Elsevier Editorial System(tm) for Parkinsonism & Related Disorders
Manuscript Draft

Manuscript Number: PARKRELDIS-D-12-00109R1

Title: Amplitude fluctuations in essential tremor

Article Type: Full Length Article

Keywords: essential tremor; tremor amplitude fluctuations; tremor long-term monitoring; tremor rating assessment scale; tremor quantitative motor assessment system

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Abstract: Objective: To assess temporal amplitude variability in patients with essential tremor (ET). Methods: Patients who satisfied the diagnostic criteria for probable or definite ET were enrolled in the study. Each enrolled patient was first rated using The Essential Tremor Rating Assessment Scale (TETRAS). Postural and kinetic tremor of the arms was then measured using a quantitative motor assessment system (QMAS) starting at 8:00AM (T0 - baseline) every 2 hours for 6 hours. Subjects were videotaped performing the tasks. Single subjects consecutively performed each assessment twice during every time-interval. At the end of the study, videos were randomized and blindly rated using TETRAS. Results: Twelve ET subjects were enrolled. QMAS and video scores were directly correlated with high test-retest reliability for each time-interval. Furthermore, the QMAS scores at T0 significantly correlated with in-person rated TETRAS scores as well as with subsequent time-intervals instrumental scores. No significant differences were detected between time-intervals QMAS average measurements using ANOVA. There was a maximal 23% absolute variation in tremor amplitude from baseline as determined by the QMAS. Test for equality of variance showed high measurement variability for subjects with high QMAS scores at T0 and throughout the 6 hours of assessment. Conclusions: Baseline measures are predictive of tremor amplitude at subsequent assessments during the day. High amplitude tremor is associated with high intra-assessment variability.

Author Declaration

Ms. Ref. No.: PARKRELDIS-D-12-00109

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All experiments on human subjects should be conducted in accordance with the Declaration of Helsinki. Papers and all procedures were carried out with the adequate understanding and written consent of the subjects involved and with the ethical approval of the Baylor College of Medicine Institutional Review Board. The manuscript is currently not under consideration by other journals.

Joseph Jankovic, MD
Corresponding author

*Cover Letter

Comments to the Reviewers

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Dear Bob,

We would like to thank you and the Referees for their helpful comments in reviewing the manuscript and we appreciate the opportunity to submit a revised version of it. We have edited the manuscript according to the Reviewers suggestions as commented below:

Reviewer #1: We have tried to better specify how we set the experimental procedure in order to avoid known factors influencing tremor amplitude assessment. Moreover, we have discussed in the text possible implications of our findings on the design of clinical trials for essential tremor as requested.

Reviewer #2: We would thank the referee for his kind help in reviewing the manuscript.

The revised manuscript has been submitted. We hope the current edited version will be suitable for publication.

With kind regards,

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Amplitude fluctuations in essential tremor

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Manuscript category: full-length article. **Abstract word count:** 219 (250). **Text word count:** 2340 (3000). **References:** 30 (30). **Tables:** 2. **Figures:** 1.

Key words: essential tremor; tremor amplitude fluctuations; tremor long-term monitoring; tremor rating assessment scale; tremor quantitative motor assessment system.

Short title: Amplitude fluctuations in essential tremor.

Disclosures: Dr. Giuffrida is the president and principal investigator of the Great Lakes NeuroTechnologies Inc.

Abstract

Objective: To assess temporal amplitude variability in patients with essential tremor (ET). Methods: Patients who satisfied the diagnostic criteria for probable or definite ET were enrolled in the study. Each enrolled patient was first rated using The Essential Tremor Rating Assessment Scale (TETRAS). Postural and kinetic tremor of the arms was then measured using a quantitative motor assessment system (QMAS) starting at 8:00AM (T0 - baseline) every 2 hours for 6 hours. Subjects were videotaped performing the tasks. Single subjects consecutively performed each assessment twice during every time-interval. At the end of the study, videos were randomized and blindly rated using TETRAS. Results: Twelve ET subjects were enrolled. QMAS and video scores were directly correlated with high test-retest reliability for each time-interval. Furthermore, the QMAS scores at T0 significantly correlated with in-person rated TETRAS scores as well as with subsequent time-intervals instrumental scores. No significant differences were detected between time-intervals QMAS average measurements using ANOVA. There was a maximal 23% absolute variation in tremor amplitude from baseline as determined by the QMAS. Test for equality of variance showed high measurement variability for subjects with high QMAS scores at T0 and throughout the 6 hours of assessment. Conclusions: Baseline measures are predictive of tremor amplitude at subsequent assessments during the day. High amplitude tremor is associated with high intra-assessment variability.

Introduction

Physiologically, an oscillatory activity of a body part is determined by its central oscillatory generators coupled with peripheral mechanical properties, modulated by a variety of mechanisms which include motor unit firing properties, synchronized motor unit activities, mechanical and stretch reflex feedback loop resonances [1, 2]. When such central and peripheral mechanisms are impaired, pathological tremors, such as essential tremor (ET) become clinically manifested. Spectral analysis of ET signal often reveals multiple peaks related to the amplitude modulation of tremor signal [3]. Tremor amplitude may vary throughout the day depending on various internal and external factors. Such variations may be measured by rating scales or they could be more objectively assessed with a quantitative motor assessment system (QMAS) [4, 5]. Tremor amplitude between assessments, even during the same day, has been reported to vary between 30% [6] and 50% [7]. Short-term variations were initially considered random since no consistent pattern of variability in amplitude was demonstrated [8], but a more predictable, diurnal profile similar to that observed in physiological tremor was described [9]. Although often attributed to stress, hypoglycemia and other possible modifiers, the observed fluctuations in tremor amplitude appear to be multifactorial in origin. The mechanism of hourly and daily variability of ET severity, however, remains unclear, representing an important source of potentially spurious or unreliable outcomes in clinical trials designed to assess efficacy of a therapeutic intervention. Therefore, this variability must be taken into account when results of such trials are analyzed and interpreted. In order to quantitatively assess tremor amplitude temporal variability in patients with ET, we prospectively evaluated in a clinical setting postural and kinetic arms tremor of patients with ET every 2 hours for 6 hours using The Essential Tremor Rating Assessment Scale (TETRAS), developed by the Tremor Research Group (TRG) [4, 10],

and the Kinesia motor assessment system (Great Lakes NeuroTechnologies Inc., Cleveland, Ohio) as QMAS [4, 11].

