Long-term Sustained Cognitive Benefits of Vagus Nerve Stimulation in Refractory Depression

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Background: Treatment-resistant depression (TRD) is a serious chronic condition disabling patients functionally and cognitively. Chronic vagus nerve stimulation (VNS) is recognized for the management of TRD, but few studies have examined its long-term effects on cognitive dysfunction in unipolar and bipolar resistant depression.

Objective: The purpose of this study was to assess the course of cognitive functions and clinical symptoms in a cohort of patients treated with VNS for TRD.

Methods: In 14 TRD patients with VNS, standardized clinical and neuropsychological measures covering memory, attention/executive functions, and psychomotor speed were analyzed prestimulation and up to 2 years poststimulation.

Results: Vagus nerve stimulation patients significantly improved on cognitive and clinical measures. Learning and memory improved rapidly after 1 month of stimulation, and other cognitive functions improved gradually over time. Cognitive improvements were sustained up to 2 years of treatment. At 1 month, improvement in Montgomery-Åsberg Depression Rating Scale scores was not correlated with changes in any of the cognitive scores, whereas at 12 months, the change in Montgomery-Åsberg Depression Rating Scale score was significantly correlated with several measures (Stroop interference, verbal fluency, and Rey-Osterrieth Complex Figure delayed recall).

Conclusions: In recent years, a growing interest in cognitive dysfunction in depression has emerged. Our results suggest that chronic VNS produces sustained clinical and cognitive improvements in TRD patients, with some mental functions improving as soon as 1 month after the initiation of the VNS therapy. Vagus nerve stimulation seems a very promising adjunctive therapy for TRD patients with cognitive impairment.

Key Words: memory, mood disorders, neuromodulation, neuropsychology, VNS

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In addition to classic clinical symptoms, it is now widely recognized that major depressive disorder (MDD) is also characterized by significant cognitive impairment.[1–4] These impairments are observed in different cognitive domains, including memory,[5] attention/executive functioning,[6,7] and general psychomotor speed.[8,9] Several studies suggest that cognitive disorders during depressive states of unipolar and bipolar disorders are relatively similar, except that bipolar patients appear to have more executive deficits than unipolar patients.[10–14] Conradi and colleagues[15] showed that up to 94% of patients report subjective cognitive problems during the acute phase of their depressive episode.

Although some of the cognitive deficits improve after successful treatment,[16,17] there is a growing body of evidence that cognitive dysfunction can persist long after the acute phase of the illness and even after the withdrawal of medication.[6,17–22] Conradi and colleagues[15] have demonstrated that up to 44% of patients still had cognitive complaints after 3 years, despite full or partial symptom remission during the treatment. Cognitive dysfunction accompanying unipolar and bipolar depression is now recognized as being a major contributor to the disruption in occupational functioning of patients and to reduced productivity at work.[23–25]

Few antidepressant treatments are known to have a positive impact on cognitive impairments. Some selective serotonin reuptake inhibitors such as paroxetine and sertraline have been shown to have cognitive benefits, but these are often limited to an increase in alertness, and many antidepressant medications have no effect or even a negative impact on cognition.[26] Electroconvulsive therapy (ECT), a treatment also recommended in treatment-resistant depression (TRD), is commonly known for causing negative cognitive adverse effects, mainly retrograde and anterograde amnesia, although some studies show improvements in other domains such as processing speed and attention.[27–31]

Vagus nerve stimulation (VNS) is a recognized treatment for TRD[32–35] with expected response rates of 15% to 42%.[32,36–39] The mechanisms through which VNS induces antidepressant effects are still not fully understood. Ascending vagal signals affect several neuromodulatory systems as well as structures involved in autonomic regulation, emotion, and cognition including the hypothalamus, amygdala, hippocampus, anterior cingulate, insula, and the frontal cortex.[40–44]

