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Targeting Trends

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Impairments in gait, posture and complex movement control in rats modeling the multi-system, cholinergic-dopaminergic losses in Parkinson's Disease

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In addition to the primary disease-defining symptoms that result from extensive loss of nigrostriatal dopaminergic neurons, approximately half of patients with Parkinson's Disease (PD) suffer from postural instability, impairments in gait control and a propensity for falls. These symptoms have been associated with losses of cholinergic neurons situated in the basal forebrain (BF) and in the brainstem pedunculopontine nucleus (PPN). We recently developed a test system (Michigan Complex Motor Control Task, MCMCT) for the assessment of fall propensity in rats. Our initial research focusing on the modeling of falls found that cholinergic lesions of the BF in combination with striatal dopamine (DA) lesions (dual lesions, 'DL') generated rats with a high rate of falls that correlated with attentional impairments on an attention task[1]. Given that PPN cholinergic projections have been associated with fall status in PD, we further sought to determine the contribution of PPN cholinergic loss to gait control and falls in rats with cholinergic BF and/or striatal dopamine system losses.

The MCMCT was designed to tax the ability to rapidly correct movement errors when traversing complex rotating surfaces (square rods). Rats were trained to traverse stationary and rotating rods, placed horizontally or at inclines. Traversing rotating rods and avoiding falls required persistent control of gait, limb coordination and carefully timed and placed steps. Following training, rats received cholinergic and/or striatal dopaminergic lesions or sham lesions. Cholinergic lesions were produced by bilateral infusions of 192 IgG-SAP (Cat. #IT-01) or Anti-ChAT-SAP (Cat. #IT-42) into the BF or PPN, respectively. Caudate dopaminergic deafferentation was achieved by bilateral infusions of 6-hydroxydopamine (6-OHDA) into the caudate nucleus. Following surgeries, rats were tested on a 14 day MCMCT test battery with increasingly complex traversal conditions (see Fig. 1).

The results indicated that rats with losses of PPN and BF cholinergic neurons and striatal dopaminergic inputs fell frequently from the rods (Fig. 1), and that these falls were associated with relatively slow traversal speed and high rate of slips. The performance of rats with losses in all three regions (PPN, BF,

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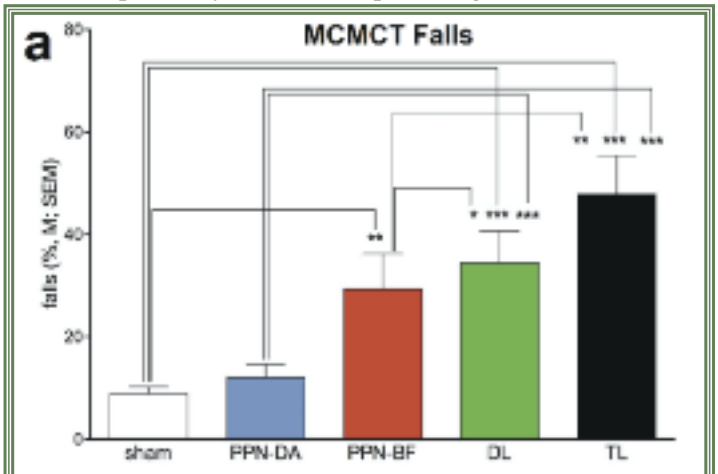

Fig. 1. Rats with PPN + BF cholinergic cell losses, with BF cholinergic and striatal dopamine lesions (DL), and with triple system lesions (TL) fell more than shams from the rotating rod (alternating directions).

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Denise Higgins, Editor

ADVANCED TARGETING SYSTEMS