Subjects and Methods

Study Population

Patients, between 18 and 75 year of age, who satisfied the TRG diagnostic criteria for probable or definite ET [12] were enrolled in the study at the Parkinson's Disease Center and Movement Disorders Clinic (PDCMDC), Baylor College of Medicine. All patients gave a written informed consent to participate in the research protocol, which was approved by the Institutional Review Board for Human Research at Baylor College of Medicine. Enrolled patients complied with the study performances requirements.

Experimental setting and procedure

All enrolled subjects were instructed not to take any medication for tremor the day of the test and to abstain from caffeinated beverages, alcohol and tobacco for at least 12 hours prior to assessment. On the day of the assessment, before the QMAS recording, each enrolled patient was first in-person rated using TETRAS by one rater (RF). Then, postural (arms outstretched) and kinetic (finger-to-nose) tremor of the arms were measured at 2-hour intervals for 6 hours from 8:00AM as baseline [8:00 (T0), 10:00 (T2), 12:00 (T4), 14:00 (T6)] using the QMAS. The Kinesia system, used as the QMAS, consists of two connected components that are worn on the finger and wrist by the subject during the assessment. The finger sensor integrates three orthogonal accelerometers and gyroscopes to detect three dimensional motion data which are transmitted wirelessly from the wrist module to a PC-unit during video-guided performances. Signal data are processed by the software to promptly provide a score which correlates with clinical scores for tremor [11].

Subjects were videotaped performing the selected tasks. Every subject performed each assessment consecutively twice during every time-interval. At the end of the study, videos were randomized and blindly rated by an independent rater (TY) using the TETRAS items for upper limb tremor. Videos recorded at each time-interval included 4 separate segments in which both patient arms were tested consecutively performing the postural and kinetic tasks using QMAS. Video segments for each time-interval were rated in random sequence to avoid systematic bias due to the time of assessment. Both raters were previously trained in TETRAS.

Data and statistical analysis

Data are presented as mean ± standard deviation (SD) for scalar measures and frequency (percent) for categorical variables. Correlation analysis was performed using Pearson's correlation. The reliability of single measures was analyzed using intra-class correlation coefficient (ICC), 95% confidence intervals (95%CI) and standard error of measurement (SEM). To check consistency of rater assessments, a 2-way mixed effects ANOVA-type model was used considering not-randomly sampled raters and absolute agreement. ICC values above 0.75 were considered indicative of good reliability [13].The SEM was calculated as the square root of the error variance, which is equal to the mean square error term obtained from ANOVA [14, 15]. The minimal detectable change (MDC) at the 95% confidence level was then computed as follow: $MDC = SEM \times 1.96 \times \sqrt{2}$ [15]. Percent absolute variations of the estimates from baseline were calculated using the formula: $(|Tn - T0|) \times 100 / T0$, where Tn is the time-interval where the maximal variation from baseline was detected. Differences in more than 2 sample means were tested using analysis of variance (ANOVA). Hartley's test was used to assess equality of variances between independent groups.

Results

Study sample clinical characteristics

Twelve ET subjects were enrolled (age: 50.25 ± 20.58 years; age at onset: 32 ± 21.66 years). Patients pharmacologically untreated for ET were 4 (33%). Treated patients were instructed to temporarily discontinue their medications the morning of the assessment. In-person rated TETRAS scores for upper limb postural (arms outstretched) and kinetic tremor were respectively 1.71 ± 0.45 and 1.79 ± 0.5 in average.

Reliability analysis of QMAS and video assessments

For each time-interval, QMAS and video scores showed high test-retest reliability. The ICC (95%CI) together with SEM and MDC values obtained by the consecutive evaluations performed at each time-interval are shown in Table 1. For postural task at T0, QMAS average scores (between consecutive evaluations) were 0.43 ± 0.58 on the right hand and 0.62 ± 0.71 on the left hand, while for the kinetic task QMAS average scores were 0.46 ± 0.55 on the right hand and 0.67 ± 0.6 on the left hand. Video average scores for postural task at T0 were 0.85 ± 0.9 on the right hand and 1.42 ± 0.67 on the left hand, while for the kinetic task video average scores at T0 were 1.58 ± 0.55 on the right hand and 1.83 ± 0.58 on the left hand. QMAS and video average scores were directly correlated (Table 2).

Baseline evaluations correlation analysis

QMAS average scores at T0 significantly correlated with task-corresponding scores obtained by in-person rated TETRAS items for upper limb tremor. Correlations were: $r = 0.64$ ($p = 0.025$) for postural task - right hand, $r = 0.7$ ($p = 0.011$) for postural task - left hand, $r = 0.59$ ($p = 0.043$) for kinetic task - right hand and $r = 0.6$ ($p = 0.039$) for kinetic

task - left hand. A significant correlation was also found between QMAS average scores and subsequent time-intervals instrumental average scores. In particular, QMAS average scores testing the postural task with right hand at T0 correlated with instrumental average scores at T2 ($r = 0.8$; $p = 0.002$), T4 ($r = 0.94$; $p < 0.001$) and T6 ($r = 0.66$; $p = 0.02$). QMAS average scores at T0 significantly correlated with instrumental average scores at T2 ($r = 0.92$; $p < 0.001$), T4 ($r = 0.85$; $p < 0.001$) and T6 ($r = 0.92$; $p < 0.001$) also considering the postural task with the left hand tested. Equivalent results were obtained evaluating the kinetic task. We found a significant correlation between QMAS average scores at T0 and T2 ($r = 0.94$; $p < 0.001$), T0 and T4 ($r = 0.94$; $p < 0.001$), T0 and T6 ($r = 0.94$; $p < 0.001$) for the right hand, and a significant correlation between QMAS average scores at T0 and T2 ($r = 0.94$; $p < 0.001$), T0 and T4 ($r = 0.95$; $p < 0.001$), T0 and T6 ($r = 0.92$; $p < 0.001$) for the left hand.

