Perfusion SPECT Changes After Acute and Chronic Vagus Nerve Stimulation in Relation to Prestimulus Condition and Long-Term Clinical Efficacy

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Left-sided vagus nerve stimulation (VNS) is an efficacious treatment for patients with refractory epilepsy. Previous studies have implicated thalamic and mesial temporal involvement in acute stimulation. In this study, acute and chronic effects of VNS in patients with refractory complex partial seizures with or without secondary generalization (CPS ± SG) were evaluated with respect to the prestimulus condition and long-term follow-up. **Methods:** Twenty-three patients (12 females, 11 males; mean age, 32.4 ± 10.6 y; mean CPS ± SG duration, 21.0 ± 11.7 y) were prospectively included. All patients were considered unsuitable candidates for resective surgery because of nonlocalizing findings in the presurgical evaluation. All underwent a split-dose ^{99m}Tc-ethyl cysteinate dimer activation study before and immediately after their initial stimulation (0.25 or 0.5 mA, 30 Hz) on a high-resolution triple-head gamma camera. Ten patients also underwent a SPECT activation study 5.7 ± 1.6 mo after implantation with an additional 0.25-mA stimulus superposed on a therapeutic intensity of 1.5 ± 0.3 mA. Data were analyzed by an automated semiquantitative volume-of-interest analysis after stereotactic anatomic standardization. **Results:** In the acute, initial setting, the left thalamus, right parahippocampal gyrus, and right hippocampus were deactivated by VNS ($P < 0.011$). Acute stimulation in the chronic state resulted in a significant left thalamic activation ($P < 0.001$). When chronic perfusion was compared with the initial pre-VNS baseline, perfusion decreases were found in both thalami (−5.3% on the left and −3.4% on the right, $P \leq 0.04$). Perfusion changes in chronic VNS correlated negatively with the prestimulus perfusion pattern, indicating the tendency toward decreased brain activity on VNS. Initial stimulation changes in the right amygdala in the group of 10 patients with chronic assessment were predictive of therapeutic response ($P = 0.018$); in addition, right chronic hippocampal perfusion changes correlated strongly with the long-term clinical efficacy of VNS ($P = 0.004$). **Conclusion:** Under initial and chronic conditions, acute VNS stimulation produces different perfusion changes that are related to the interictal perfusion pattern before stimulation. The long-term mechanism of clinically effective VNS may rely on mainly hippocampal/amygdala and thalamic inhibition. Acute amygdala and chronic hippocampal perfusion changes are predictive of long-term therapeutic response in specific patient subgroups.

Key Words: epilepsy; SPECT; vagus nerve stimulation; ^{99m}Tc-ethyl cysteinate dimer

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Neurostimulation is a rapidly evolving area for various neurologic disorders. Chronic intermittent left-sided vagus nerve stimulation (VNS) is a cost-effective and safe adjuvant treatment for patients with complex partial seizures with or without secondary generalization (CPS ± SG) who show insufficient response to anticonvulsant drugs and are unsuited for neurosurgical treatment by partial resection, subpial transsection, or corpus callosotomy (*1*,*2*). Clinical trials have shown that the duration, intensity, and frequency of CPS are reduced by VNS (*3*). Approximately 30% of patients experience a reduction of >50% from VNS (*3*,*4*), and approximately 3% become completely seizure free (*5*,*6*). Besides applications in epilepsy, other clinical applications are currently under investigation, among which is the treatment of depression (*7*,*8*). Despite increased clinical use and indications, the underlying pathophysiologic mode of action by which VNS suppresses epileptic seizures is not fully understood. Various approaches to tackle this problem are being followed, including animal models involving drug experiments, surgery, and anatomopathologic techniques (*9*–*12*) as well as human electrophysiologic and functional imaging studies with PET and SPECT (*4*,*10*,*13*–*19*). Implicated areas in the tentative mode of operation, such as the locus coeruleus, medulla, thalamus, limbic system, and cerebellum, have been described.

Specifically, all human functional neuroimaging studies published so far have shown involvement of central brain

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structures, especially the thalamus and the limbic system, but were performed on small and heterogeneous patient populations with limited characterization of the prestimulus condition. PET perfusion studies in the subacute (hours after intermittent stimulation) and chronic (>3 mo) phases showed increased thalamic blood flow during stimulation and improvement in seizure control related to a thalamic flow increase. A decrease in right mesial temporal cortex perfusion, especially in the fusiform gyrus, was also found to be related to a reduction in seizure frequency (*15*). Using SPECT functional perfusion imaging, our group previously reported on inhibited left thalamic activity using ^{99m}Tc-ethyl cysteinate dimer (ECD) in the acute, initial phase of stimulation in 12 patients (*18*). In a recent study with 8 patients, Ring et al. (*19*) found a bilateral thalamic perfusion decrease after chronic intermittent stimulation.

Because of these apparent discrepancies, and to extend and better characterize the findings in a larger series of patients, the current study had 3 aims. First, the correlation between the acute effects of initial stimulation in a larger group of 23 patients and baseline perfusion alterations was investigated by direct comparison with carefully screened age- and sex-matched healthy volunteers. Second, the perfusion effects of an additive stimulation in the chronic situation were investigated in a subgroup of 10 patients who had also undergone a SPECT activation study at VNS onset. Third, long-term regional perfusion changes were investigated by comparing the chronic perfusion state with both the baseline prestimulus SPECT data and the normal reference data. The correlation was investigated between these changes and long-term reduction in the number of CPS as the clinical outcome parameter.

MATERIALS AND METHODS

Patients and Stimulation Parameters

Twenty-three patients (12 females, 11 males) with CPS ± SG were included (group A). The mean patient age (±SD) at the time of the implantation study was 32.4 ± 10.6 y (range, 9.8–47.6 y). The average duration of disease before VNS implantation was 21.0 ± 11.7 y (range, 3.0–44.2 y). All patients underwent left-sided VNS as treatment for medication-resistant CPS ± SG (Table 1) but were considered unsuitable candidates for resective surgery because of nonlocalizing findings in the presurgical evaluation. Five had a history of febrile seizures; 2, of birth trauma; 5, of meningitis or encephalitis; 3, of Lennox-Gastaut syndrome; and 2, of head trauma. The history of 6 patients was unremarkable. The presurgical evaluation consisted of a thorough neurologic and neuropsychological investigation, electroencephalography, ictal videoelectroencephalography, MRI, and ^{18}F-FDG PET. Detailed patient characteristics with a summary of the presurgical evaluations are also given in Table 1. Some differences that were noted between the PET and SPECT evaluations were predominantly caused by the fact that the PET analysis was visual whereas the SPECT analysis was semiquantitative and based on reference data. All patients were receiving chronic treatment with antiepileptic drugs. On average, 3.3 ± 0.6 antiepileptic drugs were being taken before VNS, and that number remained unchanged at maximal follow-up (3.3 ± 0.8, paired *t* test, $P = 0.99$). Antiepileptic drug dosages were not changed during the weeks before the operation and the SPECT study. Patients continued their medication on the day of the study and were seizure free for at least 2 d before the study.

