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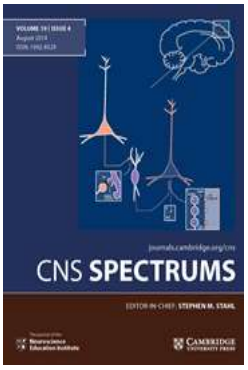

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Marked Response to VNS in a Post-Cingulotomy Patient: *Implications for the Mechanism of Action of VNS in TRD*

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ABSTRACT

Treatment-resistant major depression (TRMD, major depressive disorder that fails to respond to numerous therapies) is a relatively common and clinically challenging disorder. In many cases, the most severely affected TRMD patients have received surgical intervention (subcaudate tractotomy, limbic leucotomy, anterior capsulotomy, and anterior cingulotomy). New treatments, including vagus nerve stimulation (VNS) and deep brain stimulation, have emerged to treat individuals with TRMD. We describe the case of a woman, 53 years of age, with a long and sustained history of TRMD (33 years), which was unresponsive to numerous treatments (multiple pharmacotherapies, psychotherapy, electroconvulsive therapy [ECT]). Additionally, her TRMD failed to respond to a bilateral anterior cingulotomy. She underwent placement of a cervical vagus nerve stimulator and a brief course of ECT (3 unilateral treatments). Her depression improved markedly, and it has remained in sustained remission for 3.5 years. This case suggests a potential synergistic effect of VNS and ECT, as well as provides possible clues to the neural circuitry of VNS in TRMD.

FOCUS POINTS

- New, more invasive, treatments, (eg, vagus nerve stimulation [VNS], deep brain stimulation), are evolving for the treatment of refractory illnesses in psychiatry.
- VNS is Food and Drug Administration approved for treatment augmentation in severe, treatment-refractory depression. Studies suggest that the antidepressant effects of VNS are typically delayed by months.
- Studies demonstrate that electroconvulsive therapy (ECT) and VNS can be safely administered at the same time. Clinical experience and case reports suggest that ECT and VNS may have synergistic effects, (ie, patients who responded poorly to ECT in the past may respond better to this treatment after VNS implantation).

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INTRODUCTION

Treatment-resistant major depression (TRMD) is a variation of major depressive disorder in which patients fail to respond to numerous treatments (typically antidepressants with augmentation strategies and psychotherapy).[1] In many patients with TRMD, a variety of treatments, delivered singly or in combination, including pharmacotherapies, psychotherapies, and electroconvulsive therapy (ECT), fail to provide an adequate response. Psychiatry has begun to explore more invasive treatments for TRMD, including vagus nerve stimulation (VNS),[2] which was approved by the Food and Drug Administration as an adjunctive antidepressant therapy in 2005, and deep brain stimulation (DBS). DBS has been approved for compassionate use in obsessive-compulsive disorder and is currently experimental for TRMD.[3,4] In some severe cases, surgical interventions are used, including subcaudate tractotomy, limbic leucotomy, anterior capsulotomy, and anterior cingulotomy.[5] Unlike VNS and DBS, these neurological surgeries involve creation of a lesion. In the case of a complete bilateral cingulotomy (as described here), this lesion would limit communication between the more anterior and posterior portions of the cingulum bundle.

We describe the case of a TRMD patient whose depression did not respond to aggressive pharmacotherapy, psychotherapy, bilateral anterior cingulotomy, or ECT, but which remitted when treated with VNS in combination with ECT.

CASE REPORT

Ms M, a Caucasian woman, 53 years of age, had TRMD of 33 years duration, and posttraumatic stress disorder (PTSD) related to sexual trauma that occurred around 20 years of age. Her depression began in her early teens and resulted in multiple psychiatric hospitalizations and several serious suicide attempts during her early twenties. She denied being depression-free for >30 consecutive days, alternating between "severely depressed" and "mildly depressed" for her entire adult life. She had no history of psychosis or manic episodes. She reported limited anxiety symptoms, predominantly PTSD-related (recurrent flashbacks and avoidance), although she reported that these symptoms had not impaired her functioning during the previous 10 years. Her depressive symptoms were primarily characterized by low mood, anhedonia, anorexia, weight loss, helplessness, hopelessness, excessive guilt, and suicidal ideation. She had an extensive family history of depression, including a brother who committed suicide. She denied use of illicit drugs but reported a history of alcoholism that was 8 years in sustained remission. Her medical history was remarkable for hypothyroidism (controlled), fibromyalgia, epilepsy (controlled), and estrogen-replacement hormone therapy for oophorectomy for uterine cancer. The patient began having seizures following a closed head trauma which occurred at 46 years of age (her depression preceded her epilepsy). She reported an average of 2 seizures/year (tonic-clonic) from 46–53 years of age, and she reports that she does not recollect her depression being any worse after the seizures than before.

