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Objective measurement of activation of rigidity: diagnostic, pathogenetic and therapeutic implications in parkinsonism

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1 Quantification of the effect on rigidity of its 'activation', by isometric grip, of standardized pressure, of the contralateral hand, was explored. Torque required to move the forearm through a fixed angle of 40°, at a controlled rate of 0.5 Hz, in a horizontal plane about a pivotal axis aligned to the elbow joint, was recorded before (12 'baseline' recordings), during (10), and after (≥ 8) activation. Work required per unit displacement was calculated.

2 Specificity: Pilot serial daytime measurements gave an overall mean ratio, work required on activation over baseline, of 2.94 (95% CI 2.53, 3.42) in two elderly untreated parkinsonians, and 3.19 (2.75, 3.71) in two elderly subjects with isolated, clinically activation phenomenon, compared with 1.90 (1.64, 2.21) in two elderly without ($P < 0.001$), whilst two young adults did not activate, 0.98 (0.85, 1.14). In elderly subjects, work required under activation decreased during the day in health (-10 (-5, -14)% h^{-1}, $P = 0.0002$), showed no significant change in those with clinical activation (4 (-1, 9)% h^{-1}), and increased in parkinsonians (6 (0, 12)% h^{-1}, $P = 0.05$): there appeared to be a transitionary state.

3 Validation of methodology: Quantifying the same work ratio on a single occasion in 20 aged parkinsonians (P), their spouses (Ps), 20 index controls (C) without parkinsonism, matched to (P), and their spouses (Cs) gave corroborative evidence of a pre-clinical state, defined by other measurements, in the spouses of sufferers. Values for C, Cs and Ps, 1.89 (1.42, 2.52), 2.38 (1.79, 3.17) and 2.93 (2.20, 3.90) respectively, were in consecutive positions, from health to (P, 2.96 (2.22, 3.95)) disease ($P = 0.001$ for Ps *c.f.* C; $P = 0.1$ for Ps *c.f.* Cs). Data on change over the day may enhance discrimination.

4 Sensitivity to medicines was illustrated, in two parkinsonians, by randomised, placebo balanced and controlled challenges: 1 and 2 tablets, Sinemet CR (Du Pont Pharmaceuticals, each levodopa 200 mg/carbidopa 50 mg) and 1 tablet, Sinemet-Plus (levodopa 100 mg/carbidopa 25 mg), then two 2 mg tablets, benzhexol. The dopaminergic effect ($P < 0.001$) was selective for activation (treatment.test-condition interaction, $P = 0.004$), and showed the expected time profiles. The effect of benzhexol ($P = 0.008$) lacked such selectivity. Its onset (> 4, ≤ 6 h) was delayed, compatible with a gastrointestinal anti-muscarinic action and the subjects' ages.

5 Reliability (Fleiss's criterion) was shown to be good in 30 untreated parkinsonians.

Keywords activated rigidity objective measurement parkinsonism ageing medicines

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Introduction

Between occasion and observer variability, within-observer carryover effect, lack of sensitivity, difficulty dissociating the cardinal sign to be scrutinised from the general condition [1], and inadequate compensation for muscle mass [1] may make subjective assessment of rigidity [2] an inadequate tool for monitoring medicinal interventions and detecting changes of early parkinsonism [3]. Given the congruity of subjective and objective methods, when applied in parkinsonians with rigidity spanning the gamut of ratings [3], we explore the potential of an objective approach.

Webster described activation, 'rigidity … revealed or considerably enhanced by having the patient carry out a voluntary task with the arm contralateral to that being examined [4]', as a test which 'will enable one to detect Parkinson's disease in its earliest phase [2]'. However, his rating categorises detectable 'resting' rigidity with activation [2]. Teräväinen and colleagues [3] introduced a category, between this and 'none detectable', where rigidity is observed only during activation. Quantifying activation may allow simulation of disability (and its alleviation) during daily activity. The presence of bradykinesia during life is said to be a key predictor of the pathological diagnosis of idiopathic Parkinson's disease, but muscular rigidity, a 4–6 Hz rest tremor, or relevant postural instability aid that positive discrimination [5]. In order to define a pre-clinical state functionally, even greater reliance must be placed on complementing the discriminant ability of measures of bradykinesia [6, 7] by other variables.