In the chronic stimulation condition, a subgroup of 10 patients was restudied by SPECT imaging (group B, 4 females, 6 males). The mean patient age at the time of the implantation study was 35.1 ± 7.4 y (range, 25.2–47.6 y). The average duration of disease before VNS implantation was 21.0 ± 7.1 y (range, 13.8–33.6 y). None of these parameters was statistically significantly different from the global group. The average time between VNS onset and the chronic SPECT study was 5.7 ± 1.6 mo (range, 3.1–7.9 mo). At the time of the second SPECT study, the therapeutic current intensity had been ramped up 1–2 mA (average, 1.5 ± 0.3 mA). The chronic study was conducted by applying a 0.25-mA stimulus above the (at that time) chronic level, which had been maintained for at least 1 mo.

All patients gave informed consent based on the SPECT study protocol approved by the local ethics committee. Depending on each patient's characteristics and tolerability, a 0.25- or 0.50-mA stimulus was given initially. The surgical implantation procedure of the Neuro-Cybernetic Prosthesis (model 100; Cyberonics, Webster, TX) and stimulation parameters were as described previously (30 s on, 30 Hz, repeated every 10 min) (*18*). The SPECT study was conducted, on average, 4.1 ± 2.6 wk after implantation, depending on seizure frequency and severity, wound healing, and logistics.

During follow-up, the pulse intensity had to be adjusted by increments to improve or stabilize seizure reduction for most patients. The patients estimated the reduction in seizure severity, taking into account postictal alertness, length of seizures, injuries, and severity of the ictal state. Fractional reduction at the time of imaging or at maximal follow-up was calculated for each individual as ([number of CPS during VNS − number of CPS during baseline]/number of CPS during VNS). Because of difficulties in accountability, simple partial seizures were not included.

Activation Paradigm

Figure 1 shows a schematic overview of the study design. For the patients, 4 SPECT scans were acquired: 2 at initial VNS onset (1 off, 2 on) and 2 during chronic follow-up (3 on, 4 on). ECD (Neurolite; DuPont Pharmaceuticals Ltd., Brussels, Belgium) was used to estimate regional cerebral blood flow. A split-dose (2 × 555 MBq) SPECT technique was used to study the states without and with stimulation, as described previously in detail (*18*). From at least half an hour before to the end of SPECT acquisition, a neurologist was on-site. No clinical seizures occurred before or during the SPECT study, nor were any seizures reported during the previous 48 h. Exactly at the end of the 30-s stimulus, the second dose was injected under the same standard circumstances.

Image Acquisition and Processing

All patient and healthy volunteer SPECT images were acquired using a GCA-9300 triple-head system (Toshiba, Tokyo, Japan) with high-resolution fanbeam collimation, uniform Sörenson attenuation correction (effective attenuation coefficient, 0.09 cm^{-1}), and triple-energy window scatter correction (*20*). Reconstructed images were transferred in Interfile format onto a central image

processing system (HERMES; Nuclear Diagnostics, Ltd., Stockholm, Sweden). Intraindividual scans were automatically coregistered by means of 6 rigid parameters (shift and rotate) using a count difference minimization algorithm (MultiModality; Nuclear Diagnostics, Ltd.). The average image of each patient was then anatomically standardized onto an in-house constructed database template positioned in the coordinates of Talairach and Tournoux (*21*), using a linear 9-parameter (shift, scale, rotation) transformation (*22*).

Activity changes were calculated automatically in 39 predefined volumes of interest (VOIs) including the whole-brain gray matter. In addition, the mesial temporal cortex VOI of a previously used whole-brain VOI region map (*22*) was subdivided into the amygdala, hippocampus, and parahippocampal region (including the gyrus parahippocampus). For each individual subject and scan, the VOI activity counts were calculated per voxel and normalized onto the total number of counts in the complete VOI set of the scan. The VOIs encompassing the thalamus, brain stem, and mesial temporal cortex were included in the primary analysis because we hypothesized that in these regions, changes were to be expected from VNS. All other regions were investigated only as a secondary analysis, in order to investigate whether they might be involved in certain aspects of the VNS mechanism. For these regions, in the absence of a priori hypotheses, a correction for multiple comparisons was performed.

Age- and Sex-Matched Healthy Volunteers

The baseline, prestimulus SPECT scans of the patients were compared with those of age- and sex-matched healthy individuals (Fig. 1). Carefully screened healthy volunteers underwent the same scanning procedure with 925 MBq ^{99m}Tc-ECD under standard circumstances. For this study, 30 healthy volunteers (16 females, 14 males; mean age, 32.2 ± 8.2 y) from the GO AHEAD project (*22*) were included after randomized age and sex matching to the epilepsy patients. Because of the slightly higher average age in group B, 20 of these healthy volunteers (7 females, 13 males; mean age, 35.5 ± 7.1 y) were used for optimal age and sex matching when specifically required. To investigate the hypothesis that prestimulus or chronic SPECT findings might be related to the observed acute changes or outcome, we compared all ^{99m}Tc-ECD perfusion scans with those of the healthy volunteers and derived regional *z* scores. The *z* scores were defined as the patient's ^{99m}Tc-ECD uptake expressed in SDs from the normal template (Brass; Nuclear Diagnostics). In Table 1, the results for the baseline SPECT studies of individual patients are also included for the regions under investigation.

Statistics

After validation of normal distribution of the individual values (Kolmogorov–Smirnov test), 1-sample *t* tests were used to investigate VOI uptake ratios before and after stimulation under the null hypothesis H_0 {H_0: ratio condition 2/condition 1 = 1} for the thalamus, brain stem, and mesial temporal cortex. No correction for multiple comparisons was made for these regions. A Bonferroni correction for multiple comparisons was made so that other possible areas could be explored. Seizure occurrence preoperatively and after stimulation was assessed by paired *t* test statistics. All correlations were investigated using the Pearson coefficient. All statistics were calculated with SPSS software (SPSS Inc., Heverlee, Belgium), version 10.0 for Windows (Microsoft, Redmond, WA).

