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Kinetic tremor in Parkinson's disease – an underrated symptom

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Summary. Since the first description of the disorder which we now call ''Parkinson's Disease'' (PD) much has changed not only because of new therapeutic possibilities. Initially only the rest tremor was described. Today it is generally accepted that PD can be accompanied by different forms of tremor. Nevertheless the kinetic tremor is hardly examined and no attention is paid to it in clinical rating scales although it can already be found in old published drawings of PD-patients. To date instrumented investigations do not capture the most common kinetic tremor of PD that seems to be frequent under everyday life conditions. In order to assess the significance of kinetic tremor in PD, tremor during a spiral drawing task was investigated in an open study involving 870 patients. The results indicate that a combination of rest, postural and kinetic tremors constitute the most frequent tremor constellation in PD.

Keywords: Kinetic tremor, Parkinson's disease, spiralography.

Introduction

A pilot investigation by the authors of tremor during spiral drawing suggested that the frequency of movement-associated (kinetic) tremor in Parkinson's disease has been underestimated, a view confirmed by thorough examination of the published literature. Explanations for this underestimation suggested by the literature itself included problems with respect to both nomenclature and particular experimental methods, as well as historical perceptions regarding the various tremor types.

History

In his original monograph ''An Essay on the Shaking Palsy'' (1817), James Parkinson described resting tremor being the characteristic tremor of the disorder, which he termed 'paralysis agitans' (Parkinson, 1817). He described this tremor as ''involuntary tremulous motion, with lessened voluntary muscular power, in parts, not in action'' and ''that agitation continues in full force whilst the limb is at rest and unemployed; and even is sometimes diminished by calling the muscles into employment.'' Seventy years later, Charcot emphasized that tremor was not an essential symptom in this disorder, and argued that the term ''paralysis agitans'' was thus inappropriate and should be replaced

Table 1. Tremors in PD (adapted from Deuschl et al., 1998)

Type	Description	Comment	Incidence
I	Pure RT or RT plus PT/KT, same frequency	there is frequently a pause in the tremor during the transition from rest to posture	pure RT infrequent; combination of RT and PT/KT most common in PD
II	RT plus PT/KT, different frequencies	frequency of PT/KT higher than of RT (>1.5 Hz) but no harmonic frequency to RT often been considered to be a combination of an ET with PD	<10% of PD patients
III	pure PT/KT	frequency between 4 and 9 Hz. often considered as ET variants or found to be in-distinguishable from enhanced physiologic tremor	isolated PT/KT especially severe pure PT is rare in PD

RT rest tremor, *PT* postural tremor, *KT* kinetic tremor

by ''Parkinson's disease'' (PD). Nevertheless, Charcot, like Parkinson, clearly differentiated between the typical rest tremor of PD and the postural tremor of essential tremor (ET).

Tremors in PD

It is currently generally accepted that all behavioural types of tremor can occur in PD and, indeed, that several different types of tremor can coexist, complicating differential diagnosis (Table 1). In diagnosing PD according to the criteria of the UK Parkinson's Disease Society Brain Bank (Hughes et al., 1992), rest tremor is the only tremor type admitted as one of the cardinal signs; but while bradykinesia must be present, resting tremor is not essential for the diagnosis.

In the ''SIC Task Force Appraisal of Clinical Diagnostic Criteria for Parkinsonian Disorders'', on the other hand, rest tremor was one of the most powerful positive diagnostic predictors for PD, after asymmetry of parkinsonian signs and levodopa responsiveness (Litvan et al., 2003). Tremor, while less specific than bradykinesia, is one of the most recognizable symptoms of Parkinson's disease. However, only half of all patients present with tremor as the initial manifestation of Parkinson's disease, and 15% never exhibit tremor during the course of the illness (Martin et al., 1973). Rest tremor was present at some time during disease course in 68% to 100% of pathologically proven PD cases (depending upon disease subgroup) (Rajput et al., 1991; Hughes et al., 1992). Rest tremor (4–6 Hz) is still accepted as being the typical parkinsonian tremor, but many patients also exhibit a tremor during activity that is more prominent and disabling than classic rest tremor. It is generally recognized that severe action tremors can also persist under resting conditions (Deuschl et al., 1998). Postural tremor without parkinsonian features and without any other known aetiology is often misdiagnosed as ET, but isolated postural tremor may also be the initial presentation of PD, and it may be found with higher than expected frequency in relatives of patients with PD (Jankovic et al., 1995). Further, the results of Cohen et al. (2003) cast doubt upon the specificity of rest tremor as a clinical criterion, as twelve of sixty-four examined ET patients presented rest tremor in addition to postural tremor.

