



## Short communication

## Re-emergent tremor provocation

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## ARTICLE INFO

## Keywords:

Parkinson's disease  
Provocation  
Re-emergent tremor  
Parkinsonian tremor  
Neurophysiology  
Distraction

## ABSTRACT

**Introduction:** Rest and re-emergent tremor (RET) in Parkinson's disease (PD) are known to be markedly variable. The aim of this study is to evaluate the effect of tremor provocation on RET latency and variability.

**Methods:** We performed a prospective observational study in 21 PD patients with RET. Evaluations were conducted by accelerometric analysis of hand movements with and without provocation by counting out loud backwards from 100, in the OFF state. Differences in RET pause duration, tremor power at peak frequency, root mean square (RMS) and slope of return of the tremor after the pause was measured. Inter- and intra-subject variability were also calculated.

**Results:** RET pause duration showed a 75% decrease after provocation ( $p < 0.001$ ), which led to zero in 52% of cases, as compared to 9% in unprovoked measurements ( $p < 0.001$ ). Provocation also led to a 2.57 time increase in tremor power ( $p < 0.001$ ), 1.37 time increase in RMS ( $p < 0.001$ ) and 2.47 time increase in slope ( $p < 0.001$ ). A significant decrease in inter-subject variability was also observed ( $p = 0.001$ ).

**Conclusion:** Tremor provocation led to RET amplitude increase, pause shortening, and variability decrease. Therefore, while provocation can be recommended for the evaluation of rest tremor in clinical practice, it might well annul its value for identifying the pause prior to re-emergent tremor.

## 1. Introduction

Tremor is one of the cardinal signs of Parkinson's disease (PD). The classical presentation is of resting tremor, although postural tremor is also very common [1]. One of the characteristic features of Parkinsonian tremor is that it ceases or decreases its amplitude with movement [2]. Therefore, most patients with PD and postural tremor present a brief pause after adopting a fixed posture, with tremor re-emerging afterwards [3].

Re-emergent tremor (RET) has been given increasing attention, as pause duration has been acknowledged to be an important clinical sign, allowing different types of tremor to be differentiated [3,4]. A recent paper by our group [5] has shown that amplitude and pause duration are inversely related, and that levodopa exerts a dampening effect on re-emergent tremor, thus prolonging the pause.

On the other hand, it is widely known that certain maneuvers elicit a provocation effect on parkinsonian tremor [6,7]. Indeed, Parkinsonian tremor typically presents marked amplitude variability. Within provocation methods used in clinical practice [6], counting backwards

from 100 seems to be the most practical approach, as it combines an easy arithmetic exercise that demands attention, and a slight motor action involved in speech, showing similar tremor augmentation as more demanding tasks.

However, to the best of our knowledge, there are no studies analyzing the effect of provocation on re-emergent tremor nor its effect on pause duration, which is the aim of the current work. Following our previous results [5], we hypothesize that tremor provocation should produce an amplitude increase on RET as it does on resting tremor, and therefore an important decrease in re-emergent tremor latency, thus counteracting this phenomenon.

## 2. Methods

A prospective observational study evaluating the effect of tremor provocation on re-emergent tremor pause was conducted. Evaluations were performed by accelerometric analysis of hand movements with and without provocation, in the OFF state. The study was approved by the IRB and was conducted following Good Clinical Practice standards

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and in accordance with the Declaration of Helsinki. Written informed consent was obtained from all subjects.

Consecutive PD patients with rest and re-emergent tremor on physical exam were prospectively recruited from the Movement Disorders Service of our institution. All subjects had Hoehn and Yahr stages I–III and gave informed consent. Patients were excluded if they had other known causes of tremor, coexistence of PD and essential tremor, recent exposure to tremor-inducing drugs, anatomic or orthopedic upper limb alterations, or if they could not interrupt symptomatic medication. The current study involved further analysis performed on a study population that has already been published [9], using a similar methodology, but under different conditions and consequently, with a different aim. Primary outcomes were the modification of RET pause duration with provocation and its intra- and inter-subject variability. Secondary outcomes were the provocation effect on tremor intensity and slope of tremor increase after the pause.

