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L-DOPA treatment duration versus Parkinson's Disease progression: The dorsal-ventral divide

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Unlike other monoamine systems, the mesencephalic dopamine system is heterogeneous with respect to differential projection targets and functional effects. Thus, the nigrostriatal dopamine system that innervates the dorsolateral caudate/putamen is primarily involved in motor function, with mesolimbic striatal projections affecting some cognitive processes and reward-mediated behavior^{1, 2}. Degeneration of the dopamine system in Parkinson's disease is not uniform; in early stages primarily the nigrostriatal system is affected, leading to deficits in motor function. However, as the disease progresses, there is also a progressive involvement of the mesolimbic systems. It is the involvement of these latter systems that are proposed to contribute to deficits in reward-based learning. In treating Parkinson's disease, dopamine replacement therapy, such as L-DOPA, is administered and dosages adjusted to act primarily on the damaged dopamine system; i.e., the nigrostriatal system. However, this presents a problem, in that L-DOPA works across the entire dopamine system. Hence, its administration in the early stages of the disease could overstimulate the normal, non-impaired mesolimbic system. This is the source of the dopamine overdose hypothesis^{3, 4}, which has been proposed in animal studies to lead to alterations in reward systems^{5, 6}, and that is examined in the study by MacDonald et al in this issue⁷. A corollary of this hypothesis is that, as the mesolimbic system degenerates later in life, L-DOPA would change from having a disruptive influence on the mesolimbic system to one of restoration.

MacDonald et al showed clear differences with respect to medication effects between groups. As expected, the L-DOPA improved motor symptoms across both early and late stage Parkinson's patients⁷. However, the early Parkinson's patients also demonstrated some indication of disruption by L-DOPA only in the ON phase of medication, and showed more efficient reward learning OFF medication. This is consistent with the overdose hypothesis at a stage when the mesolimbic system is believed to be intact. Interestingly, although the late-stage Parkinson patients OFF L-DOPA showed clear learning impairment compared to controls, with L-DOPA ON, the later-stage patients did not show a differential effect when comparing between controls and early stage patient groups – i.e., the performance of early and late Parkinson's patients was identical, despite the proposed greater mesolimbic degeneration proposed to have occurred in this stage of the illness. Why there was no difference is not clear; however, this could be related to several factors.

For example, the late-stage patients also had received a longer course of L-DOPA therapy, which animal experiments suggest could in itself alter the way the system functions^{8–10}. L-DOPA exposure over years of treatment would be expected to result in substantial changes in the striatum, including decreases in D2 receptor number, decreased dopamine synthesis, and alterations in dopamine neuron autoreceptor function and activity^{10, 11}. Upon withdrawal from L-DOPA, one would expect a deficit state to be present in the mesolimbic system. Under these conditions, restoration of L-DOPA treatment may not be treating a mesolimbic degeneration, but rather reversing the effects of L-DOPA withdrawal. Such a deficit in the reward state could underlie the inability of patients ON L-DOPA from showing either a significant improvement or a substantial deficit in reward learning. With respect to controls, L-DOPA has been shown in intact rats to have a much lessened effect compared to lesioned conditions in animal studies¹⁰, presumably due to higher metabolism of the extra L-DOPA. A longitudinal study would be necessary to segregate such influences.

While this study provided unique insights into the relationship between treatment response and how it changes across time, there are several caveats that should be considered. Macdonald et al approached this by subdividing Parkinson's patients based on their duration of illness, with the hypothesis that those with the longest duration would have the greatest level of mesolimbic impairment. The division was based on 5 years or less of illness being classified as early stage, with greater than 5 years classified as late stage. On face value, this may be considered a simplification of a complex and varied disease process, in which different patients may show differential progress of the disorder over time. Moreover, there is concern that there was little separation in illness duration at the 5 year time point; with adequate patient populations, a cutoff separated by several years may have provided a better separation of effects. Nonetheless, this approach did seem to suffice to provide an adequate comparison group. Such details would require a substantially more complex experimental design, and may not be feasible due to ethical considerations related to withholding of medications.

Overall, this study extends previous work by Cools et al.^{3, 12} showing that L-DOPA can impair reward learning in early stage Parkinson's disease. However, with continued degeneration and L-DOPA administration, later-stage Parkinson's patients show disrupted cognitive performance that is not altered either ON or OFF L-DOPA. Therefore, the system appears to have stabilized to a new steady-state level that is not as responsive to L-DOPA treatment with respect to either ameliorative or disruptive actions with respect to reward, despite showing continued efficacy with respect to motor signs.

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