Temporal variations in tremor amplitude and intra-assessment variability

No significant differences were detected among time-intervals QMAS average measurements using ANOVA for both hands and tasks. There was a maximal 23% absolute variation from T0 in tremor amplitude as determined by the QMAS average estimates for postural task - right hand (at T6), 18% for postural task - left hand (at T4) and 9% for kinetic task - both hands (from T2 to T6 for the right hand, at T4 for the left hand). Test for equality of variance showed high measurement variability for high QMAS scores at T0, stratifying T0 scores in 2 independent groups by median values. Unequal variance between the 2 independent groups at T0 was found for the postural task - right hand ($F = 106.78$; $p < 0.001$), for the postural task - left hand ($F = 20.82$; $p = 0.005$), for the kinetic task - right hand ($F = 66.31$; $p < 0.001$) and for the kinetic task - left hand ($F = 18.78$; $p = 0.006$). Such difference in variability remained generally stable through the 6 hours of assessment (Figure 1).

Discussion

Temporal variations in ET severity are well recognized, often attributed to stress or some other factors, but there is paucity of data on the degree of such spontaneous fluctuations in tremor amplitude. This information is critical in designing methods and analyzing findings of clinical trials of various therapeutic interventions in ET. The aim of the current study was to determine the degree of tremor amplitude fluctuation during the day at 2-hour intervals as measured by clinical and instrumental assessments. QMAS and video-rated scores were generally reliable during the entire period of assessment in our study. Computed ICC, SEM and MDC values for both scores indicated a global higher consistency of measurements for instrumental scores compared to clinical video-rated scores. In our study sample we found action tremor amplitude variability within the 6 hours of assessment up to 23%, as determined by the QMAS. Despite any detected fluctuations, no significant differences were observed between time-interval average measurements for each hand and task in the present study, assessments at baseline being predictive of subsequent temporal evaluations. Our results are similar to those obtained by Cleeves and Findley [8], who demonstrated a small variability of tremor amplitude during a diurnal assessment. Diurnal profile of tremor amplitude fluctuation in ET may be similar to the temporal profile which characterizes physiological tremor [9]. Short and long-term temporal fluctuations of signs and symptoms severity have been well recognized in several movement disorders, such as motor and non-motor fluctuations in patients with Parkinson's disease (PD), related to a variety of factors including duration and dosage of levodopa, age at onset, stress, sleep or type of and time of food intake [16]. “Sleep benefit” and worsening disability during evening hours have been described in patients with PD as well as in patients with dystonia [17], particularly dopa-responsive dystonia due to guanosine triphosphate cyclohydrolase I deficiency [18], and dyssomnias,

specifically restless legs syndrome [19] and periodic limb movements disorder [20]. Patients with tardive dyskinesias have also shown fluctuations in intensity throughout the day [21, 22] as have those with paroxysmal dyskinesias [23], and other hyperkinesias, such as Tourette's syndrome [24]. Although these fluctuations are usually difficult to explain, they may be related to internal and external processes such as stress or fatigue. In our study we tried to create a quiet environment, avoiding as many potential stressors as possible.

It is well known that the cerebellum, which has been implicated in the pathophysiology of ET, is responsive to peripheral, external input and its dysfunction may result in wider fluctuations in amplitude, particularly in patients with more severe ET [2, 25, 26]. While variations in tremor frequency are usually small in organic tremors, such as ET, as compared to psychogenic tremors [27], variations in amplitude may be large reflecting fluctuations in the firing of individual neurons of neuronal network, such as the one responsible for generation of ET [28]. As the disease progresses, tremor signal may translate from a diffusional process [29] to a chaos-like tremor signal with a large diffusional exponent [28], further enhancing amplitude variability. Changes in fractal-like structure related to pathological processes have been already described for different biological signals, including human walking and heartbeat [30].

Spontaneous variations in tremor amplitude should be taken into account when designing future clinical trials. The 23% amplitude variability identified in our study should be considered when calculating sample size and when estimating meaningful benefit above and beyond the normal variation and placebo effect. Treatment-related acute change from baseline should be greater than the maximal spontaneous variability in tremor amplitude identified during the observational period.

In conclusion, our prospective study demonstrated that clinical rating scales, coupled with QMAS, are reliable tools in assessing severity of ET. Baseline instrumental measures of amplitude are predictive of subsequent hourly assessments and no significant differences were detected between time-intervals QMAS average measurements. There was up to 23% variability in the amplitude during the 6-hour assessment. High amplitude tremor is associated with high intra-assessment variability. Despite relatively small sample size and limited time during which tremor amplitude was monitored, we believe that the conclusions are valid and the findings have implications for the understanding of natural fluctuations of tremor and for the design, analysis and interpretation of clinical trials.

Acknowledgments. We would like to thank Anne K. Daleiden and Cathy Jankovic for their contributions to the study.

Authors roles (1. Research project: 1A. Conception, 1B. Organization, 1C. Execution; 2. Statistical Analysis: 2A. Design, 2B. Execution, 2C. Review and Critique; 3. Manuscript: 3A. Writing of the first draft, 3B. Review and Critique): Giovanni Mostile: 1A, 1B, 2A, 2B, 3A; Robert Fekete: 1B, 1C, 2C, 3B; Joseph P. Giuffrida: 1B, 2A, 2C, 3B; Toby Yaltho: 1C, 2C, 3B; Anthony Davidson: 1B, 2A, 2C; Alessandra Nicoletti: 2C, 3B; Mario Zappia: 2C, 3B; Joseph Jankovic: 1A, 1B, 1C, 2A, 2C, 3B.

