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Deep brain stimulation of the ventrointermediate nucleus of the thalamus to treat essential tremor improves motor sequence learning

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Abstract

The network of brain structures engaged in motor sequence learning comprises the same structures as those involved in tremor, including basal ganglia, cerebellum, thalamus, and motor cortex. Deep brain stimulation (DBS) of the ventrointermediate nucleus of the thalamus (VIM) reduces tremor, but the effects on motor sequence learning are unknown. We investigated whether VIM stimulation has an impact on motor sequence learning and hypothesized that stimulation effects depend on the laterality of electrode location. Twenty patients (age: 38–81 years; 12 female) with VIM electrodes implanted to treat essential tremor (ET) successfully performed a serial reaction time task, varying whether the stimuli followed a repeating pattern or were selected at random, during which VIM-DBS was either on or off. Analyses of variance were applied to evaluate motor sequence learning performance according to reaction times (RTs) and accuracy. An interaction was observed between whether the sequence was repeated or random and whether VIM-DBS was on or off ($F[1,18] = 7.89$, $p = .012$). Motor sequence learning, reflected by reduced RTs for repeated sequences, was greater with DBS on than off ($T[19] = 2.34$, $p = .031$). Stimulation location correlated with the degree of motor learning, with greater motor learning when stimulation targeted the lateral VIM ($n = 23$, $\rho = 0.46$; $p = .027$). These results demonstrate the beneficial effects of VIM-DBS on motor sequence learning in ET patients, particularly with lateral VIM electrode location, and provide evidence for a role for the VIM in motor sequence learning.

KEYWORDS
deep brain stimulation, essential tremor, motor sequence learning, serial reaction time task, ventrointermediate nucleus of the thalamus

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1 | INTRODUCTION

Motor sequence learning enables automation of frequently repeated activities, such as cycling, playing the piano, and motor rehabilitation, including relearning of old motor patterns or developing new movement patterns. Motor skills acquired through extensive repetition subsequently require neither effort nor conscious awareness. Lesion and imaging studies indicate that such procedural learning engages a different network of cortical and subcortical structures to those involved in declarative memory (Hardwick et al., 2013; Tzvi et al., 2014). Anatomical axonal tracing and imaging have revealed circuits involving the basal ganglia, cerebellum, thalamus, and motor cortex (Asanuma et al., 1983; Behrens et al., 2003; Middleton & Strick, 2000). While these circuits are engaged in motor learning (Hardwick et al., 2013; Tzvi et al., 2014), they also comprise the network involved in tremor (Fang et al., 2016; Nahab et al., 2007). Imaging and deep brain stimulation (DBS) studies document a role in tremor for the ventral intermediate thalamic nucleus (VIM) in particular (Haslinger et al., 2003; Morigaki et al., 2011), and VIM-DBS, a well-established essential tremor treatment, targets this circuit (Benabid et al., 1991; Chopra et al., 2013; Cury et al., 2017).

While anatomical, imaging, and DBS studies indicate cerebellum–VIM and VIM–motor cortex connectivity (Haslinger et al., 2003; Morigaki et al., 2011), a role for the VIM in motor sequence learning has not been established. Studies examining the effects of VIM-DBS on motor learning in essential tremor patients have shown improvement (Kronenbuerger et al., 2008), and also impairment (Chen et al., 2006; Luo et al., 2016), independent of tremor severity (Luo et al., 2016). This variation may reflect the different types of motor learning evaluated, including classical conditioning and motor adaptation. Anatomical and single-cell recordings suggest alteration of a kinaesthetic VIM subregion in patients with tremor (Morigaki et al., 2011). The variation in findings might reflect engagement of specific VIM subregions engaging in motor sequence learning networks. The cytoarchitecture in the lateral VIM differs from that medially (Hirai et al., 1989). Anatomical studies reveal termination of cerebellothalamic fibres in the lateral part (Asanuma et al., 1983), and kinaesthetic and tactile responses have been identified in neurons located in the lateral rather than the medial VIM (Ohye et al., 1989).

Here, we investigated whether the VIM is engaged in motor sequence learning by assessing whether VIM-DBS modulates serial reaction time task (SRTT) performance. The SRTT offers a well-established, robust approach for investigating implicit motor sequence learning (Nissen & Bullemer, 1987). Neuroimaging and TMS studies show SRTT performance engages the cerebellum, thalamus, and motor cortex (Hardwick et al., 2013). This task has the advantages of imposing minimal motor demands (Hardwick et al., 2013) and, with longer sequences, reducing the contribution of explicit knowledge (Pollok et al., 2021; Tzvi et al., 2014). Moreover, in the clinical context, a relatively high number of trials can be obtained in a short time period enabling on–off comparisons. Finally, its frequent clinical implementation enables comparison with other studies (Hardwick et al., 2013; Sommer et al., 1999; Tzvi et al., 2014).