RESULTS

Clinical Parameters and Therapeutic Efficacy

The average follow-up for the whole series of patients was 18.8 ± 13.6 mo (range, 4–48 mo) (Table 2, same patient as in Table 1). Stimulation had been ramped up to therapeutic output current levels in all patients (≥1 mA). In this table, clinical effectiveness is given as the reduction in the occurrence of epileptic seizures after the onset of stimulation for those patients with at least 4 mo of follow-up. In these patients, VNS significantly reduced the number of typical seizures (mean reduction at maximal follow-up, 50.1% ± 31.4%; range, 0%–100%; $P < 0.0001$). Group B was not significantly different from group A (mean reduction, 49% ± 26%; range, 17%–100%; *t* test, $P = 0.93$).

For the total group, the condition of 9 patients (39.1%) improved markedly; that is, seizures were reduced by >50%. For 6 patients, VNS resulted in a moderate reduction in seizures (30%–50%), whereas 8 (34.8%) showed only a minor effect from VNS (reduction < 30%). In group B, 3 (30%) of 10 patients showed marked improvement.

Prestimulus SPECT Findings Versus Age- and Sex-Adjusted Reference Data

The regional *z* scores for the 1-off condition are shown in Table 3. For group A, relatively hyperperfused areas were present in the left parahippocampal gyrus ($P = 0.008$), left thalamus ($P = 0.005$), left amygdala ($P = 0.012$), and both hippocampi ($P = 0.015$ [left] and $P = 0.008$ [right]). For the regions not previously implied in the mechanism of VNS, significant prestimulus hypoperfusion after Bonferroni adjustment was present in the right caudate head (corrected $P = 0.028$) and left prefrontal cortex (corrected $P = 0.036$). In group B, only the left thalamus was relatively hyperperfused ($P = 0.038$).

A significant correlation was found between relative hyperperfusion and the VNS-induced reduction in both thalami and nearly all limbic regions, including both amygdalae and the left parahippocampal region (Table 3). Also, the reductions in anterior cingulate uptake (corrected $P = 0.04$) and right superior temporal gyrus uptake (corrected $P = 0.035$) correlated significantly with the prestimulus *z* score. In Figure 2, this correlation for both thalami is shown (left: $r = -0.50$, $P = 0.015$; right: $r = -0.51$, $P = 0.016$). Similar results were obtained for group B, albeit with lower significance (Table 3). These significant correlations indicate that acute, initial VNS produces a general inhibition of subcortical neuronal activity that is relatively increased in the prestimulus condition.

Acute Perfusion Changes at Stimulus Initialization

Both the full group of 23 patients and the subgroup that underwent a renewed activation study after 6 mo were investigated. The perfusion ratio after and before stimulation (ratio of 2 on to 1 off) in the thalamus, brain stem, and mesial temporal cortex is given in Table 4.

For group A, a highly significant perfusion decrease was observed in the left thalamus (on-to-off ratio, 0.969; $P =$

TABLE 1
Patient Profiles: Demographic Features and Clinical and Paraclinical Findings

Patient no.	Age at VNS (y)	Sex	Handedness (R/L)	Disease duration (y)	History	Preoperative findings					Baseline SPECT vs. reference data
						Clinical	Neuropsychological	Ictal EEG	MRI	^{18}F-FDG PET	
1	26.7	M	R	15	Meningitis	CPS	Normal	R temp occ recr	Normal	Normal	↓ B prefrontal, ↑ L thal
2	47.4	M	R	43	Lennox-Gastaut syndrome	CPS + SG (atonic)	MR	Electro	Discrete B atrophy	Normal	↓ B severe frontal & occ, ↑ R amygdala
3	24.6	F	R	24	Lennox-Gastaut syndrome, corpus callosotomy	CPS ± SG	MR	R frontal spikes	Normal	NA	↓ Cing post, striatum, ↑ L thal, frontal
4	39.5	F	R	27	None	CPS	B temp dys (L more)	L temp recr	B hip & amygdala	↓ L hemi	↓ L frontal temp par & subcortical
5	25.5	F	R	23	Lennox-Gastaut syndrome	CPS ± SG	B memory dys	Electro, B frontal rhythmic	Normal	↓ B frontal temp cerebral & L thal	↑ R occ
6	9.8	M	R	8	Febrile seizures	CPS ± SG	NA	L & R recr	L hip scler, R ant temp atrophy	↓ L post frontal	↓ R > L temp
7	12.4	M	R	5	None	CPS ± SG	NA	R central recr	Normal	↓ L hemi	↓ L sup temp, ↑ R frontal
8	44.5	F	R	23	Meningitis, febrile seizures	CPS ± SG	R temp occ dys	R temp recr	R hip scler	Normal	↓ L prefrontal & R par, ↑ L amygdala
9	36.0	M	R	22	Traumatic birth	CPS	NA	R occ recr	B occ gliosis	NA	↑ L thal, pons
10	44.3	F	R	44	None	CPS/SPS	Auras	L hemi recr	L hip SA	↓ L temp	↑ B thal & L temp
11	40.0	M	R	3	Commotio cerebri, encephalitis	CPS ± SG	NA	B recr	B small hip	↓ global	↓ L > R frontal, ↑ L temp
12	38.4	F	R	30	Forceps birth	CPS ± SG	NA	L recr	Normal	↓ L > R frontal	↑ L frontal, ↓ B occ
13	41.5	F	R	40	Febrile seizures	CPS	Normal	L and R delta waves	Normal	↓ L temp	↓ B frontal
14	37.0	F	R	14	Meningitis	CPS ± SG	B mesial temp dys	L temp recr	B hip sclerosis	↓ L ant temp	↓ L frontal, ↑ L thal B amygdala
15	30.9	F	R	9	Febrile seizures	CPS ± SG	R post temp focus	R temp recr	R mesial temp atrophy	↓ R hemi	Normal
16	16.3	F	R	11	None	CPS ± SG/SPS	B frontal dys	R > L ant recr	Normal	↓ B temp	↓ occ, ↑ L frontal
17	31.4	M	R	11	Head trauma	CPS	Frontal temp par dys	L frontal temp recr	Scar tissue R temp neocortical	↓ R temp	↓ R temp
18	36.5	M	L	30	Encephalitis	CPS	R frontal & midtemp dys	Muscle artifact	R hip scler, cerebral atrophy	↓ L mesial temp & L cerebral	↓ R temp

