Vim stimulation as a predictor of response to deep brain stimulation in patients of severe tremor undergoing dual stimulation

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***Background*: Deep brain stimulation, targeting the ventral intermediate nucleus of the thalamus (Vim), has been shown to be an effective management tool for tremors refractory to other therapies. There is some variance in response to Vim stimulation for severe essential and rubral tremors.**

***Methods*: This study looked at dual stimulations (addition, in which the Vim is stimulated along with an additional nucleus or augmentation, in which a second lead is placed within the Vim itself) for these types of tremors. A total of eight patients, four with rubral and four with severe essential tremors, were treated with deep brain stimulation. The responses of the patients were characterized on a scale from excellent improvement to worsening of condition.**

***Results*: Two of the four patients with rubral tremor had an excellent response to Vim stimulation. These patients showed additional benefits when the prelemniscal radiation (Raprl) was stimulated, in addition to the Vim. Three of the four patients with severe essential tremor reported either a good or excellent response to Vim stimulation. One of these patients had the Raprl stimulated in addition to the Vim while another had an augmentation of the Vim, with ventralis oralis posterior (Vop) stimulation. Both showed additional benefits with the addition or augmentation performed.**

***Conclusions*: We conclude that if a patient with severe medically refractory tremor (essential or rubral tremor) responds to Vim stimulation but is still disabled he will likely also have a response to dual stimulation with an additional lead in the Raprl or an augmentation with an additional lead in the Vop. Patients who did not initially respond to Vim stimulation did not respond to the placement of a second lead. We also conclude that for severe essential tremor, Raprl stimulation showed a better response than Vim stimulation.**

tremor | Vim | Voa | Vop | Raprl | newer targets | multiple targets

Patients with tremor refractory to medical management are often sent for ventral intermediate nucleus (Vim) of the thalamus deep brain stimulation (DBS) surgery. Results are usually good. However, in cases of severe essential tremor and rubral tremor the outcomes of surgery are less predictable (1). Dual stimulations can be performed in these cases for additional benefit. They can be performed in two forms as follows: addition, in which the Vim is stimulated along with an additional nucleus or augmentation, in which a second lead is placed within the Vim itself (1-3). There is no existing paradigm to predict how a patient will respond to the second stimulation. This paper studies the responses of severe tremor to dual stimulations (additions and augmentations) and sets a paradigm that will help predict whether a second stimulation should be performed. In addition this paper compares the effects of prelemniscal radiation (Raprl) stimulation to the older and more traditional Vim target in treating tremor.

Previous work (3-7) has shown promise in targeting areas other than the Vim for essential and Holmes? tremor (rubral tremor), these include the ventralis oralis anterior (Voa) and posterior (Vop) areas of the thalamus and the globus pallidus internalis. Furthermore, it has been suggested (5) that since a Holmes? tremor involves both the cerebellothalamic and pallidothalamic circuits, combined stimulation of the subthalamic and thalamic nuclei should lead to better outcomes than Vim alone. The posterior subthalamic area, including Raprl, have shown promise as a target for amelioration of both types of tremors.

Materials and Methods

Case Selection. The study was carried out at the Center for Neurological Restoration at the Cleveland Clinic (Cleveland, Ohio). After IRB submission and approval all patients with severe rubral tremor and essential tremor undergoing stimulation of either a new target or multiple targets were selected. A new target was defined as any target other than Vim. These included Voa, Vop and Raprl. Multiple targets was defined as any combination of more than one target.

Case Evaluation. Response to stimulation of each target was characterized as: Excellent improvement (50% or greater improvement from previous functioning as judged by the patient), Good (25-49% improvement), Mild (less than 25% improvement), unchanged and worse. Response to stimulation of new targets as well as dual target stimulations was assessed similarly. The Fahn-Tolosa-Marin Tremor Rating Scale was not used as this was a retrospective study based on a chart review. This is also the reason why these patients were not followed prospectively.

Statistical Analysis. The number of cases in the series was small (eight) therefore each case was looked at individually under the broad categories of change in function that is: a) Excellent improvement, b) Good improvement, c) Mild improvement, d) Unchanged and e) Worse.