Because rest tremor is considered to be the typical parkinsonian tremor, most studies of tremor in Parkinson's disease have focused primarily upon this tremor type, and rela-

tively little attention has been paid to parkinsonian action tremor. It is the action tremor, however, which is often more disabling for the patient. In contrast to rest tremor, which may represent a social handicap, action tremor associated with Parkinson's disease is directly correlated with motor disability (Zimmermann et al., 1994) and contributes to weakness and bradykinesia (Brown et al., 1997; Carboncini et al., 2001).

Differential diagnostic problems

ET is one of the most common movement disorders, occurring worldwide with an overall prevalence of up to 4% in the general population. PD and ET are common conditions that may coexist in the same patient; estimates of coincidence range from 'rare' (less than 10% of PD patients) (Deuschl et al., 2000) to 'frequent' (Elble, 2002). The coexistence of ET and PD may be difficult to recognize as, once a patient develops parkinsonian symptoms, any postural tremor is usually attributed to PD (Jankovic, 2002). The issue of whether it is valid to define the coexistence of ET in a parkinsonian patient according to diagnostic criteria for ''classic ET'' (pure postural tremor for more than 5 years (Findley and Koller, 1995)) is controversial; on the one hand, estimated duration is no longer considered a defining criterion (Deuschl et al., 1998), while on the other, this procedure encounters problems as a result of the exclusion criterion ''no other abnormal neurological signs''.

Mono-symptomatic rest tremor as a distinct tremor form also often creates diagnostic problems. It is defined as pure or predominantly rest tremor, without signs of bradykinesia, rigidity, or postural problems sufficient for the diagnosis of PD, over a duration of at least two years (Deuschl et al., 1998).

Kinetic tremor

Tremor is usually defined as rhythmical, involuntary oscillatory movement of a body part.

Table 2. Phenomenology of tremor types (modified from Deuschl et al., 1998)

Tremor	
Rest tremor	
Action tremor	
Postural tremor	Position-independent postural tremor Position-specific postural tremor
Kinetic tremor	Simple kinetic tremor (non-goal-directed movements) Intention tremor (Tremor during goal-directed movements, not ataxia) Task-specific kinetic tremor (e.g. occupational tremors, primary writing tremor)
Force tremor	Isometric tremor

Because neither a practical etiological nor a valid physiological classification system is available, the gold standard for tremor research remains semeiological (symptomatic) classification based solely upon clinical observations (Deuschl et al., 1998), i.e. principally according to the behavioural situation in which it occurs, regardless of the underlying mechanisms.

In the past, definitions of tremor in the scientific literature have been ambiguous, leading to some confusion. Following the ''Consensus Statement of the Movement Disorder Society on Tremor'' (Deuschl et al., 1998), tremors have been divided into rest and action tremors (Table 2).

Action tremor is any tremor that is produced during voluntary contraction of muscle, including postural, isometric, and kinetic tremor (synonym: movement tremor).

Kinetic tremor (occurring during any voluntary movement) includes:

- simple kinetic tremor: (during voluntary movements that are not target-directed; may persist during voluntary, goal-directed movement without an increase in amplitude during the terminal phase;

- intention tremor: tremor during target-directed movements; amplitude increases during visually guided movements toward a target at the termination of the movement. In this case, a position-specific tremor or a postural tremor at the initiation or end of a movement must be excluded;
- task-specific kinetic tremor: tremor that may appear or become exacerbated during specific activities, such as occupational tremors and primary writing tremor.

Further, kinetic tremor may occur (alone or in combination with other tremor types) at the initiation of movement (initial tremor), during its execution (transition tremor), or at its termination (terminal tremor).