TABLE 1 (*Continued*)

Patient no.	Age at VNS (y)	Sex	Handedness (R/L)	Disease duration (y)	History	Preoperative findings			MRI	^{18}F-FDG PET	Baseline SPECT vs. reference data
						Clinical	Neuropsychological	Ictal EEG			
19	47.6	M	R	34	Febrile seizures	CPS	B frontal dys	Normal	B frontal schizencephaly, cerebral atrophy	Normal	↓ frontal hypo, ↑ B temp & L amygdala
20	26.8	M	R	14	Premature birth, trauma capitis	CPS	Normal	Indep B temp theta waves	R hip cyst	↓ L temp frontal	↑ B occ, ↓ L frontal
21	30.9	F	R	17	Febrile seizures, ALL with total cranial irradiation	CPS ± SG	R temp par focus, diffuse dys	R post temp par recr	B par atrophy	↓ R post temp	↑ B occ
22	21.4	F	R	15	None	CPS	Memory and verbal dys	R temp recr	Low-grade astr L visual cortex & hip & parahip & amygdala atrophy	↓ L frontal temp	Normal
23	36.0	M	R	20	None	CPS	B mesial temp dys	NA	Normal	↓ L lateral temp	↓ B frontal

EEG = electroencephalography; temp = temporal; occ = occipital; recr = recruitment; B = bilateral; thal = thalamus; MR = mental retardation; elect = electrodecrement; NA = not available; cing = cingulum; post = posterior; dys = dysfunction; hip = hippocampus; hemi = hemisphere; par = parietal; scler = sclerosis; ant = anterior; sup = superior; SPS = simple partial seizures; SA = structure abnormality; hypo = hypoperfusion; indep = independent; ALL = acute lymphocytic leukemia.

0.007), in correspondence with previous findings (*18*). Other regions showing a significantly reduced ^{99m}Tc-ECD uptake were the contralateral parahippocampus (0.973; $P = 0.003$) and hippocampus (0.966; $P = 0.01$). In group B, the deactivation of the left thalamus did just not reach statistical significance (0.971; $P = 0.08$), but a consistent reduction in contralateral parahippocampal uptake was seen (0.969; $P = 0.017$). For both groups, other subcortical and neocortical regions did not show significant changes after Bonferroni adjustment for multiple comparisons.

For group A, no significant correlation was found between significant initial ^{99m}Tc-ECD uptake changes and response at maximal follow-up. In the smaller subgroup that underwent scanning at chronic stimulation, the acute ^{99m}Tc-ECD uptake change in the right amygdala was significantly related to response at maximal follow-up ($r = 0.722$; $P = 0.018$), as can be seen from Figure 3.

Because only one third of the patients responded adequately to VNS, we investigated whether responders and nonresponders differed in terms of thalamic or mesial temporal perfusion. There were no differences (*t* test for independent samples) between responders ($n = 9$) and nonresponders ($n = 14$) regarding thalamic or mesial temporal perfusion decrease after acute stimulation.

Acute Perfusion Changes Caused by Stimulation in the Chronic Condition

In group B, acute perfusion changes caused by an additional 0.25-mA stimulus were investigated at an average chronic intermittent stimulation of 6 mo. The perfusion ratio between the 4-on and 3-on conditions is also given in Table 4. Highly significant ($P < 0.0001$) activation of the left thalamus because of additional acute stimulation was a consistent finding in 9 of 10 patients. On the other hand, a barely significant deactivation was found in the right hippocampus ($P = 0.048$). In the investigated regions under the chronic situation, no significant correlation was found between perfusion changes caused by additional stimulation and response at the time of the second SPECT study or at the maximal follow-up.

Chronic Perfusion Changes and Correlation with Clinical Efficacy

Differences in ^{99m}Tc-ECD uptake between the prestimulus condition and the chronic condition are shown in Table 5. Perfusion was significantly reduced in both thalami (right: 3.4%, $P = 0.04$; left: 5.3%, $P = 0.02$). Although, on average, comparable decreases in perfusion were seen in the right mesial temporal regions, the interindividual variation was larger and the group effect was not significant for the number of patients studied (Fig. 4). Long-term ^{99m}Tc-ECD uptake changes of the right amygdala and, especially, the right hippocampus correlated significantly with outcome at the time of the second SPECT examination (the 3-on condition), but the correlation with outcome at the time of maximal follow-up was the most pronounced (Table 5).

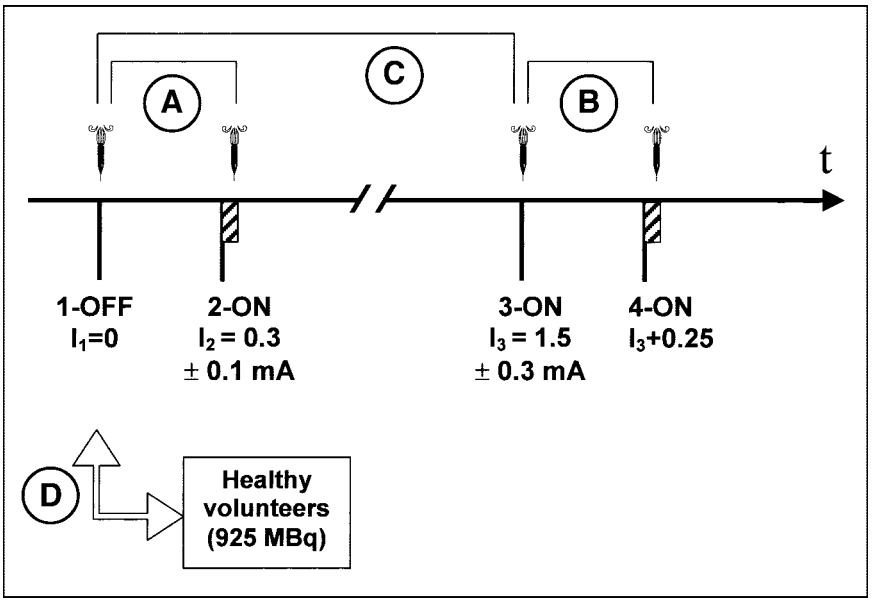

FIGURE 1. Diagram overview of study design. Maximally, 4 SPECT scans were acquired: 2 at initial VNS onset and 2 during chronic follow-up. Effect of acute stimulation was investigated in initial situation (A) and in chronic situation (B). Chronic changes were evaluated between baseline, prestimulus SPECT scan and chronic situation (C). This pre-VNS study was also compared with studies of age- and sex-matched healthy individuals (D). Below timeline, t, stimulus intensity, I, is schematically shown for different conditions.

