REMOTE MONITORING OF LEVODOPA RESPONSE IN PARKINSON'S DISEASE

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EXECUTIVE SUMMARY

We propose a simple hypothesis-driven univariate analysis of smartphone data that is able to detect treatment response in Parkinson's Disease without the use of machine learning and has immediate clinical utility.

Data/ Inputs: For each subject, 1-hour recording sessions on different days at different times of the day were randomly selected. Each recording session constituted of 1-hour records of mean acceleration in x-, y- and z-axes in 1-second time windows. We also performed validation analysis on additional sets of 4 consecutive 1-hour recording sessions on 2 separate days.

Preliminary findings: Our outcome measure (ISAD) was much higher than in patients taking levodopa medication than in those who are not (p=0.011) analysing random non-consecutive recording sessions. Repeated validation analysis of separate consecutive recording sessions demonstrated that 4 hours of recording on 2-6 separate days were ideal to distinguish the groups (p=0.004). Healthy individuals had a higher level of ISAD than Parkinson's patients not on levodopa that was approaching statistical significance (p=0.07). Preliminary ROC analysis showed good discriminatory value for screening individuals for PD (AUC=0.84) and for detecting levodopa response (AUC=0.97).

Potential Utility: ISAD is sensitive to levodopa medication in patients, and could be used as a remote marker of response to levodopa treatment avoiding the need for repeat clinic appointments. ISAD may also be a screening tool for detecting early Parkinson's Disease.

INTRODUCTION

Smartphone technology and sensor miniaturisation but have yet to significantly penetrate healthcare. Sensor miniaturisation means that most smartphones can obtain full-spectrum quantification of human activity in the real world, and their ubiquity offers the potential for a broad reach in wider society.

Parkinson's disease is a particularly attractive condition to study with smartphones, as it is characteristically a disorder of movement, measurable by accelerometers in most smart-phones. There is an acute clinical need for an objective tool to monitor disease symptoms: current practice relies on subjective clinical rating scales administered by a trained clinician taking 20-30 minutes. More significant than the subjectivity and time factor, this clinical practice does not capture the *ecological reality* for the patient: what he or she is like over the course of the day where normal human movements (and the symptoms of Parkinson's Disease) are extremely variable and context-dependent.

Smartphone-based recordings overcome these problems by recording data continuously, thereby providing detailed time-resolution of movements of patients in real-world scenarios. Additionally, with an increasing proportion of the general population owning and carrying a smartphone, developed software can not only monitor Parkinson's Disease but could also act as a screening tool.

A cardinal manifestation of Parkinson's disease is the smallness of movement: *bradykinesia*. Oddly, it is often left out of kinematic studies of Parkinson's Disease in favour of time-series analyses of rhythmic movements (tremor). This is a missed opportunity since bradykinesia is the most sensitive symptom to available drugs (dopaminergic replacement or stimulation), and so most useful to monitor for to ensure symptoms are adequately

treated. Our study seeks to illuminate this analytical blind spot by analysing the variability of movement acceleration.

Daily variability of movement amplitude

Normal human movement is extremely variable: continuous actigraphic recordings over several days show very long periods of little movement interspersed with short bursts of movement lasting seconds (e.g. getting up from chair, reaching) and longer periods of rhythmic movements (e.g. walking, cycling).

Previous actigraphic studies of Parkinson's Disease analysed mean acceleration, but this under-represents brief acceleration movement bursts that are of key interest when studying bradykinesia. **Figure 1** shows the statistical distribution of human accelerometry indicative of an extreme leptokurtic distribution. This indicates that large high force movements are brief and infrequent; therefore to analyse large force movements affected by bradykinesia, one has to capture variability rather than absolute means – it is what happens in the tails rather than the mean that is of greatest interest.

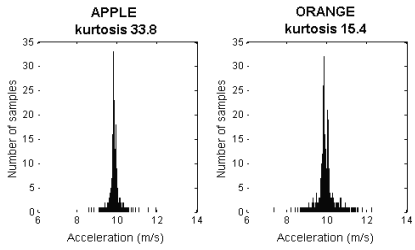

Figure 1: *Histograms of acceleration in 1-hour periods showing leptokurtic distributions in healthy controls.*

Voluntary movements are typically 1-3 seconds duration for large amplitude movements and non-rhythmic. As such, power spectra peaks, absolute deviation and standard deviation in the pilot dataset sampled at 10-100Hz frequency do not measure the movements we are predominantly interested in.