Action tremor in PD may result from a re-emergent rest tremor (Jankovic et al., 1999). Jankovic et al. found re-emergent tremor in twelve of eighteen PD patients after a mean latency of ten seconds (range: 1.0–47.0 seconds) after changing arm position from a resting to an outstretched position. A relationship of this re-emergent tremor with typical PD-related rest tremor is supported by the observation that the re-emergent tremor has the same 3- to 6 Hz frequency and also responds to dopaminergic therapy (Jankovic et al., 1999). Louis et al. (2001) found re-emergent tremor in 63 of 197 PD patients (Louis et al., 2001).

The main area of confusion is the former lack of differentiation between static (postural) and dynamic (kinetic) forms of "action"; even many papers concerning instrumental investigations of kinetic tremor (e.g. tracking experiments) employ the term "action tremor". Both the term "kinetic tremor" and its synonym "movement tremor" are thus quite rare keywords in the literature, and it might seem that this kind of tremor was a totally new concept (although the first paper with "kinetic tremor" as a keyword was published in 1968 (Tardieu et al., 1968)).

This conceptual unclarity must be taken into consideration when interpreting earlier epidemiological data, and, as a result, there is hardly any reliable information concerning the incidence of kinetic tremor in PD. An at least mild form of kinetic tremor is present in almost every parkinsonian patient (Deuschl et al., 1998). Kinetic tremor is also common in ET. Jankovic (2002) reported that 25% ET patients exhibited moderate or severe kinetic tremor, while Brennan et al. (2002) found the mean kinetic tremor rating to be even greater than the mean postural tremor rating in more than 80% of 105 ET patients.

Analysis and quantification

Wenzelburger et al. (2000) examined kinetic tremor in tremor-dominant PD-patients in a reach-to-grasp movement, and identified kinetic tremor in twelve of thirteen patients, mainly confined to the terminal phases of the movement. High amplitudes of rest or postural tremor were not necessarily associated with high amplitude kinetic tremor. Terminal kinetic tremor frequency was significantly higher than that of rest tremor before and of postural tremor after movement. Postural tremor frequency, however, was similar to that of rest tremor. Wenzelburger et al. (2000) concluded that kinetic tremor is probably related to an enhancement of physiologic tremor.

Forssberg et al. (2000) analysed oscillations in fingertip forces in ten PD patients during the grasping and lifting of an instrumented manipulandum with precision grip. They found that the force oscillations were similar in PD patients and healthy controls. They postulated the existence of common tremor-generating mechanisms and came to the conclusion that parkinsonian action tremor (here: force tremor) is an exaggerated form of physiological tremor.

Quantification of tremor is difficult because tremors have typical on/off triggers and natural fluctuations in amplitude as well

as in frequency. They are influenced by a variety of factors, such as environment and the patient's physical, mental and emotional state (Bain, 1998). Objective measurement of tremor is made possible by physiological techniques or by simple tests of the tremor's impact upon upper limb function. It can also be assessed subjectively by means of clinical rating scales. Patients with kinetic tremor can be handicapped in everyday situations, such as drinking from a glass, grasping an object, writing and other fine motor skills.

Clinical examination for kinetic tremor should include slow flexion-extension movements of the hands or any other non-visually guided and non-directed movements and repeated finger-to-nose movements. In addition, simple objective functional performance tests, such as drawing (Archimedes spirals, maze or tracing), handwriting (standard sentence), pegboard test, pouring water from one glass into another or measuring the amount of water spilled within sixty seconds from a cup, may give additional guidance for disease staging and therapy control.

Several scales have been proposed for the quantification of tremor. Most current rating scales of PD include a valid measure of rest tremor, but are less applicable in the assessment of action tremor (Zimmermann et al., 1994). For rest tremors, the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn et al., 1987), with a few supplementary questions, has been proposed as being useful (Zimmermann et al., 1994), while different scales have been proposed for postural and intention tremor. Fahn et al. (1993) published a tremor scale which distinguishes between ''rest'', ''posture'' and ''action (i.e., actually kinetic) and intention'' tremors, including additional tasks and questions concerning ''activities of daily living''. Bain and Findley developed a clinical rating scale for tremor that allows association of the magnitude of each tremor component with the affected body part (Bain and Findley, 1993) and also analysed reliability and validity (Bain et al., 1993). In addition to their rating scale, they presented a semi-standardized quantification of tremor based upon printed examples of drawn spirals (best named ''spiralography'') and handwriting by tremor patients at different grades, as rated by the authors (Bain and Findley, 1993).