All measurements were conducted in a single session, after anti-parkinsonian medication withdrawal for at least 12–24 h, depending on medication half-life and duration of action. The patients were allowed to continue with the rest of their concomitant medication. Rest tremor activity was obtained with the patient comfortably seated, with both hands in semi-prone position and with accelerometers taped to the back of both hands. The patients were asked to extend their arms to a 90° angle in front of the body, with palms facing down, and to maintain that posture for 30 s. If tremor did not re-emerge after the mentioned period of time, it was considered not to present RET in that sample. The procedure was repeated five times for consistency and comparison.

The whole procedure was then repeated after tremor provocation, which was obtained following previous reports recommendation, by counting backwards from 100, out loud and with eyes closed [6].

Accelerometric analysis was performed by evaluating the total of tremor contributions in the whole upper limb with a single axis accelerometer, which was taped to the back of each hand (0.05–100 Hz bandwidth, ATI Pentatek, Buenos Aires, Argentina). Recordings were sampled at 320 Hz and registered on an ATI Pentatek DB Vertex VX16 device (version 1.111.0.0). The digital signal of the most symptomatic hand was then analyzed offline using BIOPAC AcqKnowledge 4.2.0 software. Fast Fourier Transform (FFT) was used for Power Spectral Density (PSD) analysis and tremor power calculation [5]. Subjects with differences in dominant tremor frequency between rest and posture above 1.5 Hz were excluded from further analysis [8]. Independent low and high pass filters (FIR Butterworth) at  $\pm 2$  Hz from dominant frequency were applied. An envelope was generated by rectification and smoothing of the signal with a 1-s smoothing factor (320 samples).

Re-emergent tremor pause duration was determined measuring the time interval between the onset of the postural condition, which started after an accelerometric movement artifact produced by arm elevation, and the onset of tremor activity exceeding signal amplitude at the initiation of this condition [3,5]. The slope of gradual increase in tremor amplitude after movement-induced suppression was also calculated [5]. Root mean square (RMS) of the unfiltered postural tremor segment was calculated as a measure of tremor intensity.

RET pause duration, tremor power at peak frequency, RMS and slope was registered in every sample. Data were normalized in order to minimize absolute value variability and dispersion, as well as to prevent recordings with higher values from biasing mean results. Therefore, normalization was performed by dividing data values by the no-provocation recordings, thus expressing them as a percentage. Zero latency values were replaced with a near-zero value (0.001 s, below the sensitivity limit of the measuring device), in order to avoid normalizing errors (by zero division). Significant outliers ( $> 3SD$ ) were excluded from analysis. A paired T-test was performed comparing RET pause duration, tremor power at peak frequency, RMS and slope, with and without provocation. A one-way ANOVA was performed to compare absolute value means and variance of RET pause latency between measurements with and without provocation. Pause duration equal to

zero were excluded from variability analysis in order to avoid floor effect. A similar analysis was conducted to assess for intrasubject variability. Mean variance of each five-repetition set from each patient was compared, both with and without provocation.

### 3. Results

Twenty-four consecutive patients were evaluated. Three patients presented frequency differences between rest and posture of more than 1.5 Hz, which was interpreted as the pure postural form of PD tremor and were therefore excluded. Twenty-one patients were finally confirmed eligible and included in the study (mean age  $66.63 \pm 9.30$ ; 66.7% male). Mean MDS-UPDRS Part III (English version) scores were  $29.19 \pm 10.40$ , with a mean postural tremor score (item 3.15) of  $1.52 \pm 0.60$ , and mean rest tremor score (item 3.17) of  $1.85 \pm 0.72$ . Mean tremor frequency at rest was  $4.96 \pm 0.74$  Hz and  $5.24 \pm 0.84$  Hz during sustained posture, with a mean difference between both conditions of  $0.28 \pm 0.59$  Hz.

Provocation generated a 75% mean decrease in re-emergent tremor pause duration ( $t = 15.32$ ,  $p < 0.001$ ) as compared to baseline recordings without provocation. This latency shortening reached zero in 52% of the measured samples under provocation, leading to a loss of the pause in tremor activity, whereas only 9% of the samples with no provocation had no pause ( $p < 0.001$ ) (Fig. 1).

