Accounting for Movement Increases Sensitivity in Detecting Brain Activity in Parkinson's Disease

Štefan Holiga[1], Harald E Möller[1], Tomáš Sieger[2,3], Matthias L Schroeter[1,4], Robert Jech[2], and Karsten Mueller[1]

[1]*Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany,* [2]*Department of Neurology and Center of Clinical Neuroscience, Charles University in Prague, Czech Republic,* [3]*Department of Cybernetics, Faculty of Electrical Engineering, Czech Technical University in Prague, Czech Republic,* [4]*Clinic for Cognitive Neurology, Leipzig, Germany*

Introduction: Parkinson's disease (PD) is a progressive neurological disorder manifested by motor impairment, which may impede the ability to accurately perform motor tasks during functional magnetic resonance imaging (fMRI). In motor experiments with PD patients researchers often neglect that due to motor deficits, performance is likely to deviate from an idealized paradigm. Both temporal and amplitude deviations of movement performance affect the blood oxygenation level-dependent (BOLD) response (1, 2). Such deviations are of particular importance in areas with only tenuous BOLD signal changes of ~1%, such as the basal ganglia (BG), which are predominantly affected in PD. Finally, movement performance variability within and between sessions need to be addressed in experiments with PD patients.

Without explicit quantitative knowledge of movement performance, statistical tests relying on the generic BOLD model may be degraded by inappropriate estimates of partial regression coefficients, β, and potentially result in biased and invalid interpretations. We hypothesized that assessment and consideration of individual movements increases the sensitivity of BOLD fMRI to detect brain activity of PD patients during a motor task.

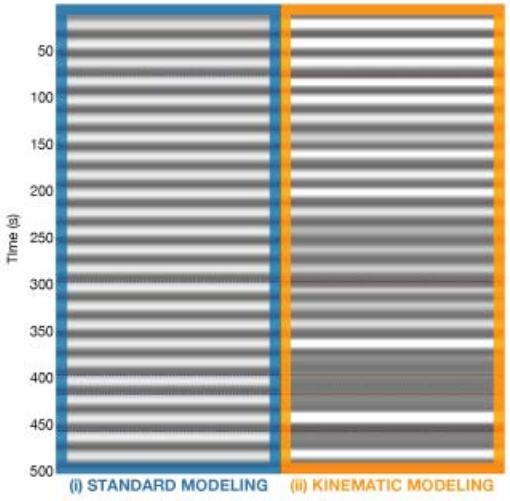

Figure 1. Comparison of session-specific predictors in fixed-effects model (left, blue: standard approach; right, orange: kinematic, mean amplitude-sensitive approach).

Methods: Twelve right-handed male patients with advanced PD (Hoehn-Yahr stages II-III, 45-64 years of age) were measured in two conditions, *(a)* after overnight withdrawal of levodopa (OFF) and *(b)* one hour after administration of 250 mg of levodopa / 25 mg carbidopa (ON). Both hands were investigated separately. A block-based motor paradigm consisting of resting and finger tapping epochs was conceived. A *T2**-weighted gradient-echo echo-planar imaging (EPI) sequence (flip angle 90°; repetition time, TR = 1 s; echo time, TE = 54 ms) was used for BOLD fMRI at 1.5T. Patients' motor outcome was recorded using MRI-compatible sensory gloves, with a set of 14 sensors measuring the flexion and abduction of fingers. Two types of fixed-effects models were generated (Figure 1). *(i)* The standard model incorporated a constant term and a predictor containing a condition-specific, constant-amplitude boxcar function characterized by onsets and durations of task-related epochs, as conventional to SPM. *(ii)* A kinematic model incorporated a constant term and a predictor computed as the envelope of the average of all kinematics' time courses (mean), or the envelope of the projection of the data to its first principal component (eigenvariate). As both varieties of kinematic predictors were sensitive to the amplitude of movement, their amplitude-invariant (AI) versions were formed to be able to show the impact of incorporating the amplitude of movement in modeling. Both types of predictors were convolved with a canonical hemodynamic response function (HRF). The standard model and four distinct kinematic models were used for fitting the mass-univariate general linear model. To evaluate the effect of dopaminergic medication to patients, we fitted a random-effects flexible-factorial model with difference between ON and OFF conditions as an effect of interest. To assess the effect size, we calculated percent signal change for each approach in a region of interest (ROI), which was formed as the intersection of parametric maps resulting from standard and all kinematic group-level approaches. Analysis of variance with repeated measures with factors 'Hand' and 'Modeling approach' for ON medication condition was calculated for quantitative assessment of the results.

