SHORT REPORT

BOLD fMRI activation induced by vagus nerve stimulation in seizure patients

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Objective: To identify the cerebral activated regions associated with the vagus nerve stimulation in epilepsy patients.

Design: Blood oxygenation level dependent functional magnetic resonance imaging (BOLD fMRI) was employed to detect areas of the brain activated by vagus nerve stimulation in five patients with documented complex partial seizures.

Methods: Functional MRI was done on a GE 1.5T Echo-speed horizon scanner. Before each patient entered the scanner, the vagal nerve stimulator was set to a specific ON–OFF paradigm so that the data could be analysed using a box-car type of design. The brains were scanned both anatomically and functionally. The functional images were corrected for head motion and co-registered to the anatomical images. Maps of the activated areas were generated and analysed using the brain mapping software, SPM99. The threshold for activation was chosen as $p < 0.001$.

Results: All patients showed activation in the frontal and occipital lobes. However, activation in the thalamus was seen only in the two patients with improved seizure control.

Conclusions: BOLD fMRI can detect activation associated with vagus nerve stimulation. There may be a relation between thalamic activation and a favourable clinical outcome.

Vagus nerve stimulation has been used to treat patients with complex partial seizures. This is achieved using an implantable nerve stimulator (NeuroCybernetic prosthesis or NCP system, Cyberonics Inc, Webster, Texas, USA).¹ Currently, more than 2000 patients with refractory epilepsy are treated each year with this device.² The mechanisms underlying this treatment are still unclear.

A PET study³ reported that patients with increased thalamic blood flow showed improvement in seizure control in response

to vagus nerve stimulation. Vagus nerve stimulation of the thalamus may play an important role in controlling seizures.

In addition to vagus nerve stimulation, studies using direct electrical stimulation of the anterior⁴ or centromedian⁵ thalamus were reported to be potential treatments for refractory epilepsy.

Recently, brain activation by vagus nerve stimulation was detected using blood oxygenation level dependent functional magnetic resonance imaging (BOLD fMRI).⁶ BOLD fMRI is a non-invasive technique that uses local changes in the concentrations of oxyhaemoglobin and deoxyhaemoglobin to identify regions of increased neural activity.⁷ Our aim in the present study was to identify cerebral regions activated during vagus nerve stimulation in a population with complex partial seizures. This information may be helpful in understanding the therapeutic mechanisms of vagus nerve stimulation.

METHODS

Patients

Five patients with documented complex partial seizures (four men, one woman; mean age 32 years) had an NCP device implanted at least one month before enrolment in the study (table 1). For each patient we calculated two seizure frequencies (from the patient's seizure diary): a preimplantation frequency for the preceding two months, and a postimplantation frequency after eight to 10 months. Anticonvulsants were not changed following NCP implantation and the patients were followed up to 16 months postimplantation.

Before the imaging, all patients signed a consent form approved by the institutional review board of our institution. On the day of scanning, they were examined by the neurologist (DM). When the stimulator was activated, all patients

Abbreviations: BOLD fMRI, blood oxygenation level dependent magnetic resonance imaging; FOV, field of view; MNI, Montreal Neurological Institute; NCP, NeuroCybernetic prosthesis; TE, time of echo; TR, time of repetition

Table 1 Demographic and thalamic activation data during vagus nerve stimulation

Patient No./age (years)/sex/seizure focus/anticonvulsant	NCP implanted before scanning	Frequency*	Clinical improvement (%)	Thalamic activation during VNS	
				Cluster extent (voxel)	p Value
1/27/M/BTL/topiramate, valproic acid	1 month	10	0%	0	$p < 2.7 \times 10^{-4}$
2/29/F/RFTL/carbamazepine	2 months	0.7	+75%	22	
3/26/M/RTL/carbamazepine	11 months	4	0%	0	
4/40/M/RTL/topiramate, valproic acid	6 months	4	0%	0	$p < 3.6 \times 10^{-6}$
5/40/M/LTL/topiramate, valproic acid	5 months	1	+50%	5	

*Number of seizures/month on average before the implantation.

BTL, bilateral temporal lobes; F, female; LTL, left temporal lobe; M, male; RFTL, right frontal temporal lobe; RTL, right temporal lobe; VNS, vagus nerve stimulation.

Figure 1 Thalamic activation and its time course during vagus nerve stimulation from two patients who showed clinical improvement during the study. (A) Brain map of thalamic activation and its time course from patient No 2. The cerebral activation was observed from thalamus (arrow), insula (1), frontal lobe (2), and temporal lobe (3). The plot shows the time course of activation in the thalamus (upper curve) and the NCP stimulation paradigm (lower curve) during vagus nerve stimulation. (B) Thalamic activation (arrow) and the time course of activation from patient No 5.

reported a tingling sensation over the left cervical region, throat irritation, and change in pitch when speaking.

Experimental design

For fMRI data acquisition, the NCP stimulation parameters were set by an external magnetic wand to a pattern of 30 seconds ON and 66 seconds OFF; all other parameters of the device—that is, signal frequency (30 Hz), pulse width (250 μ s), and output current (1.25 to 1.75 mA)—remained the same. All patients wore a 30 dB noise reduction headset to reduce loud noise (> 100 dB) generated by the magnetic resonance scanner; this also supported the head in a more stable position. Before scanning, patients were re-evaluated to determine whether they could reliably report the ON/OFF status of the stimulator.