Methods

Device and measurement protocol

Flexion/extension at the elbow was studied for reproducibility (a simple hinge movement), and the convenience of the sitting position. The device consists of a geared motor which drives a padded cradle, accommodating the forearm, about a pivotal axis, in a horizontal plane (thereby eliminating the effect of gravity on the measurement). The hand is supported in the prone position and the humero-ulnar joint positioned directly above the pivotal point. Whereas Webster [8] used an arc of 100 (60–160)°, a fixed angle of 40 (115 and 155)° proved practical in elderly parkinsonians. The adjustable height of the apparatus and position of the padded cradle supporting the upper arm allow this to be achieved in comfort: light strapping with Velcro strips discourages active movement. The speed of the motor is controlled electronically, and monitored by an optical tachometer. A single frequency of oscillation, 0.5 Hz (cycles s^{-1}), was selected: at high frequencies, measurement of torque is confounded by increasing inertia [9], whilst at low, subjects attempt to assist the motor [3, 9]. The choice was reviewed in the light of formal experimental data. Signals representing torque (from a semiconductor strain gauge) and angular position of the forearm cradle (a high quality potentiometer) are amplified, and charted on an xy recorder. The areas of hysteresis loops obtained (Figure 1) were quantified 'blind', using a graphics pad (Graphic Master, Numonics Corp., Montgomeryville, Pennsylvania, USA). Mean work required (i.e. area) per unit angular displacement was calculated (Design CAD 2-D American Small Business Computers, Pryor, Oklahoma, USA).

Activation was produced by squeezing a paediatric sphygmomanometer cuff, with the contralateral hand, to a pressure of one third of that hand's maximum grip pressure plus 20 mmHg. This isometric task was consistently within the capabilities of independently mobile parkinsonians. The pressure was pre-determined in each individual, whether there were to be one or more runs of the measurement protocol.

The basic measurement protocol consisted of acclimatisation for 2 min to the passive arm movement, six baseline recordings of the hysteresis loop at 10 s intervals, achievement of the predetermined grip pressure, a series of recordings at 15 s intervals during activation, and recovery recordings after release of grip. Subjects had a practice run prior to entry into a study.

Minimising the likelihood of provoking tremor was a facet of protocol design [10]. Tremor causes a jagged edge to the hysteresis loop, but its area will remain

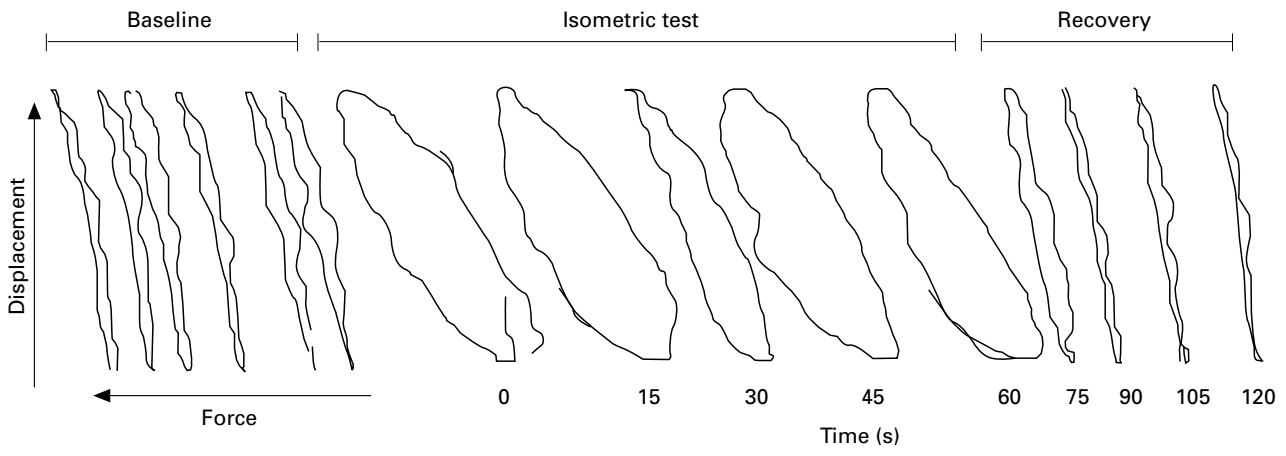

Figure 1 Serial hysteresis loops plotted under baseline test condition, during activation by contralateral isometric muscle contraction, and during recovery.

constant provided overall rigidity is unaffected. To facilitate comparison between those with and without parkinsonism, the arm judged initially to be the more rigid, or, when both sides were equal, the non-dominant arm (i.e. that of smaller muscle mass [2]) was always studied. Candidate, between-subject, covariates for the work required/unit displacement were recorded: age, gender, height, weight, arm length (shoulder to elbow, elbow to wrist), maximum forearm girth and hand grip pressure used.

