

## Case report

# Hemi-parkinsonism and return of essential tremors after MRgFUS thalamotomy: Case report and review of procedural complications affecting ventral thalamic nuclei

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## ABSTRACT

Magnetic resonance guided focused ultrasound (MRgFUS) thalamotomy targets the ventral intermediate nucleus of the thalamus and has been shown to be safe and effective to treat medication-resistant essential tremors. Improvement in tremor scores, posture and action scores, disability scores and quality of life scores have been reported in patients treated with this procedure. Adverse events are usually transient and non-severe. We present a patient who underwent MRgFUS thalamotomy of the left VIM and developed new-onset parkinsonian features predominantly on the right side and return of essential tremors a few years after the procedure. Changes in speech (hypophonia and dysarthria), gait imbalance and postural instability, bradykinesia, and cogwheeling rigidity occurred, likely due to involvement of the fiber tracts through the ventrolateral subnuclei and the adjacent ventral anterior thalamic nuclei and other surrounding structures. We describe side effects of MRgFUS thalamotomy in our patient compared to previous reports and review the thalamic nuclei and surrounding structures that can be affected during procedure, causing these effects.

## 1. Introduction

Essential tremors (ET) are due to possible neurodegenerative pathology in the cerebellum with loss of Purkinje cells [4]. An alternative hypothesis suggests that a reduction in the GABA-A and GABA-B receptors in the dentate nucleus of the cerebellum are responsible [5]. The net result is decreased inhibition of the deep cerebellar neurons with spreading overactivation into the cerebello-thalamo-cortical network and entrainment of each component in the loop [4,8]. The ventral intermediate (VIM) nucleus of the thalamus, a relay in the cerebello-thalamo-cortical tremor network, receives input from the cerebellum via the dentato-rubro-thalamic tract and has been targeted in surgical treatments of ET [9]. Magnetic resonance guided focused ultrasound (MRgFUS) thalamotomy is a relatively new technique for the ablation of the VIM in patients with ET [1,13]. We present a patient who underwent MRgFUS thalamotomy and developed parkinsonian features with a return of ET symptoms within the first three years post-procedure. We review side effects reported from previous clinical trials, outlining the tracts and thalamic nuclei involved in these outcomes.

## 2. Case report

An 84-year-old man presented with a history of ET in the hands bilaterally, with the right more affected than left, that was refractory to primidone and propranolol. He underwent a MRgFUS thalamotomy of the left VIM for essential tremors, with significant improvement of his right arm tremor. Before MRgFUS thalamotomy, he had a kinetic tremor, worsened with intention, on finger-to-nose testing, no bradykinesia, and mild ataxia on tandem gait testing. One day after the procedure, his gait testing demonstrated worsened tandem walking and a widened base. These findings persisted on 6-month follow up. He endorsed a return of his right-hand tremor to his pre-thalamotomy baseline after one year. Between 1 and 3 years after this procedure, his balance further worsened, and he developed new symptoms of bradykinesia and hypophonia.

Patient had a family history of essential tremors. He denied anosmia, or REM sleep behavior disorder symptoms. No features of psychosis, no hallucinations (visual or auditory) and no features of impulse control disorder were reported in him. His weight and appetite were stable, noted around 90 kg on initial and follow up visits. He did endorse