Potential cognitive effects of VNS therapy are still also unclear,[41] but there is evidence that chronic VNS may produce sustained improvements in various cognitive symptoms observed in TRD.[45–48] In animal studies, VNS has been shown to improve memory storage, consolidation of inhibitory-avoidance memory, and spatial and fear memory.[49–51] In epileptic patients, acute stimulation has been shown to improve recognition and consolidation in verbal memory, but chronic effects appear to be inconsistent.[48,52–56]

Unfortunately, most of the studies on the cognitive effects of VNS have been conducted on epileptic patients. It might be difficult to generalize results of VNS studies conducted in epilepsy to TRD patients, as the core pathology of their illnesses is different, and their potential for the recovery of cognitive functions is differing. Very few studies have addressed the cognitive benefits of VNS in TRD patients.[45] Sackeim and colleagues[45] observed that TRD patients treated with VNS demonstrated increases in psychomotor speed, verbal fluency, and executive functioning, but no improvement in memory after 10 weeks. They also found a correlation between cognition and mood improvement.

The goal of the present study was to examine the long-term cognitive effects of VNS in TRD patients and its relationship to changes in mood.

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MATERIALS AND METHODS

Participants

The study was conducted at the University of Montreal Health Centre. The University of Montreal Health Centre Research Ethics Board approved the protocol, and written informed consent was obtained from the patients. Fourteen patients (9 women; mean age at implantation, 50 ± 6.2 years) with TRD were selected. Patients were recruited between 2007 and 2015 from the outpatient psychiatric clinic of the hospital or were referred by psychiatrists in the community. All subjects received a diagnosis of MDD (n = 8) or bipolar disorder (n = 6). During the selection process, all patients were screened by a trained mental health nurse using the Mini International Neuropsychiatric Interview version 5.0, and the diagnosis was confirmed by a team of psychiatrists. To be included in the study, patients had to meet the selection criterion of treatment resistance, defined as a partial response or no response to at least 4 antidepressant medications, either as a monotherapy or in combination, at minimum adequate dose and duration. All patients had received at least 6 weeks of cognitive behavioral therapy psychotherapy. Exclusion criteria included psychiatric conditions, such as a borderline personality disorder, schizophrenia or history of psychosis, dementia, or alcohol or drug abuse, and medical contraindication, such as clinically relevant cardiovascular disease, active cancer, and pregnancy, as well as spontaneous remission of the major depressive episode before the surgery. One patient was removed from the study sample because his very quick response to the VNS treatment (within days of the surgery) was highly uncharacteristic of VNS patients, who usually experience a response over weeks or months of VNS therapy.

Because of the severity of the patients' depression and in accordance with Health Canada approval of VNS as an add-on treatment, concomitant medication was allowed during the study. However, medications and dosages were kept unchanged from at least 4 weeks before baseline assessment to at least 12 months after the onset of stimulation.

Treatment Parameters

Vagus nerve stimulation patients were implanted with a Cyberonics Model 102 pulse generator (Cyberonics, Inc, Houston, Tex [now LivaNova PLC, London, United Kingdom]) consisting of a subcutaneous generator delivering chronic intermittent stimulation to the left vagus nerve. Vagus nerve stimulation therapy was delivered according to recommendations by Groves and Brown[56] and Heck et al.[57] Vagus nerve stimulation activation was initiated at a 0.25 mA current and gradually increased in increments of 0.25 mA, depending on tolerability (throat discomfort or coughing). Intensity was set to the highest comfortable setting at which a clinical response was observed. At 12 months, the output currents of the VNS ranged from 0.75 to 1.75 mA (mean, 1.42 mA; median, 1.5 mA). Most patients were stimulated at a 30-Hz frequency and at a 250-microsecond pulse width. The frequency of stimulation was generally 30 seconds on and 5 minutes off, except for 1 patient who was stimulated 30 seconds on every 3 minutes because higher VNS work cycle was better tolerated than high current output.