We hypothesized that VIM-DBS would modulate sequence learning during the SRTT, supporting a causative role for VIM in motor sequence learning. The findings have potential implications for essential tremor patients receiving VIM-DBS treatment. We also evaluated whether such effects were dependent on the precise stimulating electrode coordinates, examining whether a more lateral VIM location correlates with modulation of motor sequence learning.

2 | MATERIALS AND METHODS

2.1 | Participants

Twenty-five patients with VIM electrodes previously implanted for DBS treatment of essential tremor were recruited through the Stereotactic Neurosurgery Department, University Hospital, Magdeburg and tested in the out-patient setting. Exclusion criteria were a history of epilepsy or other neurological disorder, significant alcohol, recreational drug, or medication abuse, or a psychiatric condition. The hospital's Local Ethics Committee granted ethical approval. All participants provided informed, written consent before study inclusion, in accordance with the Declaration of Helsinki, and were informed of their right to cease participation at any time without providing reasons. The stimulator can be switched on and off by the patient and is commonly stopped overnight to conserve battery power. Disease severity was quantified at the time of the study using the Fahn-Tolosa-Marin Tremor Rating Scale (FTMTRS) (Fahn et al., 1988) with stimulation off.

2.2 | Electrode implantation and postoperative localization

Surgical procedures constituted routine clinical patient management, and all patients received bilateral electrodes and impulse generators (Medtronic Inc., Minneapolis, MN or St. Jude Medical Inc., St. Paul, MN) (Klein et al., 2017). VIM targeting was performed indirectly, based on planned coordinates relative to the anterior and posterior commissures (AC, PC) (Krüger et al., 2020). Electrode placement was planned preoperatively based on individual patient structural MRI scans, confirmed intra-operatively through stereotactic x-rays and clinical response to stimulation, and re-confirmed postoperatively by co-registering postoperative CT scans with the pre-operative MRI images and the intraoperative x-rays, comparing the findings with human brain atlases. The AC–PC coordinates of the postoperative electrode locations, based on co-registering the postoperative CT images and the electrode coordinates from the intraoperative stereotactic x-rays, with the pre-operative

TABLE 1 Clinical information, stimulating electrode coordinates, and reaction times (RT) during VIM-DBS

			AC–PC coordinates			RT (ms)				
									LS-norm	LS-norm
Patient	Age, gender	FTMTRS	*x*	*y*	*z*	Learned	Random	Random-learned	On	Off
1	63.3, F	0.28	−13.1	−2.5	1.4	631.6	677.7	46.1	6.8	8.8
2	72.2, M	0.30	−12.1	−7.5	−3.0	730.6	731.6	1.0	0.14	−0.7
3	79.3, F	0.40	−12.3	−6.5	−1.4	543.3	574.7	31.4	5.5	–[a]
4	78.8, F	0.69	−12.1	−6.0	−1.6	–	–	–	–	–[a]
5	58.8, F	0.26	−12.4	−3.5	0.1	493.7	538.7	45.0	8.4	9.7
6	70.7, M	0.33	−12.2	−5.5	−2.1	543.6	599.2	55.6	9.3	2.7
7	76.4, M	0.29	−12.5	−4.0	−2.5	733.4	770.3	36.9	4.8	6.9
8	69.2, M	0.17	−12.7	−3.0	0.7	567.0	627.5	60.5	9.6	13.6
9	57.0, F	0.18	−12.1	−4.0	−0.8	541.1	598.0	56.9	9.5	2.4
10	64.2, F	0.23	−12.4	−2.5	−1.5	585.3	620.7	35.4	5.7	8.3
11	75.3, M	0.35	−14.6	−5.0	0.8	702.4	787.1	84.7	10.8	4.7
12	71.8, F	0.26	−15.3	−5.0	0.6	617.0	691.3	74.3	10.7	4.5
13	55.2, M	0.19	−11.7	−3.5	1.2	648.6	643.8	−4.8	−0.8	–[a]
14	76.1, F	0.40	−11.5	−7.0	−3.2	704.9	809.7	104.8	13.0	15.0
15	54.4, M	0.42	−12.7	−6.5	−1.9	556.4	626.9	70.5	11.3	5.0
16	76.1, M	0.24	−10.3	−6.5	−3.4	759.9	776.3	16.4	2.1	2.9
17	71.6, M	0.26	−13.2	−4.5	0.1	461.8	526.8	65.0	12.3	3.7
18	53.8, F	0.26	−13.1	−3.5	1.0	498.8	573.3	74.5	13.0	1.6
19	68.9, F	0.60	−12.3	−2.5	−1.4	621.6	594.7	−26.9	−4.5	–[a]
20	74.7, M	0.38	−14.7	−4.5	1.4	500.7	535.3	34.6	6.5	3.9
21	76.8, F	0.15	−12.0	−4.5	2.7	657.1	697.4	40.3	5.8	8.8
22	74.0, M	–	−15.4	−7.0	2.3	726.1	702.0	−24.2	−3.4	–[a]
23	63.7, M	–	−14.3	−3.0	1.63	493.6	554.7	61.1	11.0	8.1
24	38.5, F	–	−11.2	−3	1.2	422.0	480.9	58.9	12.3	5.0
25	75.8, M	–	–	–	–	529.8	582.4	52.6	9.0	5.9
Mean	70.0	0.32	−12.8	−4.6	−0.30	594.6	638.4	47.1	8.6	6.0