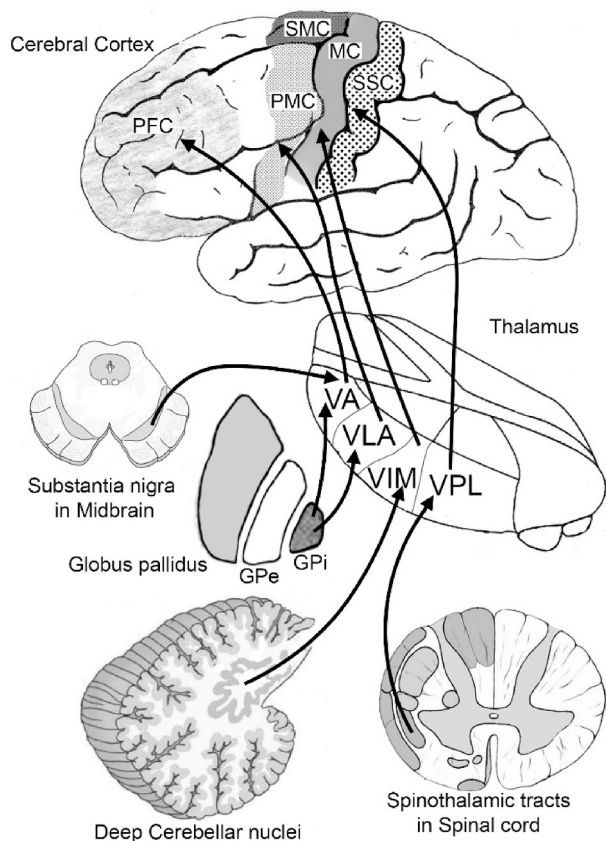
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**Fig. 1.** Afferents and efferents of ventral thalamic nuclei: The VA and the VLA are the BG-recipient zone and the VIM is the cerebellar recipient zone. PFC: prefrontal cortex, PMC- premotor cortex, SMC-supplementary motor cortex, MC-motor cortex, SSC-somatosensory cortex. GPe-Globus pallidum externa, GPi-Globus pallidum interna; VA-ventral anterior, VLA-ventrolateral anterior, VIM- ventral intermediate; VPL-ventroposterior (Lateral).

Figure Courtesy: Dr. John Cork, Computer Imaging Lab, Department of Cell Biology & Anatomy, LSU Health Sciences Center - New Orleans.

constipation that was relieved by miralax and senna. No features of urinary retention or bladder dysfunction were endorsed. He denied any orthostatic symptoms. There were no restless leg or periodic limb

movements.

On neurologic examination, his voice was hypophonic and mild-to-moderately dysarthric, though all words were intelligible. He displayed delayed responses in speech, with intact fluency, comprehension, and repetition. There was cogwheeling rigidity on the right upper extremity more than lower extremity and contralateral side. He had a moderate amplitude postural and kinetic tremor of the right hand with a delay in the emergence of the tremor with sustention. He had moderate hypokinesia and mild dysmetria on the right. Gait showed a slightly flexed posture of the right arm with some circumduction of the right leg.

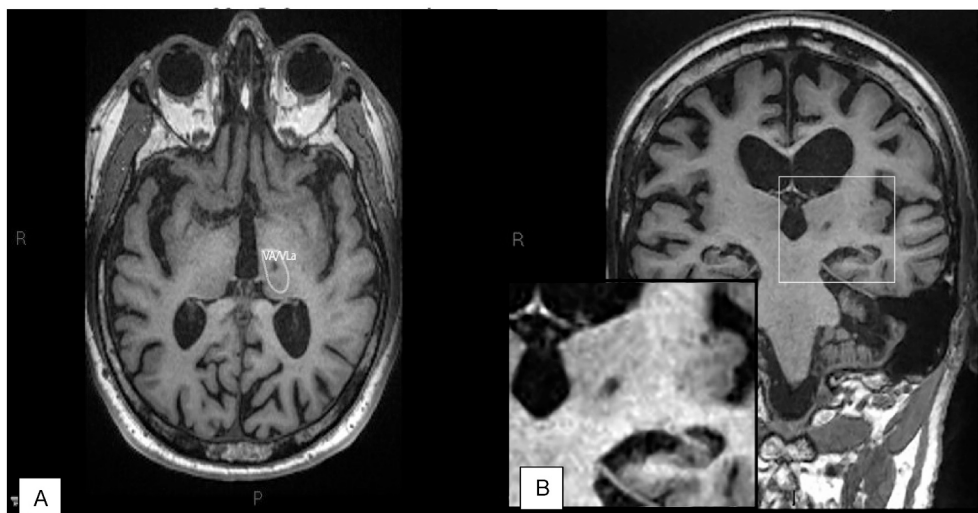
Vascular risk factors with Hba1c < 6.5%, lipid panel with LDL of 37.2 mg/dl and normal thyroid, kidney and liver function were present on laboratory work-up. He was normotensive on exam. On magnetic resonance brain imaging, mild chronic microvascular changes, and mild-to-moderate cerebral atrophy were evident.