Results

A total of eight patients were treated with deep brain stimulation for either rubral or essential tremor. There were four cases of rubral tremor and four of severe essential tremor. Relevant clinical data are

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Table 1: Clinical profile of individual patients

Pt #	Age	Gender	Tremor Type
1	34	M	rubral
2	51	M	rubral
3	55	M	rubral
4	58	M	rubral
5	74	M	essential
6	75	M	essential
7	79	F	essential
8	81	F	essential

presented in Table 1.Four of the eight cases were resolved satisfactorily after Vim stimulation. The rest required further stimulations involving Raprl, Vim/ Vop and Vop as tremor control was inadequate with Vim stimulation alone. Details of these stimulations in terms of site of stimulation and the order in which they were performed are shown in Table 2.

Table 2: Total number of surgical procedures performed on each patient

Pt #	Number of procedures	Type of procedure[a]
1	1	Right-Vim
2	1	Left Vim + Left Raprl
3	1	Right Vim + Right Raprl
4	2	Right Vim, Vim lead reimplanted (for lead break), Right Raprl added to Vim
5	3	Left Vim, Right Vim, Left Vim + Left Vim/ Vop
6	3	Left Vim, Left Raprl, Left Raprl lead replacement for lead break
7	1	Left Vim + Left Vop
8	5	Left Vim, Re-implanatation of Left Vim, Right Vim attempted, Right Raprl, Left Raprl (Left Vim left in place)

[a] Vim- Ventral intermediate nucleus of the thalamus; Rapl- prelemniscal radiation; Vop- ventralis oralis posterior nucleus of the thalamus

Rubral tremor outcomes. The four patients with rubral tremor responded differently to Vim stimulation. Two of the four (50%) had an excellent response, while the other two (50%) had a mild response. Three patients had additional stimulation (Vim + Raprl). Of these, Patient 2, who had a mild response to Vim stimulation, also showed a mild response to addition of Raprl stimulation. The two patients who showed an excellent response to Vim stimulation had an even better response (further reduction in tremor and improvement in function) with additional Raprl stimulation as compared to Vim stimulation alone. This data is summarized in Table 3.

Essential tremor outcomes. There were four patients with advanced essential tremor, and three of them (Patients 5, 6 and 8) had a good or excellent response with Vim stimulation. Of these three patients, patient 5 had an augmentation of Vim stimulation with Vop stimulation. This led to a better response than that achieved only through Vim stimulation alone. Patients 6 and 8 had Vim stimulation in addition to Raprl stimulation which led to an excellent response. In patient 8, the addition of Raprl stimulation showed additional benefits as compared to Vim stimulation alone. Patient 7 had an augmentation of Vim with Vop. The response of the augmentation was mild as was seen with stimulation of Vim alone. The patient responses are shown in Table 4.

Table 3: Rubral tremor outcomes

Pt #	First surgical session[a]		Second surgical session
1	-	Right Vim mild response	-
2	Left Vim- mild response	Left Raprl (addition)- mild response	-
3	Right Vim - excellent response	Right Raprl (addition)- excellent response with additional benefits	-
4	Right Vim - excellent response	-	Right Raprl (addition)- excellent response with additional benefits

[a] Column hyphens indicate absence of another stimulation at that surgical session

Table 4: Advanced essential tremor outcomes

Pt #	First surgical session[a]		Second surgical session		Third surgical session
5	Left Vim excellent response	-	Right Vim good response	-	Left Vim/Vop (augmentation) excellent response with additional benefits
6	Left Vim mild response	-	Left Raprl (addition) excellent response	-	-
7	Left Vim excellent response	Left Vop (augmentation) mild response	-	-	-
8	Left Vim excellent response	-	Right Raprl excellent response	-	Left Raprl (addition) excellent response

[a] Column hyphens indicate absence of another stimulation at that surgical session

Side effects. A total of 9 side effects resulted from the therapeutic interventions. These side effects are enumerated in Table 5. Of the twelve patients that had the Vim stimulated nine (75%) experienced side effects. These included dysarthria, electric sensation, limb weakness, throat constriction and hemorrhage. There was additional left-handed numbness (with Raprl stimulation) and post-operational confusion (with Vop stimulation) when augmented stimulation was used along with Vim. Of the four procedures where only the Raprl was stimulated three (75%) did not lead to any complications. One of the patients experienced seizures. The most common complication overall was dysarthria, followed by limb weakness and an electric sensation in the limbs.