On the other hand, tremor provocation led to a 2.57 time increase in tremor amplitude as measured by tremor power at peak frequency ( $t = -4.899$ ,  $p < 0.001$ ), as well as a 1.37 time increase in tremor intensity, measured by RMS ( $t = -4.047$ ,  $p < 0.001$ ). The gradual increase of tremor after the pause also showed a 2.47 time increase in its slope ( $t = -6.365$ ,  $p < 0.001$ ) following provocation (Fig. 1).

Absolute value means and variance comparison between unprovoked and provoked recordings showed a significant decrease in intersubject variability (mean 3.74 vs 0.97, variance 25.50 vs 1.43,  $p = 0.001$ ) following provocation (Fig. 2). These recordings also showed variance decrease was higher than mean decrease after provocation: 74% vs 94.4%. Intrasubject variability analysis did not achieve statistical significance (mean variance 8.36 vs 1.76,  $p = 0.29$ ).

### 4. Discussion

Our results showed that tremor provocation, while producing an amplitude increase in RET, led to an inhibition of the re-emergent phenomenon, thus reducing its clinical value.

One of the hallmarks of Parkinsonian tremor is that it ceases or decreases its amplitude with muscular activation and movement [2]. Previous work has shown that this attenuation arises from interactions between basal ganglia and cerebello-thalamo-cortical circuits [10]. Similar cortical activity has been shown to drive both rest tremor and voluntary movement, for which both seem unable to coexist at the same time [10]. In addition, pallidal activation has also been observed both during motor planning and when triggering tremor [10]. However, even though basal ganglia are known to be activated in movement plan changes, they are not involved in maintaining a fixed posture [10], which may explain why rest tremor re-emerges in this situation.

On the other hand, several tasks are known to increase Parkinsonian tremor amplitude. The method of just counting backwards was chosen following the recommendations made by Raethjen et al. [6]. In their study they found that the continuous speech production and easy arithmetic task required by counting backwards showed a significant tremor increase, comparable to other provocation methods, even those involving more demanding tasks. Interestingly, another study performed by Cleves et al. [11], showed that a more complicated arithmetic task produced a lower increase in rest tremor than the Stroop test. In conclusion, the combination of the arithmetic task and speech production seems to make counting backwards the most suitable, validated task to achieve provocation. Whether continuous speech

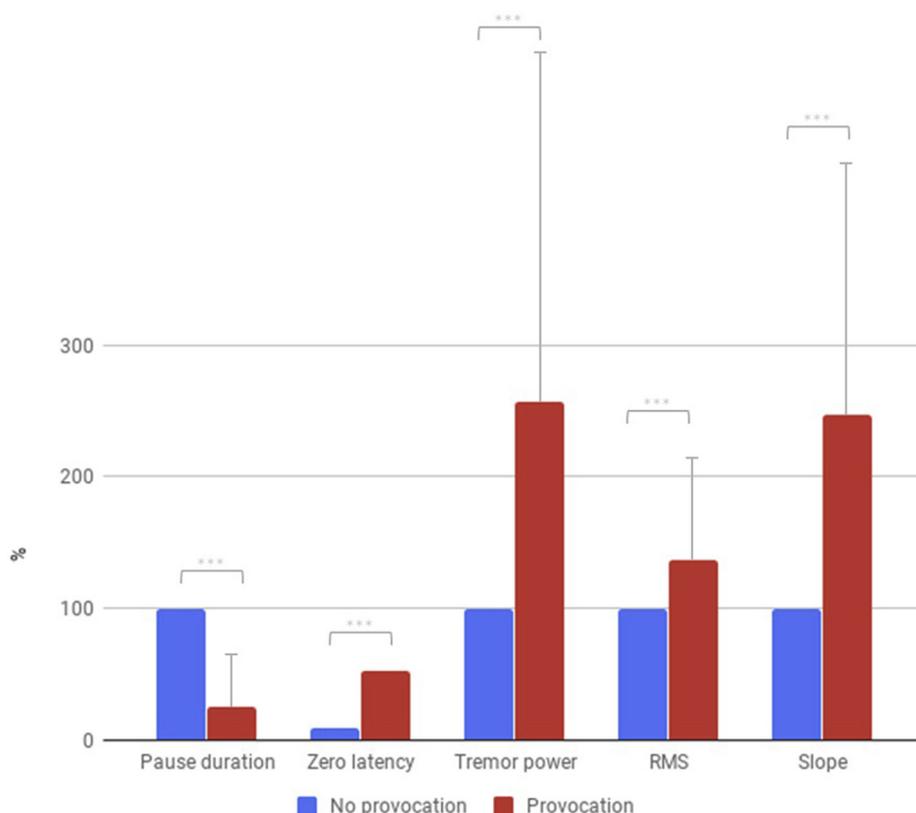


Fig. 1. Provocation effect. The graph shows the effect of provocation on RET pause duration, proportion of patients with zero latency, tremor power, RMS and slope.