Abbreviations: FTMTRS, Fahn-Tolosa-Marin Tremor Rating Scale; LS-norm, normalized learning score, based on mean RTs calculated over all sequences, with VIM-DBS on and off.

[a]Task could not be performed with stimulation off.

Negative x-coordinates: location of left VIM stimulated during right-handed button presses. The x-coordinates of the stimulating electrodes in the left-handed patients were mirrored to the left side.

structural MRI images, are provided in Table 1. These postoperative coordinates were used to examine a potential relationship between precise electrode location and effects on motor sequence learning. Tremor suppression was optimized and side-effects minimized individually postoperatively, by selecting the contact to be stimulated and adjusting current amplitude (1–6 mA), frequency (130 or 210 Hz), and pulse width (20, 40, 60, or 90 ms).

2.3 | Task

The SRTT was performed in two separate, consecutive sessions by each patient on the same day. In one session, VIM-DBS was on throughout the task performance and in the other session, the VIM-DBS was off throughout task performance, in a counterbalanced order, using Presentation software (Neurobehavioral Systems, Berkeley, CA). Participants were instructed to press buttons corresponding to the location of a red square as quickly and accurately as possible (Figure 1a), with the responses made using the four fingers of the dominant hand (compatible S-R [stimulus–response] mapping). The location of the squares either followed a fixed, 12-element sequence (locations: 1-3-2-1-4-1-2-3-1-3-2-4) or were selected at random, with the constraints that no item appeared the same consecutively, and each item appeared at least once per 12 items. We opted to use a 12-element sequence to minimize participants' awareness of the sequence when present (Overduin et al., 2014; Pollok et al., 2021).

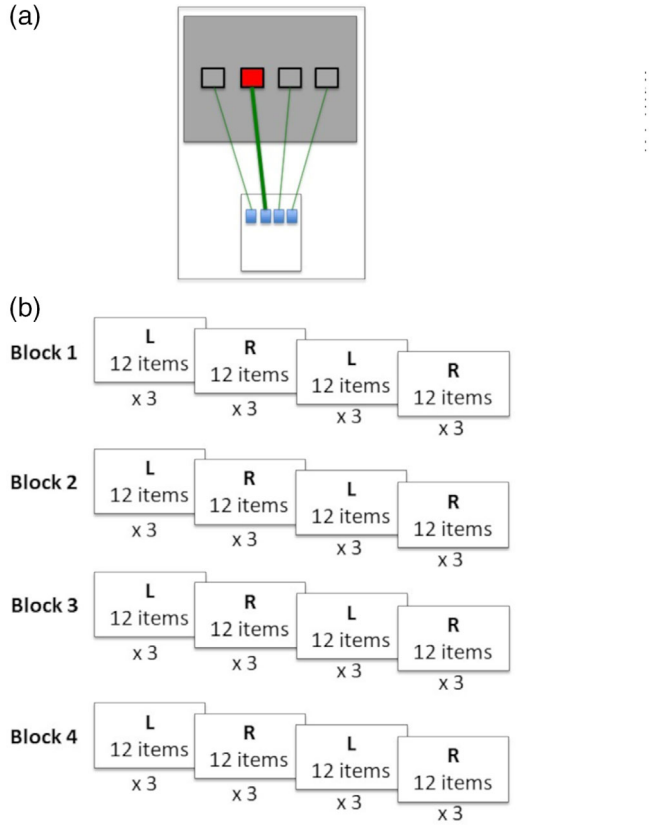

FIGURE 1 SRTT paradigm. (a) SRTT: Positions on computer screen corresponded with button locations on one-handed response pad. (b) Single SRTT session, with two learned and two random runs per block. Each patient participated in two sessions on the same day. One session was performed with the stimulation on throughout and one session was performed with the stimulation off throughout, with the order counterbalanced. L, learned sequences; R, random sequences

Participants were informed that the purpose was to evaluate motor learning based on speed and accuracy. They were not informed that there would be a repeating sequence.