Functional MR imaging

Imaging was done with a GE 1.5T Echospeed horizon scanner. Before the functional MRI, a set of high resolution T1 weighted co-planar images was obtained for overlay on the functional datasets. The parameters for the T1 weighted images were TR/TE = 550/min, FOV = 24 cm, 256×256 matrix, 28 slices with 5 mm slice thickness. For the functional images the scanning parameters were TR/TE = 4000/60 ms, FOV = 24 cm, matrix size = 64×64 , and 28 slices continuously at 5 mm slice thickness.

Functional imaging was begun 30 seconds after the patient reported that the stimulator was ON. For each patient, three consecutive scans were acquired with a 30 second pause between each scan. Each scan lasted five minutes and 56 seconds and consisted of a baseline of 66 seconds (stimulator OFF) followed by three cycles of 30 seconds ON and 66 seconds OFF.

At the conclusion of the study, the patient's stimulator was reset to the original parameters.

Data analysis

For each patient the three scans were reconstructed separately and a final brain map was generated from the average of the scans. The functional data were reconstructed off-line on a Sun Ultra60 workstation and processed and analysed using the brain mapping software, SPM99.⁸ For each scan, the reconstructed images were realigned, co-registered to the anatomical T1 images, normalised to Montreal Neurological Institute (MNI) standard brain, and then converted to Talairach brain space. Head motion artefact was accounted for by treating head displacement as a covariate. A final map for each patient was then generated by averaging the data from the three consecutive scans. The anatomical locations corresponding to the activated regions ($p < 0.001$) were identified using available digital mapping software⁹ and confirmed by the neuroradiologist (AJK).

RESULTS

Areas of activation were seen in frontal and occipital lobes (in all five patients), parietal lobe (in four patients), middle temporal lobe and cingulate gyrus (in three patients), and insula and thalamus (in two patients; fig 1). In addition, activation of the cerebellum was observed in four patients. The detailed activation areas are listed in table 2.

Both patients with clinical improvement (Nos 2 and 5) had thalamic activation. Patient No 2, with 75% improvement, had a reduction in the number of seizures from one every one to two months (0.7 seizure/month) to one in six months (0.2 seizure/month). Patient No 5, with a 50% improvement, had a decrease in seizure frequency from one seizure a month before the treatment to one every two to three months (0.4 seizure/month) following implantation of the stimulator. The remaining patients showed no change in seizure frequency (table 1).

Table 2 The activated regions observed in the left and right hemispheres for all five patients

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Cereb	3				50	14	28	72	160	251
IFG		3		28	8	4		4		
MFG						7			6	30
SFG			6	7				3	3	9
MTG		6		15				17		
STG	4			32	7	4	7		6	14
SUPMG						12			7	
SPG		3	15	9				9	9	19
AnG				10		19	3			11
Occipital		8	8	7		4	23	10	8	11
Insula				14			9			
Cingulate		5	13	37		17				
Thalamus			9	11						5

The values are the number of voxels (exceeding an extent threshold of 2 voxels and height threshold of $p < 0.001$) for each region. The voxel has a resampled unit of 2 mm³.

AnG, angular gyrus; cereb, cerebellum; cingulate, cingulate gyrus; IFG, inferior frontal gyrus; insula, insular cortex; MFG, middle frontal gyrus; MTG, middle temporal gyrus; occipital, occipital lobe; SFG, superior frontal gyrus; SPG, superior parietal gyrus; STG, superior temporal gyrus; SUPMG, supramarginal gyrus.

DISCUSSION

In our study, activation was detected in the frontal and occipital lobes in all patients. This finding has been reported in other fMRI studies examining the effects of vagus nerve stimulation.³ Anatomically, ascending pathways² from the vagus nerve in the nucleus of the solitary tract project to the parabrachial nucleus. The parabrachial nucleus projects to several forebrain areas: to the hypothalamus, amygdala, and the infralimbic cortex; to the ventroposterior thalamic complex and insular cortex; and to thalamic intralaminar and middle nuclei and the cerebral cortex. In this study, the activation we observed in frontal lobes, insula, and cingulate gyrus is consistent with the known terminal connections of the parabrachial nucleus and the thalamus. Thus activation measured by fMRI during vagus nerve stimulation appears to correspond to regions involved in the cortical processing of vagal inputs.

Although our sampling numbers are small, the two patients with thalamic activation had a more than 50% seizure reduction after implantation. Of these two patients, the one with greater seizure control had a more robust thalamic activation pattern. Thus the brain maps seemed to show a good correlation of thalamic activation with clinical improvement. This finding is in agreement with the results of a study using PET.³

The thalamocortical system is involved in generating both physiological and pathological rhythms, including sleep spindle waves and spike-wave discharges. Modulation of the thalamocortical networks by vagus nerve stimulation may influence seizure control by disrupting these neural networks.¹⁰ Our study suggests that significant thalamic activation in both spatial extent (cluster size) as well as peak intensity (p value) may have important clinical implications.

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