Title

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Finding the Sweet Spot: Fine-Tuning DBS Parameters to Cure Seizures While Avoiding Psychiatric Complications

Reversible Psychiatric Adverse Effects Related to Deep Brain Stimulation of the Anterior Thalamus in Patients With Refractory Epilepsy

Järvenpää S, Peltola J, Rainesalo S, et al. *Epilepsy Behav*. 2018;88:373-379. doi:10.1016/j.yebeh.2018.09.006

Objective: Anterior nucleus of thalamus (ANT) deep brain stimulation (DBS) is becoming a more common treatment for drug-resistant epilepsy. Epilepsy and depression display a bidirectional association. Anterior nucleus of thalamus has connections to anterior cingulate cortex and orbitomedial prefrontal cortex, hence, a possible role in emotional and executive functions, and thus, ANT DBS might exert psychiatric adverse effects. Our aim was to evaluate previous and current psychiatric symptoms in patients with epilepsy undergoing ANT DBS surgery and assess the predictability of psychiatric adverse effects. Programming-related psychiatric adverse effects are also reported. **Method:** Twenty-two patients with ANT DBS for retractable epilepsy were examined, and a psychiatric evaluation of depressive and other psychiatric symptoms was performed with Montgomery-Åsberg Depression Rating Scale, Beck Depression Inventory, and Symptom Checklist prior to surgery, concentrating on former and current psychiatric symptoms and medications. The follow-up visit was 1 year after surgery. **Results:** At the group level, no changes in mood were observed during ANT DBS treatment. Two patients with former histories of depression experienced sudden depressive symptoms related to DBS programming settings; these were quickly alleviated after changing the stimulation parameters. In addition, 2 patients with no previous histories of psychosis gradually developed clear paranoid and anxiety symptoms that also relieved slowly after changing the programming settings. **Conclusion:** The majority of our ANT DBS patients did not experience psychiatric adverse effects. Certain DBS parameters might predispose to sudden depressive or slowly manifesting paranoid symptoms that are reversible via programming changes.

Commentary

Given that most seizures in adults arise in the medial temporal lobes, a region containing critical circuits for emotional processing, it should not be surprising that both seizures and their treatment can have both positive and negative effects on psychiatric status. New-onset psychiatric issues are common following standard epilepsy surgical procedures.[1,2] In the study by Järvenpää et al, 4 (18.2%) of 22 patients developed psychiatric problems following anterior nucleus of thalamus (ANT) deep brain stimulation (DBS). They also describe that all of these symptoms resolved with alterations in stimulation intensity and contact selection. This article highlights the need to carefully monitor the mental status of patients undergoing DBS implantation so that therapeutic adjustments can be made as necessary.

The emerging use of neuromodulatory devices is creating new opportunities for understanding the neural mechanisms that support our thoughts, emotions, and behavior. For example, DBS has been used as a therapy to combat treatment-resistant depression, likely accessing some of the same networks as ANT stimulation.[3] In our own work, we have recently demonstrated that stimulation of the cingulum bundle during stereoelectroencephalography implantation can produce improved mood and anxiolysis in patients with baseline psychiatric symptomatology.[4] Stereoelectroencephalography studies and neuromodulatory therapies provide us with the opportunity to examine the spatial placement of electrode contacts and both diffusion tensor-based and electrophysiological connectivity with other cortical areas, potentially helping to elucidate the circuitry of mood and associated symptoms of emotional dysregulation (eg, apathy, neurovegetative changes, and hyperarousal). From a research perspective, obtaining pre-implantation resting state functional magnetic resonance imaging (fMRI) and diffusion tensor imaging scans, as well as thalamocortical evoked potentials during invasive monitoring, will allow us to understand the connections of areas receiving stimulation. This will in turn help us to determine whether there are differences in stimulation patterns between DBS patients developing psychiatric symptoms and those who do not, likely based on patient factors and the topography of projections from

ANT and other thalamic nuclei. Such analysis should also consider other key covariates such as the possible effects of antiepileptic and psychotropic drugs, baseline psychiatric history, seizure freedom status, and sex.

Although there was no group-level decline in psychiatric status following ANT DBS, 4 patients developed significant psychiatric symptoms over time that were alleviated by reducing the current density of stimulation or by using alternative contacts. The absence of group-level decline is of interest, as it has been noted that in postsurgical studies such changes can be obscured by having the emotional state of some individuals improve while others decline.[2] Although this may not be statistically significant, 2 patients did have markedly improved depression scores, in one case from moderately depressed to symptom-free. It is unclear whether stimulation, indirectly of the anterior cingulate area, as we have shown, led to improved affect or whether this may have been due to improved seizure control or medication changes (in one of these patients). With improved seizure control, some patients will nevertheless experience a decline in mood which has been attributed to *forced normalization*,[5] a phenomenon presently lacking a mechanistic basis, that may also result from changes in psychosocial status (eg, a patient's family structure sometimes reacts poorly to the patient's improved seizure control).

The current study found that the 2 patients experiencing depressed mood after DBS implantation each had a history of preimplantation depression. It would seem that having preexisting mood issues could contribute to posttreatment outcome, yet it was also clear that many patients with such conditions did not experience a worsening of symptoms. Two additional patients developed irritability, psychosis, and related symptoms, and both had contacts stimulated that were likely below the ANT. Both patients experienced complete symptom resolution when more dorsal contacts were used. In these patients, symptoms developed slowly and progressively, and in one case, these were associated with sleep disturbance,[6] with the causal relation between sleep disturbance and anxiety unclear. Thus, the recognized bidirectional link between epilepsy and mood disturbance[7] needs to be better explored, with further consideration given to electrode placement, stimulation parameters, and relevant covariates with relation to psychiatric symptom development.

Although the organization of efferent projections of the ANT at a histological level is incompletely determined in humans, primate and monkey studies reveal widespread projections of ANT to emotional motor and affective brain circuits, with even more extensive innervation of these networks when considering indirect projections.[8] A major target of the ANT is the cingulate area, bringing to mind the Papez circuit,[9] although relatively more neurons of the dorsomedial thalamic nucleus innervate this region.[10] Although the Papez circuit inspired ANT stimulation studies, preclinical evidence with DBS showed changes in seizure generalization with mammillary lesions and ANT stimulation,[11,12] while the SANTE trial principally examined focal seizures.[13] Recent histological work has suggested that ANT subnuclei that are easily identified in other species may be present in humans,[14] perhaps in turn suggesting that subnuclear targeting may also prove valuable. For example, in the present article, patient 3 likely had unilateral stimulation outside of the ANT, perhaps in the anteromedial or dorsomedial area and, overall, larger volumes of tissue activated were associated with psychiatric symptoms, which could suggest anatomically off-target stimulation. Although MRI-based thalamic segmentation is difficult,[15] and there is only theory in favor of a patient-based DBS approach, we wonder if future thalamic DBS may rely on segmentation and careful selection of the site of thalamic stimulation based upon each patient's epilepsy and seizure type.

Overall, DBS of the ANT represents an intriguing new tool in the treatment armamentarium of the epilepsy surgical center, and Järvenpää and colleagues add to our confidence that this tool can be used safely without undue psychiatric complication. More work is required in this area, along with more detailed assessment of the cognitive performance of DBS patients, and researchers should take advantage of this paradigm to learn more about the neural circuitry of emotion and cognition along the way. This article also highlights the need to examine the off-target effects of our interventions and provides important clinical observations as we perform more ANT DBS.

By Daniel L. Drane and Nigel P. Pedersen

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