Etiological and pathophysiological contributions of impulsivity trait and anhedonia to impulse control disorders in Parkinson’s disease

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Research Abstract
Idiopathic Parkinson’s disease (PD) is a neurodegenerative disorder resulting mainly from the loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNc), but neither the neurobiological mechanisms, nor the etiopathogenic factors of this degeneration are

understood. At the clinical level, the general wisdom has long been that early symptoms of PD are movement deficits eventually spreading later on to cognitive and psychiatric processes. However, there is increasing evidence that not only can the latter appear before the onset of the former but also that cognitive and psychiatric impairments greatly contribute to patients' morbidity and quality of life.
These non-motor symptoms range from dramatic deficits in hedonic processes, including decrease in motivated behaviors (apathy) and depression to behavioral complications such as pathological gambling or compulsive overuse of DA medication, termed as Impulsive Compulsive Behaviors (ICBs) and observed in up to 17% of – prevalently early-onset – PD patients. Interestingly, the epidemiology and phenomenology of ICBs, suggest that impulsivity, a maladaptative behavior characterized by poorly conceived, prematurely expressed, unduly risky or inappropriate actions often resulting in undesirable consequences, underlined by hyperdopaminergic activity in the mesolimbic system, lies at the core of these symptoms.
At the neurobiological level, non-motor symptoms have been considered to depend upon alterations of the DA mesolimbic system, with apathy and depression suggested to result from lesion-associated decrease in DA tone, while ICBs may result from DA Replacement (especially D2/D3 DA receptors agonists-based) Therapy (DRT). However, this wisdom has been challenged by a recent experimental model we have developed. Indeed, in rats with bilateral selective lesions of either the ventral tegmental area (VTA) or the SNc, neither resulting in major motor deficits thereby facilitating an accurate measure of the respective role of the mesolimbic vs nigrostriatal systems in motivational and affective processes, we have shown that apathetic-related behaviors may stem specifically from the loss of SNc DA neurons, suggesting a strong pathophysiological implication of the DA nigrostriatal system in the occurrence of some PD non-motor symptoms, thereby representing a major public health issue.
This whole set of data is of marked interest when considered that ICBs may depend upon altered D2/D3 DA receptors function and associated plasticity within the ventral and/or the dorsal striatum respectively. The development of ICBs following chronic DRT exposure in PD may therefore reflect a determinant interaction between the disease process itself (i.e., SNc DA loss) and the neurobiological mechanisms that underlie the propensity of individuals to expressed ICBs. If this assumption is correct, it may further imply that premorbid high impulsivity trait and its associated DA phenotype (exacerbated DA activity), may be a risk factor to develop early-onset PD and associated increased vulnerability to develop ICBs.
In this context, this proposal will lead to a better physiopathological and clinical knowledge of ICBs in PD and will address four main questions: 1) Does high impulsive trait represents a risk factor to develop early-onset PD and associated ICBs? 2) Does lesion of the SNc DA neurons interact with high impulsive trait to promote ICBs? 3) Does DRT facilitate the emergence of ICBs after SNc DA lesion in rats with or without premorbid impulsivity? 4) What are the underlying cellular and molecular mechanisms?
By implementing a unique translational strategy, we will combine correlational and dimensional studies in PD patients and causal manipulations of the DA system in rats identified as high or low impulsive in association with neuroanatomical, electrophysiological and molecular approaches

Further information available at:

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