Since the patient was exhibiting clinical signs of parkinsonism, a trial of carbidopa/levodopa (CD/LD) at 25/100 mg orally three times daily was initiated, but aborted on follow-up, as it did not improve symptoms even minimally but caused nausea and dizziness and increased his fall risk. There were no orthostatic symptoms or changes in his vitals, and systolic BP was always >120 mmHg range. There were no signs of supine hypertension, or post-prandial changes in BP.

### 3. Discussion

MRgFUS thalamotomy has been shown to be a safe and effective treatment for medication-resistant ET with improvement in tremor scores, posture and action scores, disability scores, and quality of life scores [1,2,11,13]. The typical target for MRgFUS thalamotomy is the VIM, which is a subnucleus within the ventrolateral (VL) thalamic nucleus. The role of the VIM in tremor is likely related to cerebellar input with efferent connections directly to the motor cortex, as well as relaying proprioceptive information from the deep cerebellar nuclei to the premotor cortex [9,25].

Adverse events from previous MRgFUS thalamotomy trials frequently included sensory disturbances [1–3,13] in the form of dysesthesias and paresthesias during and after the procedure. These symptoms are due to involvement of the ventroposterior [ventroposterior lateral (VPL) and ventroposterior medial (VPM)] thalamic nucleus, which has afferents that include medial lemniscal and spinothalamic tracts laterally (*trunk and extremities*), and trigeminal tract afferents medially (*face*), with efferents towards the somatosensory cortex. Sensory symptoms were not reported in our patient, likely due to anterior thalamic ablation site as we discuss further. [15].



**Fig. 2.** A/B: MRI brain axial (A) and coronal (B) slice demonstrating MRgFUS thalamotomy lesion in Left VIM with overlapping spread anteriorly.

**Table 1**  
Side effects from MRgFUS thalamotomy and thalamic nuclei involved:

	Speech Side Effects
VA nuclei	Hypophonia [10] Dysarthria [10]
VL nuclei	
BL VL lesions	Hypophonia [9]
Medial VL nucleus [L]	Anomia, perseveration [6,7]
Medial to VLp/VIM	Dysarthria* [2,10]
Posterior to VLp/VIM	Fluency deficits [6]
Central medial VL nucleus	Modulation of voice due to respiratory integration in voice production* [7,10,14]
	Motor Side Effects
VA neurons	Dystonia [10]
VA-VL complex	Rigidity* Bradykinesia
Corticospinal tracts	Spasticity*
Internal Capsule	Motor weakness [2]
VLp thalamic radiation via Genu of IC	Ataxia, postural imbalance* [18,19,23]
	Sensory Side Effects
VP nucleus	Dyesthesias, Paresthesias [1–3,13]
VPM [parvicellular]	Dysgusia [10]

\* Side effects seen in our patient.

Situated anterior to the VIM is the ventrolateral anterior (VLa) nucleus, which receives inputs from the globus pallidum. Anterior to the VLa nucleus is the ventral anterior (VA) nucleus, which also receives input from the globus pallidum, in addition to the substantia nigra (Fig. 1) [12]. The VLa and VIM are known as the motor thalamic nuclei. Efferents from these nuclei proceed to areas of the motor and premotor cortex (Fig. 1). The VA and the VL are difficult to separate resulting in physiologists dividing the VA-VL complex into the basal ganglia recipient zone (VA and VLa nuclei) and the cerebellar recipient zone (VIM nucleus); the afferents from the basal ganglia and cerebellum do not cross or overlap [24,25].