Each 144-item block was composed of alternating runs of three repetitions of the 12-item learned sequence and a 36-item random sequence (three nonrepeated sequences), starting with the learned sequence (Figure 1b). The test session consisted of eight blocks, four with stimulation on and four in which the stimulator was turned off. The on or off stimulation blocks were performed consecutively, in a counterbalanced order. Sequence learning in the SRTT is operationalized as faster RTs and/or higher accuracy on runs in which the stimuli follow a sequence compared with runs in which the stimuli are selected at random (Nissen & Bullemer, 1987). We performed a pilot study with 12 healthy participants and six patients to establish whether the stimulus presentation time length, the inter-stimulus interval, and the repeating sequence length would be suitable for assessing implicit motor sequence learning and whether patients with essential tremor would be able to perform the task. We asked these participants to write down the repeated sequence at the end of the experiment, and no participant recalled more than four of the 12 sequence items. All participants in the pilot study showed faster mean reaction times (RTs) to the repeated than the random sequences.

2.4 | Statistical analyses

Unless otherwise stated, the data were normally distributed, permitting parametrical tests. To establish whether an inability to perform the experiment depended on disease severity, we performed a one-way ANOVA with the between-subject factor *Task completed* (yes, no). Pearson's correlation coefficient (*r*) was calculated between FTMTRS and mean RTs during learned and random sequences with the stimulation off and on, to evaluate whether disease severity had an impact on RTs, and between the FTMTRS and the mean normalized learning scores with and without stimulation, to assess whether disease severity is associated with motor sequence learning.

A repeated measures two-way ANOVA with the within-subject factors *Sequence type* (learned, random) and *Stimulation* (on, off), and the between-subject factor *Stimulation order* (on first, off first) was applied to the mean RTs to indicate whether implicit motor sequence learning took place, as reflected by faster RTs to learned (repeated) than random sequences, and whether learning was modulated by VIM-DBS. The mean RT was calculated across blocks for responses to learned and to random sequences, with VIM-DBS on and off. We additionally corrected for the factor *Handedness*, as three participants were left-handed, and for *Age* and *Sex* and for *Stimulation amplitude*. As only two patients received a stimulation frequency of 210 Hz (all others received 130 Hz), we also performed the ANOVA excluding these two patients. The patients were stimulated at one of four pulse widths. Spearman's correlation was calculated between pulse width as an ordinal variable and RTs to learned and to random sequences, with stimulation on. Given the range of RTs between individuals, mean normalized learning scores ([mean RT to random − mean RT to learned]/mean RT to random) were also compared. The normalized learning score was calculated per run, as each run was performed continuously, then averaged over each block. To examine whether learning increased over time, a repeated measures ANOVA was applied with the within-subject factors *Stimulation* (on, off) and *Time* (Blocks 1 to 4). We also corrected for *Age* and *Sex* and for *Stimulation amplitude*. The mean RT was calculated for each sequence, then averaged over each run. *T*-tests, including those used for post hoc comparisons, were two-tailed. Where data were not normally distributed, a two-sided Wilcoxon rank sum test was additionally applied. Post hoc evaluations of correlation between *Age* and RTs and mean normalized learning scores, using Pearson's coefficient, were performed to explore a potential influence of *Age* on the findings.

To establish whether any effect on RT resulted from a speed–accuracy trade-off, we performed an analogous repeated measures two-way ANOVA for accuracy. There were no outliers in RT or accuracy (exceeding three times the interquartile range above the third or below the first quartile).

Spearman's correlation coefficient (ρ) was calculated between the stimulation coordinates with respect to the AC–PC line, which were not normally distributed, and the difference between the mean RT during random and learned sequences during stimulation. The coordinates of the stimulating electrodes in the right VIM of the left-handed patients were reflected to the left hemisphere for inclusion in the group analysis.

3 | RESULTS

Unless specified, the data were normally distributed according to the Shapiro–Wilk test, and there were no outliers.