Disclosures: Dr. Fekete has served as a consultant for Lundbeck, Inc. and has received honoraria from Medlink, Inc. Dr. Giuffrida is the president and principal investigator of Great Lakes NeuroTechnologies Inc. Dr Yaltho has served as a consultant for Merz Pharmaceutics, speakers bureau for Teva Pharmaceutical Industries Ltd and he has received research support from EMD Serono. Dr Zappia has received compensation for consulting services from Boehringer-Ingelheim, Lundbeck, and UBC and has received scientific grants from AIFA, Novartis, and Lundbeck. Dr. Jankovic has received research

support from Allergan, Inc; Allon Therapeutics; Biotie; Ceregene, Inc; Chelsea Therapeutics; Diana Helis Henry Medical Research Foundation; EMD Serono; Huntington's Disease Society of America; Huntington Study Group; Impax Pharmaceuticals; Ipsen Limited; Lundbeck Inc; Medtronic; Merz Pharmaceuticals; Michael J Fox Foundation for Parkinson Research; National Institutes of Health; National Parkinson Foundation; Neurogen; St. Jude Medical; Teva Pharmaceutical Industries Ltd; University of Rochester; and the Parkinson Study Group. He has served as a consultant or advisory committee nember for Allergan, Inc; Chelsea Therapeutics; EMD Serono; Lundbeck Inc; Merz Pharmaceuticals; Michael J Fox Foundation for Parkinson Research; Neurocrine Biosciences, Inc; Teva Pharmaceutical Industries Ltd. Dr. Jankovic has also received honoraria for serving as an editor for Elsevier; Medlink: Neurology; Neurology in Clinical Practice; Neurotoxin Institute; Scientiae; and UpToDate. Dr Mostile, Dr Davidson and Dr Nicoletti report no disclosures.

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Table 1. QMAS and video scores test-retest reliability

		QMAS Scores					
		Postural Task			**Kinetic Task**		
N = 12		**ICC (95%CI)**	**SEM**	**MDC**	**ICC (95%CI)**	**SEM**	**MDC**
T0	**Right Hand**	0.87 (0.6 - 0.96)	0.23	0.63	0.92 (0.76 - 0.98)	0.15	0.41
	Left Hand	0.9 (0.69 - 0.97)	0.24	0.67	0.84 (0.54 - 0.95)	0.26	0.72
T2	**Right Hand**	0.78 (0.4 - 0.93)	0.22	0.61	0.85 (0.55 - 0.95)	0.19	0.53
	Left Hand	0.75 (0.36 - 0.92)	0.33	0.9	0.95 (0.85 - 0.99)	0.16	0.46
T4	**Right Hand**	0.58 (0.05 - 0.86)	0.45	1.24	0.91 (0.72 - 0.97)	0.19	0.54
	Left Hand	0.76 (0.35 - 0.93)	0.31	0.85	0.93 (0.79 - 0.98)	0.2	0.57
T6	**Right Hand**	0.85 (0.58 - 0.96)	0.18	0.51	0.88 (0.65 - 0.96)	0.23	0.65
	Left Hand	0.81 (0.47 - 0.94)	0.34	0.95	0.98 (0.92 - 0.99)	0.09	0.25
		Video Scores					
		Postural Task			**Kinetic Task**		
N = 12		**ICC (95%CI)**	**SEM**	**MDC**	**ICC (95%CI)**	**SEM**	**MDC**
T0	**Right Hand**	0.78 (0.39 - 0.93)	0.46	1.28	0.93 (0.78 - 0.98)	0.15	0.42
	Left Hand	0.75 (0.33 - 0.92)	0.37	1.02	0.88 (0.66 - 0.96)	0.2	0.57
T2	**Right Hand**	0.6 (0.56 - 0.87)	0.59	1.63	0.8 (0.46 - 0.94)	0.25	0.7
	Left Hand	0.74 (0.32 - 0.92)	0.36	1.01	0.93 (0.79 - 0.98)	0.15	0.42
T4	**Right Hand**	0.53 (0 - 0.84)	0.63	1.75	0.81 (0.48 - 0.94)	0.29	0.82
	Left Hand	0.72 (0.31 - 0.91)	0.41	1.14	0.8 (0.45 - 0.94)	0.23	0.64
T6	**Right Hand**	0.55 (-0.02 - 0.85)	0.54	1.5	0.76 (0.34 - 0.92)	0.34	0.94
	Left Hand	0.83 (0.53 - 0.95)	0.33	0.92	0.97 (0.91 - 0.99)	0.1	0.28

Notes: data are ICC (95%CI), SEM and MDC. T0, T2, T4 and T6 are 2-hour time-intervals. Analysis was performed for each tested hand and task. **Legend:** QMAS = quantitative motor assessment system; ICC = intra-class correlation coefficient; SEM = standard error of measurement; MDC = minimal detectable change.

