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TWO AUTOCOVARIANCE-BASED MEASURES OF BALANCE IN PARKINSONIANS AND NORMAL CONTROLS

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Abstract: Center of pressure electronic platform testing is proposed as an affordable early diagnostic tool for persons at risk of Parkinson's disease. A stiffness measures and crossing time statistic are studied for possible use in such a diagnosis.

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1. Neurological Background

Parkinson's disease (PD) is a common and disabling neurodegenerative disorder affecting millions of people worldwide. Recent positron-emission tomography (PET) studies have shown a loss of over 90% of dopamine in the posterior putamen (basal ganglia) in the brain already at the time of first clinical symptom manifestation. This indicates the presence of a long pre-clinical period of the disease, estimated at between 6 to 10 years; cf. Hoehn and Yahr stage I PD [9]. We are currently witnessing a time of scientific optimism where new treatments, such as neuroimmunophillins and stem cell transplantation, are emerging that have the potential to reverse the natural history of this otherwise progressive disorder. These treatments are likely more effective when given early in the course of the disease rather than late. Therefore, identification of early or preclinical disease has become crucial to selecting patients for these novel therapies. Early identification of disease requires a sensitive and cost-effective screening method that can be applied to a large number of persons.

Generalized psychomotor changes may appear before typical limb Parkinsonian motor abnormalities of tremor and loss of dexterity. Other prodromal symptoms of PD include impaired olfaction, depression, visuomotor control abnormalities, personality disorders, musculoskeletal pain or sensory dysfunction, such as paresthesias. Depression, anxiety, fibromyalgia, and shoulder pain were most frequently documented with symptoms beginning 4 to 6 years before the onset of diagnostic symptoms (Gonera et al [7]). However, these prodromal symptoms are not specific enough to serve as diagnostic markers of PD. Because the signs of early PD may be subtle and imperceptible to the patient and non-expert physician, it is not clear whether signs of Parkinsonism are absent during the prodromal phase or are frequently overlooked. Patients with hemiparkinsonism provide a unique learning opportunity to study subclinical symptoms where the healthy body side can be used as a model for the presymptomatic patient. In patients with unilateral disease (Hoehn and Yahr stage I [9]), degeneration of dopaminergic neurons innervating the ipsilateral striatum compared with the affected side of the body has not yet resulted in contralateral Parkinsonian signs. Motor test abnormalities of peg board performance, writing time, and finger dexterity could be detected on the so-called "normal" side in 53% of hemiparkinsonian patients (Horstink and Morrish [10]). These results show that motor abnormalities may be detectable in subjects who are unaware of motor abnormalities. In addition to this, Albin et al [1] in a recent VMAT-2 PET study reported significant striatal monoaminergic reductions in patients with REM sleep behavior that were most prominent in the posterior putamen

but below the threshold of clinical Parkinsonism. The aforementioned neurological studies motivated us to develop several measures of balance impairment from registered trajectories of the center of pressure during quiet stance on an electronic platform. The two measures studied in this paper are shown to discriminate effectively between persons with PD of varying degrees of severity and normal controls. We intend to use these measures as early diagnostic tools for people that may be at risk of developing PD; more detailed correlation studies are required in order to ascertain direct causality or direct correlation with the (much more expensive) PET scans that can accurately determine the amounts of dopamine in the brain. Identification of very early disease has become crucial to select subjects for treatments that may have the potential of secondary prevention of PD. A biomarker, to be useful in screening large populations to identify preclinical disease, should be inexpensive, easily administered, and sufficiently sensitive and specific to avoid unacceptable false negatives or positives. Measures of dopamine nerve terminal integrity with positron emission tomography (PET) have allowed preclinical disease to be detected in relatives of patients with PD (Brooks [3]). However, there is a need for less expense and more cost-effective screening tests. This paper focuses on the development of measures of postural stiffness and motor dysfunction by making use of a Kistler electronic platform. We present evidence of two measures that are significantly correlated with descriptive clinical assessments, such as those used in the Universal Parkinson's Disease Rating Scale (UPDRS), particularly the Motor Option of that scale. Based on this, and known evidence that some of the known UPDRS measures, such as the peg test, show high correlation with the amount of dopamine in the brain, we hope to directly validate a significant correlation between the platform measures and the amount of dopamine. The platform measures provide a higher resolution and are more objective than those offered by the UPDRS. PET measurements of the dopamine in the brain is an expensive procedure. The measures on the electronic platform, by contrast, are inexpensive and can be easily done in a doctor's office. They are of considerable importance in themselves, since they provide clinically useful measures of postural stability. By having a high correlation coefficient with the scores on peg tests, some of these platform measure are likely to be good covariates of the amount of dopamine in the brain as measured by a PET scan. This would provide an inexpensive means of correctly assessing the status of PD in preclinical cases by inexpensive means; hence the interest in studying and developing these measures.