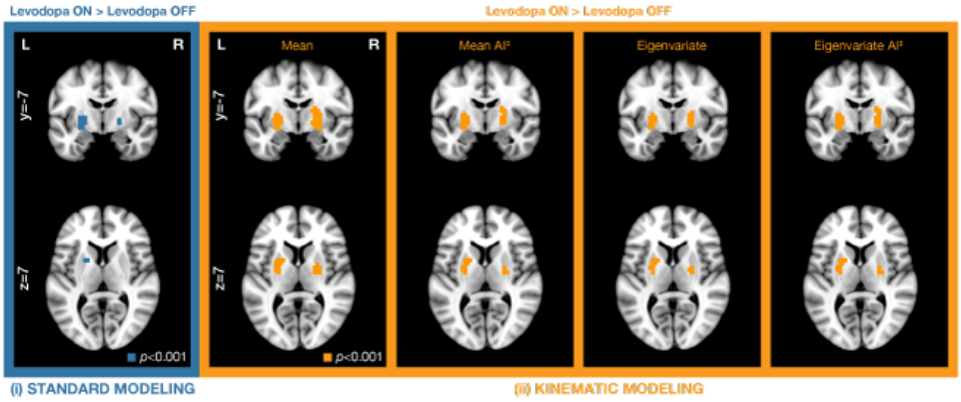

Figure 2. Group-level response to levodopa treatment in PD patients as random effect parametric maps (p<0.001; uncorrected).

Results & Discussion: Strikingly, all variations of kinematic modeling outperformed standard modeling and resulted in an extensive sensitivity increase (Figure 2). They provided a larger spatial extent of activity and higher family-wise error (FWE) corrected cluster p-values. In contrast, the right subcortical cluster obtained with standard modeling did not remain significant after FWE multiple test correction. All kinematic approaches provided significantly higher (p<0.05) amplitudes of activity (Figure 3). In addition, all kinematic approaches except 'mean' showed a significant interaction (p<0.05) between factors 'Hand' and 'Modeling approach'. Interestingly, a significant difference (p<0.05) between amplitude-sensitive and amplitude-invariant versions of eigenvariate kinematic approach was discovered. Our results provide a clear evidence of increasing sensitivity in detecting brain activity in PD patients compared to generic fMRI statistics, when quantitatively accounting for their movement.

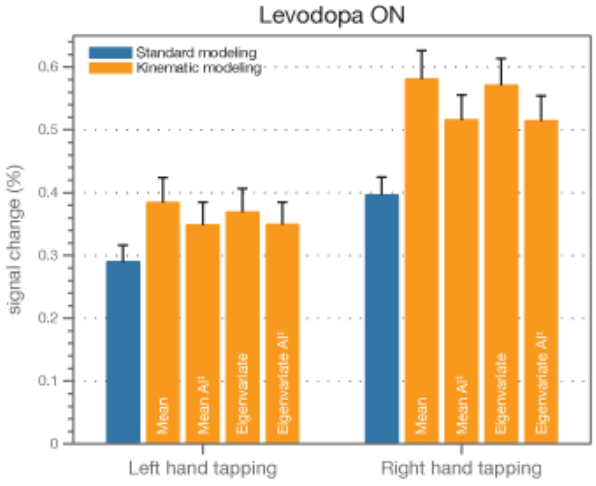

Figure 3. Average effect size in basal ganglia functional ROI.

References: [1] Bandettini PA. 1991, In: Functional MRI of the brain, Berkeley: SMRM, 143. [2] Waldvogel D et al. 1999, J Cereb Blood Flow Metab 19: 1209-1212