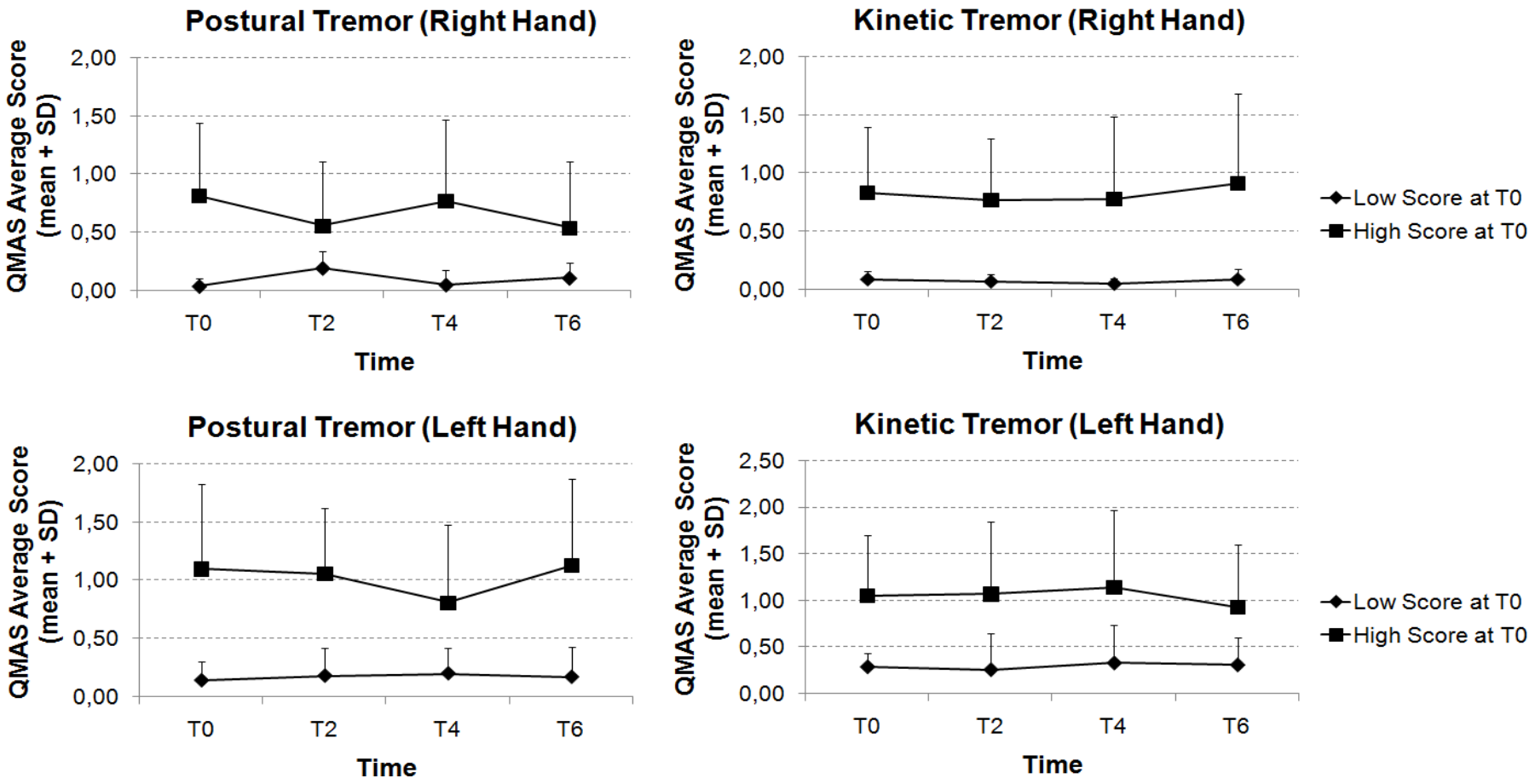
Table 2. Correlation between QMAS and video average scores for time-intervals

N = 12	**Postural Task**	**Kinetic Task**
T0		
Right Hand	0.71 (0.01)	0.77 (0.003)
Left Hand	0.78 (0.003)	0.73 (0.007)
T2		
Right Hand	0.66 (0.018)	0.91 (< 0.001)
Left Hand	0.78 (0.003)	0.72 (0.008)
T4		
Right Hand	0.74 (0.006)	0.85 (< 0.001)
Left Hand	0.72 (0.009)	0.8 (0.002)
T6		
Right Hand	0.9 (< 0.001)	0.78 (0.003)
Left Hand	0.86 (< 0.001)	0.73 (0.007)

Notes: data are Pearson r (p value). T0, T2, T4 and T6 are 2-hour time-intervals.

Analysis was performed for each tested hand and task.

Figure 1. QMAS average scores variability among time-intervals (T0 score cut-offs are median values)



Amplitude fluctuations in essential tremor

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Manuscript category: full-length article. **Abstract word count:** 219 (250). **Text word count:** 2340 (3000). **References:** 30 (30). **Tables:** 2. **Figures:** 1.

Key words: essential tremor; tremor amplitude fluctuations; tremor long-term monitoring; tremor rating assessment scale; tremor quantitative motor assessment system.

Short title: Amplitude fluctuations in essential tremor.

Disclosures: Dr. Giuffrida is the president and principal investigator of the Great Lakes NeuroTechnologies Inc.

Abstract

Objective: To assess temporal amplitude variability in patients with essential tremor (ET). Methods: Patients who satisfied the diagnostic criteria for probable or definite ET were enrolled in the study. Each enrolled patient was first rated using The Essential Tremor Rating Assessment Scale (TETRAS). Postural and kinetic tremor of the arms was then measured using a quantitative motor assessment system (QMAS) starting at 8:00AM (T0 - baseline) every 2 hours for 6 hours. Subjects were videotaped performing the tasks. Single subjects consecutively performed each assessment twice during every time-interval. At the end of the study, videos were randomized and blindly rated using TETRAS. Results: Twelve ET subjects were enrolled. QMAS and video scores were directly correlated with high test-retest reliability for each time-interval. Furthermore, the QMAS scores at T0 significantly correlated with in-person rated TETRAS scores as well as with subsequent time-intervals instrumental scores. No significant differences were detected between time-intervals QMAS average measurements using ANOVA. There was a maximal 23% absolute variation in tremor amplitude from baseline as determined by the QMAS. Test for equality of variance showed high measurement variability for subjects with high QMAS scores at T0 and throughout the 6 hours of assessment. Conclusions: Baseline measures are predictive of tremor amplitude at subsequent assessments during the day. High amplitude tremor is associated with high intra-assessment variability.