Table 5: Complications from stimulation of various areas

Area Stimulated	No. side effects	Complications									Total Proced-ures
		Dys-arthria	Left hand numbness	Electric sensation	Limb weakness	Throat constriction	Post-op confusion	Postural instability	Seiz-uses	Hemor-rage	
Vim	3	3		2	2	1				1	2
Vim + Raprl		1	1					1			3
Vim + Vop	1	1					1				3
Raprl	3								1		4
Total complications	7(no comp-lications 5)	5	1	2	2	1	1	1	1	1	

Discussion

Additions and Augmentations. DBS of the Vim is very effective in managing medication refractory essential tremor (8-11). With medications tremor control is at best 50% (12) but with Vim DBS tremor-control is achieved in around 80% of patients (13,14). In some patients with severe tremor however the effect of Vim stimulation is less predictable. These are patients with rubral tremor and severe essential tremor (15). In these patients additions and augmentations of stimulation have been performed with additional benefit in some (5,6). Additions consist of stimulation of an additional nucleus e.g. If a patient has had Vim stimulation then an addition would consist of Vim + Raprl stimulation (See Fig. 1 below). In some patients augmentation was performed, e.g. Vim + Vop (See Fig. 1 below). The issue so far has been the absence of an available algorithm to predict whether performing an addition or augmentation will provide additional benefit to the initial Vim stimulation. In our series of patients we found that, in both rubral tremor as well as severe essential tremor, if Vim stimulation produced a good response then an addition or an augmentation produced additional benefit. However, if there was an absence of a good response to Vim, additions and augmentations did not show additional benefit. Additions and augmentations act by increasing the inhibition of thalamic output to the cortex (4, 5, 15). It is unclear how this may be taking place but in all probability it is due to an additive frequency being provided by the second stimulator through the second lead (4, 5, 16). This frequency can be delivered to another spot in the same nucleus (augmentation) or to another spot in the tract like the Raprl (addition) which inputs into the Vim. The electrical effect is of providing double the frequency (two stimulators providing around 130Hz each) as compared to a single stimulation (1-3, 5-7). For some reason most patients cannot tolerate turning up the frequency very high through a single lead but can do so if fractionated over 2 spots in the same nucleus or one in the nucleus and another in an afferent tract (Raprl) (17). Doubling the frequency provides increased inhibition and therefore a better therapeutic effect (4,6). With the new stimulators it is possible to produce this effect by interleaving, that is running two programs on the same lead in the Vim so that the overlapping area gets double the frequency. The basic question still remains as to why some of these tremors show a good response to the initial Vim stimulation and others do not. It appears that the physiology of tremor in the non-responders is different (4-7). These patients may have the tremor generating oscillator outside the stimulated circuit which has traditionally been thought of as being the cerebello-thalamic and pallido-thalamic pathways (5,15). It has been shown that the Raprl has fibers that originate from the mesencephalic reticular formation, connecting it to the thalamus via the ascending cerebellothalamic fibers (17-23). These fibers project onto the ventrolateral thalamus, including the Vim. Stimulation of the Raprl is a good point to catch these ascending cerebellothalamic fibres as they converge together here before entering the thalamus. The Vop, the pallidal afferent pathway, have been shown to be an effective target