Assessment

Data for mood and cognition were collected before implantation (baseline) and then at 1, 3, 6, 12, and 24 months after the onset of stimulation. At baseline, at an average of 4 months before implantation of the device, a short neuropsychological battery was performed, and patients underwent an investigation of biological factors. Baseline mood was assessed 2 weeks before implantation. At each assessment, patients' cognitive functions were evaluated by a trained neuropsychologist. Cognitive dysfunctions in refractory depression are reported to be stable over time, unless the patient experiences a spontaneous remission or deterioration of his depressive symptoms.[58,59] There was no spontaneous remission or severe deterioration in our patients' symptoms while on the VNS waiting list; therefore, we did not expect significant changes in the cognitive profile of our patients immediately before VNS implantation.

The cognitive battery included measures of verbal and visuospatial memory, attention/executive functions, and psychomotor speed. Verbal learning was evaluated by the total immediate recall score of the Rey Auditory Verbal Learning Test (RAVLT),[60] composed of the total words recalled in the 5 learning trials. Verbal memory was assessed with the delayed free recall scores (30-minute delay) of the same verbal memory task. The RAVLT recognition scores were not used here because they were already very high at baseline (mean, 13.3 words out of 15) and are known to show poor reliability in repeated measures.[61] Visuospatial memory was evaluated using the Rey-Osterrieth Complex Figure (ROCF) test[62] using the delayed free recall score (30-minute delay). Attention and executive functions were evaluated with verbal phonemic fluency[63] and the interference condition of the Stroop Color and Word Test.[64] Information-processing speed was assessed by the color naming performance of the Stroop test and the total score of the Symbol Digit Modalities Test (SDMT).[65]

To minimize practice effects, alternate forms of the cognitive tasks were used at each test session except for the Stroop test, as it is a proven method for reducing practice gains.[61–66]

The Montgomery-Åsberg Depression Rating Scale (MADRS) was used by a trained psychiatrist to measure depressive symptoms.[67]

Statistical Analyses

Analyses were performed using IBM SPSS Statistics version 21 (IBM Corporation, Armonk, NY). Data were analyzed using descriptive statistics and Student *t* tests to compare unipolar and bipolar patients on different demographic and clinical characteristics. Longitudinal effects were examined for all mood and cognitive measures between baseline (preimplantation), 1-month, 3-month, 12-month, and 24-month evaluations. For mood scores, effects of VNS stimulation at different time points were evaluated with repeated measures analyses of variance (ANOVAs). For cognitive scores, Pearson correlations revealed that several cognitive variables were correlated at 1 or more time points ($P > 0.05$). Based on the results, cognitive tasks were regrouped in 3 functional categories: memory (RAVLT verbal learning, RAVLT verbal memory, and visual memory), information-processing speed (SDMT and Stroop color), and attention-executive function (phonemic fluency and Stroop interference). Repeated measures multivariate ANOVAs (MANOVAs) were performed on each of the categories of cognitive measures to evaluate the effect of time. Planned repeated contrasts were used to make comparisons between the different evaluation times. To explore whether pre- to post-VNS treatment changes were clinically relevant, the reliable change index (RCI) was also calculated for clinical and cognitive scores (see Jacobson and Truax[68] and Jacobson et al[69] for methodology). A significance level of 0.05 was chosen for all statistical tests.

RESULTS

Sample Characteristics

Demographic and clinical characteristics of patients are summarized in Table 1. Mean age at baseline (preimplantation) was

TABLE 1. Demographic and Clinical Characteristics of VNS Patients

Patients	Sex	Age, y	Education, y	Diagnosis	Age at 1st Episode, y	Age at Present Depressive Episode, y	Length of Current Episode, mo	No. Episodes	MADRS Baseline	MADRS % Change at 1 mo	MADRS % Change at 12 mo	MADRS % Change at 24 mo	No. Mood Disorder Treatment Trials
1	F	53	13	MDD	17	49	60	5	23	57	52	83	4
2	M	50	16	MDD	17	37	156	2	29	21	24	52	6
3	F	49	18	MDD	41	46	48	3	29	35	38	72	6
4	F	41	13	MDD	36	36	55	1	31	23	23	45	6
5	M	54	11	MDD	16	53	13	4	29	38	45	90	4
6	F	49	14	MDD	27	43	72	4	23	35	61	48	6
7	M	57	22	MDD	35	56	18	3	21	24	67	67	5
8	M	54	22	MDD	47	57	36	2	25	52	72	84	4
9	F	35	14	BD II	20	29	81	3	23	83	83	83	4
10	F	53	17	BD II	17	51	26	4	34	53	88	88	6
11	M	56	11	BD II	16	51	66	4	27	−11	56	22	4
12	F	51	16	BD II	16	48	36	3	21	86	86	90	4
13	F	54	16	BD I	26	52	24	4	41	56	90	56	6
14	F	44	13	BD I	30	41	42	4	24	92	92	83	4
Mean (SD)		50 (6.2)	15.4 (3.5)		25.8 (10.5)	46.4 (8.1)	52.4 (36.3)	3.3 (1.1)	27.1 (5.6)	45.8 (28.5)	62.5 (24.0)	68.8 (21.0)	4.9 (1.0)

