Frontal cognitive impairments and saccadic deficits in low-dose MPTP-treated monkeys.

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Created 11/13/2011
By elscl_admin November 13, 2011


Abstract:

There is considerable overlap between the cognitive deficits observed in humans with frontal lobe damage and those described in patients with Parkinson’s disease. Similar frontal impairments have been found in the 1-methyl-4-phenyl-1,2,3, 6-tetrahydropyridine (MPTP) primate model of Parkinsonism. Here we provide quantitative documentation of the cognitive, oculomotor, and skeletomotor dysfunctions of monkeys trained on a frontal task and treated with low-doses (LD) of MPTP. Two rhesus monkeys were trained to perform a spatial delayed-response task with frequent alternations between two behavioral modes (GO and NO-GO). After control recordings, the monkeys were treated with one placebo and successive LD MPTP courses. Monkey C developed motor Parkinsonian signs after a fourth course of medium-dose (MD) MPTP and later was treated with combined dopaminergic therapy (CDoT). There were no gross motor changes after the LD MPTP courses, and the average movement time (MT) did not increase. However, reaction time (RT) increased significantly. Both RT and MT were further increased in the symptomatic state, under CDoT. Self-initiated saccades became hypometric after LD MPTP treatments and their frequency decreased. Visually triggered saccades were affected to a lesser extent by the LD MPTP treatments. All saccadic parameters declined further in the symptomatic state and improved partially during CDoT. The number of GO mode (no-response, location, and early release) errors increased after MPTP treatment. The monkeys made more perseverative errors while switching from the GO to the NO-GO mode. Saccadic eye movement patterns suggest that frontal deficits were involved in most observed errors. CDoT had a differential effect on the behavioral errors. It decreased omission errors but did not improve location errors or perseverative errors. Tyrosine hydroxylase immunohistochemistry showed moderate (approximately 70-80%) reduction in the number of dopaminergic neurons in the substantia nigra pars compacta after MPTP treatment. These results show that cognitive and motor disorders can be dissociated in the LD MPTP model and that cognitive and oculomotor impairments develop before the onset of skeletal motor symptoms. The behavioral and saccadic deficits probably result from the marked reduction of dopaminergic neurons in the midbrain. We suggest that these behavioral changes result from modified neuronal activity in the frontal cortex.

Journal:
Journal of neurophysiology

Volume:
81

Issue:
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