Ms M's pharmacotherapy treatment history for TRMD was extensive. Over the previous 30 years, she had been treated with various combinations of 2–5 antidepressants and numerous augmentation agents. She had failed adequate dose-duration antidepressant trials with several different classes of antidepressant including selective serotonin inhibitors (citalopram, paroxetine, fluvoxamine, and escitalopram), tricyclic antidepressants (imipramine, amitryptyline), serotonin-norepinephrine reuptake inhibitors (venlafaxine extended release, duloxetine), buproprion, nefazodone, as well as antidepressant augmentation trials with lithium, aripiprazole, and olanzapine. She had multiple courses of ECT (bilateral and unilateral) from 1970–2006, with generally limited immediate benefit and no sustained or long-term benefit. In 1981, she underwent bilateral anterior cingulotomy for TRMD, which had no effect on depressive symptoms. She attempted suicide on several occasions after the cingulotomy. In 1983 she underwent a course of bilateral ECT (10 treatments) with no response. Two years later, another course of 10 bilateral ECT treatments also failed.

With regards to history of *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* axis II pathology: none of her outpatient records lists her as having an Axis II diagnosis. Two psychiatric hospitalizations (1999 and 2000) listed the diagnosis of "borderline personality disorder"; a subsequent hospitalization (2005) listed "rule out borderline personality disorder". She underwent a Minnesota Multiphasic Personality Inventory assessment in 2000, while hospitalized, which concluded: "nonspecific findings—marked anxiety, neediness, feelings of inadequacy, and ruminations over past trauma."

In late 2005 and early 2006 Ms. M failed another

three month antidepressant combination trial: duloxetine (90 mg QD) combined with quetiapine (300 mg HS) and lithium (300 mg TID), as well as topiramate (200 mg QHS) for epilepsy. In March 2006, having failed an extensive list of antidepressant and mood stabilizers, Ms M underwent implantation of a VNS device for TRMD. Her previously described medications (ie, duloxetine, quetiapine, lithium, and topiramate) were unchanged. VNS was initially ineffective, with her depression (suicidal thoughts) resulting in a psychiatric hospitalization in May 2006. While in hospital, with VNS ongoing, she underwent three unilateral ECT treatments (VNS was temporarily deactivated only during the interval in which she received the ECT treatments), with considerable acute antidepressant benefit. At discharge, medications were duloxetine (60 mg QD), temazepam (15 mg QHS), and quetiapine (400 mg QHS).

After discharge, the patient experienced continued improvement in her depressive symptoms. In June of 2006, she reported that her depression was "much better," and that her core primary symptoms (anhedonia, decreased energy, hopelessness, helplessness, suicidal ideation) were "gone." At this time, quetiapine was discontinued and zolpidem (for sleep) was added; otherwise, only limited dose adjustments occurred during the subsequent months. Three and one-half years later, she remains depression-free with no residual depressive symptoms. During a recent (December 2009) assessment, she scored 4 on the Montgomery-Åsberg Depression Rating Scale, which is consistent with depression remission. At that time, she reported stable mood, good sleep and appetite, social activity, good energy, and motivation. In addition to VNS, her medications were duloxetine (60 mg PO QD), temazepam (15 mg QHS), and zolpidem (10 mg QHS). She also continued to participate in weekly cognitive behavioral psychotherapy sessions, which began five years ago. Additionally, she reports she has not had any seizures following the implant of her VNS device.

