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# Early serotonergic lesion promotes the emergence and severity of motor symptoms in monkeys.

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## Résumé

**Context:** Serotonergic (5-HT) neurons degenerate in Parkinson's disease (PD). We and others have highlighted strong relationships between the alteration of the serotonergic (5-HT) system and the expression of motor and non-motor symptoms on both parkinsonian patients and monkeys. It is therefore crucial to investigate the precise implication of 5-HT besides dopamine (DA) in the parkinsonian symptomatology.

**Aim:** To assess the impact of an early serotonergic (5-HT) lesion on the development and severity of motor symptoms induced by a dopaminergic lesion in non-human primates.

**Methods:** 5-HT fibers (not somas) were lesioned by using 3,4-methylenedioxy-N-methamphetamine (MDMA) while DA neurons were lesioned by using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in two groups of macaque monkeys (MDMA/MPTP and MPTP alone). Lesions were assessed by positron emission tomography (PET) imaging using the following tracers: [11C]DASB for the 5-HT transporter (SERT), [11C]PE2I for the DA transporter and [11C]Raclopride for DA D2/D3 receptors. Lesions were also assessed by immunohistochemistry using tyrosine hydroxylase, tryptophan hydroxylase 2 and SERT antibodies. The severity of parkinsonian symptoms was assessed longitudinally using the rating scale of Schneider and Kovelowski. The higher the score, the more symptomatic the monkey.

**Results:** As expected, MDMA led to a decrease of [11C]DASB binding around 40% in the brain, except in the raphe. MPTP led a strong decrease of [11C]PE2I binding in the striatum, independently of the groups. More surprisingly, a strong increase of [11C]Raclopride was evidenced in the striatum after MPTP in MDMA/MPTP lesioned monkeys compared to MPTP lesioned ones. Assessment of motor symptoms showed that MDMA/MPTP monkeys exhibited more rapidly and severely rigidity, tremor and postural abnormality compared to MPTP ones.

**Conclusion:** All together, these results demonstrate that the early lesion of serotonergic fibers promotes the emergence and severity of parkinsonism in response to MPTP in macaque monkeys.

**Mots-Clés:** motor symptoms, serotonergic lesion, monkeys

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