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Deep Brain Stimulation for the Treatment of Aggressive Behaviour: Considerations on Pathophysiology and Target Choice

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The experience of Giordano et al. [1] contributes to shedding a light in the field of the neurosurgical treatment of aggressive behaviour (hereby called "intermittent explosive behaviour, IED," following the DSM-V). The case of a patient presenting with IED, intellectual disabilities, and obsessive ritualistic behaviours is described.

Pathophysiology

The authors propose deep brain stimulation (DBS) of the ventral capsule/ventral striatum (VC/VS), a well-known target for other psychiatric disorders, as effective for the treatment of IED [2, 3]. Bilateral VC/VS DBS was successfully used after the temporary efficacy of bilateral posterior hypothalamus (pHyp) DBS in another single case of IED [4]. Stimulation of the right "orbitofrontal projections" (VC/VS) has been reported with success in a case of IED [5].

Bilateral pHyp DBS has been extensively used with efficacy [6–12]. Some disputations about the fact that the pHyp target of Sano et al. [13] be at the level of the diencephalon-mesencephalic junction (the "posterior hypothalamic region") [14] or definitely in the ventral tegmental area (VTA) have to be considered [15, 16] in order to better understand the anatomical substrate of the disorder.

Following studies of rodents and primates [17], but also functional imaging human studies on aggressive patients [18], the authors sustain the hypothesis of Davidson et al. [19] that a dysfunction of the "emotional brain" plays a pivotal role in aggressive behaviour pathophysiology. This circuit includes the anterior cingulate cortex, the orbitofrontal cortex, the amygdala, the insular cortex, and the VS. Still, the hypothalamus is only marginally cited as having a pathophysiological role in aggressive behaviour [19, 20].

Nevertheless, Cannon and Bard in the 1920s, Papez in the 1930s, MacLean in the 1940s, and other more recent "affective neuroscientists" considered the hypothalamus a key region in the emotional response to stimuli and aggressive behaviour expression [17, 21]. The experimental low-frequency (8 Hz) stimulation of the posteromedial hypothalamus led to autonomic system arousal and defence-like behaviour in cats [22]. Following these observations, Miyazaki et al. [23] and Sano et al. [13], in the 1960s, popularized with success the technique of pHyp lesioning in patients with severe aggressive behaviours.

Given these considerations, both the pHyp region and the VC/VS probably belong to the brain systems involved in the processing and expression of emotions. In order to further define the anatomical regions involved in the generation of aggressive behaviour, DBS-related literature data are of paramount relevance, even though they are not often considered. The reported efficacy of both the VC/VS and the pHyp targets led us to consider the possible structure connecting the 2 above-mentioned DBS target regions. The only well-described anatomical bundle of fibres connecting these 2 areas is the mesolimbic pathway, a dopaminergic pathway primarily connecting the VTA (located in the so-called "posterior hypothalamic region" defined by Starr [14]) with the nucleus accumbens, part of the VS complex.

This pathway is also known as the "reward pathway" because it is activated during the processes of rewarding, by which appetitive and consummatory behaviours are induced. This pathway has been extensively studied in addiction, and it is supposed to have a role in the positive symptoms of schizophrenia [24, 25].

Animal studies have already shown a role of this pathway in the pathophysiology of aggressive behaviour, but this was never delineated in humans (also given the obstacles in performing invasive studies). Panksepp and Zellner [26] hypothesized 2 distinct categories of aggression, RAGE and SEEKING, the former describing offensive/defensive rage and the latter predatory and methodical aggression. The rage response is mediated by the corticomedial amygdala, the medial hypothalamus, and the periaqueductal grey. Periaqueductal grey would generate the autonomic arousal, thanks to its brainstem nuclei connections, by means of the dorsal longitudinal fasciculus. The core of this system seems to be glutamatergic. The SEEKING response is mediated by the lateral hypothalamus and the mesolimbic dopaminergic system (VTA and nucleus accumbens). Panksepp and Zellner [26] also proposed interrelations between these 2 systems, mediated by an intrahypothalamic system between the medial and the lateral part. Both animals and humans would react with rage (RAGE system involvement) when an expected reward was not received (SEEKING system involvement), generating frustration. So, the electrical stimulation of DBS targets in the mesolimbic pathway could introduce a "noise" in the rewarding system, blocking an aggressive behaviour.