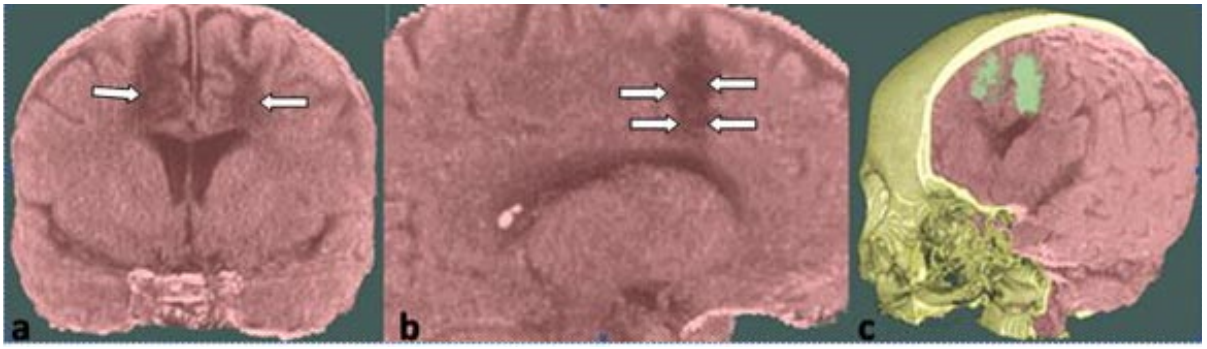
A high resolution computed tomography (CT scan; Figure 1), acquired using a General Electric LightSpeed VCT 64-Slice CT scanner (30 cm FOV, no gantry tilt, 1024 x 1024 matrix, 1.5 mm slice thickness) was obtained following placement of VNS. Review of the CT scan and comparison to standard brain atlases demonstrates a bilateral lesions (from the 1981 cingulotomy surgery) in the mid-portion of the cingulate gyrus with complete obliteration of the structure in the superior inferior and medial lateral dimensions.

DISCUSSION

This case report highlights a woman, now 56 years of age, with a lifelong history of profound and debilitating TRMD characterized by numerous failed antidepressant medication trials, failed ECT trials (both before and after cingulotomy), and failed bilateral anterior cingulotomy, who has experienced sustained remission of her TRMD after VNS and a brief course (3 treatments) of ECT.

This case also highlights the potential synergis-

FIGURE 1.
Three different high resolution CT views of the cingulotomy lesion*



Panel A: Coronal view of the cingulotomy lesion demonstrating the near-complete superior-inferior ablation of the cingulate gyrus. Panel B: sagittal view of the medial surface of the left hemisphere. Note the near complete transection of the cingulate extending from the superior surface to the corpus callosum. Panel C: An oblique view leaving skull in place with lesion area highlighted in green. CT images acquired using a General Electric LightSpeed VCT 64-Slice CT scanner (30 cm FOV, no gantry tilt, 1024 x 1024 matrix, 1.5 mm slice thickness). CT images created using the Dextroscope® platform (Volume Interactions, Bracco Industries, Buckinghamshire, UK).

* Arrows denote the edges of cingulotomy lesion.

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tic effect of VNS and ECT and allows for consideration of the neural pathways that may be essential for a VNS response in TRMD, including the fact that a completely transected anterior cingulate did not prevent an antidepressant response to VNS.

Several articles describe the concomitant use of ECT with VNS.[6-8] ECT is not contraindicated in VNS, but it is recommended that the device be deactivated during the ECT procedure to avoid potential complications involving cardiac or pulmonary side effects.[6] Some reports have suggested that ECT and VNS may have a synergistic antidepressant effect.[7,8] Our group has observed a similar antidepressant synergistic effect between VNS and ECT in 3 cases as well (patients with lifelong histories of requiring recurrent ECT, no longer requiring ECT as frequently or requiring fewer ECT with the addition of VNS). Sharma and colleagues[8] described two patients (unipolar, bipolar depression) for whom ECT had previously been unsuccessful. In both patients, VNS, was initially unsuccessful until ECT was reintroduced. It is also possible, in the case described above, that the ECT simply coincided with the patient's response to VNS.

Demonstrating a direct causal relationship between our patient's sustained depression remission and VNS is not possible. Her history, however, lacked any sustained antidepressant response to any treatment. Before she received VNS, ECT had not previously elicited a response. Although some patients may experience an acute antidepressant response with only 3 ECT treatments, the typical recommended effective "dose" of ECT, in order to sustain the antidepressant response, is >3 treatments.[9,10] Her initial early response to ECT, as well as her sustained euthymia suggest that VNS may have played a synergistic role with ECT. Ms. M is currently depression-free, and has been for 4 years. Before receiving VNS, she reported no depression-free period >1 month over her entire life. Sackeim and colleagues[11] studied the effectiveness of ECT in TRMD in which ECT had been discontinued, and they reported a very high relapse rate (~70% at 1 year).