To investigate whether chronic VNS normalizes the prestimulus hyperperfusion in these areas, we compared the data for group B in the 3-on condition with those for the reference group. These data are included in Table 4. Most regional uptake values normalized, except for the left parahippocampal region, where a relative hyperperfusion was observed.

The left prefrontal cortex VOI, which was significantly hypoperfused when compared with reference values, was normalized in the chronic situation (from $z = -5$ [corrected $P = 0.03$] to $z = -2$ [corrected $P =$ not statistically significant]). These results confirm the hypothesis that chronic VNS normalizes thalamic and (right) mesial temporal hyperperfusion present in the prestimulus (1-off) condition.

A significant correlation was present between the long-term change (3-on vs. 1-off) and the individual *z* score of the prestimulus condition, the latter being compared with a subsample of 20 age- and sex-matched healthy volunteers (Table 5). The most pronounced correlation was found in the amygdala and hippocampus bilaterally. The thalamic chronic changes were not related to the pre-VNS ^{99m}Tc-ECD uptake. In all regions, a negative correlation coefficient was found, confirming the general tendency toward decreased perfusion on VNS preferentially in those areas that are overactive in the prestimulus condition.

There were no differences (*t* test for independent samples) between responders ($n = 3$) and nonresponders ($n = 7$) regarding chronic intraindividual perfusion decrease in the thalamic region. However, there was a highly significant difference for responders regarding chronic perfusion decrease in the right amygdala ($P = 0.001$).

DISCUSSION

The vagal nerve has medullary afferents mainly to the nucleus tractus solitarius (NTS) in the medulla, where each vagus nerve synapses bilaterally on the NTS. Most of the ascending NTS projections are to ipsilateral structures, but some ascending NTS projections less densely innervate contralateral structures. The NTS projects to several structures within both cerebral hemispheres, including the hypothalamic nuclei, thalamic nuclei, central nucleus of the amygdala, and nucleus accumbens.

The body of evidence pointing toward a central role for the thalamus in epilepsy is large and increasing. Thalamic lesions in experimental models suppress seizure activity (*11*); pharmacologic manipulations of the anterior midline thalamus can modulate seizure activity (*23*); and during partial seizures, thalamic perfusion is increased (*24,25*). It is therefore not surprising that experiments are being conducted on deep-brain stimulation of thalamic nuclei, in particular the anterior nucleus (*26*) and centromedian nucleus (*27*), with promising results.

Although, from this study, we were not able to show a direct relationship between thalamic activity changes and seizure reduction, such a relationship did exist for the mesial temporal cortex. This region has been shown to be involved in the mechanism of seizure spread (*28*). Through the projection of the amygdala, the NTS gains access to the amygdala–hippocampus–entorhinal cortex pathways of the limbic system. Through the commissura anterior and anterior regions of the hippocampus, secondary connections to the contralateral hippocampus can thus also exist, as supported by the evoked-potential studies that have shown bilateral effects in the brain from left-sided VNS and by the PET studies that have shown bilateral mesial temporal cortical deactivation from left-sided VNS (*14,15*).

In this study, we investigated, first, whether a pre-VNS thalamic or mesial temporal abnormality was present and correlated with the observation of thalamic hypoperfusion

TABLE 2
VNS Characteristics and Clinical Efficacy at Time of Chronic Study and at Maximum Follow-Up

Patient no.	Baseline stimulus level at second SPECT (mA)	Follow-up (mo)	Seizure frequency (CPS/mo)				
			Before VNS	At second SPECT	% Change	At maximum follow-up	% Change
1	1.50	28	30	20	−33	20	−33
2	—	7	30	—	—	20	−33
3	—	22	180	—	—	60	−67
4	1.75	23	15	4	−73	4	−73
5	—	15	90	—	—	3	−97
6	—	7	50	—	—	50	0
7	—	30	12	—	—	9	−25
8	1.75	26	10	5	−50	0	−100
9	1.50	15	30	25	−17	25	−17
10	—	4	5	—	—	0	−100
11	—	5	8	—	—	6	−25
12	—	44	8	—	—	4	−50
13	—	5	4	—	—	4	0
14	1.50	29	3	1	−67	1	−67
15	—	48	16	—	—	5	−69
16	—	40	200	—	—	0	−100
17	—	4	4	—	—	1	−75
18	1.25	26	4	4	0	2	−50
19	2.00	25	30	15	−50	15	−50
20	1.50	5	4	3	−25	3	−25
21	1.00	5	8	6	−25	6	−25
22	—	12	10	—	—	8	−20
23	1.25	7	30	15	−50	15	−50

caused by VNS and, second, whether the presence of such an abnormality was related to clinical response. We found that the 1-off study showed a significantly increased interictal thalamic and mesial temporal perfusion when compared with an age- and sex-matched reference template. The *z* scores for several mesial temporal subregions and both thalami were directly related to the relative uptake changes after VNS, expressed as ratios before and after stimulation. Because all correlation coefficients were negative, this finding implies that the more active a specific region was, the more did VNS elicit a reduction in that region. However, the exact reason for relative hyperperfusion in these regions in

TABLE 3
VOI Comparison for VNS Epilepsy Patients in Acute Phase (Group A) and for Patients Who Underwent Activation in Chronic Situation (Group B)

Area	VOI size (voxels)	Acute								Chronic, group B (n = 10)			
		Group A (n = 23)				Group B (n = 10)							
		Ratio (on-to-off)	SD	t (df = 22)	P (2-tailed)	Ratio (on-to-off)	SD	t (df = 9)	P (2-tailed)	Ratio (on-to-off)	SD	t (df = 9)	P (2-tailed)
Left parahippocampus* (BA 19, 35, 36)	104	0.978	0.059	−1.79	0.09†	0.992	0.067	−0.39	NS	0.998	0.049	−0.12	NS
Left amygdala (BA 34)	44	1.011	0.133	0.38	NS	1.018	0.121	0.47	NS	1.008	0.073	0.35	NS
Left hippocampus	67	1.002	0.073	0.13	NS	1.012	0.061	0.62	NS	1.031	0.068	1.44	NS
Left thalamus	131	0.969	0.049	−2.98	0.007	0.971	0.046	−1.96	0.08†	1.044	0.030	4.59	0.001
Right parahippocampus* (BA 19, 35, 36)	105	0.973	0.036	−3.57	0.002	0.969	0.033	−2.91	0.017	0.990	0.035	−0.91	NS
Right amygdala (BA 34)	47	1.025	0.112	1.07	NS	1.038	0.133	0.90	NS	1.037	0.068	1.71	NS
Right hippocampus	74	0.966	0.059	−2.78	0.011	0.964	0.057	−1.98	0.08†	0.961	0.050	−2.33	0.048
Right thalamus	120	0.990	0.069	−0.66	NS	1.008	0.031	0.82	NS	1.008	0.041	0.64	NS
Brain stem	137	1.006	0.060	0.47	NS	1.012	0.038	0.91	NS	1.012	0.056	0.65	NS

