

Cerebello-Cortical Control of Tremor Rhythm and Amplitude in Parkinson's Disease


The pathophysiology of Parkinson's disease (PD) tremor involves both the basal ganglia and a cerebello-thalamo-cortical circuit.^{1,2} It remains unclear how tremor rhythm and amplitude emerge from these circuits and whether these mechanisms depend on tremor phenotype. Previous data suggest that the cerebellum is specifically involved in PD postural tremor.³ However, different postural tremor types (re-emergent or pure postural tremor)⁴ were included, and region-specific effects on tremor amplitude were not assessed. Here, we investigated the role of the motor cortex (M1) and cerebellum in generating rhythm versus amplitude of PD rest tremor compared with re-emergent tremor.

We tested the effect of single-pulse transcranial magnetic stimulation (TMS) on tremor rhythm (tremor reset index [TRI]) and tremor power (electromyography) in 14 patients with PD (Table S1; Appendix S1). All patients had rest tremor and electrophysiologically proven re-emergent tremor: wrist extension suppressed tremor amplitude for up to 3000 milliseconds ($F_{1,20} = 11.7$, $P < 0.001$; $\text{part.}\eta^2 = 0.47$; Fig. 1A,B). Cerebellum-TMS reset re-emergent tremor, but not rest tremor ($t_{13} = 2.1$, $P = 0.026$; Cohen's $d = 0.57$; TRI vs. 0 [re-emergent tremor: $t_{13} = 3.0$, $P = 0.010$; rest tremor: $t_{13} = 1.0$, $P = 0.33$]; Fig. 1C–E). In re-emergent tremor, the TRI after cerebellum-TMS decreased with subsequent tremor bursts (1–5 after TMS), indicating transient resetting (time: $F_{4,52} = 3.61$, $P = 0.011$; $\text{part.}\eta^2 = 0.22$; Table S2). M1-TMS, but not cerebellum-TMS, reduced tremor power for both rest tremor and re-emergent tremor (site \times time interaction: $F_{8,104} = 8.77$, $P < 0.001$; $\text{part.}\eta^2 = 0.40$; Fig. 1F,G [no 3-way interaction with tremor type]). Specifically, M1-TMS reduced tremor power up to


1500 milliseconds in both tremor types (rest tremor, time: $F_{8,104} = 8.17$, $P < 0.001$; $\text{part.}\eta^2 = 0.39$; re-emergent tremor, time: $F_{8,104} = 13.24$, $P < 0.001$, $\text{part.}\eta^2 = 0.50$), whereas cerebellum-TMS did not influence tremor power ($F < 1.4$).

Our findings suggest that the cerebellum is part of the oscillator controlling the rhythm of re-emergent tremor, but not rest tremor. Compared with previous data, the TRI after cerebellum-TMS was smaller (0.1 vs. 0.5), and tremor reset was transient instead of permanent.³ This may relate to the postural tremor types included (here, re-emergent tremor; previously, all postural tremors),³ to the stimulation intensity (here, 56% stimulator output; previously, 68%),³ or both. Re-emergent tremor and resting tremor have been hypothesized to be a continuum ("tremor of stability"),² and they share clinical features.⁵ However, re-emergent tremor has a smaller dopamine response and slightly higher frequency than rest tremor.⁴ Our data suggest that these differences may be explained by the cerebellum, which comes in with voluntary movement and transiently modulates the tremor oscillator and possibly tremor frequency, while the fundamental character of the tremor remains unchanged.

Our data further suggest that M1, but not the cerebellum, controls tremor amplitude, independent of tremor phenotype. This finding is in line with previous data.⁶ M1-TMS effects on tremor power were shorter compared to wrist extension (1500 vs. 3000 milliseconds), suggesting that mechanisms involved in voluntary actions may have an additional role in tremor suppression. TMS pulses were given at intensities that produce motor-evoked potentials, so the effects may be driven in part by somatosensory afferents related to small muscle twitches. Intriguingly, thalamus interventions effectively reduce PD tremor amplitude,⁷ while cerebellum-TMS did not. This may suggest that the effects of thalamus interventions are not (only) explained by the interruption of cerebello-thalamo-cortical projections, but potentially also by the interruption of cortico-thalamo-cortical projections.⁸ ●