VNS has well-established efficacy in treatment-resistant epilepsy. Additionally, there is a clear association between epilepsy and depression; hence it is possible that the patient's partially-controlled epilepsy was contributing to her depression.[12] However, her depressive symptoms (including hospitalizations and suicide attempts) clearly preceded her traumatic epilepsy onset. It is noteworthy that in addition to her depression resolution, the patient also reports no further seizures following VNS implantation.

This case report may provide some key insights into the critical neuroanatomical network components "required" for successful VNS treatment in TRMD. The mechanism of action of VNS in TRMD, as in epilepsy, is incompletely understood. There is evidence that the effects of VNS on the brain systems associated with mood are mediated both through primary brainstem nuclei projections (dorsal raphe, locus ceruleus, nucleus tractus solitarius) and limbic system and direct cortical pathways.[13,14] Current models of depression hypothesize that depression represents a dysregulation of several interconnected structures in the frontal and limbic circuitry.[15-17] Key structures in this network include the prefrontal cortex (medial, orbital, and dorsolateral), the amygdala, the cingulate cortex, the hippocampus, striatum, dorsal thalamus, and the hypothalamus. Many of these structures intersect with the upstream afferent pathway of the vagus (Figure 2).

The cingulate cortex, fully transected in Ms. M's case, is considered a pivotal region in depression neuroimaging studies. Visual inspection of the high resolution CT scans (Figure 1) demonstrates that the patient's cingulate gyrus was transected at the junctional region of the dorsal anterior cingulate and the mid-cingulate. The transection occurred well forward of the posterior cingulate cortex.

The cingulate (and underlying cingulum bundle) is a critical structure in mood disorders. Structural neuroimaging studies have demonstrated a reduction in gray matter volume in the left subgenual anterior cingulate in individuals with depression.[18-20] Functional neuroimaging studies of the subgenual anterior cingulate cortex (Brodmann's area [BA] 25) in depression have also shown this region to be hypometabolic compared with non-depressed controls.[20] Other studies have demonstrated that when corrected for the volume loss occurring in this region with depression, BA 25 is actually hypermetabolic compared with nondepressed controls.[21] Further, numerous treatment modalities, including medications,[22] DBS,[3] and sleep deprivation[23] have demonstrated decreased metabolism of BA 25. More dorsal regions of the cingulate also have been identified as involved in depression. Studies have found that the dorsal anterior cingulate (dorsal to the corpus callosum and posterior to the genu of the corpus callosum) also undergoes change with depression: positron-emission tomography imaging studies assessing antidepressant and DBS

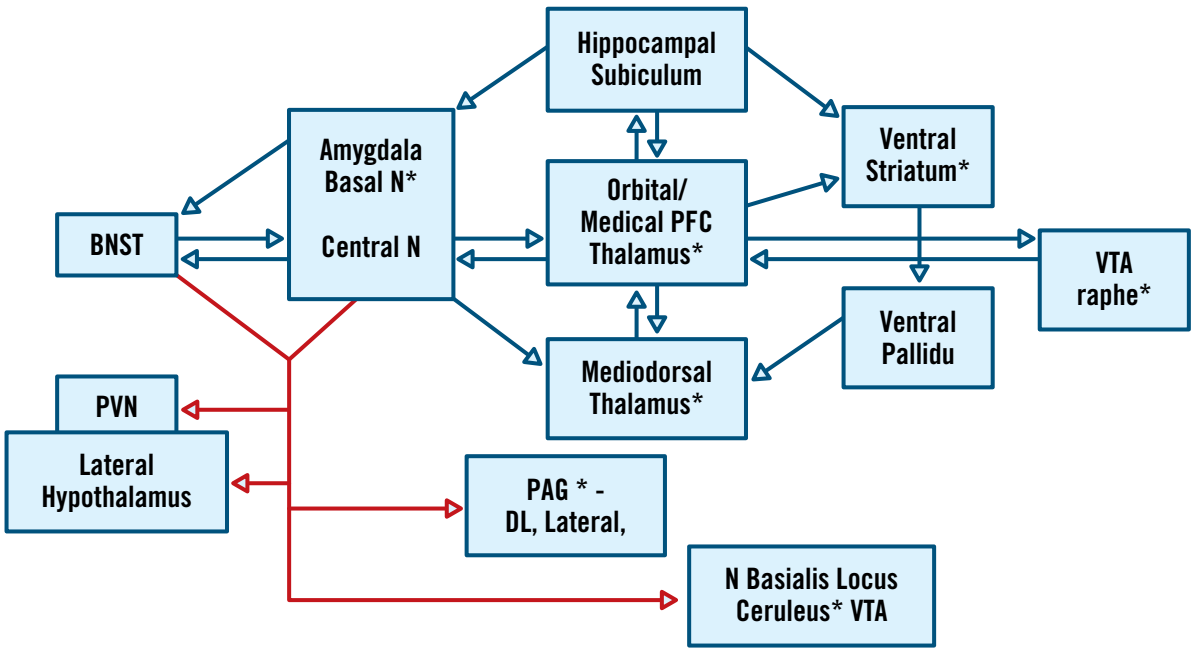
antidepressant response demonstrate increased activation of this region.[24,25]