The patients ($N = 25$; 12 female) had an average age at electrode implantation of 67.8 years (standard deviation [*SD*]: 10.2) and at assessment of 70.0 (*SD*: 10.2) years. Three patients (Patients 16, 23, and 24) were left-handed. FTMTRS scores were available for 21 and stimulation coordinates for 24 patients (Table 1). Due to tremor severity, four patients were unable to perform the task without stimulation, and one patient could not perform the task with or without stimulation, leaving 20 participants for statistical analysis. Applying a one-way ANOVA including the latter five patients, with the between-subject factor *Task completed* (yes, no), the FTMTRS scores showed more severe disease in those unable to carry out the task ($F[1] = 11{,}39$, $p = .003$). The FTMTRS scores did not correlate with RTs with the stimulation off, reflecting the patients' ability to perform the task without intervention (learned: $r(17) = 0.30$, $p = .24$; random: $r(17) = 0.32$, $p = .22$) (Figure S1). Furthermore, they did not correlate with RTs with the stimulation on (learned: $r(20) = 0.010$, $p = .97$; random: $r(20) = -0.048$, $p = .84$) or with the mean normalized learning scores (without stimulation: $r(20) = -0.075$, $p = .78$; with stimulation: $r(20) = -0.22$, $p = .35$).

A main effect of *Sequence type* was observed ($F[1,18] = 69.0$, $p < .001$) but no main effect of *Stimulation* ($F[1,18] = 0.42$, $p = .53$) or of *Stimulation order* ($F[1,18] = 0.48$, $p = .50$). The interaction of *Sequence type* × *Stimulation* was significant ($F[1,18] = 7.89$, $p = .012$). Post hoc comparison showed that the RT difference for random and sequence runs was greater with the stimulation on compared with stimulation off ($T[19] = 2.34$, $p = .031$, Figure 2a). No other interactions were significant. The interaction *Sequence type* × *Stimulation* remained significant if *Handedness* was added as a factor ($F[1,17] = 5.48$, $p = .032$), as well as correcting for *Age* and *Sex* as a covariate and a between-subject factor, respectively ($F[1,17] = 6.74$, $p = .019$), if correcting for the additional covariate *Stimulation amplitude* ($F[1,13] = 5.18$, $p = .040$), and if excluding the two patients receiving stimulation at 210 Hz ($F[1,13] = 4.82$, $p = .047$). The pulse width applied did not correlate with RTs (learned: $\rho(20) = -0.12$, $p = .62$; random: $\rho(20) = -0.16$, $p = .50$).

Similarly, the normalized learning score was greater with the stimulation on than off (Figure 2b). The normalized learning scores were not normally distributed according to the Shapiro–Wilk test. An examination of these data revealed that if the data from the three participants with mean scores over twice the interquartile range above the third or below the first quartile were excluded, the remaining data