There are a number of papers concerning the employment of digitizing tablets for the quantification of tremor and/or movement disorders. None of these has focused specifically upon kinetic tremor in PD, although it could be shown that this technique allows quantification and analysis of tremor in movement tasks (such as spiral drawing and handwriting) under methodological aspects (Pullman, 1998; Eichhorn et al., 1996) and in ET (Elble et al., 1990; Eichhorn et al., 1996).

Materials and methods

Subjects

870 patients with a prior diagnosis of Parkinson's disease were included in the study. All were receiving conventional anti-parkinsonian medication at the time of the investigation but symptom management was no longer satisfactory, so that supplementation with pramipexole was envisaged. Inclusion criteria were the presentation of light to moderate parkinsonian symptoms under stable therapy, including at least light akinesia. Only 52 patients did not exhibit rest tremor. The tremor-dominant side was assessed for the purposes of this investigation.

Rating scales

Evaluation of clinical symptoms was conducted according to the items of the Short Parkinson Evaluation Scale (SPES) (Rabey et al., 1997, 2002), with stages 0 to 3 corresponding to 'absent', 'mild', 'moderate' and 'severe'.

Subjects were required to draw freehand on a sheet of paper a spiral with at least five turns (example: Fig. 2); the task was executed consecutively by each hand of the patient. Tremor during spiral drawing was evaluated according to Bain and Findley (1993) by a colleague of the authors experienced with this instrument and blind to further patient details. Bain and Findley emphasized that 95 of 100 normal subjects (aged

between 3 and 80 years) achieve a rating of grade 1 or lower in this test. A clear tremor is discernible in drawn spirals presented by Bain and Findley as exemplary for values higher than grade 4. According to the experience of the current investigators, grades 2 and 3 correspond to light tremor, and grade 4 to moderate tremor. For the evaluation of the current results, the authors therefore conservatively defined clinically relevant kinetic tremor as that producing a rating of 5 or above.

Statistics

Statistical methods for the analysis of kinetic tremor were planned before the data were examined. The nature of the collected data led to choose non-parametric comparisons (Kruskal-Wallis) to test for significant differences between stages of rest and postural tremor for the spiral rating grades. Correlation between the different tremor types was analysed with Spearman-rho (rank correlation). For a better understanding of interrelationship between the different tremors we used linear regression analysis with rest and postural tremor as predictors and the Bain-Findlay rating as outcome.

Results

Only 11 of 870 patients (1.3%) drew spirals which were evaluated as corresponding to normal persons according to Bain and Findley (1993); 47.1% exhibited a marked to very severe kinetic tremor (grades 5–10; example: Fig. 1). The summary of the total raw data in the accompanying histograms indicates that kinetic tremor can be associated with pure rest tremor as well as with pure postural tremor (Fig. 3). Somewhat surprising was

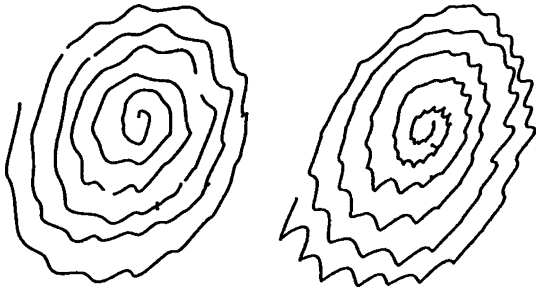

Fig. 1. Original spiral drawing (Bain and Findley, 1993): Examples for grades 5 (left) and 6 (right) (with kind permission of authors and publisher)

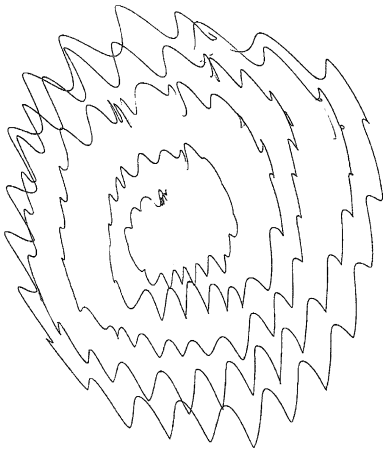

Fig. 2. Spiral drawing of a PD patient with severe kinetic tremor

the fact that, of the 29 patients who presented akinesia without postural and rest tremor, eight also showed moderate and four even a marked kinetic tremor during spiral drawing.

