prefrontal cortex including the subgenual cingulate region. Although the amygdala is also implicated in major depression, only one group found significant decreases in metabolism in the bilateral amygdale. Further studies with a larger number of subjects and greater spatial and temporal resolution are needed to clarify to role of these structures in both acute and chronic VNS for TRD.

The use of VNS for both epilepsy and depression raises the question of how one peripheral nerve can modulate two distinct disease states. In reviewing the imaging correlates of VNS for epilepsy and depression we find that differences in stimulation parameters can result in distinct brain activation patterns. In addition, structural and functional differences within neuronal networks between and within patients with epilepsy and depression may lead to the differences in regional brain activation between these patient populations. There is also a likely interaction effect between the physician-controlled stimulation parameters and patient-specific factors such as type and severity of disease. Finally, one cannot rule out the possibility of common neuroanatomical networks underlying seemingly distinct disease states.

**Occipital and trigeminal nerve stimulation**

Functional neuroimaging has also been used to study occipital nerve stimulation (ONS) for occipital neuralgia and migraine headache as well as trigeminal ganglion stimulation for neuropathic trigeminal pain. Pain is a common modality in these disorders. In order to place this review and discussion in context, it is critical to understand the brain regions affected by painful stimuli. Lanz et al. performed a meta-analysis studying the fMRI and PET correlates of painful stimuli. Specifically, different types of pain were studied including “normal”, thermal, mechanical, hyperalgesia, allodynia, clinical neuropathic, and experimentally-induced pain. The authors found greater activation in bilateral secondary somatosensory cortex (S2), ipsilateral cingulate cortex, contralateral prefrontal cortex, contralateral basal ganglia, and contralateral cerebellum in response to allodynia and hyperalgesia. However, “normal pain” induced greater activation in the ipsilateral insula, contralateral anterior cingulate, contralateral prefrontal cortex, bilateral thalamus, and bilateral basal ganglia. Clinical neuropathic pain was associated with activation of the contralateral S2 and supplementary motor area (SMA) and ipsilateral cerebellum. Thus, nerve stimulation for various pain syndromes would be expected to modulate these brain regions, including the insula, cingulate cortex, prefrontal cortex, thalamus and somatosensory regions.

Kovacs et al. used 3 T fMRI to visualize the central effects of occipital nerve stimulation in a single healthy volunteer. Activation was found in the hypothalamus, thalamus, orbitofrontal cortex, prefrontal cortex, periaqueductal gray, inferior parietal lobule, and cerebellum. Deactivation occurred in primary cortices such as M1, V1, A1, and S1, the amygdala, paracentral lobule, hippocampus, S2, and SMA. This was mainly a feasibility study and was limited in that only one subject was studied. Matharu et al. used PET in chronic migraine patients implanted with bilateral suboccipital stimulators to show changes in rCBF in the dorsal rostral pons, anterior cingulate cortex, cuneus, and left pulvinar.
Thus limbic, sensory and motor regions appear to be modulated by ONS.

Magis et al. assessed the effects of chronic ONS in a cohort of drug resistant chronic cluster headache (dCCH) patients using 18FDG-PET. Compared to healthy volunteers, chronic ONS resulted in decreased metabolism in the anterior cingulate cortex (ACC), mid-cingulate, left visual cortex, left pulvinar, cerebellum, midbrain, and left lowerpons. There was increased metabolism in the bilateral sensorimotor cortices. When patients with ONS for dCCH were segregated into responders vs. nonresponders, there was a significant increase in metabolism in the perigenual ACC of responders. In addition, the authors found persistent hypothalamic activation despite a reduction in cluster headache attack frequency. The authors conclude that the persistence of hypothalamic activation suggests that ONS for cluster headache is only a symptomatic therapy with patients still experiencing recurrent autonomic attacks. Thus limbic, sensory and motor regions appear to be modulated by ONS.