When standing quietly, the center-of-pressure (COP) beneath the feet moves in a stochastic manner. Based on the mathematical models of posture control

described in this paper, quantitative postural stiffness measures are computed from the autocovariance function obtained from these trajectories. Our data, collected at the Pittsburgh Veteran's Administration Hospital, indicate that electronic platform balance testing is able to objectively distinguish Parkinsonian imbalance from normal controls on the basis of a total body stiffness factor. We have also data that a subgroup of otherwise normal volunteers, especially elderly, have increased total body stiffness showing striking overlap with the Parkinsonian pattern yet in the absence of clinical symptoms of Parkinsonism. It appears likely that this subgroup of apparently normal persons may be at risk of having or developing PD. Validation of the electronic platform efficiency is done with the much more costly PET scans; Gunn et al [8].

The paper is organized as follows. A measure of stiffness, described in Lauk et al [11], is studied in more detail in the next section. Our investigation of this measure led us to adjust it for drift when applied to our data. The resulting stiffness measure is, therefore, a drift adjusted version of that given in Lauk et al [11]. A correlation study of this measure with the UPDRS is then presented. Computational issues associated with the stiffness measure are described in Section 3. A measure that is much easier to obtain in practice than the measure of stiffness is introduced in Section 4; it is the time required for the autocovariance function to become negative; we call this the first crossing time. Whereas the stiffness measure has a direct physical interpretation, as equation (1) shows, the first crossing time has a simple clinical meaning that is explained in Section 4, and it can easily be extracted from data. Preliminary results also show significant correlations between both these measures and individual ratings of rigidity, bradykinesia, posture impairment, gait and leg agility as rated by the Universal Parkinson Disease Rating Scale (UPDRS) in patients with PD; Fahn et al [6]. These data provide evidence that a higher intrinsic muscle stiffness factor may contribute to the specific Parkinsonian symptoms; Bohnen et al [2]. From a clinical standpoint, this suggests that the COP-based postural stiffness measure increases with increased severity of the respective motor system disabilities associated with PD. We trust that some of the measures derived from the COP trajectory analyses will improve or superceed the existing subjective evaluations currently used by UPDRS. We are in the process of developing other platform measures as well, in the hope of capturing as many relevant clinical or non-clinical features of balance impairment as possible.

2. The Stiffness Measure

Chow and Collins [4] proposed a mechanical model of posture control from which an analytical form for the autocorrelation function of the COP motion was obtained. Later, a stiffness measure was derived from this model (Lauk et al [11]). Here, we outline the calculations. To simplify the problem, we consider only motion in the $y-z$ plane, where y denotes the axis of medio-lateral movement. Such movement was shown to be consequential in Parkinsonians and the elderly, cf. Mitchell et al [12]. We suppose the body can be modeled by a flexible rod. We assume the body is close to being upright and that the combination of the destabilizing effects of gravity and the stabilizing effects of the imperfect control system are captured by a simple stochastic forcing term. This hypothesis is based on the observation that the dynamics of the COP obey a correlated random walk. We represent the COP motion as a single point on the rod. The resulting equation is

$$\beta\frac{\partial^2}{\partial t^2}y(z,t)+\frac{\partial}{\partial t}y(z,t)=\nu\frac{\partial^2}{\partial z^2}y(z,t)-\alpha y(z,t)+\eta(z,t). \tag{1}$$

