Dr Passamonti’s research focuses on apathy and impulsivity, two severe and distressing behavioural problems in dementia and neurodegenerative disorders. These encompass the full spectrum of frontotemporal lobar degeneration (FTLD) syndromes, Alzheimer’s disease (AD) including mild cognitive impairment (MCI), and the typical and atypical Parkinsonian diseases. The harmful combination of apathy and impulsivity in these neurodegenerative conditions significantly reduces patients' and carers' quality of life and represents an important economic burden for national health systems. There is thus a pressing need to better understand the etio-pathogenesis of these behavioural problems, to facilitate the development of appropriate therapies that specifically target these neuropsychiatric symptoms.

**Research themes and objectives are:**

1. To study apathy and impulsivity in neurodegenerative disorders via disaggregating their molecular, pharmacological, neuropsychological, and brain mechanisms.
2. To provide new and effective tools for early identification and treatment of distressing behavioural problems in neurodegenerative disorders, for use in early-phase clinical trials.

To achieve these aims, Dr Passamonti employs a type of structural equation modelling (‘watershed’ model) that combines multi-dimensional data spanning different, but hierarchically organised, layers of pathogenesis. This statistical framework offers a clear model to test for the cascade of events leading to behavioural changes in neurodegenerative disorders, despite the absence of a one-to-one mapping between the neurobiological causes and the clinical phenotypes.

Dr Passamonti’s research is organized in three work-packages, linking Macro-, Meso- and Micro-scopic scales:

1. Behavioural tasks are used to assess motivation, action selection, and cognitive control in patients with FTLD syndromes, AD, MCI, and Parkinsonian disorders. Apathy and impulsivity represent important behavioural problems in these conditions; hence, Dr Passamonti employs a ‘trans-diagnostic’ approach to study these neuropsychiatric symptoms across distinct, although behaviourally related, neurodegenerative illnesses. The data from neuropsychological testing are decomposed with computational approaches, to derive the latent cognitive variables of apathy and impulsivity. Computational modelling offers a parsimonious approach to study apathy and impulsivity in neurodegenerative disorders, from which to test the efficacy of therapies restoring the monoaminergic transmission (i.e., noradrenergic, dopaminergic, and serotonergic function).

2. The psychological constructs (i.e., motivation, action selection, and cognitive control) that converge to mediate apathy and impulsivity in neurodegenerative disorders are linked to dysfunctions within distinct limbic, pre-motor, and cognitive fronto-striatal circuits. This is achieved by employing network models based on functional magnetic resonance imaging (MRI) data. Patients with neurodegenerative disorders are studied ‘at rest’ and while performing tasks that assess motivation, action selection, and cognitive control. These functional MRI studies are performed ON and OFF treatment with pharmacological agents that enhance the serotoninergic, dopaminergic, and noradrenergic transmission.

3. Dysfunctions within limbic, pre-motor, and cognitive networks are linked, within the ‘watershed’ model, to cell loss in brainstem nuclei that mediate monoaminergic transmission and brain atrophy in fronto-striatal areas. To this end, Dr Passamonti employs high-resolution structural MRI to quantify brain atrophy and the amount of neuromelanin in the substantia nigra and locus coeruleus in the brainstem.
Together, Dr Passamonti’s studies inform early-phase clinical trials by: 1) providing the necessary background for their psychopharmacology, which can exploit an improved understanding of the influence of monoaminergic deficits on apathy and impulsivity in neurodegeneration, 2) allowing new and brain-based tools to assess neuropsychiatric symptoms in a broad spectrum of neurodegenerative conditions, in which apathy and impulsivity represent a common and distressing problem.

References:


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