*Including gyrus parahippocampus and fusiform gyrus.
†Two-tailed significance level: $P < 0.05$; values up to $P = 0.10$ are displayed; NS = $P > 0.10$ (not statistically significant).
df = degrees of freedom; BA = Brodmann's area.

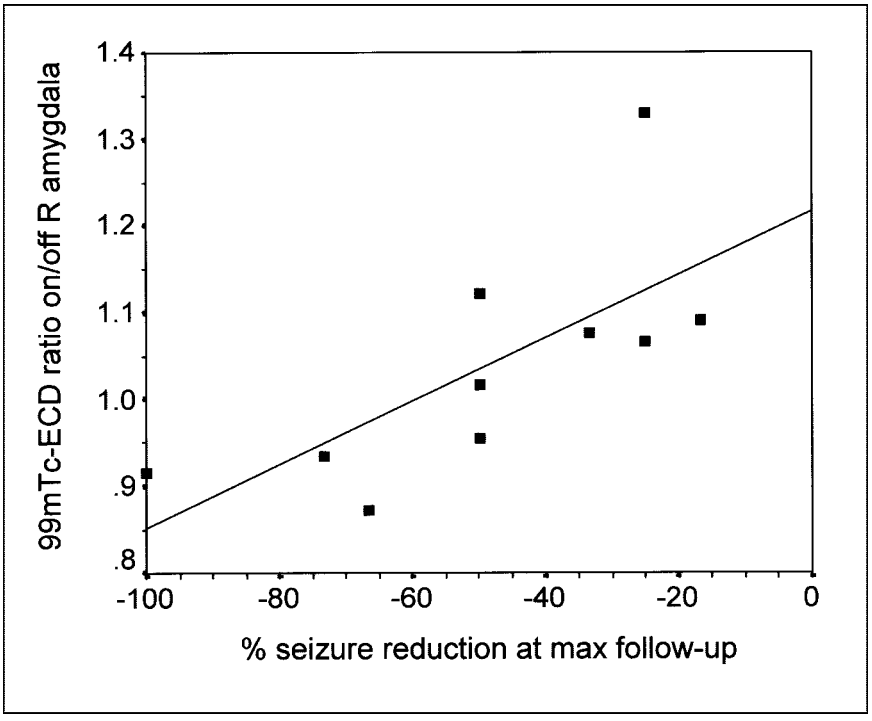

FIGURE 2. Relationship between ^{99m}Tc-ECD uptake in right amygdala at initial, acute VNS stimulation and long-term seizure reduction in group of 10 patients for whom long-term perfusion measurements were assessed.

the prestimulus condition is unclear for several reasons. First, postictal hyperperfusion is unlikely to be responsible for this observed phenomenon because no clinical signs of seizures were present before or after the study. Even in the absence of strict electroencephalography monitoring before and during the study, systematic subclinical epileptiform brain activity would be statistically unlikely to affect the whole group of patients studied. Second, interictal thalamic hypoperfusion has been studied mainly in the context of temporal lobe epilepsy. A recent study by Yune et al. (*29*) found that only 26% of subjects showed thalamic hypoperfusion. Juhasz et al. (*30*), in a high-resolution PET study of temporal lobe epilepsy, showed that in the interictal state, although left hypometabolism was present in the dorsomedial thalamic nucleus, bilateral hypermetabolism was present in the lateral part of the thalamus. Moreover, the patients that we studied were unsuited for epilepsy surgery; only a few showed (inconsistent) arguments for pure tem-

TABLE 4
Regional Prestimulus, Interictal *z* Score Versus Healthy Volunteers and Pearson Correlation with Acute Perfusion Changes Caused by VNS

	Acute										Chronic, group B (n = 10)		
	Group A (n = 23)					Group B (n = 10)							
Area	z	t (22 df)	P_z	r	P_r	z	t (9 df)	P_z	r	P_r	z	t (9 df)	P_z
Left parahippocampus (BA 19, 35, 36)	0.8	2.9	0.008	−0.51	0.01	0.5	1.2	NS	−0.56	NS	0.8	2.9	0.016
Left amygdala (BA 34)	1.1	2.7	0.01	−0.71	0.001	1.3	1.3	NS	−0.46	NS	1.5	2.2	0.06*
Left hippocampus	0.6	2.7	0.02	−0.51	0.013	0.5	0.9	NS	−0.26	NS	0.5	1.6	NS
Left thalamus	0.9	3.1	0.005	−0.50	0.015	1.0	2.5	0.038	−0.82	0.006	0.1	0.2	NS
Right parahippocampus (BA 19, 35, 36)	0.1	0.7	NS	−0.26	NS	0.6	2.2	0.06*	−0.64	0.06*	0	−0.2	NS
Right amygdala (BA 34)	0.3	1.3	NS	−0.49	0.02	0.0	0.0	NS	−0.73	0.02	−0.3	−0.5	NS
Right hippocampus	0.6	2.9	0.008	−0.24	NS	0.8	2.2	0.06*	−0.53	NS	0.4	1.1	NS
Right thalamus	0.5	1.4	NS	−0.51	0.01	0.6	1.5	NS	−0.72	0.02	0.2	0.5	NS
Brain stem	0.2	0.5	NS	−0.18	NS	0.8	1.5	NS	−0.62	0.07*	0.7	1.5	NS

*Two-tailed significance level: $P < 0.05$; values up to $P = 0.10$ are displayed; NS = $P > 0.10$ (not statistically significant).
df = degrees of freedom; $P_z = P$ for Z score; $P_r = P$ for Pearson correlation coefficient; BA = Brodmann's area.