Clinical evaluation of methodology

Subjects gave informed consent to participate in studies, which had local Ethics Committee approval. All were independently mobile. Clinical parkinsonism was diagnosed on the presence of two or more of the cardinal signs of hypo/bradykinesia: 'resting' rigidity, tremor and postural instability. There was evidence of three or more of the UK Brain Bank supportive criteria [5] for diagnosis of definite Parkinson's disease. Clear-cut, non-idiopathic parkinsonism, and patients in whom there were reservations, were excluded [5, 11].

1 Specificity with respect to subject category and time of day: a pilot study Eight females were studied: two young (24 and 32 years) and healthy; two elderly (67 and 68 years) and healthy; two elderly (both 66 years) who exhibited activation phenomenon, but had no increase in resting tone or other cardinal sign of parkinsonism; and two elderly (67 and 85 years) with untreated parkinsonism and mild to moderate resting rigidity. Those in the latter two categories were otherwise healthy on screening. Hysteresis loops were recorded at five time points between 10.00 and 16.00 h (36 per subject: six baseline, five during activation and seven over the first 4 min following release of grip, with immediate repeat).

2 Validation of methodology in relation to the definition of a pre-clinical state

(i) Reference categories studied. These [7] were twenty treated sufferers (P) from idiopathic parkinsonism (five men and five women in the age groups 70–79 and 80–89 years) and their spouses (Ps), and 20 control couples, comprising index partners (C), found to have no, or only one, cardinal sign of parkinsonism on screening, and their spouses (Cs). Ps and Cs could have parkinsonism. P and C were matched for age band and sex. Statistical analysis [7] showed that Ps and controls did not differ significantly in age, height, weight or mental test score [12]. However, a prognostic index for parkinsonism, based on hypo/bradykinesia of gait, showed Ps to be intermediate between P and controls, and highly significantly different ($P < 0.0001$) from the latter. Postural abnormality, as measured by an increase in standing sway and decrease in foot separation during walking, was also greater in Ps than in controls ($P = 0.0007$ and 0.02). Marked differences remained after correction for relevant covariates (tabulated in [7]). A modified Webster [2] rating of rigidity (with a separate score for rigidity observed only during activation), 'blind' to subject identity and category, was greater in Ps than controls ($P = 0.01$), tremor was not. No significant difference was detected between C and Cs with respect to the variables studied.

(ii) Summary of inclusion and exclusion criteria applied to consecutively presenting couples. Subjects [7] were Caucasian, had English as their first language, were free from cardiovascular and respiratory symptoms during normal daily activities, and did not use a walking aid. Those with overt abnormality of limbs, a history of orthopaedic surgery to, or with any pain in, joints of spine or limbs were excluded. A history of specific neurological disorder (other than parkinsonism where indicated/allowable), musculoskeletal disorder, or a condition which might mimic a cardinal sign; clinical dementia (or a mental test score [12] $< 50\%$); depression or other mental illness; and receipt of hypnotics or sedative drugs led to exclusion.

(iii) Ranking of categories by work per unit displacement. Hysteresis loops were recorded in P, Ps, C and Cs (30 per subject: protocol as in Study 1, except initial and repeat recovery recordings restricted to four, at 15 s intervals).