Introduction

Physiologically, an oscillatory activity of a body part is determined by its central oscillatory generators coupled with peripheral mechanical properties, modulated by a variety of mechanisms which include motor unit firing properties, synchronized motor unit activities, mechanical and stretch reflex feedback loop resonances [1, 2]. When such central and peripheral mechanisms are impaired, pathological tremors, such as essential tremor (ET) become clinically manifested. Spectral analysis of ET signal often reveals multiple peaks related to the amplitude modulation of tremor signal [3]. Tremor amplitude may vary throughout the day depending on various internal and external factors. Such variations may be measured by rating scales or they could be more objectively assessed with a quantitative motor assessment system (QMAS) [4, 5]. Tremor amplitude between assessments, even during the same day, has been reported to vary between 30% [6] and 50% [7]. Short-term variations were initially considered random since no consistent pattern of variability in amplitude was demonstrated [8], but a more predictable, diurnal profile similar to that observed in physiological tremor was described [9]. Although often attributed to stress, hypoglycemia and other possible modifiers, the observed fluctuations in tremor amplitude appear to be multifactorial in origin. The mechanism of hourly and daily variability of ET severity, however, remains unclear, representing an important source of potentially spurious or unreliable outcomes in clinical trials designed to assess efficacy of a therapeutic intervention. Therefore, this variability must be taken into account when results of such trials are analyzed and interpreted. In order to quantitatively assess tremor amplitude temporal variability in patients with ET, we prospectively evaluated in a clinical setting postural and kinetic arms tremor of patients with ET every 2 hours for 6 hours using The Essential Tremor Rating Assessment Scale (TETRAS), developed by the Tremor Research Group (TRG) [4, 10],

and the Kinesia motor assessment system (Great Lakes NeuroTechnologies Inc., Cleveland, Ohio) as QMAS [4, 11].

Subjects and Methods

Study Population

Patients, between 18 and 75 year of age, who satisfied the TRG diagnostic criteria for probable or definite ET [12] were enrolled in the study at the Parkinson's Disease Center and Movement Disorders Clinic (PDCMDC), Baylor College of Medicine. All patients gave a written informed consent to participate in the research protocol, which was approved by the Institutional Review Board for Human Research at Baylor College of Medicine. Enrolled patients complied with the study performances requirements.

Experimental setting and procedure

All enrolled subjects were instructed not to take any medication for tremor the day of the test and to abstain from caffeinated beverages, alcohol and tobacco for at least 12 hours prior to assessment. On the day of the assessment, before the QMAS recording, each enrolled patient was first in-person rated using TETRAS by one rater (RF). Then, postural (arms outstretched) and kinetic (finger-to-nose) tremor of the arms were measured at 2-hour intervals for 6 hours from 8:00AM as baseline [8:00 (T0), 10:00 (T2), 12:00 (T4), 14:00 (T6)] using the QMAS. The Kinesia system, used as the QMAS, consists of two connected components that are worn on the finger and wrist by the subject during the assessment. The finger sensor integrates three orthogonal accelerometers and gyroscopes to detect three dimensional motion data which are transmitted wirelessly from the wrist module to a PC-unit during video-guided performances. Signal data are processed by the software to promptly provide a score which correlates with clinical scores for tremor [11].

Subjects were videotaped performing the selected tasks. Every subject performed each assessment consecutively twice during every time-interval. At the end of the study, videos were randomized and blindly rated by an independent rater (TY) using the TETRAS items for upper limb tremor. Videos recorded at each time-interval included 4 separate segments in which both patient arms were tested consecutively performing the postural and kinetic tasks using QMAS. Video segments for each time-interval were rated in random sequence to avoid systematic bias due to the time of assessment. Both raters were previously trained in TETRAS.

Data and statistical analysis

Data are presented as mean ± standard deviation (SD) for scalar measures and frequency (percent) for categorical variables. Correlation analysis was performed using Pearson's correlation. The reliability of single measures was analyzed using intra-class correlation coefficient (ICC), 95% confidence intervals (95%CI) and standard error of measurement (SEM). To check consistency of rater assessments, a 2-way mixed effects ANOVA-type model was used considering not-randomly sampled raters and absolute agreement. ICC values above 0.75 were considered indicative of good reliability [13].The SEM was calculated as the square root of the error variance, which is equal to the mean square error term obtained from ANOVA [14, 15]. The minimal detectable change (MDC) at the 95% confidence level was then computed as follow: $MDC = SEM \times 1.96 \times \sqrt{2}$ [15]. Percent absolute variations of the estimates from baseline were calculated using the formula: $(|Tn - T0|) \times 100 / T0$, where Tn is the time-interval where the maximal variation from baseline was detected. Differences in more than 2 sample means were tested using analysis of variance (ANOVA). Hartley's test was used to assess equality of variances between independent groups.

Results

Study sample clinical characteristics

Twelve ET subjects were enrolled (age: 50.25 ± 20.58 years; age at onset: 32 ± 21.66 years). Patients pharmacologically untreated for ET were 4 (33%). Treated patients were instructed to temporarily discontinue their medications the morning of the assessment. In-person rated TETRAS scores for upper limb postural (arms outstretched) and kinetic tremor were respectively 1.71 ± 0.45 and 1.79 ± 0.5 in average.

Reliability analysis of QMAS and video assessments

For each time-interval, QMAS and video scores showed high test-retest reliability. The ICC (95%CI) together with SEM and MDC values obtained by the consecutive evaluations performed at each time-interval are shown in Table 1. For postural task at T0, QMAS average scores (between consecutive evaluations) were 0.43 ± 0.58 on the right hand and 0.62 ± 0.71 on the left hand, while for the kinetic task QMAS average scores were 0.46 ± 0.55 on the right hand and 0.67 ± 0.6 on the left hand. Video average scores for postural task at T0 were 0.85 ± 0.9 on the right hand and 1.42 ± 0.67 on the left hand, while for the kinetic task video average scores at T0 were 1.58 ± 0.55 on the right hand and 1.83 ± 0.58 on the left hand. QMAS and video average scores were directly correlated (Table 2).

Baseline evaluations correlation analysis

QMAS average scores at T0 significantly correlated with task-corresponding scores obtained by in-person rated TETRAS items for upper limb tremor. Correlations were: $r = 0.64$ ($p = 0.025$) for postural task - right hand, $r = 0.7$ ($p = 0.011$) for postural task - left hand, $r = 0.59$ ($p = 0.043$) for kinetic task - right hand and $r = 0.6$ ($p = 0.039$) for kinetic

task - left hand. A significant correlation was also found between QMAS average scores and subsequent time-intervals instrumental average scores. In particular, QMAS average scores testing the postural task with right hand at T0 correlated with instrumental average scores at T2 ($r = 0.8$; $p = 0.002$), T4 ($r = 0.94$; $p < 0.001$) and T6 ($r = 0.66$; $p = 0.02$). QMAS average scores at T0 significantly correlated with instrumental average scores at T2 ($r = 0.92$; $p < 0.001$), T4 ($r = 0.85$; $p < 0.001$) and T6 ($r = 0.92$; $p < 0.001$) also considering the postural task with the left hand tested. Equivalent results were obtained evaluating the kinetic task. We found a significant correlation between QMAS average scores at T0 and T2 ($r = 0.94$; $p < 0.001$), T0 and T4 ($r = 0.94$; $p < 0.001$), T0 and T6 ($r = 0.94$; $p < 0.001$) for the right hand, and a significant correlation between QMAS average scores at T0 and T2 ($r = 0.94$; $p < 0.001$), T0 and T4 ($r = 0.95$; $p < 0.001$), T0 and T6 ($r = 0.92$; $p < 0.001$) for the left hand.