These observations on the pathogenesis of IED led us to consider the disease as a circuitopathy or a system disease, in which the mesolimbic "reward" system has a central role. This observation allows clarifying the possible reason why both VC/VS and pHyp targets are successfully used in the DBS of aggressive behaviour.

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It is also worth mentioning that aggressive behaviour in humans is under a fine cortical control, mostly involving the orbitofrontal cortex [17, 20, 21]. The implanted patients come with moderate to severe intellectual disabilities, which can further explain the failure of cortical control over the frustration-rage mechanism.

Choice of the Target

The modulation of different neural nodes in the same circuit can potentially give different therapeutic responses. Indeed, the targets generally do not just lie on one circuit.

The VC/VS target also allows the modulation of the fibres connecting the orbitofrontal cortex and the subgenual cortex to the medial, dorsomedial, and anterior nuclei of thalamus, which are supposed to have a role in the pathogenesis of obsessive-compulsive disorder (OCD) [27]. These considerations are the theoretical basis of the efficacy of capsulotomy for OCD [28]. In the reported case, the authors show how the modulation of VC/VS generates a clear improvement of "ritualistic obsessions."

The pHyp target was reported to be effective in the palliative treatment of drug refractory seizures in different series [8, 10]. The mechanism of action probably relies on the modulation of the mammillothalamic tract of Vicq d'Azir, which lies just anterior to the pHyp target. The mammillothalamic tract projects to the anterior thalamic nuclei, which has diffuse projections to frontal and temporal lobes. Bilateral anterior thalamic nuclei DBS is a CE-marked procedure for the treatment of drug refractory epilepsy [29].

Another aspect which has to be considered is that the stimulation of the pHyp allows a direct modulation of the autonomic system, probably via the modulation of the dorsal longitudinal fasciculus arising there. Still, the pHyp region can be considered as a node of both the limbic and the autonomic system. This aspect can be taken into account in patients presenting with autonomic system disorders, such as trigeminal autonomic cephalalgias.

Since IED is often associated to other disorders, such as intellectual disabilities, OCD, and epilepsy [30], a patient-tailored target can be chosen.

We also want to discuss the following statement from Giordano et al. [1]: "this target is approximately the same used for OCD and has indeed the advantages of avoiding neurovegetative side effects as in the posteromedial hypothalamus." In this case the authors refer to the experience of the Torres group and that one of our group [8, 11]. Out of the 7 patients treated by our group, only 1 patient had vegetative side effects, which prevented us from looking for optimal stimulation parameters [8]. Only a transient sympathetic response was observed in 1 out of 6 patients in the Torres group [11]. The possible autonomic side effects have to be taken into account in target selection. It is probably true that these side effects prevented physicians from getting optimal stimulation parameters in a single case.

Before choosing the target, another key point concerns the stimulation intensity necessary for effective pHyp DBS, which is generally lower than that used in VC/VS DBS. The experience of Franzini et al. [8] shows that voltage is always under 3 V (between 1 and 3 V in our group), the frequency is between 130 and 180 Hz, the pulse width is between 60 and 117 μs, and the stimulation is monopolar with the contact 0 as the negative contact, or bipolar using the 2 farthest contacts. Giordano et al. [1] set the following therapeutic parameters: 2.5 V, 130 Hz, 210 μs, using bilateral 4-contacts monopolar stimulation, with the internal pulse generator (IPG) as the cathode. The other group reporting VC/VS DBS for the treatment of aggressive behaviour used higher stimulation intensities, as generally reported in DBS for OCD [4, 5]. So, using less energy-demanding parameters is relevant in this population because of the less frequent episodes of IPG end-of-life issues and surgical replacement necessity. In our experience the end of battery life is challenging for patients, caregivers, and hospital carers because of the nature of the disease. Sudden aggressive reactions are generally observed. So, a strategy to reduce the number of these occurrences has to be seriously considered. Unfortunately, the use of a rechargeable IPG would be, at least, a weekly challenge due to the scarce patient compliance in IPG recharging.

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