3 Sensitivity to medicines: potential in characterizing pharmacodynamic profiles of (a). Single doses of levodopa/carbidopa combinations, with conventional and controlled release properties Two (64 and 68 year) female parkinsonians, with mild resting rigidity, each received four placebo-balanced, single dose challenges in a different random order. As in a previous study of hypokinesia [13], three challenges contained an active component [two tablets Sinemet CR (Du Pont Pharmaceuticals Ltd, each levodopa 200 mg/carbidopa 50 mg); one tablet *Sinemet CR*; and one tablet Sinemet-Plus (levodopa 100 mg/carbidopa 25 mg)]. The other challenge was of placebo only. Both patients were on maintenance therapy with combined levodopa (total daily doses: 1 g and 600 mg)/carbidopa, but received no medication after 22.00 h on the day before a study, and only the 10.00 h challenge on the study day, until recording had been completed. A dose of Sinemet Plus was then given and the normal regimen resumed. Challenges were at least 2 days apart.

Hysteresis loops (36 per subject: as in Study 1) were recorded immediately before each challenge and at four time points, up to 6 h post-dose.

(b). Single dose of benzhexol. One week after Study (a), the same patients received two single dose challenges, two tablets of Artane (Lederle Laboratories, each two mg benzhexol) and two placebo tablets, in a different order. The study design was, otherwise, as in Study (i).

4 Reliability Hysteresis loops (30 per subject: as in *Study 2*) were recorded, and immediately repeated, in each of 30 newly diagnosed, untreated parkinsonians.

Further development of methodology

Effect of different frequency of oscillation, compatible with comfort: hysteresis loops (16 in a single run per

subject: six baseline, four during activation, and six at 30 s intervals after grip release) were recorded in four subjects (two with, two without, parkinsonism), at five frequencies in different random sequence.

Statistical analysis

The analysis of variance [14] used measurements of mean work required per unit displacement, under each test condition (baseline, activation or recovery), or the increment (see below) in work required on activation over baseline, as the dependent variable. The number of data points in each study is specified. In Study 1, serial time points were incorporated as a candidate covariate, allowing any time trends to be compared between subject categories. In Study 2, subject characteristics and time of day were considered as covariates. In Study 3, pre-treatment values were employed as a covariate, to increase the precision with which within-patient treatment effects could be defined and reduce the effect of any difference in state between study days. It can be assumed, from the pharmacokinetics of the preparations, that the pre-treatment measurement in a consecutive period will be unaffected by the previous challenge. Studies 1 and 2 are explanatory, not pragmatic: they are intended to generate hypotheses. Study 3 tests an hypothesis.

To make valid the assumptions of normally distributed residuals [15] and equality of variance [16], a $\log_e$ transformation was made for work required. Thus, figures give geometric means and their 95% confidence intervals (CI), and, in the text, changes with test condition are expressed as ratios to baseline values, linear time trends as percentage changes.

Results

The ratio, work required on activation to baseline value, was of much greater discriminant value between subject categories (Studies 1 and 2) than the absolute value for work under a given condition. This may reflect a lack of standardisation for individual characteristics: no between-subject covariate was identified. Within-subject, test condition, serial time points (Study 1 and 3) and frequency of oscillation (Further development …) proved important covariates. There was no difficulty maintaining the inflation pressure for the one minute duration of the isometric test, even with the serial time points and range of frequencies.