Electrical stimulation of the trigeminal ganglion (TGES) has been shown to have a therapeutic effect for trigeminal neuropathic pain. In order to map the central mechanisms involved, Willoch et al. measured H215O-PET activation in a group of ten patients implanted with trigeminal ganglion stimulators for chronic trigeminal neuropathic pain. Patients were studied in three conditions: Stimulator off (chronic pain), short-term stimulation (stTGES), and long-term stimulation (ltTGES) (85 to 130 Hz, pulse width 210 to 400 ms, and amplitude range 0.5 to 2.0 V). The minimal time interval between implantation and the PET study was eight weeks. Short-term TGES (stTGES) showed increased rCBF in the ipsilateral superior parietal and superior frontal cortices. Significant reduction in rCBF was found in the cerebellum, and medial orbitofrontal cortex. Long-term TGES (ltTGES) likewise showed increased rCBF in the superior prefrontal and superior parietal cortices and decreased rCBF in the cerebellum, and medial orbitofrontal cortex. In addition, there was an increase in rCBF in the bilateral medial frontal cortices, and the rostral and mid-ACC. Compared to short-term changes, ltTGES showed an increase in rCBF in the orbitofrontal and medial frontal cortices that extended into the rostral cingulate cortex with decreased metabolism in the caudal ACC. Again, this study supports a central role for medial frontal and anterior cingulate cortex in pain modulation. In addition, the differences between metabolism between the anterior and caudal ACC suggest that they encode different aspects of pain perception. The authors suggest that while the caudal ACC is involved in the actual encoding of pain, the rostral ACC mediates pain anticipation and modulation.

**Sacral nerve stimulation**

The final paradigm of peripheral nerve stimulation that has been studied with functional neuroimaging is sacral nerve stimulation for incontinence. Chronic unilateral stimulation of the sacral S3 nerve has been described as a treatment for urge incontinence and bladder hyperactivity refractory to conservative treatment. Previous studies have shown that urge during bladder distension has been associated with activation of the periaqueductal gray (PAG), anterior cingulate gyrus, insula, thalamus, and cerebellum. Sacral nerve stimulation has been used to treat Fowler’s syndrome, a condition seen in young women characterized by urinary retention and a lack of sense of urgency despite large bladder volumes. Dasgupta et al. studied eight patients with Fowler’s syndrome that had been implanted with a sacral nerve stimulator and compared rCBF using H215O PET in the stimulator on and off states. They found that bladder filling in healthy controls lead to increased rCBF in midbrain, anterior cingulate and posterior cingulate regions. In contrast, patients with Fowler’s syndrome had an increase in rCBF in only the anterior and posterior cingulate without midbrain activation with the stimulator turned off. Turning the stimulator on lead to additional rCBF in the midbrain. The authors suggest a role for an abnormal interaction between brainstem and cortical centers in patients with this syndrome.

Blok et al. studied a group of 20 patients implanted with sacral nerve stimulators (SNS) for detrusor hyperactivity using 18F215O-PET. They found important differences in brain activity between acute and chronic SNS. Acute SNS lead to decreased rCBF in the medial cerebellum, right postcentral gyrus, right insula, and ventromedial orbitofrontal cortex. On the other hand, with chronic SNS there was a significant decrease in rCBF in the middle cingulate gyrus, ventromedial orbitofrontal cortex, right dorsolateral prefrontal cortex, left amygdala/hippocampal complex, midbrain, midline thalamus, and left cerebellum. Group analysis between the acute and chronic states showed significant differences in the sensory, premotor and cerebellar regions. A major conclusion of this study was that acute sacral neuromodulation leads to changes in structures known to be involved in sensorimotor learning such as the premotor cortex and cerebellum; and, with chronic neuromodulation, these become less active while other regions involved in central control of micturition become more active. Similar changes in activity between acute and chronic stimulation were seen by Lundby et al. when they studied PET activation in a group of 10 patients implanted with sacral nerve stimulators for fecal
incontinence. While initial stimulation lead to activation of the contralateral frontal cortex, after 2 weeks, there was a shift in activation to the ipsilateral caudate nucleus.[24]

CONCLUSIONS

Taken together, the following conclusions can be drawn from the above studies. First, investigator-controlled factors such as stimulation frequency and pulse width are major determining factors in which brain regions are activated and the degree of their activation. Second, brain activation is an interaction between investigator-controlled stimulation parameters and the patient-specific neurophysiological state of various brain regions. Thus, the same regions may show discordant activity in different diseases as networks with a different baseline activity may respond differently to stimulation. Third, changes in brain activity over time may represent learning and plasticity in neuronal networks in which initial changes in one set of structures ultimately leads to chronic changes in a second set of structures. Thus, we must be cautious in interpreting a role for structures that may only be temporarily involved or represent a secondary phenomenon. Finally, diseases with diverse behavioral phenomenology such as epilepsy, depression, pain and incontinence may share common neuroanatomical substrates in ways that we do not yet fully understand.