Temporal variations in tremor amplitude and intra-assessment variability

No significant differences were detected among time-intervals QMAS average measurements using ANOVA for both hands and tasks. There was a maximal 23% absolute variation from T0 in tremor amplitude as determined by the QMAS average estimates for postural task - right hand (at T6), 18% for postural task - left hand (at T4) and 9% for kinetic task - both hands (from T2 to T6 for the right hand, at T4 for the left hand). Test for equality of variance showed high measurement variability for high QMAS scores at T0, stratifying T0 scores in 2 independent groups by median values. Unequal variance between the 2 independent groups at T0 was found for the postural task - right hand ($F = 106.78$; $p < 0.001$), for the postural task - left hand ($F = 20.82$; $p = 0.005$), for the kinetic task - right hand ($F = 66.31$; $p < 0.001$) and for the kinetic task - left hand ($F = 18.78$; $p = 0.006$). Such difference in variability remained generally stable through the 6 hours of assessment (Figure 1).

Discussion

Temporal variations in ET severity are well recognized, often attributed to stress or some other factors, but there is paucity of data on the degree of such spontaneous fluctuations in tremor amplitude. This information is critical in designing methods and analyzing findings of clinical trials of various therapeutic interventions in ET. The aim of the current study was to determine the degree of tremor amplitude fluctuation during the day at 2-hour intervals as measured by clinical and instrumental assessments. QMAS and video-rated scores were generally reliable during the entire period of assessment in our study. Computed ICC, SEM and MDC values for both scores indicated a global higher consistency of measurements for instrumental scores compared to clinical video-rated scores. In our study sample we found action tremor amplitude variability within the 6 hours of assessment up to 23%, as determined by the QMAS. Despite any detected fluctuations, no significant differences were observed between time-interval average measurements for each hand and task in the present study, assessments at baseline being predictive of subsequent temporal evaluations. Our results are similar to those obtained by Cleeves and Findley [8], who demonstrated a small variability of tremor amplitude during a diurnal assessment. Diurnal profile of tremor amplitude fluctuation in ET may be similar to the temporal profile which characterizes physiological tremor [9]. Short and long-term temporal fluctuations of signs and symptoms severity have been well recognized in several movement disorders, such as motor and non-motor fluctuations in patients with Parkinson's disease (PD), related to a variety of factors including duration and dosage of levodopa, age at onset, stress, sleep or type of and time of food intake [16]. “Sleep benefit” and worsening disability during evening hours have been described in patients with PD as well as in patients with dystonia [17], particularly dopa-responsive dystonia due to guanosine triphosphate cyclohydrolase I deficiency [18], and dyssomnias,

specifically restless legs syndrome [19] and periodic limb movements disorder [20]. Patients with tardive dyskinesias have also shown fluctuations in intensity throughout the day [21, 22] as have those with paroxysmal dyskinesias [23], and other hyperkinesias, such as Tourette's syndrome [24]. Although these fluctuations are usually difficult to explain, they may be related to internal and external processes such as stress or fatigue. In our study we tried to create a quiet environment, avoiding as many potential stressors as possible.

It is well known that the cerebellum, which has been implicated in the pathophysiology of ET, is responsive to peripheral, external input and its dysfunction may result in wider fluctuations in amplitude, particularly in patients with more severe ET [2, 25, 26]. While variations in tremor frequency are usually small in organic tremors, such as ET, as compared to psychogenic tremors [27], variations in amplitude may be large reflecting fluctuations in the firing of individual neurons of neuronal network, such as the one responsible for generation of ET [28]. As the disease progresses, tremor signal may translate from a diffusional process [29] to a chaos-like tremor signal with a large diffusional exponent [28], further enhancing amplitude variability. Changes in fractal-like structure related to pathological processes have been already described for different biological signals, including human walking and heartbeat [30].

Spontaneous variations in tremor amplitude should be taken into account when designing future clinical trials. The 23% amplitude variability identified in our study should be considered when calculating sample size and when estimating meaningful benefit above and beyond the normal variation and placebo effect. Treatment-related acute change from baseline should be greater than the maximal spontaneous variability in tremor amplitude identified during the observational period.

In conclusion, our prospective study demonstrated that clinical rating scales, coupled with QMAS, are reliable tools in assessing severity of ET. Baseline instrumental measures of amplitude are predictive of subsequent hourly assessments and no significant differences were detected between time-intervals QMAS average measurements. There was up to 23% variability in the amplitude during the 6-hour assessment. High amplitude tremor is associated with high intra-assessment variability. Despite relatively small sample size and limited time during which tremor amplitude was monitored, we believe that the conclusions are valid and the findings have implications for the understanding of natural fluctuations of tremor and for the design, analysis and interpretation of clinical trials.

Acknowledgments. We would like to thank Anne K. Daleiden and Cathy Jankovic for their contributions to the study.

Authors roles (1. Research project: 1A. Conception, 1B. Organization, 1C. Execution; 2. Statistical Analysis: 2A. Design, 2B. Execution, 2C. Review and Critique; 3. Manuscript: 3A. Writing of the first draft, 3B. Review and Critique): Giovanni Mostile: 1A, 1B, 2A, 2B, 3A; Robert Fekete: 1B, 1C, 2C, 3B; Joseph P. Giuffrida: 1B, 2A, 2C, 3B; Toby Yaltho: 1C, 2C, 3B; Anthony Davidson: 1B, 2A, 2C; Alessandra Nicoletti: 2C, 3B; Mario Zappia: 2C, 3B; Joseph Jankovic: 1A, 1B, 1C, 2A, 2C, 3B.