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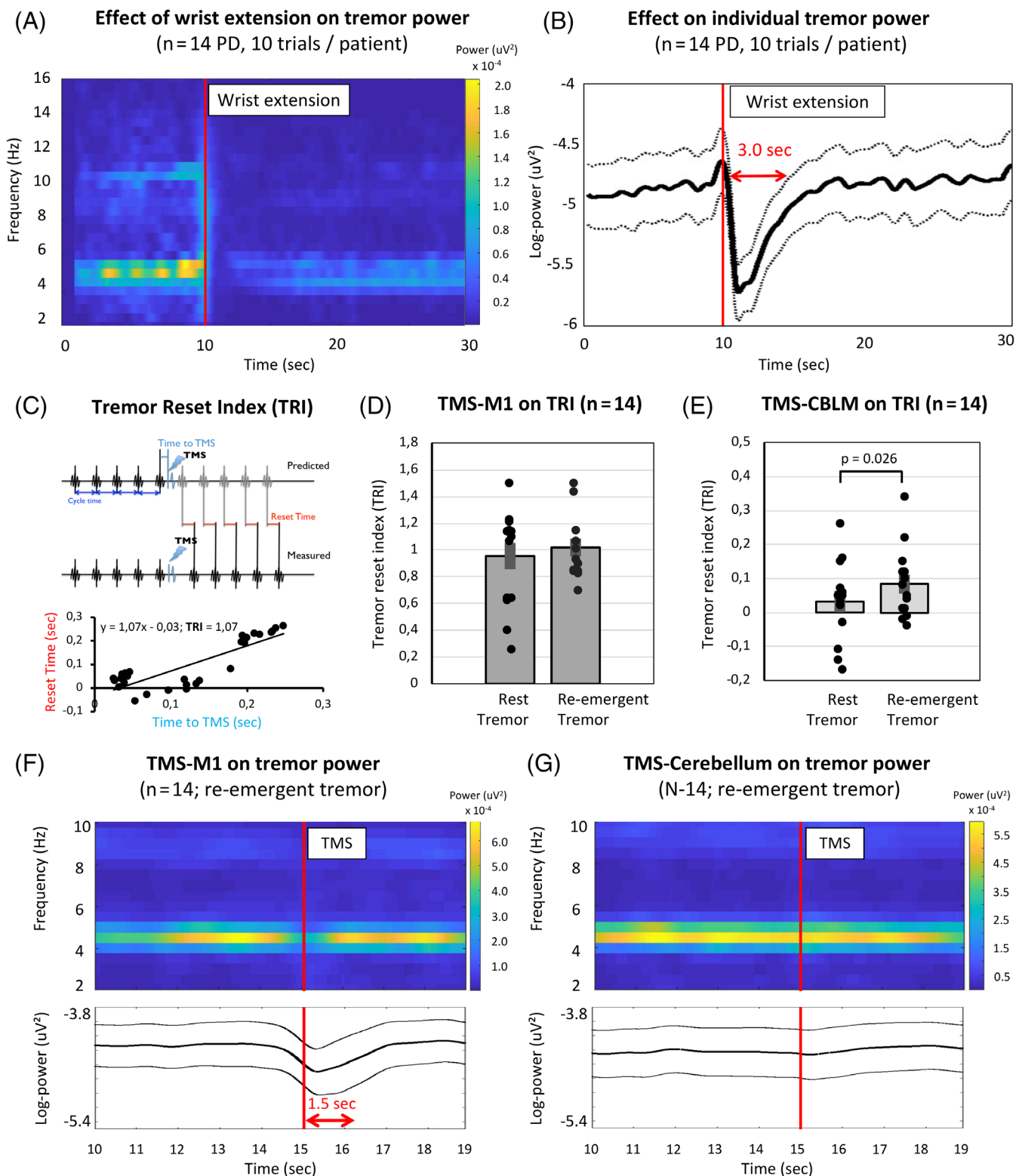