The vast majority of studies of central neuromodulation in response to direct peripheral nerve stimulation involve VNS for epilepsy and depression. On the other hand, there is a relative dearth of functional neuroimaging studies related to stimulation of other peripheral nerves. As more patients are implanted with peripheral nerve stimulators, it will become imperative to perform functional neuroimaging studies with greater power to delineate the regions involved in their therapeutic effect. This will hopefully lead to advancements in the targeting of these areas for further neuromodulation. The peripheral nervous system is the integral link between the external world and our internal neuronal representation of that world. These studies will not only delineate the mechanisms underlying various disease states but also help us to understand how the brain represents our interaction with the our physical environment.

REFERENCES

1. Athwal BS, Berkley KJ, Hussain I, Brennan A, Cragg M, Sakakibara R, et al. Brain responses to changes in bladder volume and urge to void in healthy men. Brain 2001;124:369-77.
2. Barnes A, Duncan R, Chisholm JA, Lindsay K, Patterson J, Wyper D. Investigation into the mechanisms of vagus nerve stimulation for the treatment of intractable epilepsy, using 99mTc-HMPAO SPET brain images. Eur J Nucl Med Mol Imaging 2003;30:301-5.
3. Beckstead RM, Morse JR, Norgren R. The nucleus of the solitary tract in the monkey: Projections to the thalamus and brain stem nuclei. J Comp Neurol 1980;190:259-82.
4. Bertram EH, Mangan PS, Zhang D, Scott CA, Williamson JM. The midline thalamus: Alterations and a potential role in limbic epilepsy. Epilepsia 2001;42:967-78.
5. Blok BF, Groen J, Bosch JL, Veltman DJ, Lammersma AA. Different brain effects during chronic and acute sacral neuromodulation in urge incontinent patients with implanted neurostimulators. BJU Int 2006;98:1238-43.
6. Bohning DE, Lomarev MP, Denslow S, Nahas Z, Shastri A, George MS. Feasibility of vagus nerve stimulation-synchronized blood oxygenation level-dependent functional MRI. Invest Radiol 2001;36:470-9.
7. Bosch JL, Groen J. Sacral nerve neuromodulation in the treatment of patients with refractory motor urge incontinence: Long-term results of a prospective longitudinal study J Urol 2000;163:1219-22.
8. Chae JH, Nahas Z, Lomarev M, Denslow S, Lorberbaum JP, Bohning DE, et al. A review of functional neuroimaging studies of vagus nerve stimulation (VNS). J Psychiatr Res 2003;37:443-55.
9. Conway CR, Sheline YI, Chibnall JT, Bucholz RD, Price JL, Gangwani S, et al. Brain blood-flow change with acute vagus nerve stimulation in treatment-refractory major depressive disorder. Brain Stimul 2012;5:163-71.
10. Conway CR, Sheline YI, Chibnall JT, George MS, Fletcher J, Mintun MA. Cerebral blood flow changes during vagus nerve stimulation for depression. Psychiatry Res 2006;146:179-84.
11. Dass Gupta R, Critchley HD, Dolan RJ, Fowler CJ. Changes in brain activity following sacral neuromodulation for urinary retention. J Urol 2005;174:2268-72.
12. Fahoum F, Lopes R, Pittau F, Dubeau F, Gotman J. Widespread epileptic networks in focal epilepsies-EEG-MRI study Epilepsia 2012.
13. Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia 2010;51:899-908.
14. Garnett ES, Nahmias C, Scheffel A, Firmau G, Upton AR. Regional cerebral blood flow in man manipulated by direct vagal stimulation. Pacing Clin Electrophysiol 1992;15:1579-80.
15. Henry TR, Votaw JR, Pennell PB, Epstein CM, Bakay RA, Faber TL, et al. Acute blood flow changes and efficacy of vagus nerve stimulation in partial epilepsy. Neurology 1999;52:1166-73.
16. Henry TR, Bakay RA, Pennell PB, Epstein CM, Votaw JR. Brain blood-flow alterations induced by therapeutic vagus nerve stimulation in partial epilepsy: II. prolonged effects at high and low levels of stimulation. Epilepsia 2004;45:1064-70.
17. Kandel E, Schwartz J, Jessell T. Principles of Neural Science. 4th ed. McGraw-Hill Medical; 2000.