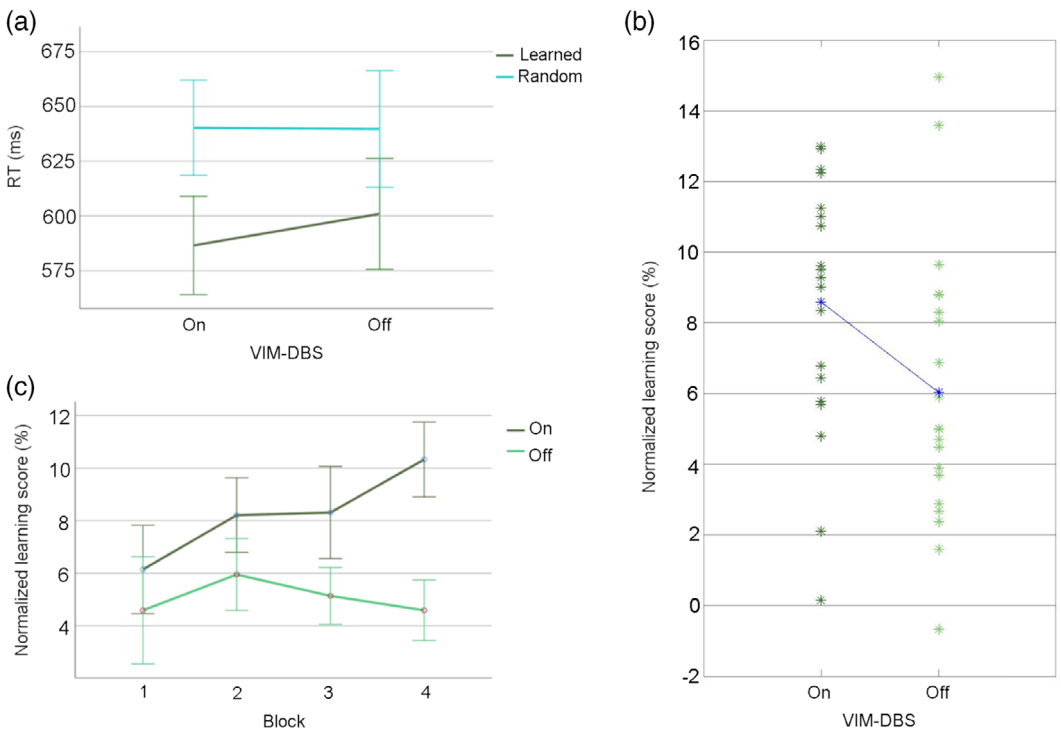

FIGURE 2 SRTT performance. (a) Interaction between within-subject factors *Stimulation* (on/off) and *Sequence type* (learned/random) ($F[1,18] = 7.89$, $p = .012$). (b) The normalized learning score was greater with the stimulation on than off ($T[19] = 2.47$, $p = .023$). (c) The learning score increased over time when the stimulation was on and not off, but neither *Time* ($F[1,14] = 1.83$, $p = 0.20$) nor an interaction between *Stimulation* and *Time* ($F[1,14] = 2.13$, $p = 0.17$) was significant

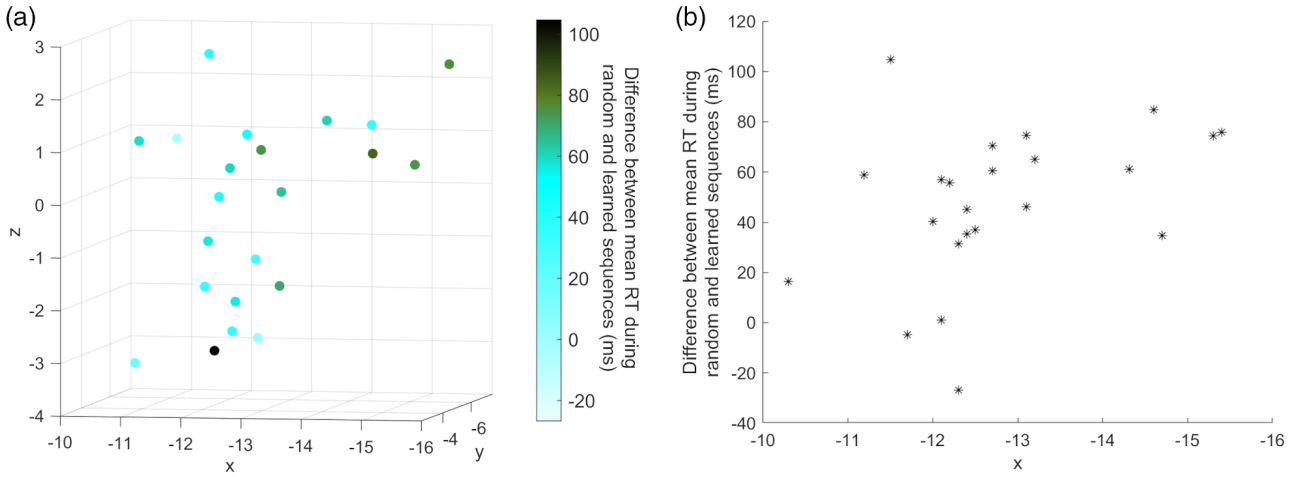

FIGURE 3 Electrode location. (a) Stimulated electrode coordinates relative to AC–PC line, color-coded according to within-patient mean RT difference with stimulation on. (b) Correlation between RT difference with stimulation on and x-coordinates of stimulated electrodes (Spearman's $\rho = 0.46$; $p = .027$)