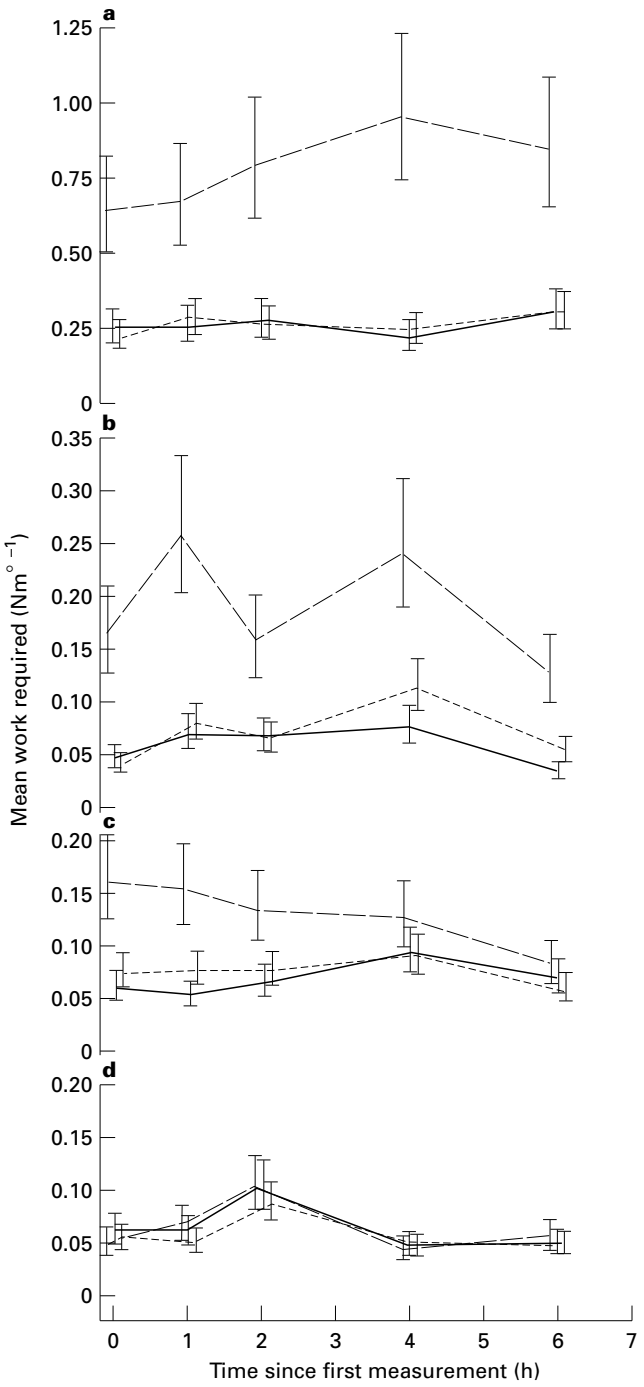

Figure 2 Work required per unit displacement of the forearm, with respect to time of day, in two elderly subjects with untreated parkinsonism (a), two healthy elderly with an isolated clinical finding of activation phenomenon (b), two healthy elderly without activation on examination (c) and two healthy young adults (d). Mean values and 95% C.I. are given, under each test condition. N.B. Contracted scale on y-axis in upper graph. — baseline; –– activation; --- recovery.

1 Specificity: a pilot study.

Parkinsonians (Figure 2) were distinguished by greater baseline values for work required per unit displacement. The proportional increase in the work on activation provided additional discrimination between subject categories (category.test-condition interaction, $P < 0.001$). The overall mean ratio, work on activation to baseline value, was 2.94 (95% CI; 2.53, 3.42) in those with parkinsonism, 3.19 (2.75, 3.71) in the elderly with isolated activation phenomenon and 1.90 (1.64, 2.21) in the elderly without, and 0.98 (0.85, 1.14) in the healthy young adults. Thus, activation of rigidity was not found in the healthy young, but could be demonstrated objectively in the elderly, irrespective of its clinical presence. Those elderly with clinical activation had a

greater proportional increase in work on activation than those without ($P<0.001$). However, parkinsonism was not associated with a greater proportional increase than found in those with just activation phenomenon.

The daytime profile of work required in the activated condition (Figure 2) varied between subject categories (category.time-point interaction, $P<0.001$; category.time-point.test-condition interaction, $P<0.01$). It decreased significantly over the study period in the healthy elderly (% decrease per hour, 10 (95% CI; 5, 14), $P=0.0002$), showed no significant trend in the elderly with clinical activation (% decrease per hour, 4 (-1, 9)), and increased significantly in the parkinsonians (% increase per hour 6 (0, 12), $P=0.05$).

2 *Validation of methodology in a pre-clinical state*

Ranking (as in Study 1) on the basis of the ratio, work on activation to baseline value, placed the three categories, C, Cs and Ps, in consecutive positions from normal ageing towards parkinsonism. Category C had a considerably lower mean (95% CI) ratio, 1.89 (1.42, 2.52), than did Ps, 2.93 (2.20, 3.90) ($P=0.001$). Whilst the ratio for Cs, 2.38 (1.79, 3.17), was intermediate between Ps and C, the contrast between Ps and Cs reached significance only at the 0.1 level. However, the ratio in P, 2.96 (2.22, 3.95), was virtually identical to that in Ps. A finite limit to the proportional increase in tone on activation might be approached in Ps, but the ratio in P could be submaximal due to anti-parkinsonian medication (see Study 3). The absolute work required, under baseline, activation or recovery conditions, had no predictive value for subject group, either in itself or in addition [17] to that of the ratio. Adjustment for the time of day of these 'spot' measurements and the candidate, between-subject covariates did not aid discrimination.

