The role of early motor cortex changes in Parkinson's disease progression: a 4-year longitudinal neurophysiological study

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OBJECTIVES

Previous cross-sectional neurophysiological studies depicted the pathophysiological basis of early-stage Parkinson's disease (PD), reporting an abnormal cortical excitability and plasticity as well as an altered kinematic performance. However, the prognostic relevance of early pathophysiological features of people with PD (PwPD) remains unknown. This 4-year longitudinal multitechnique neurophysiological investigation aimed to assess whether pathophysiological abnormalities in the primary motor cortex (M1) observed in PwPD correlate with clinical severity at different stages and predict disease progression.

AIMS

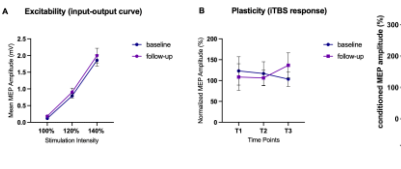
We enrolled 60 early-stage, drug-naïve PwPD patients and 50 healthy controls (HC). PD patients underwent clinical, neurophysiological, and kinematic assessments at baseline and after a 4-year follow-up

METHODS

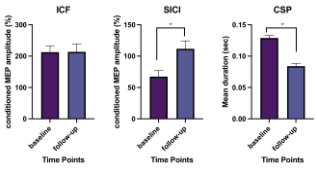
The clinical assessment included the administration of standardized clinical scales aimed at evaluating motor and non-motor symptoms. Neurophysiological assessment included various transcranial magnetic stimulation protocols used to evaluate M1 excitability (input/output curve), intracortical inhibitory (short-interval intracortical inhibition – SICI and cortical silent period- CSP), faciliatory mechanisms (intracortical facilitation - ICF) and plasticity (intermittent theta burst stimulationl); kinematic analysis quantified finger movement performance. Statistical analyses assessed group differences, longitudinal changes, and correlations between neurophysiological and clinical data.

RESULTS

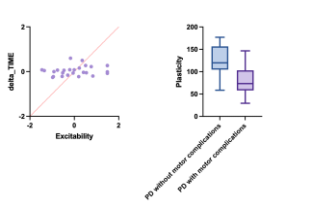
At baseline, PwPD showed increased M1 excitability, reduced SICI, and impaired plasticity compared to HC, while ICF and CSP were preserved. Kinematic performance was also significantly worse in PD. Over 4 years, clinical and kinematic measures worsened significantly. While excitability and plasticity remained stable, inhibitory markers (SICI and CSP) declined. M1 excitability and plasticity at baseline predicted worsening of motor performance and the development of motor complications, respectively



Longitudinal assessment of M1 excitability and plasticity.
(A) I/O curves of MEPs at baseline and follow-up
(B) Cortical plasticity evaluated by iTBS-induced modulation of MEP amplitude



Longitudinal Changes in Measures of Cortical Facilitation and Inhibition



Measures of Cortical Excitability and Plasticity as Predictive Markers of Motor Worsening
(A) Linear regression analysis illustrating significant associations between baseline measures of primary motor cortex excitability and kinematic motor worsening in Parkinson's disease patients.
(B) Box plot highlighting reduced motor cortex plasticity at baseline in patients developing motor complications compared to patients not presenting motor complications at the 4-year follow-up.

DISCUSSION

Our findings suggest that increased cortical excitability and impaired plasticity are early and stable pathophysiological features of PD , supporting their role as disease-trait markers. In contrast, progressive deterioration in cortical inhibition aligns with clinical worsening, identifying SICI and CSP as potential disease-state markers.

CONCLUSIONS

This longitudinal study highlighted a potential role for cortical excitability and plasticity as intrinsic disease traits, while declining inhibitory control could reflect disease progression. These findings support the use of TMS measures as potential biomarkers for tracking and predicting PD progression.

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