In our patient, adverse events of parkinsonism included changes in speech, tone, and bradykinesia. Anterior placement of the thalamotomy lesion, resulting in involvement of the afferents from the globus pallidus interna (Gpi) and substantia nigra (SN) and their efferent connections to motor and premotor cortex, likely caused the parkinsonian-like motor and speech changes. In Fig. 2 are shown the MRI brain axial and coronal slices, which demonstrate the lesion site, targeting the VIM with overlapping involvement of the anteriorly located ventral thalamic nuclei (VLa and VA). Extrathalamic structures, such as the pyramidal tract and the internal medullary lamina, can help identify the ventral motor thalamic nuclei from the ventral sensory thalamic nuclei [27]. The VIM can be identified by the dentorubrothalamic tract (DRT), a hypointense structure surrounded by the VIM [28].

Studies have shown that VL thalamotomy increases bradykinesia [20–22] with interruption of the nigral-pallidal connections via thalamus to premotor cortex which normally facilitates desired movement and inhibits unwanted movements [26]. Inferolateral to the motor thalamic nuclei, involvement of the corticospinal and pyramidal tracts can cause changes in tone and motor strength in an individual [2]. Proprioceptive afferents from the deep cerebellar nuclei via the VIM nucleus can indirectly produce ataxia and truncal instability/postural imbalance [18,19,23], which was noted in our patient.

Our patient also developed expressive language changes after thalamotomy. Speech and language changes, including dysarthria, modulation in voice rhythm and tone are well-described complications of ablation and deep brain stimulation of the VIM in Parkinson's Disease [2,16,17]. Mild deficits in verbal fluency and executive functions following lesions anterior to the VIM [6] are seen due to efferent connections from the ventral anterior thalamic nuclei projecting towards the temporo-parieto-occipital cortex overlapping Wernicke's area [7]. Dysarthria can also be from involvement of passing pallidal fibers in the VA-VL thalamus complex which terminate in the prefrontal cortex

(Broca's area). Laterality to the left hemisphere may explain the expressive language changes noted after the procedure. Changes in tone of the muscles of the tongue and larynx, due to pallidal afferents terminating in motor homunculi, have occurred from left medial central VL thalamic lesions causing modulation of voice and its tone [7,10,14].

Disruption of cerebellar, basal ganglia, and nigral connections via the left VL and possibly overlapping with VA nuclei from anterior lesional placement likely produced a combination of speech changes, postural instability, and parkinsonism in our patient. We review the other side effects reported during and after the procedure and elucidate the possible thalamic nuclei involved (Table 1).

The prevalence of parkinsonism is increased in the elderly population (> 65 yrs), with speech changes, rigidity and changes in gait simulating PD [29]; and these changes may be exacerbated due to the natural history of neurodegeneration in elderly patients. Vascular parkinsonism can be seen in patients with lacunar/small deep subcortical infarcts and white matter changes [31]. In our patient, vascular risk factors were well-controlled. Brain imaging showed mild to moderate microvascular sequelae and mild to moderate cerebral volume loss (without lobar predominance), which could have exacerbated the symptoms. In our patient, hemiparkinsonism (right) occurred concurrently with recurrence of ET shortly after a thalamic lesion (left) that affects the pathways as discussed. Therefore, we consider this case as a potential consequence of MRgFUS VIM thalamotomy.

The etiology of tremor relapse after thalamotomy is not entirely clear. One mechanism may be retraction of the thalamic ablation site post procedure and has been described before [11]. After a repeat procedure at the same site, some patients show lasting improvement at 12-month follow up [11]. Our patient did not undergo a repeat procedure. There may also be a resynchronization of the cerebello-thalamo-cortical circuit that causes recurrence of tremor after thalamotomy and deep brain stimulation (DBS) of the VIM. This may explain why there is a short duration of effect from changes to stimulation parameters in some patients.