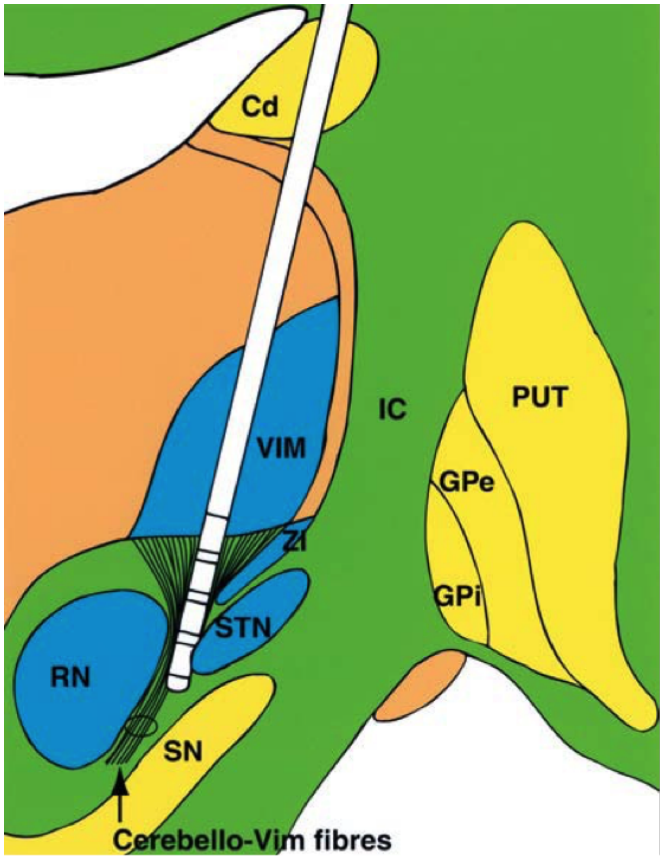

Fig. 1: Sagittal section through the thalamus. Schematic diagram showing the position of the DBS electrode in relation to the path of the cerebello?Vim fibers from the dentate and interpositus nuclei on the left side. The electrode is placed where these fibers are concentrated together in the subthalamic region before ?fanning out? to the large body of the Vim above. Cd = caudate nucleus; GPi = globus pallidus internus; IC = internal capsule; PUT = putamen.

area for amelioration of essential tremor (4). While the exact pathological loop that connects the Vim and Vop is not known, it has been shown that the Vop might have a greater effect on tremor control than previously imagined. The Vop has been hypothesized to be a cerebellar receiving area (24) and some cells of this area have been implicated in tremor related activity (25). This would explain the additional benefits from Vop stimulation in addition to Vim.

Raprl stimulation alone had a better outcome than Vim stimulation alone in advanced essential tremor. Raprl stimulation alone for advanced essential tremor had a better success rate than Vim alone. The explanation for this is two-fold. Firstly, it has been shown that more energy is required for exciting cell bodies than for myelinated fiber tracts (17). Secondly, the fibers from the interposed nucleus of the cerebellum are more abundant and more compactly packed in the posterior subthalamic area than in the thalamus (18). For these reasons a single electrode stimulation of the Raprl leads to a better response than stimulation of the Vim. A larger number of cases will have to be systematically studied to validate this conclusion.

Loss of benefit over time in advanced essential tremor. In all the above patients the effect of DBS in essential tremor wore off with time due to tolerance. In some of these patients the benefit can be regained by reprogramming (11-14). However an initial poor response to DBS could not be fixed by conventional reprogramming and therefore dual stimulations were used. This suggests that those tremors that are responsive to DBS have a different electrical physiology from those that are not responsive. DBS can overwrite the abnormal discharge in the responsive patients. In these patients if the abnormal signal re- emerges it can again be taken down by a new DBS program. However patients who are unresponsive seem to have a different electrical signal that cannot be overwritten by DBS.

Resistance to DBS. Most tremors are generated by central oscillators. In essential tremor it is most likely the inferior olive (26). In rubral tremor it is thought to be the thalamus (27). One question remains: In patients who do not respond to DBS could the oscillators be located outside the cerebellothalamicocortical pathway? This is unlikely as it has repeatedly been shown (28, 29) that the central oscillatory circuit in essential tremor is the olivo?cerebello?thalamic circuit. The failure to respond to DBS is possibly due to a different form of electrical signal or a different signal to noise ratio in these patients which seems to bypass the suppressive effect created by electrical noise from the DBS. This hypothesis will have to be proven by further studies.

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