How might activation of the left vagus affect the fronto-limbic mood circuitry? Upstream vagal projections synapse with anterior components of these fronto-limbic circuits: most of the upstream afferent fibers of the vagus travel via the nucleus tractus solitaries (NTS).[13] Fibers from the NTS project to the central nucleus of the amygdala as well as the nucleus accumbens. Additionally, animal models demonstrate the NTS, synapsing through the parabrachial nucleus, also send projections to the thalamus, the amygdala (particularly the central nucleus of the amygdala, but also the basolateral and other amygdalar nuclei), the anterior insula, and infralimbic cortex, lateral prefrontal cortex, and other cortical regions.[13,26] Of note, the predominance of upstream vagal afferent pathways target regions in the anterior/temporal portions of these circuits (ie, amygdala, nucleus accumbens, insula, and prefrontal cortex). The connections between these regions would have been spared in the cingulotomy described in this case report (location of surgical lesion depicted in Figure 3).

Neuroimaging studies of VNS in TRMD demonstrate that most of the acute effects of VNS in TRMD occur in anterior and temporal regions.[27-30] These regions include the anterior cingulate, the insular region, lateral and medial prefrontal cortex, and orbitofrontal cortices.

Given the known neuroanatomy and evidence from neuroimaging studies, two distinct (though by no means exclusive) methods by which VNS acts on the fronto-limbic mood circuitry emerge: amygdalar and lateral orbital-insular synaptic pathways. The amygdala is known to have extensive cortical projections, including the rostral insula and temporal pole; however, the strongest of these connections are with the medial prefrontal cortex rostral and ventral to the genu of the corpus callosum.[17] Similarly, vagal projections to the lateral orbital cortex (and adjacent anterior

FIGURE 2.
Intersection between the affarent vagal pathway and the frontolimbic model of depression[15]



The model emphasizes how orbital and MPFC dysfunction leads to disinhibition of neural transmission through the amygdala (efferent paths from amygdala in red). Animal and human neuroimaging studies have determined that the upstream pathways of the vagus have multiple intersections with the brain regions in this model (depicted by asterisks alongside the structure). The majority of these regions are anteriorly positioned in the brain.

Figure adapted from Drevets WC, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Struct Funct.* 2008;213(1-2):93-118.

BNST=bed nucleus of the stria terminalis; Basal N=basal nucleus of the amygdala; Central N=central nucleus of the amygdala; PAG=periaqueductal gray; PVN=peraventricular nucleus of the hypothalamus; VTA=ventral tegmental area; MPFC=medial prefrontal cortex.

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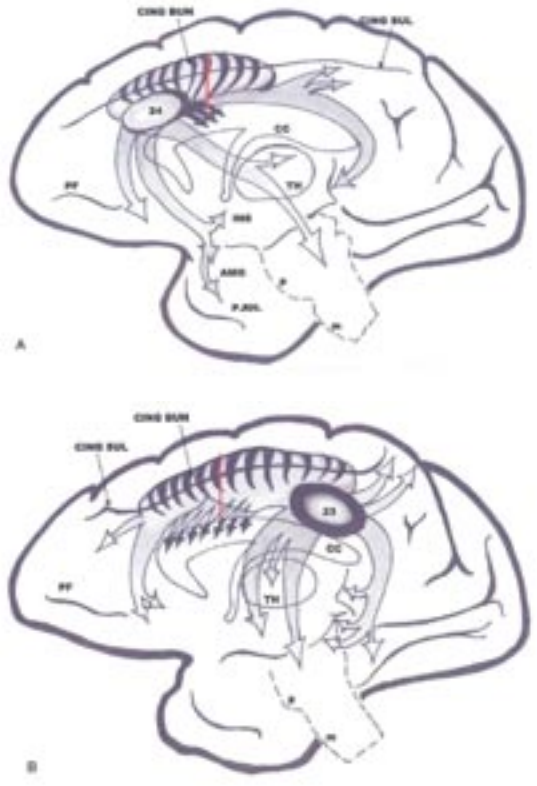
insular regions), which likely interact with medial prefrontal regions, may be another mechanism by which VNS acts in TRMD. In both instances, these mechanisms of action seem to have minimal involvement with the posterior limbic/paralimbic circuitry and would not be affected by a bilateral cingulotomy.

