Biological Determinants of Impulsivity in Parkinsons Disease

https://neurodegenerationresearch.eu/survey/biological-determinants-of-impulsivity-in-parkinsons-disease/

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USA

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Biological Determinants of Impulsivity in Parkinsons Disease

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The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

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Research Abstract

PROJECT SUMMARY Motor symptoms in Parkinson’s disease (PD) are effectively managed by dopamine-based therapies, yet behavioral changes in patients can arise as an unintended consequence. Symptoms characterized by persistent participation in reward-driven activities

result in significant morbidity to patients and caregivers. The descriptive term for these symptoms, impulsive and compulsive behaviors, captures the aberrant, goal- directed, decision-making phenomenology typified in this clinical condition. Symptoms range from hypersexuality to compulsive eating, gambling, shopping, and excessive participation in certain hobbies. Impulsive and compulsive behaviors are more commonly manifest in patients taking dopamine agonist therapy, and behaviors can abate with reduction or discontinuation of their use. Indeed, other therapeutic interventions, including deep brain stimulation and levodopa, are associated with the genesis of maladaptive behaviors, and overall, these symptoms appear to localize to a dysfunctional, or `overdosed', mesocorticolimbic dopamine system. This proposal will characterize the biological determinants of impulsive and compulsive behaviors in PD, with specific focus on the role of dopamine agonist therapy and the mesolimbic dopamine network. We propose a series of experiments that will determine distinct functional brain changes in response to dopamine agonist use in patients with and without impulsive and compulsive behaviors. Our first aim is to identify how the cerebral hemodynamic response to dopamine agonists distinguishes patients with impulsive and compulsive behaviors. We hypothesize that these patients have an exaggerated, or increased, mesolimbic hemodynamic response to dopamine agonist therapy. Hemodynamic changes will be linked to neurocognitive assessments of reward-based decision making and risk preference, emphasizing the coherence between physiologic brain changes and the behavioral response to medication. Next, we aim to determine how dopamine therapy can differentially alter inhibitory gamma-aminobutyric acid (GABA) neurotransmission in patients susceptible to impulsive and compulsive behaviors. Finally, we will test the hypothesis that releasable dopamine stores in the mesolimbic dopamine system are greater in patients susceptible these behaviors, thus linking a biological mechanism the etiology of these maladaptive behaviors. Completion of this study will pave the way for the use of non-invasive, quantitative outcomes in PD necessary for future target validation studies and early-phase drug discovery. Also, we will provide direct evidence that dopamine therapy acts on extra-striatal neural networks, linking regional changes in neural activity to dopamine-induced alterations to GABA levels. This work will advance the field to engaging novel therapeutic targets essential to effective treatment of impulsive and compulsive behaviors. Ultimately, this work will guide the development of improved, individualized therapies, advancing the therapeutic goals of personalized medicine, which is vital for patients suffering from PD.

Lay Summary
NARRATIVE Impulsive and Compulsive Behaviors (ICB) in Parkinson's disease (PD) are characterized by maladaptive, reward-driven behaviors that occur in a subset of patients as a consequence of dopamine therapy. The work assesses the biophysical, physiological and molecular relationships determining susceptibility to medication- induced behavioral changes in PD. Completion of this study will provide the basis for a novel cognitive and imaging approach that will ultimately improve the quality and care of PD patients.

Further information available at:

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