production with a more demanding arithmetic task achieves higher tremor amplitude is yet to be determined. The final recommendation is that patients should be evaluated under provocation methods in order to avoid tremor intensity underestimation. Our results showed a similar RET amplitude increase as that shown in rest tremor by Raethjen et al. Another study by Zach et al. [12], has concluded that cognitive stress increases tremor intensity, reduces the effect of levodopa on resting tremor, and significantly decreases tremor variability.

The central mechanisms involved in tremor provocation remain still unclear [7]. Psychological stress is known to increase dopaminergic transmission in the basal ganglia, for which the most plausible

explanation is that non-dopaminergic mechanisms are involved in the modulation of tremor under stressful situations [7]. Moreover, it has been suggested that the noradrenergic system might modulate the cerebello-thalamo-cortical network during tremor under stress [12].

A recent study by our group [5], evaluating the influence of levodopa on re-emergent tremor pause duration has shown an inverse relation between re-emergent tremor latency and its amplitude, meaning that with lower amplitude, the pause gets longer, and vice versa. The analysis of the current study is in line with those previous results.

A limitation of this study is that we only relied on accelerometry in the back of both hands for the evaluation of tremor. This method

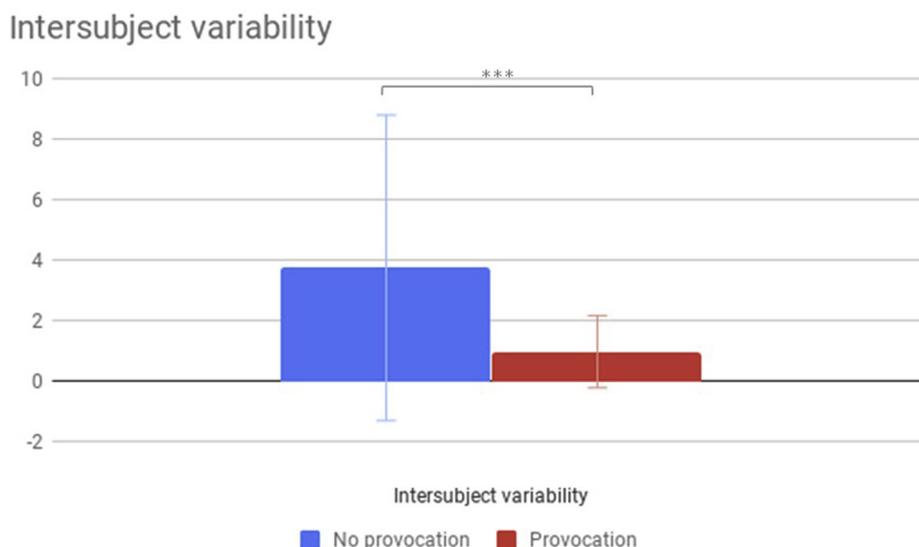


Fig. 2. Effect of provocation on inter-subject pause duration variability.

evaluated the total of tremor contributions of the whole upper limb, thus leading to possible overestimations of pause disappearance in cases of continuous tremor in other limbs with mechanical spread into our measurement. However, this bias was equally present in both situations: with and without provocation.

In conclusion, we have observed that tremor provocation leads to an increase in postural tremor intensity, with a steeper slope of tremor return after the pause, and a consequent decrease in re-emergent tremor pause duration. This latency decrease has led to the disappearance of the pause in approximately half of the samples. Tremor provocation has also led to a variability decrease in re-emergent tremor pause duration. Our results show that RET latency can be effectively modulated by provocation.

#### Conflicts of interest

None declared.

#### Disclosures

None reported.

#### Declarations of interest

None.

#### Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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