were normally distributed. The main effect of *Stimulation* on the normalized learning score was significant ($F[1,14] = 6.46$, $p = .023$). Although the increase in the learning score over time was greater when the stimulation was on, neither the effect of *Time* ($F[3,42] = 0.88$, $p = .46$) nor the interaction between *Stimulation* and *Time* ($F[3,42] = 0.68$, $p = .57$) was significant (Figure 2c). The main effect of *Stimulation* remained significant when correcting for *Age* and *Sex* as a covariate and a between-subject factor, respectively ($F[1,12] = 4.83$, $p = .048$), and the main effect of *Time* was significant ($F[3,36] = 2.88$, $p = .049$). There was a trend towards a *Stimulation* × *Time* × *Age* interaction ($F[3] = 2.84$, $p = .052$) but no significant *Stimulation* × *Time* × *Sex* interaction ($F[3] = 1.75$, $p = 0.18$). The interactions *Stimulation* × *Time* ($F[3,36] = 2.58$, $p = .068$), *Stimulation* × *Age* ($F[1] = 3.45$, $p = 0.088$), and *Time* × *Age* ($F[3,36] = 2.88$, $p = .050$) showed trends. There were no main effects of *Age* ($F[1] = 1.95$, $p = .19$) or *Sex* ($F[1] = 0.035$, $p = .85$). Including the additional covariate, *Stimulation amplitude*, the main effect of *Stimulation* was still observed ($F[1,9] = 5.21$, $p = .048$). There was no significant main effect of *Stimulation amplitude* ($F[1] = 1.83$; $p = .21$). Note that the normalized learning score was also greater with the stimulation on when all patients were included ($T[19] = 2.47$, $p = .023$). Finally, the finding was unaltered on application of a nonparametric test (Wilcoxon rank sum test [$n = 20$]: $p = .037$). Note also that block 1 contains three repetitions of the learned sequence, so learning is already reflected in faster RTs.

Given the trends towards the interactions *Stimulation* × *Age* and *Time* × *Age*, we performed a post hoc evaluation of correlations between *Age* and RTs. *Age* correlated with RTs for both *Sequence types* in both *Stimulation* conditions (learned, on: $r = 0.55$, $p = .005$; learned, off: $r = 0.59$, $p = .007$; random, on: $r = 0.54$, $p = .006$; random, off: $r = 0.62$, $p = .003$). *Age* did not correlate with the mean normalized learning score, either examining the mean normalized learning scores overall or in the four *Time* blocks separately.

There was no main effect of *Sequence type* or of *Stimulation* on accuracy and no significant interaction between *Sequence type* and *Stimulation*. Although the difference was not significant, accuracy was higher during learned than random sequences, excluding a speed–accuracy trade-off.

A correlation was observed between the difference between the mean RT to random and learned sequences when the stimulation was on and the x-coordinates of the stimulating electrode locations ($n = 23$, $\rho = 0.46$; $p = .027$) (Figure 3a,b). In Figure 3b, darkening green reflects a within-patient mean RT difference between responses to random and learned sequences, with the stimulation on, exceeding the patient group median (54.1 ms). More lateral placement was associated with greater motor sequence learning, as reflected by enhancement of RTs to learned sequences. The median was considered, as a nonlinear (Spearman's) correlation was investigated. The mean RT difference to random and learned sequences did not correlate with the disease severity ($n = 20$, $\rho = 0.033$; $p = .89$) (Figure S1).

4 | DISCUSSION

Motor sequence learning was modulated during VIM-DBS, as reflected by the interaction between stimulation state and sequence type: the RT advantage observed when the stimuli followed a fixed sequence, compared with when the stimuli were selected at random, was greater when VIM stimulation was on. Importantly, the interaction indicates that the RT reduction does not simply reflect tremor improvement through stimulation but rather a specific modulation of motor sequence learning. The normalized learning score was also greater when the stimulation was on than off, suggesting that individual learning was greater with the stimulation. The finding provides support for the hypothesis that the VIM is a part of the network of brain structures engaged in motor sequence learning. It also suggests that effects on motor learning may be relevant when patients with essential tremor are treated with VIM-DBS.

We consider two potential limitations arising from inter-individual variability in performance among patients. First, while the mean RT

difference between learned and random sequences during stimulation was consistent with implicit learning, which is usually deemed to yield a ~40–60 ms difference, the greater difference in some individuals could suggest improved performance due to enhanced attention. We consider this interpretation unlikely, however, based on known VIM connectivity with cerebellum and M1 (Haslinger et al., 2003; Morigaki et al., 2011), resulting in its being deemed a motor integration zone (Greene et al., 2020), in contrast with other thalamic nuclei, which are engaged in attentional networks, such as the pulvinar (Saalmann et al., 2012) and the dorsomedial nucleus (van der Werf et al., 2003). Second, while the learning score increased over time when the stimulation was on but not when it was off, the increase was only significant when correcting for age and sex. We suggest that this finding could reflect the inter-individual variability in performance over the course of the experiment in the patient group, which may be due not only at least in part to the tremor, but also possibly to the effects of age. However, while RTs correlated with age and were slower in older patients, this was the case for RTs to both the learned and random sequences. Moreover, the mean normalized learning score did not correlate with age whether stimulation was on or off. The latter finding is consistent with previous studies indicating that motor sequence learning may remain intact in older individuals (King et al., 2013; Meissner et al., 2016). The initial small increase in learning score when the stimulation was off may also simply result from inter-individual variability. Finally, the full effects of stimulation may not have been reached in patients starting with stimulation off, as the task was performed within minutes of switching on. However, there was no significant interaction between stimulation order and sequence type, suggesting the effect of stimulation on motor learning did not depend on how long the stimulation had been on.