The major analysis revealed in the two independent analyses of the stages of resting and postural tremor a significant difference for the associated kinetic tremor rating grades ($p = 7.8 * 10^{-17}$ for rest tremor; $p = 2.3 * 10^{-14}$ for postural tremor).

A continuous increase in the mean rank was thereby evident, suggestive of a clear functional relationship (Fig. 4). Results of the correlation analysis (Spearman) are shown in Table 3. Although highly significant especially the correlation between kinetic tremor with both other tremor types shows only low strength of the relationship (explained variance).

Regression analysis similarly detected significant contributions by each of the predictors 'rest tremor' and 'postural tremor' to the adjudged value for spiral drawing. The variance explained by this model amounted to a total of 11.0% for the two predictors combined, (for comparison: rest and postural tremor have a common variance of 17.6% also in the linear regression model). Figure 4 depicts graphically the relationship between

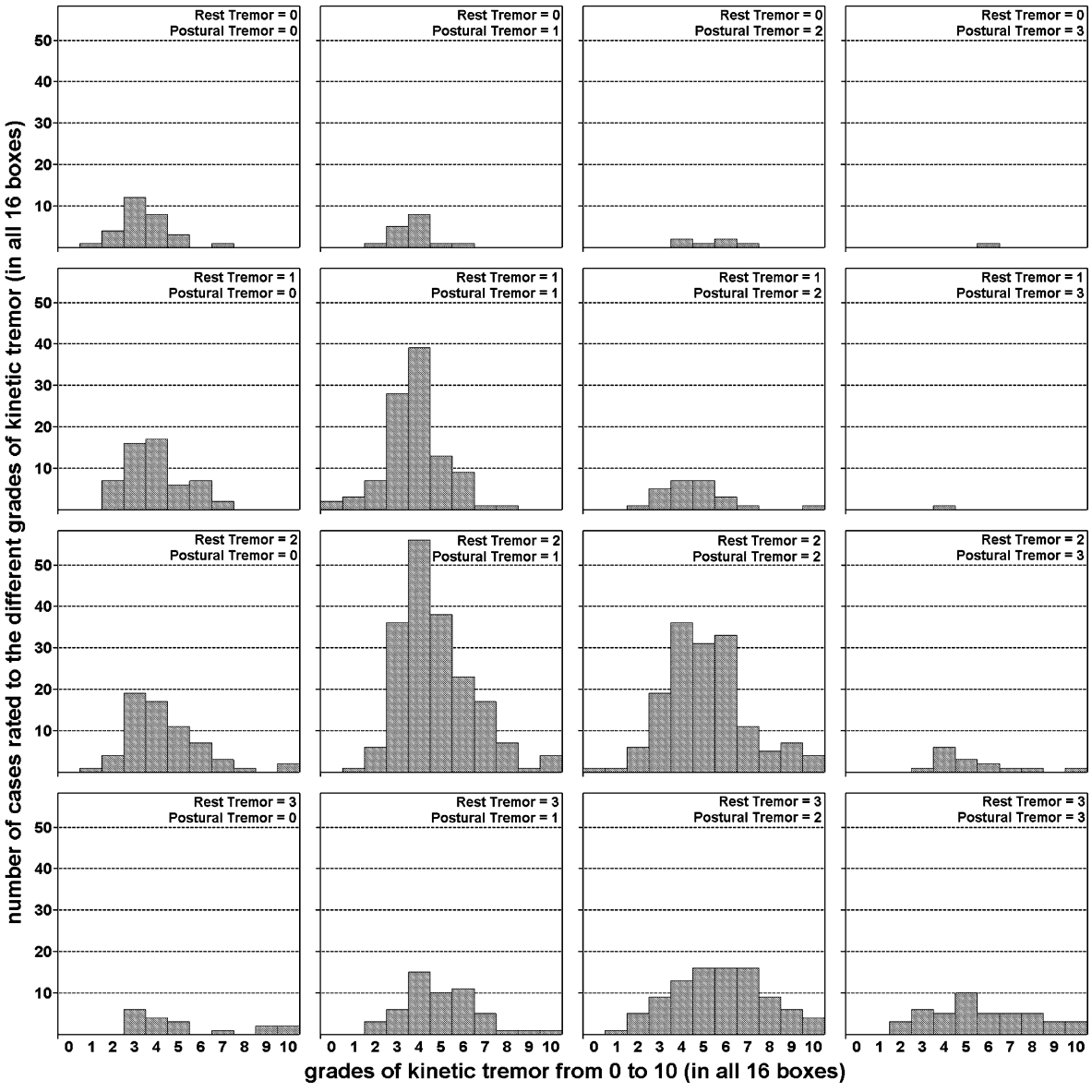

Fig. 3. Tremor triad in PD: Overall view of all combinations. Rest tremor (stages 0 to 3 in 4 lines), postural tremor (stages 0 to 3 in 4 columns) and kinetic tremor (within each box: grades 0 to 10 (x-axis)). Stages of postural and rest tremor are given in the boxes. Bars represent number of cases, total n = 870

kinetic tremor and each of rest and postural tremor.

Discussion