We therefore developed a very simple analysis, 'sessional absolute deviation' (SAD), that captures the variability of human movement during a recording session by simply assessing the variability of the second-by-second accelerometer mean. To capture variation across recording sessions (since Parkinson's Disease symptoms vary with treatment over time), we also analysed 'intersessional absolute deviation' (ISAD). Our method therefore captures the width of the distribution across different time scales.

What do SAD and ISAD reflect?

SAD is weighted towards high acceleration movements composed of a mixture of non-rhythmic movements and rhythmic low-frequency (<1Hz) movements (e.g. walking). A recording block with high SAD would therefore reflect a period with higher levels of physical activity than a recording block with low SAD.

On the other hand, ISAD reflects differences in movement patterns over several recording sessions. Thus, an individual with low ISAD would be someone with only periods of low force movements, i.e. patients in a sedentary state such as akinetic-rigid untreated patients or the elderly disabled. It is theoretically possible that the low ISAD might reflect an individual with only periods of minimally varying high force movements, but this would be an unusual pattern of behaviour (e.g. walking steadily on a treadmill continuously for several hours). Conversely an individual with high ISAD would be someone with periods with frequent force-varying movements and other periods with predominantly low force movements. This person would be similar to Parkinson's Disease patients with ON-OFF periods.

The bradykinesia of Parkinson's Disease is specifically targeted by dopaminergic drug-treatments—the most potent drug being levodopa (Madopar®, Sinemet®, Stalevo®)—and responsiveness to levodopa is so typical of Parkinson's Disease that lack of response suggests an alternative diagnosis. Levodopa can rapidly treat the symptoms but has unpredictable absorption so the timing of action can be unpredictable and chronic use is associated with wearing-off phenomenon (shorter ON periods), and episodic excess of movement (dyskinesias). One could therefore hypothesise that patients with untreated Parkinson's Disease would have less movement and thus more regular levels of activity (low ISAD) compared with treated patients who have ON-OFF cycles and dyskinesias (high ISAD).

RESULTS

Analysis of random sessions

The recording sessions were randomly selected in the discovery analysisand there were no gross

timing differences between PD and healthy controls **(Appendix-I Figure 1)**. SAD did not significantly differ between healthy controls and patients with Parkinson's Disease (p>0.05) (**Appendix-I Figure 2**); ISADalso did not differ significantly between patients with Parkinson's Disease and healthy controls (p>0.05) but there was a linear relationship between age and ISAD in healthy controls that was not reproduced in a subsequent validation analysis **(Appendix-I Figure 3**).

Effect of medication in Parkinson's Disease

Six of the patients with Parkinson's Disease were taking levodopa while three were not (but were taking other less potent agents). **Figure 2** demonstrates that patients on levodopa are more likely to have high ISAD with a clear segregation between the groups (student's unpaired t-test, p=0.011). ISAD potentially represents a simple metric that captures a medication treatment effect.

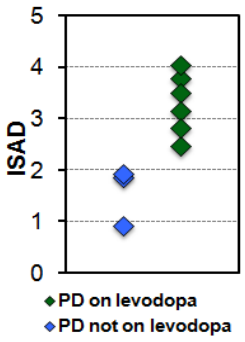

Figure 2: *Discovery analysis of ISADshowing segregation of patients not taking levodopa and patients taking levodopa (student's unpaired two-tailed t-test, p=0.011)*

Analysis of consecutive sessions

To validate our results and to avoid selection bias, we performed a validation analysis on a separate set of datapoints obtained from 6 consecutive 50-60min recording sessions on different dates for the patients with Parkinson's Disease (**Figure 3a & 3b**). **Figure 3a** demonstrates the varying values of SAD over consecutive sessions. The short plasma half-life of levodopa makes it likely that levodopa plasma peaks and troughs were captured in the 5-6 hours analysed. Recording sessions lasting 3-4 hours in total were sufficient to demonstrate statistical significant difference (**Figure 3c**). However, the overlap in ISAD values between patients indicates reduced accuracy meaning that ISAD analysis over long duration consecutive sessions may be less useful clinically.