3 *Sensitivity to medicines: illustrative data*

(a) Single doses of levodopa/carbidopa combinations A significant ($P<0.001$) difference was found between challenges in the work per unit displacement, but the effect appeared (Figure 3) to be confined to the activation test condition (treatment.test-condition interaction, $P=0.004$). Two tablets of Sinemet CR, by comparison with placebo alone, had a significant ($P=0.03$) effect on activation: the ratio, work on activation to baseline value, was 0.70 (95% CI; 0.51, 0.96) of that after the placebo challenge. No effect, over all time points, was found with one tablet of Sinemet CR or with Sinemet-Plus, the ratios being, respectively, 1.05 (0.75, 1.48) and 0.80 (0.57, 1.12) of that after placebo. However, the response/time profiles of the different active challenges did reflect the expected levodopa concentration/time profiles of the preparations and dosages used (nature of treatment.test-condition.time-point interaction, $P<0.001$), but with a lag in response,

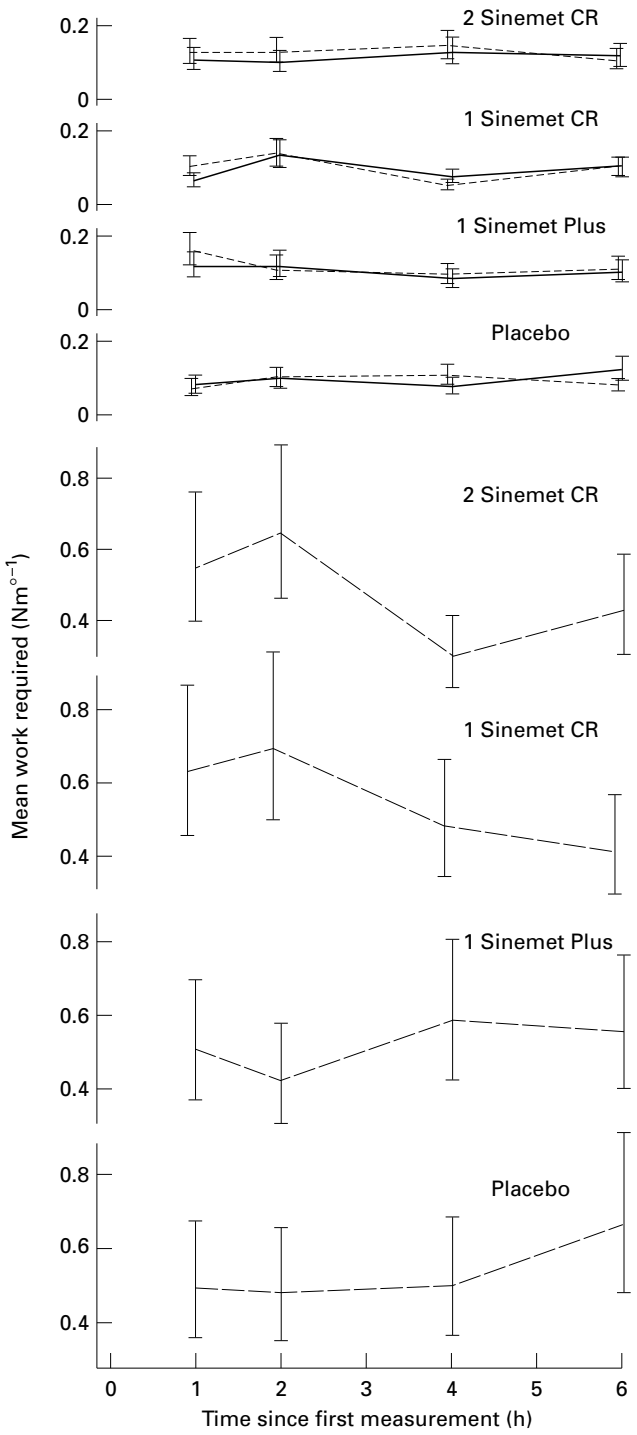

Figure 3 Response-time profiles for single doses of Sinemet CR (one and two active tablets) and Sinemet-Plus (one) and placebo, with respect to work required per unit displacement of the forearm, under baseline (— upper series of graphs), activation (––– lower series) and recovery (----- upper series) test conditions. Mean values and 95% CI are given for two parkinsonians at four time points after each challenge: they are corrected to remove any effect of pre-treatment differences in mean work required (see *Statistical analysis*).

as reported for hypokinesia [13]. The profile for the placebo challenge echoed the increase in rigidity with time of day of the untreated sufferers in Study 1.