Parkinsonian features and recurrence of ET on the right, corresponding to left VIM lesion in our patient, raises the question of whether hemiparkinsonism can be a side effect of unilateral MRgFUS thalamotomy. Dysarthria and ataxic changes in gait can be seen with DBS of the VIM thalamus, more commonly with bilateral DBS surgeries, however, these complications can be minimized by programming adjustments [30]. Hence, while MRgFUS thalamotomy may be appealing as a less-invasive procedure, the possibility of irreversible side effects must be discussed with the patient when considering MRgFUS versus DBS as potential treatment options for essential tremor.

## References

- [1] J.W. Chang, C.K. Park, N. Lipsman, et al., A prospective trial of magnetic resonance-guided focused ultrasound thalamotomy or essential tremor: results at the 2-year follow-up, *Ann Neurol* 83 (1) (2018 Jan) 107–114.
- [2] A. Boutet, M. Ranjan, J. Zhong, et al., Focused ultrasound thalamotomy location determines clinical benefits in patients with essential tremor, *Brain* 141 (12) (2018 Dec 1) 3405–3414.
- [3] P.S. Fishman, W.J. Elias, P. Ghanouni, et al., Neurological adverse event profile of magnetic resonance imaging-guided focused ultrasound thalamotomy for essential tremor, *Mov Disord* 33 (5) (2018 May) 843–847.
- [4] E.D. Louis, P.L. Faust, J.P. Vonsattel, et al., Neuropathological changes in essential tremor: 33 cases compared with 21 controls, *Brain* 130 (2007) 3297–3307.
- [5] S. Paris-Robidas, E. Brochu, M. Sintès, et al., Defective dentate nucleus GABA receptors in essential tremor, *Brain* 135 (Pt 1) (2012 Jan) 105–116.
- [6] G.A. Ojemann, P. Fedio, J.M. Van Buren, Anomia from pulvinar and subcortical parietal stimulation, *Brain* 91 (1968) 99–116.
- [7] G.A. Ojemann, A.A. Ward Jr., Speech representation in ventrolateral thalamus, *Brain* 94 (1971) 669–680.
- [8] M. Najac, I.M. Raman, Integration of Purkinje cell inhibition by cerebellar nucleo-olivary neurons, *J Neurosci* 35 (2) (2015 Jan 14) 544–549.
- [9] L. Milosevic, S.K. Kalia, M. Hodaie, et al., Physiological mechanisms of thalamic ventral intermediate nucleus stimulation for tremor suppression, *Brain* 141 (7) (2018 July) 2142–2155.
- [10] J.D. Schmahmann, Vascular syndromes of the thalamus, *Stroke* 34 (9) (2003 Sep) 2264–2278.