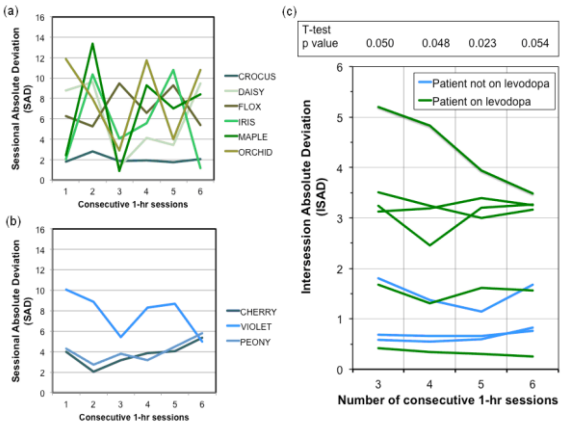

Figure 3: *Analysis of consecutive sessions of sessional absolute deviation, SAD over 6 consecutive sessions for* ***(a)*** *patients on levodopa and* ***(b)****patients not on levodopa;* ***(c)*** *ISAD showing statistical significance (unpaired t-tests with uncorrected p-values displayed).*

Due to the reduced accuracy, we analysed another 4 consecutive sessions on a separate day. There was immense variability in SAD within a day and between days for patients on levodopa **(Figure4a)**, which is absent with patients not on levodopa **(Figure 4b)**. This is verified with ISAD of all 8 sessions with clear separation (unpaired two-tailed t-test, p=0.004). This demonstrates that multiple day analyses over several hours increase the accuracy of this technique dramatically (**Figure 4c)**.

Relationship with UPDRS scale

UPDRS scores recorded in this study used the self-reported Activities of Daily Living (UPDRS-II-ADL) scale which provides a global picture of function and symptoms. In this data, there was a significant correlation between ISAD and UPDRS-II-ADL scores (Spearman rho 0.736, p=0.028), but this correlation is likely to be spurious as more disabled patients with higher UPDRS-II-ADL would be much more likely to be started on levodopa by their neurologists. When correcting for levodopa use, partial correlation between ISAD and UPDRS-ADL was not significant (Spearman rho 0.555, p=0.153) **(Appendix-I Table 1).**

This is not surprising as UPDRS-II-ADL captures non-motor parameters and is known to be poorly responsive to levodopa.

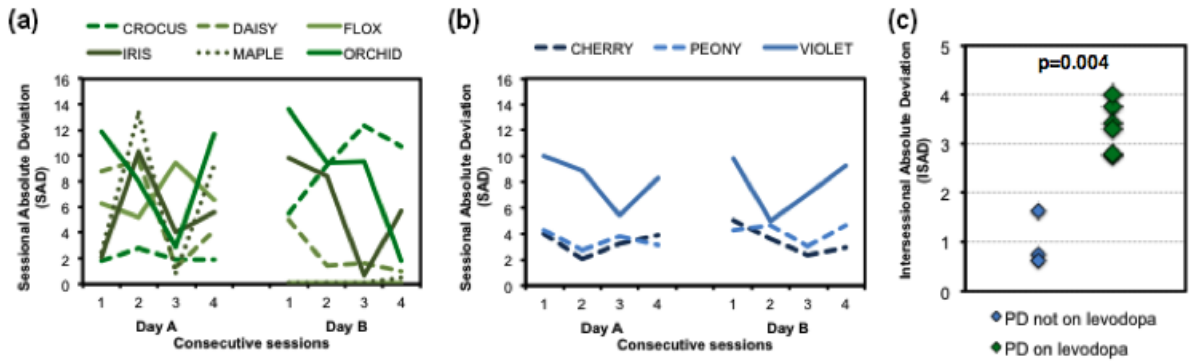

Figure 4: *Analysis of consecutive sessions of sessional absolute deviation, SAD over 4 consecutive sessions on two separate days for* ***(a)*** *patients on levodopa and* ***(b)*** *patients not on levodopa; and* ***(c)*** *intersessional absolute deviation, ISAD of all 8 sessions showing clear separation (unpaired two-tailed t-test, p=0.004).*

Re-analysis of healthy controls and patients with Parkinson's Disease

Due to the improved accuracy with two sets of 4 consecutive sessions, we re-analysed the healthy controls using the same method. We found that healthy controls have an intermediate level of ISAD in between patients on levodopa and not on levodopa **(Figure 5)**. Of note, there is one outlier in the healthy controls (Sunflower) generating the overlap between healthy controls and Parkinson's Disease patients not taking levodopa. This intermediate ISAD level supports the hypothesis that as an individual develops the symptoms of bradykinesia, ISAD measurements are lower. Once started on levodopa, ISAD rises to overshoot healthy individuals due to ON-OFF cycles.