(b) Single dose of benzhexol Here the significant ($P=0.008$) treatment effect on work per unit displacement was irrespective of test condition. The ratio, mean work

required, over all test conditions and time points, after benzhexol to that after placebo, was 0.84 (0.74, 0.95). This ratio was 0.87 (0.66, 1.16) at 1 h post-challenge, 0.89 (0.67, 1.18) at 2 h, 1.18 (0.89, 1.57) at 4 h and 0.50 (0.38, 0.67) at 6 h (nature of treatment.time-point interaction, $P < 0.001$). The onset of clinical benefit from benzhexol appeared to be affected by its anti-muscarinic action on the gastrointestinal tract and/or the age of the patients.

4 *Reliability*

The calibration of the device did not drift over the studies described. There was no significant difference between initial and repeat measurements of mean work per unit displacement under any of the three test conditions. The reliability coefficient (one-sided 95% CI) was, under baseline conditions, 0.77 (0.62); for activation, 0.81 (0.68); and for recovery, 0.83 (0.71): values of greater than 0.4 but less than 0.75 are rated as fair to good, and greater than 0.75 as excellent [18].

Further development of methodology: optimal frequency

The average work per unit displacement, over all test conditions, was markedly greater at the higher frequencies (Figure 4) in the parkinsonians (subject-category.frequency interaction, $P < 0.001$). Moreover, their recovery from activation was slower at the higher frequencies (category.frequency.test-condition interaction, $P < 0.005$), taking as long as 3 min. Discrimination between those with and without the condition appeared to be best at 0.58 Hz (35 cycles min^{-1}): adoption of a slightly higher frequency, than the 0.5 Hz of the preceding studies, may enhance specificity and sensitivity.

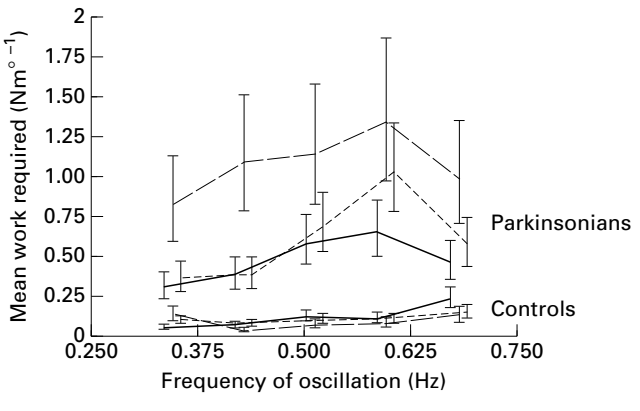

Figure 4 Effect of frequency of oscillation on the work required per unit displacement of the forearm. Mean values and 95% C.I. are given for two subjects with and two without parkinsonism, under each test condition (— base line; –– activation; --- recovery), at frequencies of 0.333, 0.417,0.500, 0.583 and 0.667 Hz (20 to 40 cycles min^{-1}).

Discussion

A device and protocol for measuring the work required to displace the forearm is presented, developing the work of Webster [2], with particular reference to quantifying the increment in work under activation. The validity of the method is tested in a demanding context, reliability verified and insights given into its sensitivity and specificity. Overall, congruency has been demonstrated between such objective assessment and subjective rating [3]. In practice, it is constrained by the grossness of the clinical categorisation [1], differences in what is being assessed (mid-line [2] or limb rigidity), the assessment manoeuvre and conditions (resting, activated or recovery), and incorporation of a global impression into the subjective judgement [1].