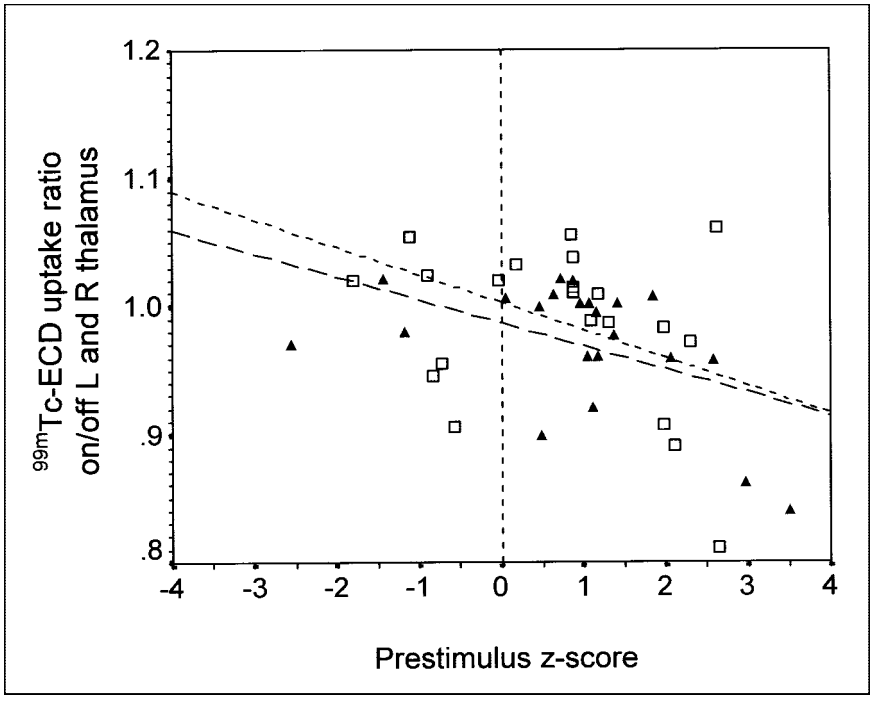

FIGURE 3. ^{99m}Tc-ECD uptake difference caused by acute, initial VNS in thalamus (right [□] and left [▲]) in relation to prestimulus *z* score and to age- and sex-matched template of 20 healthy volunteers.

poral lobe epilepsy in the presurgical work-up, and little is known about the thalamic or mesial temporal correlates of patients with non–temporal lobe epilepsy. Third, to our knowledge, only very few studies have investigated interictal perfusion or metabolism in epilepsy compared with a carefully screened age- and sex-matched reference template.

For the 1-off/2-on activation study, these results for the thalamus confirm previously published data that conflicted with excitation found in small series of comparable patients but in a subacute and chronic state (*14,15,17*). The current findings reconcile, in part, these discrepant results and also imply that adaptation occurs after a (possibly short) period of intermittent VNS. The contradictory activation of the left thalamus in the chronic state is superimposed on a reduction in activity, in comparison with the pre-VNS state, that partly normalizes the hyperactivity present before VNS. It is known that cerebral processing of acute and chronic stimuli can be very different (*31,32*) and that this difference may be

TABLE 5
Chronic Changes Caused by VNS in 10 Patients and Correlation with Follow-Up and with Initial Prestimulus Interictal *z* Score

	Group B (n = 10) activity ratio, chronic vs. pre-VNS				Correlations					
					Clinical efficacy, second SPECT		Clinical efficacy, maximum follow-up		Prestimulus *z* score	
Area	Ratio, 3/1	SD	*t* (9 df)	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Left parahippocampus (BA 19, 35, 36)	1.002	0.086	0.06	NS	−0.24	NS	−0.01	NS	−0.30	NS
Left amygdala (BA 34)	1.016	0.142	0.35	NS	0.11	NS	0.25	NS	−0.86	0.006
Left hippocampus	0.990	0.110	−0.28	NS	0.41	NS	0.28	NS	−0.84	0.009
Left thalamus	0.947	0.062	−2.69	0.025	0.28	NS	0.01	NS	−0.23	NS
Right parahippocampus (BA 19, 35, 36)	0.974	0.066	−1.23	NS	0.38	NS	0.12	NS	−0.81	0.009
Right amygdala (BA 34)	0.968	0.159	−0.60	NS	0.66	0.05	0.70	0.04	−0.70	0.05
Right hippocampus	0.945	0.096	−1.71	NS	0.58	0.09*	0.85	0.004	−0.76	0.03
Right thalamus	0.966	0.046	−2.35	0.044	0.11	NS	0.53	NS	0.29	NS
Brain stem	0.994	0.065	−0.29	NS	0.08	NS	0.26	NS	−0.41	NS

*Two-tailed significance level: $P < 0.05$; values up to $P = 0.10$ are displayed; NS = $P > 0.10$ (not statistically significant).
df = degrees of freedom; BA = Brodmann's area.

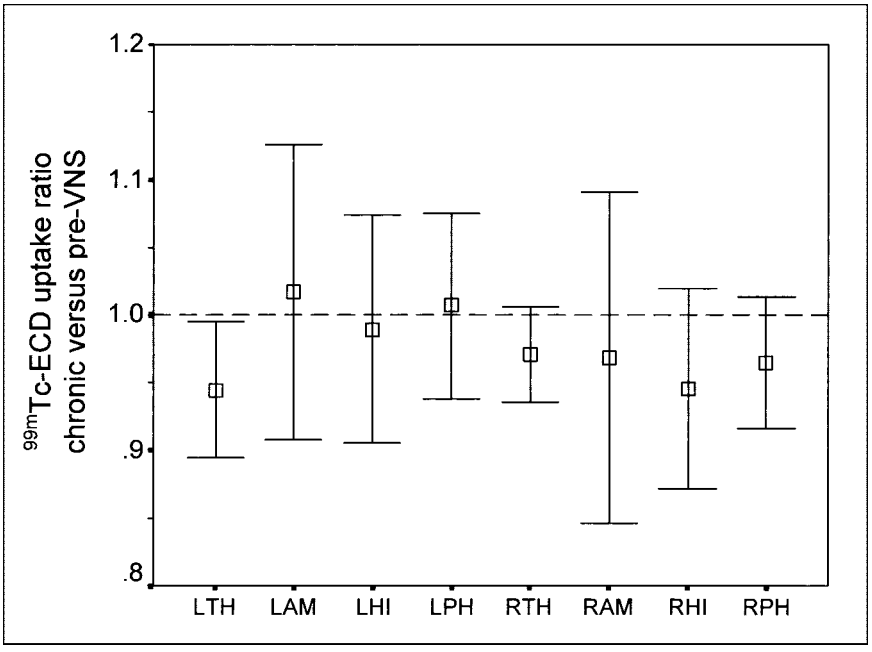

FIGURE 4. Chronic ^{99m}Tc-ECD uptake changes in thalamus and mesial temporal cortex (95% confidence interval for mean). Significant decreases are indicated with asterisk. LAM = left amygdala; LHI = left hippocampus; LPH = left gyrus parahippocampus (+ fusiform gyrus); LTH = left thalamus; RAM = right amygdala; RHI = right hippocampus; RPH = right gyrus parahippocampus (+ fusiform gyrus); RTH = right thalamus.

attributed to local adaptation effects that alter synaptic neurotransmission.

