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Unlocking the secrets of dopamine in Alzheimer's Disease

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Dopamine (DA) is a neurotransmitter belonging to the catecholamine family that plays essential functions in the central nervous system. The main source of DA in the brain derives from dopaminergic neurons in the ventral tegmental area (VTA) and *substantia nigra pars compacta* (SNpc) that project to different brain regions and exert distinct functions. The VTA targets the hippocampus, *nucleus accumbens* and cerebral cortex and mediates the control of motivation and reward. In contrast, the SNpc projects mainly to the caudate and putamen nuclei of the striatum and is involved primarily in the control of voluntary movement.

The notion that DA modulates hippocampal functions, including synaptic plasticity and memory [1,2], has been known for sometime now. Also, its role in Alzheimer's Disease (AD) is supported by tantalizing experimental observations conducted either in AD mouse models or in AD post-mortem brains [3]. Moreover, stimulation of primary motor cortex (M1) by transcranial magnetic stimulation (TMS) in AD patients demonstrated an impairment of central cholinergic activity that can be transiently restored by the administration of Levodopa or rotigotine, a dopamine D2/D3 agonist. More recently, it has been demonstrated that alteration of LTP-like cortical plasticity is rescued in AD patients treated with rotigotine, thus confirming that dopaminergic stimulation might reveal a therapeutic strategy for AD [3,4].

Despite this array of data, the putative pathogenic mechanisms underlying the dopaminergic dysfunction in AD still remains to be clarified. In a recent report, Nobili and colleagues provide experimental evidence showing that also the VTA is a key brain region involved in AD pathogenesis [5]. Indeed, authors show for the first time that dopaminergic neuron loss in the VTA could be detected in the Tg2576 model of AD at the early "pre-plaque" stage in which no cell death occurs in the hippocampus. The progressive dopaminergic degeneration in the VTA results in lower DA outflow in the hippocampus and *nucleus accumbens*, which correlates with impairments in CA1 synaptic plasticity, memory performance and reward processing [5].

This nonclinical observation might somehow be associated with the clinical "dopaminergic" symptomatology including either apathy, a common neurobehavioural feature associated with AD [6], or anhedonia, which has been suggested to increase the risk of AD-related markers.

Although the molecular underpinnings of VTA dopaminergic degeneration in AD remain to be