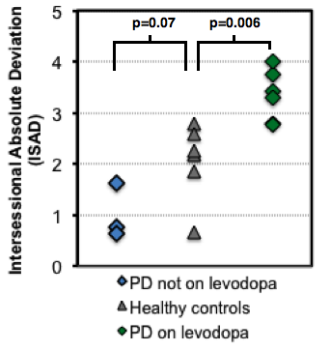

Figure 5:*ISAD analysis of 2 x 4 consecutive sessions showing segregation of patients not taking levodopa and patients taking levodopa, and an intermediate level for healthy controls(one-factor ANOVA, $F_{2,12}$=15.1, p=0.0005). Patients not on levodopa (mean 1.004 ±0.541SD), healthy controls (mean 3.341 ± 0.499SD) and PD patients on levodopa (mean 2.049 ± 0.761SD).*

CLINICAL UTILITY

Can the data help distinguish PD patients from control subjects?

ISAD has potential as a screening tool as patients not on levodopa (i.e. analogous to undiagnosed PD patients) have a lower level compared to healthy controls (**Figure 5**).We tested its discriminatory ability using a Receiver Operating Characteristic (ROC) Curve with the means and standard deviations from the pilot dataset assuming that further data collected are consistent with pilot; the area under ROC curve 0.837 – a good screening test)**(Appendix-I Figure 4a)**.

However even if ISAD is a good discriminator, caution is advised for use as a screening tool: participants who download the App for personal screening may not be adequately counselled, risking psychological trauma (even despite recommendations for face-to-face confirmation assessment by a neurologist).

Can the data help measure change or variability of symptoms in PD subjects? Can the data be used in other creative ways to inform patient treatment and care?

Our analysis from patients on and off levodopa medication show that ISAD can measure symptom variability in PD subjects with as little as 4 hours recording on 2 separate days. This suggests that ISAD change following initiation of treatment could be used to determine responsiveness to levodopa (area under ROC curve 0.968) **(Appendix-I Figure 4b)**.

In the clinical setting, determining levodopa-responsiveness is important in distinguishing Parkinson's Disease from Parkinson-mimics which do not respond to levodopa. Current practice is a

repeat clinician assessment after starting treatment (i.e. a 2nd clinic appointment in several weeks to months). With our approach, a clinician of the future would prescribe levodopa medication and the smartphone would then record ISAD before and after starting the medication. The smartphone can then remotely alert the clinician if there has not been a response therefore prompting an earlier follow-up clinic appointment.

Additionally, imprecise drug dosing, poor dose scheduling or long-term use risk producing excessive movements (dyskinesias), wearing OFF phenomenon and unpredictable ON-OFF fluctuations (40% of patients develop dyskinesias within 5 years of starting treatment). Our analysis could detect this: one would predict that patients with extreme levels of ISAD would have levodopa-induced dyskinesias or marked ON-OFF cycles. The patient with the highest ISAD in our analysis was also taking amantadine suggesting that he or she experiences dyskinesias. Dosing ON-OFF cycles can also be captured from long recordings allowing personally tailored dosing schedules to maintain continuous dopaminergic stimulation and thus less long-term complications.

Together with self-reported UPDRS-II scores, a nuanced picture of patient function can be formed remotely (**Figure 6**).

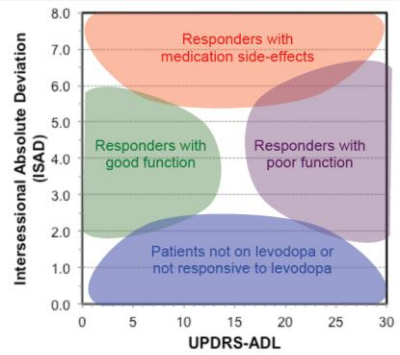

Figure 6:*Categorising patients using ISAD and UPDRS*

Do the analyses and proposed uses of the data use innovative approaches and methods?

Our analysis focuses on the variability of movement acceleration rather than time-series rhythmic data to address clinically relevant questions. Our technique uses a minimal dataset needing only brief recordings (8-24 hours in total) encouraging patient and volunteer compliance.

An additional merit of our technique is its simplicity: the low computational needs means that analysis of the recorded data can be performed on the user's own smartphone rather than being transmitted to a remote server if privacy is desired.

CONCLUSION

The next critical step is to validate our uniquely simple analysis in a larger patient population and garner patient and clinician interest. This can be achieved using a new model of doing research with patient, clinician and developer cooperation (**Appendix-II**). As active research neurologists, we are valuable partners in taking this forward.