BD indicates bipolar disorder; F, female; M, male.

50 years (35–57 years), mean age of depression onset was 25 years (16–47 years), duration of the current episode was 52 months (13–156 months), and education level averaged 16 years (11–22 years). Baseline MADRS score averaged 26, a moderate level of depression. The proportion of patients diagnosed with a bipolar disorder was 43% (n = 6). Unipolar and bipolar patients were similar in terms of age (unipolar = 50.9 years, bipolar 48.8 years) ($P = 0.6$), number of depressive episodes (unipolar = 3, bipolar = 3.7) ($P = 0.3$), age at the current episode (unipolar = 47.1, bipolar = 45.3) ($P = 0.13$), length of the current depressive episode (in months) (unipolar = 57.3, bipolar 45.8) ($P = 0.58$), and severity of the current depressive episode (MADRS score: unipolar = 26.3, bipolar = 28.3) ($P = 0.51$). For their current episode, unipolar and bipolar patients were also similar in terms of use of selective serotonin reuptake inhibitors ($P = 0.76$), serotonin-norepinephrine reuptake inhibitors ($P = 0.57$), tricyclic antidepressants ($P = 0.89$), and atypical antipsychotics ($P = 0.67$). Two patients had received previous ECT.

Mood Variables

Percent change in MADRS score averaged 46% (–11%–92%) after 1 month, 62% (26%–96%) at 3 months, 63% (23%–93%) at 12 months, and 70% (22%–90%) at 24 months. Ten patients showed a clinically significant response (>50% improvement in MADRS) at 3, 12, and 24 months. Remission rate (MADRS score ≤10) was 29% (4/14) at 1 month, 50% (7/14) at 3 months, 57% (8/14) at 12 months, and 64% (9/14) at 24 months. Analyses on the entire sample showed a significant improvement in MADRS score over time ($F_{4,48} = 30.4$, $P < 0.001$, $\eta^2 = 0.72$), with planned contrasts showing a significant improvement at 1 month ($P < 0.001$) and no significant change from 1 month to the following evaluations. There was no difference between bipolar and unipolar patients in terms of depression severity at baseline ($P = 0.322$, $t_{13} = 1.03$). Also, patients with bipolar disorder showed a similar antidepressant response to other patients at all time points except at 12 months, where unipolar patients averaged 48% change in MADRS score, whereas bipolar patients averaged 82% change.

Cognitive Measures

Results on cognitive measures are shown in Table 2. Baseline scores varied between mild deficit and normal range but on average were within 1 SD of normative data for their age. No significant differences were found between unipolar and bipolar patients on baseline cognitive scores. These normal results may be linked to the fact that our clinical sample had an average of 15 years of education and included several highly skilled professionals.