Clinicians tend to regard 'tone' in a limb as representing neurogenic muscle activity. However, resistance to passive stretch [9, 19–27] and recovery towards the rest position is an inherent property of muscle and support structures. Such resistance does not generate electromyographic (EMG) activity in the relaxed, normal individual [21–27]. It persists after nerve block [23], during general anaesthesia [23, 25], even after 'muscle relaxants' [25]. The mechanical properties of muscle and/or connective tissue change with age [21], and, more markedly, with parkinsonism, where they contribute to clinical rigidity [27]. This is not just a feature of advanced disease [26–28], with contractures: a reduced range of passive joint movement occurs early [7]. Changes in non-neurogenic resistance lack specificity, and neurogenic may be difficult to isolate from non-neurogenic. Arousal is an important covariate of objectively-measured resistance to passive movement [19, 25, 29], failure to relax may increase resistance [19, 22, 24–27], but to test for arousal is to provoke it.

Rigidity implies increased resistance to passive movement [2, 8, 28, 29]. In parkinsonism, increased neuronal activity mediates increased tone. Here stretch-related EMG activity has been correlated with clinical rating of rigidity [28], but is not a *sine qua non* for diagnosis [4, 20, 27]. Parkinsonian rigidity measured under 'baseline' conditions is responsive to medicinal therapy [1]. Historically, it has been relieved by thalamotomy [4, 28, 29], destruction of specific parts of the globus pallidus [10, 28], dorsal root section [28], infiltration of muscles with local anaesthetic [20, 28], light general anaesthesia and sleep [10, 29].

The change in resistance to movement produced by activation is evidently neurogenic, but elucidating details of the mechanism(s) is beyond the scope of the present study. Activated rigidity is found throughout the course of parkinsonism [4], and, historically, has been lastingly reduced by specific lesioning of the thalamus [4, 29] and globus pallidus [10], indicating dependency on the underlying extrapyramidal disease. Indeed, there is a direct quantitative relationship between activated rigidity and the magnitude of the long-latency EMG stretch response to suddenly-applied loads in parkinsonism [30]. A less marked EMG response to stretch in the activated condition, found in some 'control'

subjects, may reflect the change from health to disease.

Obtaining objective evidence of response to medicinal intervention, and being able to titrate dosage, are important where the onset of effects is slow and delayed, and the therapeutic window may be small, as with benzhexol in the elderly. The illustration of selectivity for activated rigidity is encouraging, since it suggests that cumulative disability during the day is not inevitable in the actively-mobile sufferer. Dopaminergic selectivity is likely to be partial: had baseline rigidity been markedly increased, it may well have been responsive [3, 31]. In apparent contrast, Webster [4] described only baseline rigidity to be responsive during open follow-up, but activation stimuli and timing of test in relation to dosing were not standardized. Long term, progressive improvement in objectively measured rigidity, not just maintenance of the *status quo*, has been described with selegiline [1]: neuronal rescue cannot be dismissed as an explanation. A pre-clinical state, with rigidity manifest only on activation, potentially uncomplicated by irreversible damage, may be a better testing ground for neuroprotection and neuronal rescue.

In the healthy elderly, activated rigidity decreased during the day, as if a negative feedback mechanism was operating. In the healthy young, there was no activation, any such a mechanism being totally effective. In those elderly with isolated activation phenomenon, feedback appeared to be failing, whilst in untreated parkinsonism, baseline rigidity was present and activated rigidity appeared to be cumulative. (Many sufferers do complain of particular incapacity in the early afternoon, sometimes attributed to a post-prandial effect. They may become aware of cumulative activated rigidity at this time). Further characterization of these changes is needed: they, like those in distance/time measures of gait [6], may reflect the age-related decline in striatal dopamine [32]. The age-related neuronal attrition might be subject to genetic variability and interaction with xenobiotic influences, in repeated or chronic exposure [31, 33–36, 37].

As an epidemiological tool in investigating the aetiology of parkinsonism, measuring the tendency towards it [7] has the advantage of not depending on any particular theory or mechanism of causation. The constellation of early evidence of rigidity, hypo/bradykinesia and postural instability (and even the seborrhoeic dermatitis [38] associated with parkinsonism) in spouses of sufferers is difficult to explain by selective mating, learned or reactive behaviour. Reciprocation, rather than congruity, of disability is expected in aged partners. Additional data on diurnal changes in activated rigidity may enhance the definition of their tendency towards parkinsonism. These couples had cohabited for half a century: influences, operating in the home environment in adult life, may contribute to the pathogenesis of idiopathic parkinsonism.

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