- [11] E.K. Weidman, M.G. Kaplitt, K. Strybing, et al., Repeat magnetic resonance imaging-guided focused ultrasound thalamotomy for recurrent essential tremor: case report and review of MRI findings, *J Neurosurg* 25 (2019 Jan) 1–6.
- [12] G. Schaltenbrand, W. Wahren, *Atlas for Stereotaxy of the Human Brain*, Thieme, Stuttgart, Germany, 1977.
- [13] W.J. Elias, N. Lipsman, W.G. Ondo, P. Ghanouni, et al., A randomized trial of focused ultrasound thalamotomy for essential tremor, *N Engl J Med* 375 (8) (2016 Aug 25) 730–739.
- [14] F. Lhermitte, Language disorders and their relationship to thalamic lesions, *Adv Neurol* 42 (1984) 99–113.
- [15] A. Sinai, M. Nassar, A. Eran, M. Constantinescu, M. Zaaroor, E. Sprecher, I. Schlesinger, Magnetic resonance-guided focused ultrasound thalamotomy for essential tremor: a 5-year single-center experience, *J Neurosurg* 5 (2019 Jul) 1–8.
- [16] S. Skodda, Effect of deep brain stimulation on speech performance in Parkinson's disease, *Parkinsons Dis* 2012 (2012) 850596.
- [17] J.D. Putzke, R.J. Uitti, A.A. Obwegeser, Z.K. Wszolek, R.E. Wharen, Bilateral thalamic deep brain stimulation: midline tremor control, *J Neurol Neurosurg Psychiatry* 76 (5) (2005) 684–690.
- [18] Sinai A, Nassar M, Eran A, et al. Magnetic resonance-guided focused ultrasound thalamotomy for essential tremor: a 5-year single-center experience [published online ahead of print, 2019 Jul 5]. *J Neurosurg* 2019;1–8.
- [19] B. Sieveritz, M. García-Muñoz, G.W. Arbuthnott, Thalamic afferents to prefrontal cortices from ventral motor nuclei in decision-making, *Eur J Neurosci* 49 (5) (2019) 646–657.
- [20] G. Selby, Stereotactic surgery for the relief of Parkinson's disease. Part 2. An analysis of the results in a series of 303 patients (413 operations), *J Neurol Sci* (1967) 343–375.
- [21] C.D. Marsden, J.A. Obeso, The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease, *Brain* 117 (4) (1994) 877–897.
- [22] L.V. Laitinen, A.T. Bergenheim, M.I. Hariz, Ventroposterolateral pallidotomy can abolish all parkinsonian symptoms, *Stereotact Funct Neurosurg* 58 (1–4) (1992) 14–21.
- [23] R. Nakamura, Postural dependence of reaction time in normal subjects and patients with focal brain lesions, *Appl Neurophysiol* 39 (3–4) (1976) 321–325.
- [24] J.M. Deniau, H. Kita, S.T. Kitai, Patterns of termination of cerebellar and basal ganglia efferents in the rat thalamus. Strictly segregated and partly overlapping projections, *Neurosci Lett* 144 (1–2) (1992) 202–206.
- [25] M. Gaidica, A. Hurst, C. Cyr, D.K. Leventhal, Distinct populations of motor thalamic neurons encode action initiation, action selection, and movement vigor, *J. Neurosci.* 38 (2018) 6563–6573.
- [26] C. Duval, M. Panisset, A.P. Strafella, A.F. Sadikot, The impact of ventrolateral thalamotomy on tremor and voluntary motor behavior in patients with Parkinson's disease, *Exp Brain Res* 170 (2) (2006) 160–171.
- [27] K. Yamada, K. Akazawa, S. Yuen, et al., MR imaging of ventral thalamic nuclei, *AJNR Am J Neuroradiol* 31 (4) (2010) 732–735.
- [28] V.T. Lehman, K.H. Lee, B.T. Klassen, et al., MRI and tractography techniques to localize the ventral intermediate nucleus and dentatorubrothalamic tract for deep brain stimulation and MR-guided focused ultrasound: a narrative review and update, *Neurosurg Focus* 49 (1) (2020), E8.
- [29] D.A. Bennett, L.A. Beckett, A.M. Murray, K.M. Shannon, C.G. Goetz, D.M. Pilgrim, D.A. Evans, Prevalence of parkinsonian signs and associated mortality in a community population of older people, *N Engl J Med* 334 (2) (1996 Jan 11) 71–76.
- [30] R.F. Dallapiazza, D.J. Lee, P. De Vloot, A. Fomenko, C. Hamani, M. Hodaie, S. K. Kalia, A. Fasano, A.M. Lozano, Outcomes from stereotactic surgery for essential tremor, *J Neurol Neurosurg Psychiatry* 90 (4) (2019 Apr) 474–482.
- [31] M. van Zagten, J. Lodder, F. Kessels, Gait disorder and parkinsonian signs in patients with stroke related to small deep infarcts and white matter lesions, *Mov Disord* 13 (1) (1998 Jan) 89–95.