Monitoring and modulating neuropsychiatric symptoms

Knowledge valorisation

This first part of this thesis focused on Deep brain stimulation (DBS) studies in obsessive-compulsive disorder (OCD) and Parkinson's disease (PD) in order to study underlying mechanisms of neuropsychiatric symptoms. The second part of this thesis focused on mood symptoms in PD by exploring the usability of the experience sampling method (ESM) in PD patients, and by developing a treatment programme for anxiety in PD patients. This valorisation paragraph describes how the obtained knowledge from the research in this thesis can be made valuable for clinical and societal use.

Societal relevance

Neuropsychiatric symptoms include a broad range of psychiatric symptoms that are believed to be mediated by changes in brain functions. Certain conditions that were once considered to be manifestations of psychodynamic conflict are now considered neuropsychiatric disorders, such as OCD. Moreover, it is increasingly recognised that neuropsychiatric symptoms, such as anxiety and a depressive mood, are an integral part of PD, the second most common neurodegenerative disorder.

Neuropsychiatric symptoms have a large impact on health-related quality of life, which reflects the impact of a disease or symptoms on several aspects of a patient's life, including their physical, mental and social well-being. Moreover, according to the World Health Organization (WHO), neuropsychiatric disorders are the third leading cause of disability-adjusted life years (DALYs). According to the National Institute of Mental Health, DALY is a measure of overall disease burden, expressed as the total number of years lost to illness, disability, or premature death within a given population. This high disease burden of neuropsychiatric symptoms has a considerable impact on the global economic burden. In PD, for example, neuropsychiatric symptoms complicate treatment and require additional and complex interventions.

Despite the impact of neuropsychiatric symptoms on the health status of patients and global health care costs, treatments specifically developed and validated for neuropsychiatric symptoms are still scarce. This is partly because underlying mechanisms of neuropsychiatric symptoms are largely unknown. The findings reported in this thesis improve our understanding of underlying mechanisms of neuropsychiatric symptoms in PD and OCD, which is crucial in order to adapt and tailor treatment. Moreover, new methods and interventions have been introduced to improve care for

patients. Improved care will in turn contribute to an increase in quality of life of patients, and eventually to a decrease in health care costs and societal burden.

Target audience

Our findings are relevant for OCD and PD patients, clinicians, psychologists, health insurance companies and researchers.

The findings from the DBS studies (chapter 2 to 5) are relevant for patients, since the findings might improve the surgical procedure, and subsequently improve treatment outcome. Knowledge of the neural substrates underlying obsessive and compulsive symptoms (chapter 2), as well as observed side-effects following DBS of a specific target, the STN, (chapter 3) might help clinicians to achieve maximal therapeutic effect. The same holds for DBS for PD. Studying underlying mechanisms (chapter 4) and potential risk factors (chapter 5) of emotional and cognitive side-effects following DBS might be helpful for patient selection and improving the surgical procedure. In chapter 5 we show that neurosurgeons do not have to feel restrained by fear of cognitive side-effects when using multiple MERs in order to attempt to have more possibilities for postoperative stimulation settings.

The findings from the ESM studies (chapter 6 and 7) are relevant for PD patients and their health care team, as ESM has to potential to improve care. Due to the unpredictable fluctuating nature of both motor and mood symptoms in PD, it is challenging to capture and study their association, and adjust treatment accordingly. In chapter 7 we showed that ESM allows to study associations between affective state, motor symptoms and contextual factors on a group level in PD. Findings on a group level may lead to more general treatment recommendations. Moreover, we showed that on an individual level ESM can be used to visualise and monitor symptom change over the course of the day. In chapter 6 we showed that ESM data collected over a longer period of time can be used to generate symptom networks displaying prospective associations between mood and motor symptoms. The information collected by ESM can lead to an increased awareness and understanding in patients and clinicians regarding particular circumstances in which symptoms occur or are perceived as more disabling. This might benefit collaborative decision making between the patient and clinician, help personalising treatment and give the patient a ‘sense of

control'. Our findings could also be of interest to insurance companies and policy makers, given that ESM has proven potential as an E-health tool for PD patients.