Our own analysis of drawing spirals has revealed that kinetic tremor often occurs in PD patients. The results indicate that a combination of rest, postural and kinetic tremors constitute the most frequent tremor constellation in PD. It was even found that a number of PD patients without any sign of tremor during clinical examination presented evidence for a clear kinetic tremor in their drawn spirals. The relatively small explained variance found in the regression

Table 3. Correlation between ratings of the different tremor types

Ratings	Spearman-rho	Explained variance
Postural/rest tremor	0.420**	17.6%
Kinetic/rest tremor	0.296**	8.8%
Kinetic/postural tremor	0.274**	7.5%

** $p < 0.01$ (two-sided), $n = 870$

models may indicate that, kinetic tremor possesses at least a significant autonomous component within the tremor triad in PD.

It thus appears that impairment caused by kinetic tremor in PD may be underestimated by instrumented examinations which employ more ballistic, shorter movements.

In conclusion, it can be emphasized that more attention should be paid to kinetic tremor in PD, as it is frequently present and quite disabling with respect to important everyday tasks, such as writing. A better understanding of pathophysiologic and pharmacologic processes can be expected from a more precise differentiation of the different tremor forms at PD furthermore.

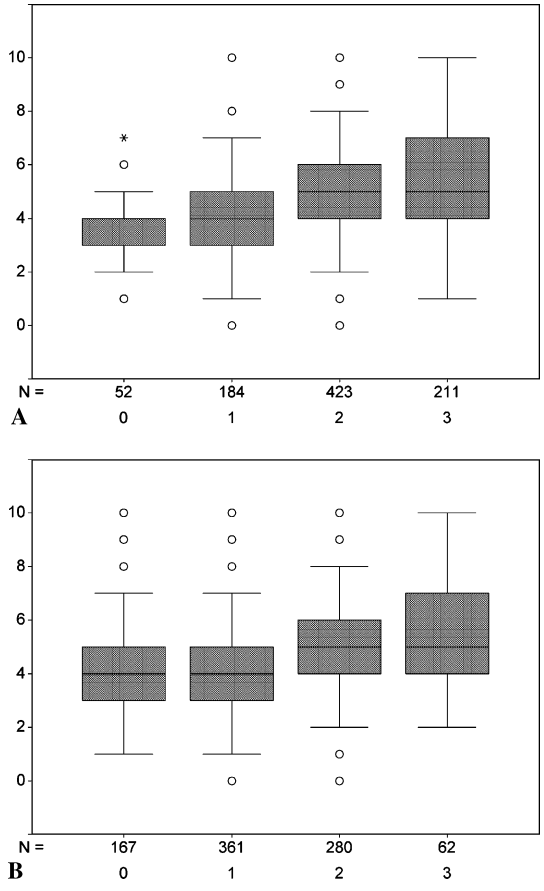

Fig. 4. The box plots indicate the (statistically significant) functional relationship of kinetic tremor rating (y-axis) with each of the other tremor forms. **A** rest tremor; **B** postural tremor (extreme values: "o" and "*")

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