Memory

Results of the MANOVA for memory tests show a significant difference among the testing sessions across the 4 memory measures ($\Lambda = 0.218$, $F_{16,125.895} = 5.081$, $P < 0.001$, $\eta^2_{partial} = 0.78$). Univariate tests revealed that verbal learning scores showed a significant effect of evaluation time ($F_{4,44} = 10.933$, $P < 0.001$, $\eta^2_{partial} = 0.50$) with a significant improvement between the baseline and the 1-month evaluation ($P < 0.001$, $t_{11} = 25.9$) and maintenance of the response until 24 months of stimulation. For verbal memory (RAVLT delayed recall), there was a significant effect of evaluation time ($F_{4,44} = 5.892$, $P = 0.001$, $\eta^2_{partial} = 0.35$), with a significant improvement between the baseline and the 1-month evaluation ($P = 0.007$, $t_{11} = 10.735$) and a maintenance of the response until 24 months. For visuospatial memory (ROCF delayed memory recall), the univariate analysis showed a significant effect of evaluation time ($F_{4,44} = 17.737$, $P < 0.001$, $\eta^2_{partial} = 0.62$), and planned contrasts revealed a significant difference between the

TABLE 2. MANOVA and ANOVA Results of VNS Patients on Cognitive Measures

	Baseline			1-mo Evaluation			3-mo Evaluation			12-mo Evaluation			24-mo Evaluation					
Measures	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**	**RCI**	***P***	**Partial η^2**
Memory																		
RAVLT learning (total 5 trials)	45.4	10.2	29–64	57	8	48–73	57.2	7.9	45–70	58.5	5.6	51–71	58.3	8.4	42–71	1.78	<0.001	0.5
RAVLT delayed recall	10.5	3.3	6–15	12.7	1.7	9–15	12.4	2.5	9–15	13	2.2	8–15	12.8	2	10–15	0.80	0.001	0.35
ROCF delayed recall	18.7	5.8	9–29	25.5	4	19.5–32	28.4	5.1	15–35	22.9	3.7	15.5–33	29.3	5	16–35	1.38	<0.001	0.62
Information-processing speed																	<0.001	0.33
SDMT score	46	10.7	18–60	47.6	8.1	33–60	48.4	11.5	30–61	52.4	7.9	38–65	52.3	8.9	34–64	0.69	0.009	0.22
Stroop color	76.3	18.1	28–96	77.4	18.7	44–107	81.6	17.2	54–106	87.7	14.9	57–112	88.6	12.8	61–110	0.95	0.002	0.28
Attention/executive functions																	<0.001	0.43
Phonemic fluency (total 3 letters)	36.6	9.6	18–50	39.6	8.7	20–51	43.9	12.1	22–59	43.9	8.9	22–55	44.07	11.2	24–64	0.66	0.011	0.22
Stroop interference	39.7	12.3	8–60	40.4	11.5	14–60	43.6	10.7	36–65	47.6	8.4	40–72	50.2	8.6	31–64	1.01	<0.001	0.36

baseline and 1-month evaluation ($P = 0.001$, $t_{11} = 18.184$), as well as a significant difference between the 3-month and the 12-month evaluation ($P = 0.014$, $t_{11} = 8.539$), and between the 12- and 24-month evaluation ($P < 0.001$, $t_{11} = 41.605$).

Information-Processing Speed

The MANOVA on measures of information-processing speed showed a significant effect of evaluation time ($\Lambda = 0.672$, $F_{8,102} = 2.808$, $P = 0.007$, $\eta^2 = 0.33$). Univariate results revealed that the Stroop color naming score showed a significant effect of evaluation time ($F_{4,52} = 5.102$, $P = 0.002$, $\eta^2_{partial} = 0.28$), but there was no significant difference between any of the consecutive evaluations. The Symbol Digit Modalities Test showed a significant effect of evaluation time ($F_{4,52} = 3.758$, $P = 0.009$, $\eta^2_{partial} = 0.22$), but there was also no significant difference between any of the consecutive evaluations.

Attention and Executive Functions

The MANOVA on attention and executive functions tests showed a significant effect of evaluation time across the 2 tests ($\Lambda = 0.572$, $F_{8,104} = 4.108$, $P < 0.001$, $\eta^2 = 0.43$). Univariate results demonstrated that the interference score of the Stroop interference test showed a significant improvement over time ($F_{4,52} = 7.214$, $P < 0.001$, $\eta^2_{partial} = 0.36$), but there was no significant difference between any of the consecutive evaluations. Verbal fluency scores also showed a significant effect of evaluation time ($F_{4,52} = 3.661$, $P = 0.011$, $\eta^2_{partial} = 0.22$), but there was also no significant difference between any of the consecutive evaluations.