Other limbic regions that showed marked perfusion decreases on acute VNS included the contralateral parahippocampus. In contrast to our previously published results using a similar VOI technique but with a less detailed region map for the mesial temporal cortex, significant changes and correlations were found in mesial temporal substructures. The nucleus of the tractus solitarius projects to several nuclei of the thalamus and hippocampus (*9*,*14*), and both the hippocampus and the amygdala have been implied as possible electrostimulation targets for epilepsy. The reason that effects were predominantly contralateral in our population and that left hippocampal or parahippocampal effects were not observable is unclear. The patients formed quite a heterogeneous population (Table 1), as was expected because they were, by definition, not suitable candidates for surgical resection (having no accessible or demonstrable defect or having the epileptogenic region in functional or eloquent areas). A tendency toward left-sided functional abnormality was seen: 12 of 23 PET studies showed left-sided hypometabolism, whereas only 4 showed right-sided abnormalities and 7 showed normal findings.

In this study, we found that chronic intermittent VNS increased left prefrontal blood flow, which was impaired in the prestimulus condition. It has been suggested that noradrenergic or serotonergic deficits, as well as other abnormalities, may contribute to a predisposition to some types of epilepsy and depression, although more evidence supports the concept that some genetic mammalian models of human epilepsy exhibit analogous manifestations of depression (*33*). The effect of prefrontal increased perfusion could tentatively be related to the clinical results that have been obtained with VNS in depression, currently under investigation in phase III trials (*7*,*8*). Nevertheless, these preliminary findings need to be further elaborated and correlated with clinical depression ratings.

The ability to test the likelihood of reducing seizures by VNS could obviate long periods of trial and error in the adjustment of VNS settings. In the group that was also studied by SPECT after 6 mo, a highly significant correlation was found between the acute perfusion changes in the right amygdala and long-term clinical follow-up. This finding implies that SPECT imaging at the time of initial VNS may be predictive of response at least in a subgroup of patients. The long-term perfusion changes in the right amygdala and right hippocampus correlated significantly with long-term seizure reduction. Both results indicate an important pathophysiologic role for these regions in the mechanism of seizure suppression by VNS, compatible with the known seizure spread pathways (*28*). Recently, a study by Olejniczak et al. (*34*) showed that VNS was able to suppress interictal sharp-wave activity in the human hippocampus, whereas a study involving cats found that epileptogenesis by amygdala electric kindling was counteracted by VNS (*35*).

Some methodologic issues need further discussion. The changes observed in this study were on the order of 3%–6%. For these to be of clinical value for possible predictions in individual patients, it is important that the test–retest reproducibility of the applied split-dose activation paradigm be known. Although we are not aware of any test–retest or sham stimulation activation studies acquired for healthy volunteers or patients under the same circumstances as in this study, an upper limit on reproducibility may be set from the intrasubject test–retest values for ^{99m}Tc-ECD SPECT under approximately the same circumstances as in this study, as previously described (*22*). In this study, for 925-

MBq injections and the same VOI analysis procedure, intrasubject reproducibility in 12 healthy volunteers with an average scanning interval of 2 wk ranged from 1.4% to 6.2% (average, 3% ± 1.4%), was inversely related to VOI size, and was <3% for VOI sizes > 200 voxels. For the thalamus and mesial temporal cortex, this intrasubject medium-term reproducibility was 5%–6%. Although we used a smaller injection dose per scan, the variability may be comparable because the split paradigm has no variability caused by physiologic differences that may be present when scanning after a 14-d interval. One can assume that in the absence of strong mental activation, the only significant differences between baseline and stimulation conditions in the single-day split-dose paradigm stem from the stimulation itself. In conclusion, the changes from pooled group effects observed here were of the same magnitude as the expected test–retest variability of the split-dose technique. In the absence of more specific test–retest values for the split-dose single-day activation paradigm, prospective patient studies of small perfusion changes in the mesial temporal cortex are needed to show whether the sensitivity of the SPECT split-dose paradigm is sufficient to discriminate responders from nonresponders.

SPECT activation studies are suboptimal in terms of the number of subjects and the constraints on multiple repetitions of tasks at short intervals because of ^{99m}Tc-ECD activity accumulation and are thus characterized by few degrees of freedom. Because correlation with clinical *z* score data was an aim, only an automated, anatomically standardized method was followed. No second-order statistical parametric mapping results were tried, because when the degrees of freedom are relatively few, results tend to be overly conservative and possibly false-negative (*36*). Nevertheless, functional SPECT imaging may allow imaging of larger groups of patients and therefore has the potential to define subgroups of patients that show a favorable clinical response to VNS.

CONCLUSION

VNS effectively decreased seizure frequency in patients with intractable epilepsy. Measurements of regional cerebral blood flow at the onset of VNS indicated that left thalamic perfusion and contralateral parahippocampal and posterior neocortical perfusion were decreased. However, in the chronic situation, a (paradoxical?) increase in left thalamic flow was present and was in agreement with existing literature. Chronic intermittent VNS, in comparison with the prestimulus condition, resulted in a marked perfusion decrease in the contralateral hippocampus and amygdala that correlated with clinical efficacy. The thalamus in these patients was generally overactive preoperatively, and VNS did reset this activity after chronic stimulation.

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Erratum

The authors of the article titled "Comparison of (+)-^{11}C-McN5652 and ^{11}C-DASB as Serotonin Transporter Radioligands Under Various Experimental Conditions" (*J Nucl Med.* 2002;43:678–692) accidentally omitted 2 of the authors from the Acknowledgments section. The names of those authors are Jie Yuan, MD, and George Hatzidimitriou, MS. The authors regret the error.