Finally, results from the CBT studies are valuable for PD patients who suffer from anxiety, psychologists working with these patients, health insurance companies and researchers. The CBT treatment, if proven effective, will hopefully provide PD patients with behavioural and anxiety management techniques that may give lasting benefits on anxiety symptoms, well-being, quality of life, and possibly on motor symptoms. The findings from the focus group interviews are particularly relevant for psychologists working with PD patients, as it provides insight into the specific needs of PD patients and potential barriers of undergoing therapy. Psychologists might tailor their method based on these findings. Moreover, the paper provides a detailed description of the CBT programme that was developed for PD patients suffering from anxiety, including factors that may complicate treatment, as well as ways how to deal with these during therapy. On top of that, the workbook and manual for therapists are available upon request in three different languages and we aim to develop a website to distribute our manual, so we hope that PD patients around the world benefit from the therapy. While the paper discussing the effectiveness of the intervention is currently in preparation, the findings are relevant for health insurance companies, as most health insurance companies apply evidence-based approaches to coverage decisions. Finally, the protocol describing the methodology of the study (chapter 8) might be relevant for researchers by facilitating the development of similar trials studying the effect of psychotherapeutic interventions for different target groups.

Products/innovation

The research described in this thesis can be considered innovative in several ways. First of all, we were the first to report severe and persistent motor side-effects following STN-DBS in an OCD patient. Reporting these side-effects are of crucial importance, as it might guide neurosurgeons in target selection.

Another innovative approach within this thesis concerned the usability of ESM in PD patients. The ESM method originated in psychiatry, and has recently been applied in a number of other diseases, such as migraine, stroke and COPD. In this thesis, we demonstrated that ESM is useful to study associations between motor and mood

symptoms, and contextual factors on a group and individual level in PD. Moreover, we were the first to study prospective associations between motor and mood symptoms in PD in an n=1 design. The findings demonstrate how recall bias can be prevented and they bring us one step closer to personalise treatment to the individual patient.

Despite its high prevalence, there is currently no evidence-based treatment available for anxiety in PD. Psychotherapeutic interventions that are available have not been studied in a controlled design or only in small sample sizes. The primary focus of our study was to assess the clinical effectiveness of a specialised CBT programme for anxiety in PD and possible changes in cerebral connectivity (chapter 8). The development of the CBT programme was based on literature, existing CBT modules and focus group interviews with patients, in order to tailor the programme to better serve their specific needs, concerns and circumstances (chapter 9). This study is the first in its kind to test both CBT effectiveness in a controlled trial and to record possible structural and functional brain changes induced by CBT, which may lead to an increased understanding of the underlying neurobiological mechanisms of both anxiety and response to treatment in PD patients.

Implementation

The knowledge acquired from the studies in this thesis will be implemented in health care practice on one hand, and used for continuation of research on the other hand. The findings from the OCD studies contributed to a shift in target selection for DBS in our hospital from the STN to the ventral capsule/ventral striatum. Moreover, a database has been created for all OCD patients who received DBS in our hospital, in order to collect data regarding target location, active electrodes, symptom improvement, side-effects, medication, etc. This dataset is now used for research purposes with the aim to uncover best practices and improve outcome. The findings from the studies regarding the cognitive side-effects following STN-DBS in PD resulted in the continuation of the use of microelectrode recording as a way of optimising lead implantation. Moreover, we continue to collect data from PD patients who received STN-DBS in order to increase our sample size and apply advanced statistical methods and machine learning algorithms to discover underlying mechanisms of side-effects and clinical outcome.

The application of ESM in the field of PD care is still in its infancy. This thesis provides a valuable contribution to our knowledge of the usability of ESM for research purposes and health care practice in PD. ESM can be used to capture the fluctuating nature of motor and mood symptoms in PD and to study their association in relation to contextual factors. Moreover, revealing population based patterns via ESM may lead to more general treatment recommendations, while individual analyses of ESM data can be used to establish a personalised treatment plan. However, we also found that the sensitivity of the method needs to be improved for further implementation, for which we have made several recommendations. In the future, ESM data may potentially serve as a parallel ground truth to objective data, such as obtained by monitoring motor symptoms by wearable sensors, since these alone may not be representative for the experienced disability. In addition, combining objective and subjective data on motor and non-motor symptoms can potentially be used as input signal for adaptive DBS. Adaptive DBS aims to automatically adapt stimulation parameters to the fluctuating clinical state of the patient, where stimulation is only provided when necessary. The idea is that adaptive DBS results in fewer stimulation-induced side-effects compared to conventional DBS.

The CBT programme aimed at treating anxiety in PD is currently in use in our hospital. To disseminate our findings among health care professionals we gave presentations and workshops at conferences. Moreover, we presented our programme at several Parkinson café’s in the region in order to create awareness regarding anxiety and its treatment among PD patients and health care professionals. The CBT programme, including the workbook and manual for therapists, is available in three different languages so we hope it will find its way into widespread clinical use. We are currently finalising our paper regarding the clinical effectiveness of the programme. Meanwhile, we are studying the cost-effectiveness of the treatment, as well as changes in cerebral connectivity associated with successful treatment in order to unravel the underlying neurobiological mechanisms of anxiety in PD.