Reliable Change Indices

Table 2 lists the RCIs at 24 months for all cognitive measures. There was no clinically significant change for any of the cognitive measures (RCI <1.96). For the MADRS score, the improvement was clinically significant at 12 months (RCI = 2.14) and at 24 months (RCI = 3.25).

Associations Between Cognitive and Clinical Improvement

We examined whether cognitive improvements were linked to clinical changes at different time points. At 1 month, the improvement in MADRS scores was not significantly correlated with changes in any of the cognitive scores (all r's < −0.443, all P's < 0.15). At 12 months, the change in MADRS score was significantly correlated with several measures (Stroop interference: $r = -0.65$, $P = 0.01$; verbal fluency: $r = -0.63$, $P = 0.01$; ROCF: $r = -0.58$, $P = 0.05$).

DISCUSSION

The results of this naturalistic longitudinal study suggest that chronic VNS therapy produces sustained positive effects on cognitive function in TRD patients, as well as antidepressant effects.

Most of the antidepressant effect was observed during the first month of stimulation, and some patients saw additional clinical improvement at 12 months, and clinical benefits were sustained for at least 2 years. The early and sustained clinical effect observed here confirms previous results of a 2-year follow-up of VNS in TRD[34] and that of a 5-year observational study of 795 TRD patients treated with VNS.[70] Our response rate (71% of responders at 12 months) was relatively high compared with other samples.[29,33,34] This difference may be linked to the moderate severity of depression in our sample, a higher ratio of bipolar cases in our cohort (6/14 patients), and a thorough selection by our multidisciplinary team with regard to personality disorders, as well as frequent appointments for parameter adjustments in the first 2 years of VNS therapy. Similar to the study of Aaronson et al,[71] unipolar and bipolar patients in our cohort showed similar clinical responses at all evaluations except at 12 months, where bipolar patients showed higher response rates, suggesting that VNS is indicated for both subgroups of patients.

Our results indicate that chronic VNS treatment is associated with sustained cognitive gains. Improvements were observed in measures of psychomotor speed, verbal fluency, attention, and executive functioning, as well as verbal and visual memory. We observed clear differences in improvement rate between cognitive measures. Memory measures, such as recall of a complex figure, as well as learning and recall of a word list, show more than 25% improvement after 1 month of treatment. Other cognitive measures, such as the phonemic fluency, the SDMT, and the Stroop task, showed improvements of less than 12% after 1 month. The memory improvement observed cannot be attributed to consolidation processes as recognition scores were high at baseline. The fact that list learning also improved suggests that improvements in encoding contributed to changes in memory performance. Encoding is often affected by changes in alertness and attention, and VNS is known to affect alertness,[72,73] yet we observed only modest changes in the attentional measures examined after 1 month.

These results on cognitive measures are globally consistent with those reported of Sackeim and colleagues[45] after 10 weeks of VNS treatment. However, in contrast to the study of Sackeim et al,[45] we found significant improvements in verbal and visual memory. This discrepancy between the 2 studies may be linked to differences in the memory measures used. For example, the verbal memory measure used here (RAVLT) involves more inter-item interference during encoding than the Buschke Selective Reminding Test used in the study of Sackeim et al.[45] Vagus nerve stimulation studies in epilepsy have reported improvements in memory during acute VNS.[53,55] More work will be needed to clarify the long-term effects of VNS on encoding processes.