FIG. 1. Effects of TMS on rhythm and power of rest versus re-emergent tremor. **(A)** Average TFR of EMG power. The red line indicates voluntary wrist extension. This transiently reduces tremor power at ± 5 Hz. **(B)** Average log-transformed tremor power (from EMG) at individual re-emergent tremor frequency (\pm SEM). The red arrow indicates a significant drop in tremor power (up to 3.0 seconds after TMS). **(C)** The TRI is the slope of the regression line between “time to TMS” and “reset time” (over multiple trials in each individual), here shown for 1 patient (M1-TMS, re-emergent tremor). **(D,E)** TRI (mean \pm SEM) for M1 stimulation **(D)** and cerebellum stimulation **(E)** during rest and posturing. **(F,G)** Effect of TMS over M1 **(F)** and the cerebellum **(G)** on re-emergent tremor. Effects for rest tremor are similar (supplement). Upper panels show the average TFR of EMG tremor power (n = 14); lower panels show the average (\pm SEM) log-transformed tremor power (derived from EMG) over time at individual tremor frequencies (n = 14). Red arrow indicates a significant drop in tremor power for up to 1.5 seconds after TMS. APB, abductor pollicis brevis; CBLM, cerebellum; ECR, extensor carpi radialis; EMG, electromyography (from muscle showing clearest tremor in each patient); FCR, flexor carpi radialis; FDI, first dorsal interosseus; M1, primary motor cortex; PD, Parkinson’s disease; SEM, standard error of mean; TFR, time-frequency representation; TMS, transcranial magnetic stimulation; TRI, tremor reset index. [Color figure can be viewed at wileyonlinelibrary.com]

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Saccadic Bradykinesia in Parkinson's Disease: Preliminary Observations

Bradykinesia (low velocity) and hypokinesia (reduced amplitude) of limb movements are features of Parkinson's disease (PD) exacerbated when patients perform self-guided, repetitive limb movements, such as finger tapping—the so-called “sequence effect.” In the oculomotor system, both hypometria and slowing of voluntary saccades have been described in PD¹ but never as a change *over time*, which is the defining feature of this phenomenon.

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We examined 6 mildly- or moderately impaired PD patients (Unified Parkinson's Disease Rating Scale-motor, 11 ± 2.8 points; duration of illness, 2.2 ± 0.4 years) aged 69 ± 5 years (1 woman) and 7 age-matched healthy controls (5 women, 56 ± 7 years). Eye movements were recorded using infrared binocular videonystagmography (VNG) (Micromedical Visual Eyes 525 system) sampled at 250 Hz. We recorded reflexive horizontal saccades toward 20° visual targets projected onto a screen 1 m away followed by voluntary horizontal saccadic eye movements over a 60-second epoch in the light but without visual targets. Here, participants faced a white screen and were asked to “look right, then left, and continue looking right and left in your own time and to a similar location as the previous targets” until instructed to stop.

Voluntary horizontal saccadic eye movements without visual targets led to a progressive decrease in PD saccadic amplitude over time (hypometria) (Fig. 1A, bottom trace; Video VIDEO S1; Fig. 1B).¹ In addition, PD saccadic velocity progressively decreased over time, even when accounting for smaller saccadic amplitudes (cf. main sequence effect; Fig. 1C–E). Group (PD vs. controls) and time (first six vs. final six saccades) interacted for both amplitude and velocity ($F(1,11) > 6.1$; $P < 0.0031$), with a decrease over time in PD ($P \leq 0.001$) but not controls ($P > 0.110$; Fig. 1B, C). PD saccadic velocity in the final six saccades was lower than normative amplitude-matched velocities ($P = 0.039$), whereas no difference was present in the first six saccades ($P = 0.547$; Fig. 1D,E). In contrast, reflexive saccadic amplitude (Fig. 1A, middle trace) and velocity were normal in PD. Healthy controls displayed normal saccadic function across all saccadic tasks (Fig. 1A, top trace).

Self-paced saccades are usually more affected than reflexive (or “automatic”) saccades in PD, that appear to be relatively normal.² Voluntary saccades are cognitively complex responses that require higher-order control processes and are perhaps more vulnerable to neurodegeneration in PD than reflexive saccades with more direct sensorimotor transformations.³

Human electrophysiological studies suggest that the sequence effect in PD may relate to changes in long-term potentiation, where a decline in corticospinal output as movement progresses results in a gradual decrease in movement amplitude.⁴ While based on appendicular rather than oculomotor data, a similar neural mechanism may account for the sequence effect in voluntary self-paced saccades in PD, although other mechanisms involving omnipause neurons or direct effects on the superior colliculus are possible.⁵

In summary, our data suggest that saccadic bradykinesia can be elicited at the bedside (here also documented formally using VNG) and was apparent in all consecutive patients but absent in age-matched controls. “Saccadic bradykinesia” may be a useful and early clinical sign of PD, but future studies should confirm these findings and assess its specificity as a clinical biomarker of disease progression. ■

Patient Consent

Written informed consent was obtained from the patients for publication of the case history and videos. ■