It is likely that stimulation disrupts the pathological processes causing disease-related deficits, as indeed is the case when stimulation improves tremor. Tremor is associated with cortical hypersynchrony (Crowell et al., 2012; Schnitzler et al., 2009; Thompson et al., 2014). It is plausible that excessive synchronization has a detrimental effect on the cortical processing underpinning motor sequence learning, and its interruption by VIM stimulation enables motor cortical neuronal discharging units to engage in motor learning processes. VIM-DBS is a well-established treatment for tremor in pharmacoresistant ET (Cury et al., 2017). Motor learning deficits have been observed in ET patients (Kronenbuerger et al., 2007; Shill et al., 2009), and the RTs here are slower than in an SRTT in healthy controls of a similar age (Hong et al., 2020). A modulation in motor sequence learning performance during VIM-DBS therefore has important implications for this treatment option.

The results of the current study indicate that motor sequence learning benefits from VIM stimulation in patients with essential tremor. Although not formally assessed, we assume that this form of learning was implicit based on our use of a 12-element sequence. This finding is consistent with a previous report showing that VIM-DBS has a positive effect on eye-blink conditioning (Kronenbuerger et al., 2008). However, this form of stimulation has been shown to be detrimental to adaptive motor reaching (Chen et al., 2006). At present, there is insufficient data to account for these discrepancies, although the results suggest that it is important to consider the type of motor learning. Disruption in adaptive reaching has been proposed to result from impairment of the ability to form internal models (Chen et al., 2006). Although cerebellum–VIM–cortical pathways are also engaged in adaptive reaching, forming internal models for single, continuous actions is a fundamentally different aspect of motor learning to the discrete movements involved in eye-blinks and button-pressing. While the combinatorial processes needed in implicit acquisition of motor sequences also require establishment of a model, in contrast to sequence learning, the model underpinning adaptive reaching involves corrective visuo-proprioceptive feedback mechanisms to control the movement itself, while the movements themselves in button pressing and blinking are stereotyped. Different underlying processing is also suggested both by the lack of correlation between individual performances in these two types of motor learning (Stark-Inbar et al., 2021), and the absence of interference or facilitation when integrated into a single task (Overduin et al., 2014). The neural correlates of motor sequence learning appear closer to those of conditioning than adaptive reaching, given the effects of VIM stimulation. Differential performance impairment in these types of learning, for example, in Parkinson's disease patients (Sommer et al., 1999), further underlines differences in neural correlates.

We postulated that lateral electrode location would have a greater effect on motor sequence learning. The lateral part of the VIM differs histologically from the medial part (Hirai et al., 1989). Connectivity studies indicate that cerebellothalamic fibres terminate in the lateral part (Asanuma et al., 1983), and electrophysiological recordings document kinaesthetic and tactile responses in the lateral region (Ohye et al., 1989), features that may be necessary components for motor learning. Motor sequence learning correlated with the x-coordinates of the stimulating electrode locations, a measure of the lateral distance from the AC–PC midline (Klostermann et al., 2003). Studies examining the relationship between lead location and tremor improvement have estimated an optimal distance of 12.3 mm (Papavassiliou et al., 2004) as well as 13.4 ± 1.5 mm (Vassal et al., 2012) lateral to the midline. Our finding of improved motor sequence learning with more lateral placement is consistent with the hypothesis that particular VIM subregions are engaged in motor learning. A recent review reported the VIM target x-coordinate as 15 mm lateral to the mid-commissural point (Iorio-Morin et al., 2020). This lateral position is also consistent with electrode location relevant to tremor suppression. The relationship between the precise stimulating electrode location and modulation of motor sequence learning suggests that the laterality of the target electrode location should be considered in pre-operative stereotactic planning.

5 | CONCLUSIONS

In summary, we present evidence based on VIM-DBS for a role for the VIM in motor sequence learning. The finding has important implications for DBS treatment of tremor. Tremor modulation depends on precise electrode location (Cury et al., 2017), and our study reveals

that lateral VIM electrode placement improves motor sequence learning in essential tremor patients.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The Local Ethics Committee of the University Hospital Magdeburg granted ethical approval. All participants provided informed, written consent before study inclusion, in accordance with the Declaration of Helsinki, and were informed of their right to cease participation at any time without providing reasons.

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