

**Title: The role of motor learning in dopaminergic therapy of Parkinson's disease**

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The long duration response (LDR) is the most desirable component of dopaminergic therapy in PD <sup>1</sup>. The mechanism underlying LDR is unknown. Our recent data on a mouse model of early PD demonstrate LDR (Beeler et al, *Ann Neurol*, tentatively accepted) in its slow build up of improvement after the initiation of therapy and gradual degradation of performance. We hypothesize that motor learning may play a significant, under-appreciated role in the symptoms of Parkinson's disease as well as in the therapeutic effects of dopaminergic medications. We suggest that the important, yet enigmatic LDR to chronic levodopa treatment is a manifestation of rescued motor learning. Based on these findings, we propose to data-mine two clinical trials to demonstrate the effect of active hand use and dopaminergic medications on motor learning and performance. We hypothesize that levodopa therapy restores motor learning in early PD (ELLDOPA) whereas D2 class dopamine agonist does not and simply restores motor performance (PATCH). We also hypothesize that active hand use in dopamine-deficient state facilitates aberrant learning and worsens performance. This study will provide a clinical relevance of the motor learning hypothesis and a theoretical basis for novel therapeutic approaches enhancing learning component.