18. Ko D, Heck C, Grafson S, Apuzzo ML, Coulwdwell WT, Chen T, et al. Vagus nerve stimulation activates central nervous system structures in epileptic patients during PET H2(15)O blood flow imaging. Neurosurgery 1996;39:426-30.
19. Kovacs S, Peeters R, De Ridder D, Plazier M, Monenovsky T, Snaaert S. Central effects of occipital nerve electrical stimulation studied by functional magnetic resonance imaging. Neuromodulation 2011;14:46-55.
20. Krauss GL, Koubiessi MZ. Cerebellar and thalamic stimulation treatment for epilepsy. Acta Neurochir Suppl 2007;97(Pt 2):347-56.
21. Lanz S, Seifert F, Maihofner C. Brain activity associated with pain, hyperalgesia and allodynia: An ALE meta-analysis. J Neural Transm 2011;118:1139-54.
22. Liu W-C, Mosier K, Kainin AJ, Marks D. BOLD fMRI activation induced by vagus nerve stimulation in seizure patients. J Neurosurg Psychiart 2003;74:811-3.
23. Lomarev M, Denslow S, Nahas Z, Chae JH, George MS, Bohning DE. Vagus nerve stimulation (VNS) synchronized BOLD fMRI suggests that VNS in depressed adults has frequency/dose dependent effects. J Psychiatr Res 2002;36:219-27.
24. Lundby L, Møller A, Buntzen S, Krogh K, Yang K, Gjedde A, et al. Relief of focal incontinence by sacral nerve stimulation linked to focal brain activation. Dis Colon Rectum 2011;54:318-23.
25. Magdaleno-Madrigal VM, Martínez-Vargas D, Valdés-Cruz A, Almazán-Alvarado S, Fernández-Mas R. Preemptive effect of nucleus of the solitary tract stimulation on amygdaloid kindling in freely moving cats. Epilepsia 2010;51:438-44.
26. Magis D, Bruno M-A, Fumai A, Géraldy P-Y, Hustinx R, Laureys S, et al. Central modulation in cluster headache patients treated with occipital nerve stimulation: An FDG-PET study BMC Neurol 2011;11:25.
41. Slavin KV. Peripheral nerve stimulation for neuropathic pain. Neurotherapeutics 2008;5:100-6.
42. Stanton-Hicks M, Panourias IG, Sakas DE, Slavin KV. The future of peripheral nerve stimulation. Prog Neurol Surg 2011;24:210-7.
43. Sucholeiski R, Alsaadi TM, Morris GL Jr, Ulmer JL, Biswal B, Mueller WM. fMRI in patients implanted with a vagal nerve stimulator. Seizure 2002;11:157-62.
44. Tatum WO, Malek A, Recio M, Orlowski J, Murtagh R. Diffusion-weighted imaging and status epilepticus during vagus nerve stimulation. Epilepsy Behav 2005;4:411-5.
45. Theodore WH, Fisher RS. Brain stimulation for epilepsy. Lancet Neurol 2004;3:111-8.
46. van Laere K, Vonck K, Boon P, Brans B, Vandekerckhove T, Dierckx R. Vagus nerve stimulation in refractory epilepsy: SPECT activation study. J Nucl Med 2000;41:1145-54.
47. van Laere K, Vonck K, Boon P, Versijpt J, Dierckx R. Perfusion SPECT changes after acute and chronic vagus nerve stimulation in relation to pre-stimulus condition and long-term clinical efficacy. J Nucl Med 2002;43:733-44.
48. Vonck K, Boon P, Van Laere K, D’Havé M, Vandenckhove T, O’Connor S, et al. Acute single photon emission computed tomographic study of vagus nerve stimulation in refractory epilepsy. Epilepsia 2000;41:601-9.
49. Vonck K, De Herdt V, Bosman T, Dedeuwaerdere S, Van Laere K, Boon P. Thalamic and limbic involvement in the mechanism of action of vagus nerve stimulation, a SPECT study. Seizure 2008;17:699-706.
50. Willoch F, Gamringer U, Medele R, Steude U, Tölle TR; PET activation study. Analgesia by electrostimulation of the trigeminal ganglion in patients with trigeminopathic pain: A PET activation study. Pain 2003;103:119-30.
51. Zempleni MZ, Michels L, Mehnert U, Schurch B, Kollias S. Cortical substrate of bladder control in SCI and the effect of peripheral pudendal stimulation. Neuroimage 2010;49:2983-94.
52. Zhang DX, Bertram EH. Midline thalamic region: Widespread excitatory input to the entorhinal cortex and amygdala. J Neurosci 2002;22:3277-84.
53. Zobel A, Joe A, Freymann N, Clusmann H, Schramm J, Reinhardt M, et al. Changes in regional cerebral blood flow by therapeutic vagus nerve stimulation in depression: An exploratory approach. Psychiatry Res 2005;139:165-79.