# Emotion and cognition in Parkinson's disease

# KNOWLEDGE VALORIZATION

The goal of this valorization paragraph is to describe how the knowledge resulting from the research in this thesis can be made valuable for clinical and societal use. This thesis focuses mainly on the etiology and neurobiological mechanisms of emotional disturbances and cognitive disorders in Parkinson's disease (PD).

### SOCIETAL RELEVANCE

Non-motor symptoms of PD are now more and more recognized as being an integral part of the disease, with a significant impact on the quality of life of patients and their caregivers and leading to greater health care expenses. This thesis focuses on a subgroup of non-motor symptoms that are particularly disabling for patients: neuropsychiatric symptoms, and emotional disturbances and cognitive disorders in particular.

Although the impact of these disorders on a patient's health status has been widely recognized, treatments are still scarce and non-optimal. As such, the search for effective treatments is still ongoing. However, in order to develop effective interventions, both pharmacological and psychotherapeutic, it is essential that we first unravel the underlying neurobiological mechanisms of neuropsychiatric disorders in PD. The research in this thesis showed that a large network of subcortical limbic areas and cortical frontal areas is involved in emotional processing and that a disbalance in this system may lead to disturbances in emotion regulation. Taking into account the complexity and diversity of the disease, pharmacological and non-pharmacological treatments should be tailored to the needs and capabilities of PD patients in order to be effective. As such, knowledge about the neurobiological correlates of emotional dysfunction as well as potential compensation mechanisms in PD may provide an important base for successful treatment, as PD patients may for instance benefit from these compensational mechanisms with respect to emotion regulation. Consequently, successful treatment will contribute to an increase in quality of life of patients and caregivers, and eventually also to a decrease in health care costs and societal burden.

For cognition, we see a large spectrum of cognitive disorders where PD patients with different cognitive phenotypes show specific cognitive deficits. By exploring the neural correlates of these cognitive phenotypes we may be able to promptly identify patients who are at risk for developing more severe cognitive decline and PD dementia. As such, more specific and patient tailored pharmacotherapy and cognitive training options can be developed and provided in

early stages of cognitive decline. Moreover, PD patients whose cognitive profile can be associated with comorbid Alzheimer's disease (AD) pathology may benefit from additional therapy directed at AD.

### TARGET AUDIENCE

The results of this thesis are relevant for various target groups who are confronted with emotional disturbances and cognitive disorders in PD and it's consequences.

The results can be particularly important for health care professionals, such as neurologists, (neuro-)psychologists, psychiatrists and other clinicians who work with PD patients suffering from these symptoms. Information about the nature, risk factors and underlying causes of neuropsychiatric disorders will aid them in recognizing symptoms and early indicators of affective and cognitive disorders. As a result, they can provide patients and their caregivers with information about specific treatment options at an early stage. Also, they may consider regular MRI scans in PD patients who start to show signs of slight cognitive decline, and inform about early pharmacotherapy and cognitive training options that can help prevent further cognitive deterioration.

Furthermore, fellow scientists and clinicians who aim to develop new interventions for neuropsychiatric symptoms in PD can use the results and recommendations made in this thesis. As stated before, the complexity and diversity of the disease requires pharmacological and non-pharmacological treatments that are tailored to the needs and capabilities of PD patients. Knowledge about the etiology and neurobiological correlates of neuropsychiatric disturbances in PD is very relevant to this respect.

Finally, results from this thesis can be valuable for researchers and clinicians who work with neurodegenerative diseases other than PD. Symptoms of anxiety, depression and apathy are for instance very common in Alzheimer's disease and other types of dementia, but also in other movement disorders such as Huntington's disease.

### PRODUCTS / INNOVATION

The research described in this thesis can be considered innovative in several ways. First, we applied an alternative approach of measuring and analyzing functional imaging data that enabled us to reveal for the first time potential compensatory activation during implicit emotional processing in PD patients. This finding can be

particularly relevant for the development of new therapeutic interventions as PD patients may benefit from these compensatory mechanisms when being treated for affective disorders.

Another innovative approach within this thesis concerned the investigation of cognitive disorders in PD as a continuum rather than using diagnostic categories. This enabled us to revealed a pattern of cerebral atrophy that could already be detected in PD patients with slowed mental speed but otherwise intact cognition. Instead of searching for signs of mild cognitive impairment, clinicians should consider mental slowing as an early “red flag” for potential further cognitive decline. Hence, they should consider closely following the course of decline in these PD patients and offering them treatment options in an early phase in order to prevent further cognitive deterioration.

In order to explore the relative contribution of PD-specific and nonspecific risk factors in a model for depression in PD, we used an advanced statistical model that also takes into account mutual correlations among factors and their influence on the outcome. Unlike previous research and theories that focus on the effect of disease-specific factors on the risk for developing depression in PD, this model showed us that it is equally important, if not more important, to take into account general risk factors for depression. This new approach may drastically change our current view on etiology, prevention and treatment options for depression in PD.

### IMPLEMENTATION

The knowledge acquired from the studies in this thesis will be used for continuation of our research into underlying neurobiological mechanisms of neuropsychiatric disorders in PD. As became apparent from this thesis, PD patients show altered emotion regulation that can be partly associated with the progressive degeneration of dopaminergic systems that is characteristic for the disease. In addition, brains of PD patients deviate in general from healthy brains due to factors like cell death and other degenerative processes. Therefore, we aim to develop more advanced methods for analyzing imaging data from PD patients that take into account the neural alterations caused by the disease. Consequently, we intend to apply these methods for exploring another area in PD that urgently needs further research: anxiety disorders. With no evidence-based treatment available at present, it is again essential to first unravel the underlying neurobiological mechanisms of anxiety in PD. To this end, we will focus on functional connectivity patterns among areas within the neural emotional

network. In addition, we aim to study structural and functional features of subregions of the amygdala, as they appear to play a central role in emotion regulation. Finally, we will use our findings for the development of a new psychotherapeutic intervention for anxiety in PD. To this end, we recently obtained a research grant from the Michael J. Fox Foundation for Parkinson's research to develop and investigate the clinical effectiveness of a specialized Cognitive Behavioural Therapy module for anxiety in PD. In addition, we will use structural and functional neuroimaging techniques to study changes in cerebral connectivity associated with successful treatment. Our main future goal is that this treatment module will be recognized and accepted as an effective non-pharmacological intervention for the treatment of anxiety symptoms in PD patients, and that it will find its way into widespread clinical use.

We further intend to follow-up the PD patients with different cognitive profiles in order to longitudinally explore the extent to which neural substrates associated with early markers of cognitive impairment (e.g., slowed mental speed) can be used as a predictor of severe cognitive decline and conceivable conversion to dementia in PD. Ultimately, this may open the door to early identification of PD patients who are at risk of severe cognitive decline or conversion to dementia and offers better treatment opportunities that can eventually delay the onset of dementia in these patients.