The RCI at 24 months for all neuropsychological measures suggests that some cognitive changes are not clinically meaningful at any testing time (<1.96). This result may be linked to our sample, which contained several skilled professionals with baseline cognitive scores within the reference range. Other indices of functional improvement, such as measures of quality of life and the proportion of patients who were able to return to work in skilled professional positions (9/14), suggest that cognitive improvements were clinically meaningful.[74] Some studies have suggested a lack of correspondence between clinician-administrated tests and patient-rated reports of cognitive functioning in some situations, and the low severity of cognitive deficits observed at baseline may contribute to this dissociation between cognitive tests and functional improvement.[75]

One may argue that the repeated cognitive evaluations used in the present study may have produced practice effects.[76,77] However, the use of alternate forms at each evaluation session is known to minimize practice effects, especially for verbal memory measures.[42,61,66–92] Also, the amount of time between the baseline evaluation and the first postoperation evaluation averaged 150 days, and the effects were sustained during intervals as large as 12 months (from the 12-month to the 24-month evaluation), which suggests that practice effects cannot account alone for the cognitive improvements obtained. Our results suggesting that VNS produces sustained cognitive improvement in TRD are supported by the fact that most our patients (9/14) returned to work in skilled professional positions. Cognitive deficits are an important debilitating factor in everyday functioning in major depression, often responsible for impaired work productivity, and they are

correlated with functional impairment.[81,82] In this light, improvement of cognitive deficits should be an important issue in treatment choice. Treatment for refractory depression is often challenging and can include a combination of medications, ECT, or adjuvant somatic therapies such as deep brain stimulation and repetitive transcranial magnetic stimulation. Until now, these therapies have demonstrated limited cognitive benefits.[83–85] The cognitive benefits of VNS therapy argue for a more systematic consideration of the cognitive effects of different treatment modalities in TRD. Vagus nerve stimulation should be considered in TRD patients with cognitive deficits, as they seem to improve dramatically with VNS, and some cognitive dysfunctions might even be a good predictor of VNS treatment response.

One could also suggest that the cognitive improvements observed are secondary to improvements in mood. However, we found no significant correlation between changes in cognitive scores and improvement on the MADRS at 1-month post-VNS onset, which is when the largest improvements in mood were observed. Studies report that during a depressive episode, specific cognitive domains could recuperate faster than others during remission. For instance, Boeker et al[86] observed learning and memory improved after clinical recovery, whereas working memory, executive functions, and sustained attention showed no improvement. In their study, Douglas and Porter[87] also observed that memory, verbal learning, verbal fluency, and psychomotor speed improved faster than executive functions and attention. Cognitive deficits persisting after the remission of depressive symptoms could be part of the phenotype of depression.[88] One potential cause behind the lack of correlation between mood and cognitive improvement at 1 month is that VNS therapy is reported to have a faster effect on norepinephrine than on serotonin.[42] Therefore, VNS therapy could sometimes give rise to an effect on cognition before the patients can actually report an effect on mood. This dissonance between rate of improvement in cognition and mood seems to disappear later on during the treatment, as cognitive improvements were correlated with mood improvements at 12 months. However, these correlations may also stem from VNS effects on alertness, which can influence both cognition and mood.

Because of the absence of control group, placebo effects could have affected the results. Double-blind sham-controlled studies are difficult to conduct in VNS research because most patients have throat discomfort during the stimulation[42] and are impractical and ethically challenging for long-term studies. However, placebo effects are minimal on objective cognitive tests in depression.[89,90] Also, cognitive improvements in our study were sustained over 2 years of VNS, minimizing the probability that they are due to a placebo effect. A placebo effect may have affected the MADRS measure, although placebo effects may be smaller in refractory depression than nonrefractory depression.[91] The reversibility of depressive symptoms after cessation of the VNS treatment was not systematically tested in the present study. However, 1 patient (patient 14) with a stable antidepressant response had a temporary malfunction of the stimulator approximately 2 years after implantation, and there was a significant return of depressive symptoms within 2 days that was reversed by the replacement of the stimulator.

The present results should be interpreted within the context of certain study limitations including a sample size that was small, which may have lowered statistical power, and the lack of double-blind placebo control. However, the present findings suggest additional evidence of persistent clinical and cognitive improvements with VNS therapy as a treatment for TRD. Preliminary data on 10 of our patients still show sustained cognitive improvements after 5 years of VNS therapy. Future work should include larger studies with controls and should integrate neuroimaging measurements to parallel the effects of rapid changes in cognition.

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