Understanding the anatomy of the cingulate gyrus and underlying white matter (cingulum bundle) and the mechanism by which this structure integrates with other components of the frontolimbic mood network may provide insights into the reasons for the success of VNS in an individual with a complete bilateral cingulotomy.

FIGURE 3.
Regional course of the cingulum fibers in the anterior and posterior cingulate cortex (Rhesus monkey)[31]



The red vertical line represents approximate anterior margin of the cingulotomy lesion in this case. Using autoradiographic tracer injection studies Mufson and Pandya[31] were able to analyze the constituent white matter components of the cingulum bundle. They found fibers arising from both the anterior and posterior portions of the cingulate cortex projected into prefrontal cortex; however, only fibers from the anterior portion (BA 24; Panel A) projected into the insula and amygdala. In contrast, fibers originating from the posterior cingulate cortex (BA 23; Panel B) did not project to these structures. These tracer studies suggest that the principal direct communication between cingulate cortex and other central components (eg, the AMG) of the frontal-limbic circuitry implicated in mood disorders predominantly involves the more anterior cingulate regions, which would not be affected by the cingulotomy lesion (anterior margin of lesion depicted with dotted vertical line).

AMG=amygdala; CC=corpus callosum; CING BUN=cingulum bundle; CING SUL=cingulate sulcus; PF=prefrontal cortex; INS=insula; p=pons; PRH=parahippocampal gyrus; m=medulla; TH=thalamus; BA=Brodmann's area.

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The anatomy and interconnections of fibers making up the cingulate gyrus are very complex and beyond the scope of this case report. Mufson and Pandya[31] used an autoradiographic tracer injection studies in Rhesus monkeys to analyze the constituent white matter components of the cingulum bundle. They found that most cingulum fibers arise from the thalamus, the cingulate cortex itself, and association areas (Figure 3). Fibers from all three origins project both rostrally and caudally. Interestingly, fibers arising from both the anterior and posterior portions of the cingulate cortex projected into prefrontal cortex; however, only fibers from the anterior portion (BA 24; Figure 3, panel A) project into the insula and amygdala. In contrast, fibers originating from the posterior cingulate cortex (BA 23; Figure 3, panel B) did not project to these structures.[31] These tracer studies suggest that the principal direct communication between cingulate cortex and other central components (eg, amygdala) of the frontal-limbic circuitry implicated in mood disorders predominantly involves the more anterior cingulate regions.

On the basis of this case report, it appears that direct communication between the posterior and anterior cingulate is not necessary for VNS to be efficacious in TRMD. Unlike DBS or VNS, a cingulotomy involves physically lesioning neuronal pathways: a complete bilateral transection of the cingulate cortex would likely cut at least much if not all of the synaptic communication between anterior and posterior components of the "default mode system" (medial and dorsal prefrontal cortex and posterior cingulate cortex).[32] Recent studies[33] suggest individuals with depression have problems "shifting out" of the default mode system when challenged. Because the default mode system has been associated with self-referential function, it can be suggested that persistent activity in the system may be associated with rumination on self-related, possibly negative thoughts.

CONCLUSION

To our knowledge, this study is the first reported case of a patient with a failed cingulotomy for TRMD who subsequently experienced an antidepressant response to VNS. Based on the computed

tomography confirmed, near-complete obliteration of the bilateral cingulate, this case suggests an intact cingulum (in the anterior-posterior axis) is not necessary to respond to VNS. Considering that the most aggressive of treatments had failed for Ms. M's TRMD, this case study highlights the potential efficacy of VNS in very treatment resistant clinical depression and emphasizes the need for further studies to determine the mechanism of action of VNS in TRMD. ***CNS***

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