This equation describes the motion of an infinitely long rod or polymer that is elastically pinned to a single location and driven stochastically. Parameters β and α^{-1} have dimensions of time and ν has a dimension of length squared divided by time. The stochastic force is assumed to have statistics $E(\eta(t))=0$ and $E(\eta(z',t')\eta(z,t))=2D\delta(t-t')\delta(z-z')$, with E denoting expectation.

From dimensional analysis, we find that α and β are related to the stiffness of the rod through the relation $\nu\sim(\alpha/\beta)L^2$, where L is the length of the original rod, from which we obtain a parameter we call the normalized *stiffness* $k=\alpha/\beta$ (Lauk et al [11]).

Consider the spatiotemporal autocorrelation function $S(z-z',t-t')=E(y(z,t)y(z',t'))$. The autocorrelation function desired is given by $S(z_0,\tau)$ where z_0 is an arbitrary point on the polymer and without loss of generality we can choose $z_0=0$. We solve (1) using Fourier-Laplace transform methods. In transformed space the correlation function is given by

$$\hat{S}(k,\omega)=E(|\hat{y}(k,\omega)|^2)=\frac{2D}{|-\beta\omega^2-i\omega+\alpha+\nu k^2|^2}. \tag{2}$$

The Green's function is given by

$$\hat{G}(k,\omega)=\frac{1}{-\beta\omega^2-i\omega+\alpha+\nu k^2}. \tag{3}$$

From (2) and (3), we find that

$$\operatorname{Im}\hat{G}(k,\omega) = \frac{i\omega}{2D}\hat{S}(k,\omega).$$

In the time domain, this implies

$$G(z,t) = -\frac{1}{2D}\frac{dS(z,t)}{dt}, \qquad t > 0.$$

The autocorrelation is $S(0,t) = \langle y(0,t)y(0,0)\rangle$. Inverse Fourier transforming the Green's function gives in the time domain (Chow and Collins [4])

$$G(0,t) = \frac{e^{-t/2\beta}}{2\sqrt{\nu\beta}}\, J_0\left(\frac{\sqrt{4\alpha\beta-1}}{2\beta}\, t\right), \tag{4}$$

where $J_0(x)$ is the zeroth-order Bessel function. For $4\alpha\beta < 1$, J_0 is replaced by the zeroth-order modified Bessel function I_0.

3. Statistical and Computational Aspects Associated with the Stiffness Measure

From the COP trajectory of a patient, obtained as a sequence of 50 readings per second for a total of 120 seconds, we aim to estimate the parameters α and β, and subsequently the measure of stiffness as α/β. The $y-$component of the COP trajectory, viewed as a time series, allows immediate computation of the autocovariance $A(t)$. We use lags of up to 90 seconds, since after that $A(t)$ flattens out to zero. Its numerical derivative, $\frac{d}{dt}A(t)$ is an estimate of the theoretical expression written in (4). We aim to find those values of α and β in (4) which give the best (nonlinear) fit to the data ecapsulated in $\frac{d}{dt}A(t)$. Though estimation of derivatives is unstable, ability to collect data at high frequency, coupled with suitable smoothing, allows us to produce sufficiently reliable estimates. We trim the first three seconds of data to allow the autocovariance to be fitted to an oscillatory pattern of a Bessel function. Bessel functions, when viewed as power series, become quickly numerially unstable. We therefore opted for an optimization package to carry out the task. Using *Mathematica* to perform the nonlinear fit, we obtained the least squares estimates for α, β and ν. We start with the person's mass as an estimate for β, which is consistent with what model (1) describes. The standard errors for the parameters of the fitted functions can be obtained from the covariance matrix of the fit. The rest of the numerical optimization routines are written in *C* and *Splus*. Some of the *C* routines borrow from Press et al [13]. In addition to this, we added a drift parameter to the model which is not present in Lauk et al [11]. It provides for

a significantly better fit to the data.