Disclosures: Dr. Fekete has served as a consultant for Lundbeck, Inc. and has received honoraria from Medlink, Inc. Dr. Giuffrida is the president and principal investigator of Great Lakes NeuroTechnologies Inc. Dr Yaltho has served as a consultant for Merz Pharmaceutics, speakers bureau for Teva Pharmaceutical Industries Ltd and he has received research support from EMD Serono. Dr Zappia has received compensation for consulting services from Boehringer-Ingelheim, Lundbeck, and UBC and has received scientific grants from AIFA, Novartis, and Lundbeck. Dr. Jankovic has received research

support from Allergan, Inc; Allon Therapeutics; Biotie; Ceregene, Inc; Chelsea Therapeutics; Diana Helis Henry Medical Research Foundation; EMD Serono; Huntington's Disease Society of America; Huntington Study Group; Impax Pharmaceuticals; Ipsen Limited; Lundbeck Inc; Medtronic; Merz Pharmaceuticals; Michael J Fox Foundation for Parkinson Research; National Institutes of Health; National Parkinson Foundation; Neurogen; St. Jude Medical; Teva Pharmaceutical Industries Ltd; University of Rochester; and the Parkinson Study Group. He has served as a consultant or advisory committee nember for Allergan, Inc; Chelsea Therapeutics; EMD Serono; Lundbeck Inc; Merz Pharmaceuticals; Michael J Fox Foundation for Parkinson Research; Neurocrine Biosciences, Inc; Teva Pharmaceutical Industries Ltd. Dr. Jankovic has also received honoraria for serving as an editor for Elsevier; Medlink: Neurology; Neurology in Clinical Practice; Neurotoxin Institute; Scientiae; and UpToDate. Dr Mostile, Dr Davidson and Dr Nicoletti report no disclosures.

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Table 1. QMAS and video scores test-retest reliability

		QMAS Scores					
		Postural Task			**Kinetic Task**		
N = 12		**ICC (95%CI)**	**SEM**	**MDC**	**ICC (95%CI)**	**SEM**	**MDC**
T0	**Right Hand**	0.87 (0.6 - 0.96)	0.23	0.63	0.92 (0.76 - 0.98)	0.15	0.41
	Left Hand	0.9 (0.69 - 0.97)	0.24	0.67	0.84 (0.54 - 0.95)	0.26	0.72
T2	**Right Hand**	0.78 (0.4 - 0.93)	0.22	0.61	0.85 (0.55 - 0.95)	0.19	0.53
	Left Hand	0.75 (0.36 - 0.92)	0.33	0.9	0.95 (0.85 - 0.99)	0.16	0.46
T4	**Right Hand**	0.58 (0.05 - 0.86)	0.45	1.24	0.91 (0.72 - 0.97)	0.19	0.54
	Left Hand	0.76 (0.35 - 0.93)	0.31	0.85	0.93 (0.79 - 0.98)	0.2	0.57
T6	**Right Hand**	0.85 (0.58 - 0.96)	0.18	0.51	0.88 (0.65 - 0.96)	0.23	0.65
	Left Hand	0.81 (0.47 - 0.94)	0.34	0.95	0.98 (0.92 - 0.99)	0.09	0.25
		Video Scores					
		Postural Task			**Kinetic Task**		
N = 12		**ICC (95%CI)**	**SEM**	**MDC**	**ICC (95%CI)**	**SEM**	**MDC**
T0	**Right Hand**	0.78 (0.39 - 0.93)	0.46	1.28	0.93 (0.78 - 0.98)	0.15	0.42
	Left Hand	0.75 (0.33 - 0.92)	0.37	1.02	0.88 (0.66 - 0.96)	0.2	0.57
T2	**Right Hand**	0.6 (0.56 - 0.87)	0.59	1.63	0.8 (0.46 - 0.94)	0.25	0.7
	Left Hand	0.74 (0.32 - 0.92)	0.36	1.01	0.93 (0.79 - 0.98)	0.15	0.42
T4	**Right Hand**	0.53 (0 - 0.84)	0.63	1.75	0.81 (0.48 - 0.94)	0.29	0.82
	Left Hand	0.72 (0.31 - 0.91)	0.41	1.14	0.8 (0.45 - 0.94)	0.23	0.64
T6	**Right Hand**	0.55 (-0.02 - 0.85)	0.54	1.5	0.76 (0.34 - 0.92)	0.34	0.94
	Left Hand	0.83 (0.53 - 0.95)	0.33	0.92	0.97 (0.91 - 0.99)	0.1	0.28

Notes: data are ICC (95%CI), SEM and MDC. T0, T2, T4 and T6 are 2-hour time-intervals. Analysis was performed for each tested hand and task. **Legend:** QMAS = quantitative motor assessment system; ICC = intra-class correlation coefficient; SEM = standard error of measurement; MDC = minimal detectable change.

Table 2. Correlation between QMAS and video average scores for time-intervals

N = 12	Postural Task	Kinetic Task
T0		
Right Hand	0.71 (0.01)	0.77 (0.003)
Left Hand	0.78 (0.003)	0.73 (0.007)
T2		
Right Hand	0.66 (0.018)	0.91 (< 0.001)
Left Hand	0.78 (0.003)	0.72 (0.008)
T4		
Right Hand	0.74 (0.006)	0.85 (< 0.001)
Left Hand	0.72 (0.009)	0.8 (0.002)
T6		
Right Hand	0.9 (< 0.001)	0.78 (0.003)
Left Hand	0.86 (< 0.001)	0.73 (0.007)

Notes: data are Pearson r (p value). T0, T2, T4 and T6 are 2-hour time-intervals.

Analysis was performed for each tested hand and task.

Figure 1. QMAS average scores variability among time-intervals (T0 score cut-offs are median values)