Commentary: Posteromedial Hypothalamic Deep Brain Stimulation for Refractory Aggressiveness in a Patient With Weaver Syndrome: Clinical, Technical Report, and Operative Video

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Received, June 13, 2021.
Accepted, July 6, 2021.
Published Online, September 1, 2021.

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The authors have provided a detailed description on treating drug-resistant aggressiveness in patients with Weaver syndrome. This operative case study is a significant contribution to the existing yet limited body of literature on stimulation of the posteromedial hypothalamus (PMH) as it provides a detailed contemporary description of the surgical technique along with its pearls and pitfalls.

Sano et al. was the first to describe the use of stereotactic radiofrequency ablation for the treatment of pathological aggressiveness by targeting the PMH in the 1960s. His work formed the basis for high-frequency stimulation of PMH, and his stereotactic coordinates were used in several other studies with reasonable success. The PMH “region,” adeptly named the “Triangle of Sano,” is located at the midpoint of the intercommissural line, the anterior border of the mammillary bodies, and rostral portion of the cerebral aqueduct. Its proximity to other vital structures of the hypothalamus can lead to a variety of side effects, including seizures, cardiovascular changes, hypertension, and dysregulation of body temperature, with some of these side effects aiding in intraoperative target refinement.

Hyperaggressive behavior is thought to develop when there is hyperstimulation of the limbic system without appropriate higher order cortical inhibition. Studies involving stimulation of the anterior and posterior hypothalamic regions suggest connections between the amygdala, hypothalamus, prefrontal/orbitofrontal cortices, and the limbic circuit of Papez all play a role in modulating aggressive behavior. The amygdala in particular has connections to the PMH region (via the fornix and stria terminalis), which renders both of these structures’ attractive targets for neuromodulation in the treatment of aggressive behavior.

Narabayashi et al. published a series of papers detailing the effectiveness of stereotactic amygdalotomy in the treatment of epilepsy and hyperaggressive behavior. There have been limited studies involving the deep brain stimulation (DBS) of the amygdala for the treatment of patients with aggressive tendencies; however, one case report by Strum et al. demonstrated good treatment effects on a 13-yr-old boy with autism and self-injurious behavior. Other regions of interest in the treatment of hyperaggressive behavior have included the thalamus, hippocampus, fornix, anterior limb of the internal capsule, supragenual cingulum, and more recently the nucleus accumbens.

Advancements in neuroimaging have allowed for diffusion tensor imaging (DTI) and tractography to be used in identifying pathways involved in PMH circuitry. Torres et al. was the first to use deterministic tractography to assess the connectivity of the PMH in hyperaggressive patients who were treated with DBS. The modeled stimulation field generated affected a wide network beyond the PMH, including the ventral tegmental area, dorsal longitudinal fasciculus, and medial forebrain bundle. Such preliminary work suggests that therapeutic benefits of PMH DBS modulation of aggressive behavior are likely mediated by affecting the aforementioned neural networks. In addition, DTI and tractography will likely aid in target selection and refinement.

Neurosurgical intervention for the treatment of hyperaggressive and self-injurious behaviors poses unique challenges. These patients are rare, and the few studies published so far include single case or small cohorts with inconsistent outcome measures. Some have employed the Inventory for Client and Agency Planning (ICAP) or Overt Aggression Scale (OSA) to measure clinical aggressiveness, but the majority base their results on subjective improvements.

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in patient behavior.\textsuperscript{10} Additionally, ethics committees and large multidisciplinary teams of medical professionals are needed to effectively manage and treat these complex patients. This can be costly and time-consuming, further limiting the accessibility of treatment. Lastly, hyperaggressive behavior is heterogeneous, involving different networks in different patients, which renders a particular case study difficult to generalize. Although the present study suffers from some of the same pitfalls, we commend the authors for providing a rigorous description of their surgical technique, objectifying their outcomes using the ICAP, and providing follow-up data at 6 and 12 mo.

As mentioned, the authors have done an excellent job in providing a very detailed operative methodology on targeting the PMH using contemporary techniques along with microelectrode recording. They use Sano’s\textsuperscript{2,3} coordinates for initial targeting and refine that by micro-electrode recording (MER) recordings and stimulations with 5 electrodes.\textsuperscript{18} This is significant as few authors have reported detailed MER characteristics of the PMH and even fewer have utilized that information in operative planning.\textsuperscript{19,20}

In addition, the authors used scalp electroencephalogram to identify frontal theta rhythms induced by hypothalamic stimulation in order to confirm correct electrode placement. They also combined this with previously explored use of electrocardiogram, electromyogram, and clinical exam to fine-tune lead placement within the PMH. The methodology developed by the authors can be used in future large-scale investigations to help further refine the target within the PMH.

A notable concern in this study is their use of 5 electrodes for MER. The use of multiple tracts in a compact region of the brain raises concerns for microlesion effects (MLEs) induced by MER placement alone. An MLE refers to improvement in the patient’s preoperative symptoms observed after electrode placement but prior to onset of stimulation, likely due to the lesion induced by placement of the electrode in the intended nucleus. This phenomenon has been well described in the Subthalamic nucleus/Globus Pallidus internus literature for Parkinson’s disease, with effects lasting up to about 3 wk postoperatively.\textsuperscript{21-24} However, the continued improvement in the patient’s preoperative symptoms at follow-up 6 mo and 1 yr following surgery shows promise in the targeted area chosen by the authors.

We again commend the authors on their contemporary operative technique in the treatment of pathologic aggressiveness in a patient with Weaver syndrome through the targeting of the PMH for DBS lead placement. We believe this study provides much needed evidence for surgical treatment of medically intractable aggressiveness not only in patients with this disorder but also for those afflicted by similar syndromes. Literature on this topic has been limited by small sample sizes, ethical concerns regarding patient autonomy, and a lack of standardized validated metrics for measuring treatment response. Further studies on the neural circuits involved in aggression, the use of neuroimaging in operative targeting, optimal stimulation parameters to obtain treatment response, and the influence of the MLE has on patient outcomes need to be elucidated before this technique, and others like it, can be more readily available for this population.

Funding
This study did not receive any funding or financial support.

Disclosures
The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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