We first use the stiffness measure to discriminate between the two groups: Parkinsonians and normal controls. The two groups were matched for age and other phisiological characteristics. In our Pittsburgh study, so far we had 26 Parkinsonians and 17 normal controls. The research protocol collects information on the platform variables in addition to the UPDRS data. We obtain an average of 15.2 for the stiffness measure in Parkinsonians; the estimated standard deviation of this average is 0.86. The normal controls have a mean of 10.3 with a standard error of 0.28. A formal test for equality of means rejects this hypothesis with a p-value less than 0.01 This shows that the stiffness measure provides good separation between the two populations.

The Spearman correlation of the stiffness measure with the motor portion of the UPDRS is 0.57 with a p-value of 0.026. Foot agility yields the highest correlation with the stiffness measure; it is 0.65 for this data.

4. Statistical Analysis of the First Crossing Time

The time required for the autocovariance function of the movement in the medio-lateral direction to first cross the time axis, that is, to hit zero for the first time, is an indication of how fast the person loses balance control. We call this variable the first crossing time.

To obtain estimates of the variance of the crossing time for a subject, we compute the crossing time for each of the five 2-minute trials, and compute the sample variance in the five readings. Inspection of the data shows that the variance in the crossing time changes from subject to subject; a formal test rejects the hypothesis of equality of variances (the p-value 0.016). This makes computation of confidence intervals for differences in the crossing times between the two populations groups a bit nonstandard. The 26 Parkinsonians yield an average crossing time of 20.2 whereas the 16 normal controls have a mean crossing time of 26.9. Even the most conservative approach (using the larger estimate of the variance among the two groups) yields the result that the Parkinsonians have, on average, the crossing time significantly greater than normal controls (p-values less than 0.01 in both cases, using a Gaussian test). Nonparametric tests offer similar conclusions. A one-sided Wilcoxon rank test finds that the median of the Parkinsonian average residual is significantly greater than the corresponding median of normal controls; the p-value is again less than 0.01.

The stiffness measure and crossing time show a Pearson correlation of -0.72. The crossing time has the clear advantage of being very easy to extract from data. By contrast, the stiffness measure (in spite of its attractive physical interpretation) is privy to pitfalls, such as estimational subjectivities regarding the amount of smooting used to estimate the derivative. In addition, the trimming of the first few seconds of the autocorrelation curve so that Bessel fuction can be fitted to the resulting oscillatory pattern is also subjective. The crossing time has a Spearman correlation of -0.62 with the UPDRS motor portion. It also shows a Spearman correlation of -0.53 with the right hand peg test and -0.58 with the left hand peg test; it yields a -0.55 correlation with bradykinesia. An interesting correlation for the crossing time is with the number of falls and near falls per month. Specifically, the Spearman correlation with the near falls is -0.59. This high correlation may allow the identification of patients prone to falling by using this platform measure supplemented by other clinical variates.

In addition to the stiffness measure and crossing time, several other statistics of the autocovariance function can be derived from the electronic platform data. These measures would then all be used to classify the state of PD in a subject and study correlations with measures obtained from the UPDRS scales. Data suggests that the following features of the covariance curve as particularly informative*:* (1) *The area under the autocovariance curve* from the trigger point to the first time the autocovariance hits zero. This statistic measures the overall balance control displayed by the individual. A small area indicates lack of balance and large area is sign of good balance control. (2) *The rate of decay of the autocovariance function.* Preliminary evidence suggests that PD patients show a much faster rate of decay than normal controls, though they also seem to rebound more. (3) *The oscillatory pattern of the autocovariance.* PD patients rebound more in order to regain balance. Such motion is reflected in the autocovariance as critical points, that is, as local extrema or points of inflection. Furthermore, a study of the acceleration, provided by the original two-dimensional trajectories, provides measures of "slips" that are helpful in the assessment of the probability of falls in the elderly. Details of the specific findings shall appear elsewhere.

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