Final report

SNN125143: Impulse control disorders in Parkinson's disease: epidemiology, biomarkers, risk factors and treatment possibilities

With the financial support of the SNN125143 project, we have published 28 articles with a cumulative impact factor of 105.9. Of these articles, 7 were graded as D1, 10 as Q1 and three as Q2.

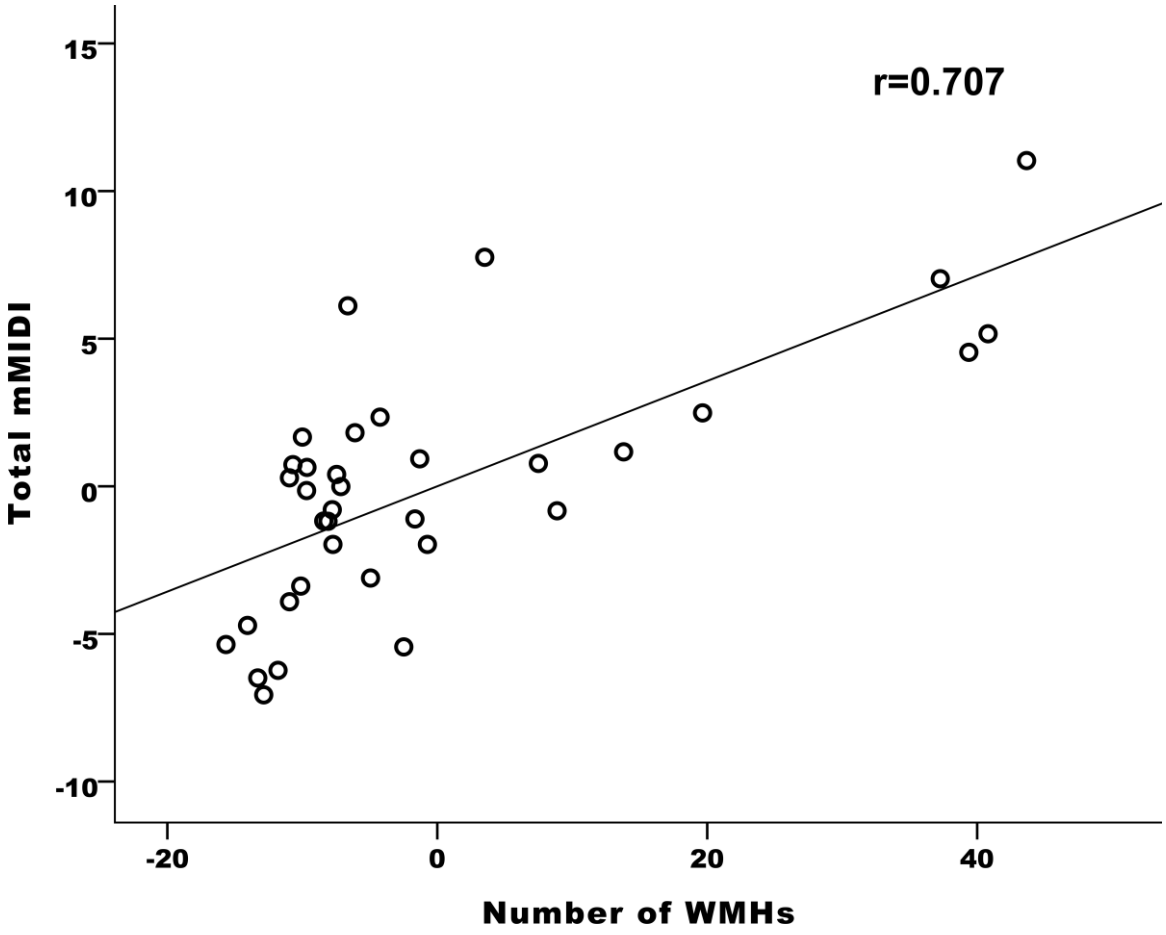
Briefly, we screened 1000 Parkinson's disease (PD) patients for impulse control disorders (ICDs) and performed detailed neuropsychological testing. Meanwhile, in order to evaluate MRI-based risk factors, we performed high-resolution MRI scans on these ICD cases.

Our main results are the following in relation to the original project plan:

1. 1. We first showed that screening for problematic Internet use may help identify impulse control disorders in Parkinson's disease. Impulsive control disorders in Parkinson's disease (PD) are emerging problems with potentially devastating consequences. Standard methods used to screen for these disorders are clinically imperfect. Although rarely reported, many patients use the Internet to engage in compulsive behaviors. The Internet is easily accessible. We designed a study to test the hypothesis that active screening for excessive Internet use and addiction might improve the sensitivity of identifying impulse control disorders. The standard screening method included the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease and the modified Minnesota Impulsive Disorders Interview. In the second round, the Problematic Internet Use Questionnaire was also assessed to detect excessive Internet use. Our results suggest that screening for problematic Internet use with the Problematic Internet Use Questionnaire is an effective, feasible, and easy-to-use adjunctive method for identifying patients with Parkinson's disease with impulse control disorders more efficiently and probably at an earlier stage.(BEHAVIORAL NEUROLOGY 2019: 4925015, IF: 2,093, Q2 prestige)
2. For the identification of risk factors for ICD we also investigated healthy volunteers and smokers. We published these results in the JOURNAL OF BEHAVIORAL ADDICTIONS 8: (1) pp. 35-47, 2019 (IF=5,143, D1 prestige).
3. We have published a study on the identification of highly reliable and representative MRI patterns for addiction in non-Parkinsonian subjects. (JOURNAL OF BEHAVIORAL ADDICTIONS 8: (1) pp. 162-168., 2019, IF=5,143, D1 prestige, and SCIENTIFIC REPORTS 9: (1) 15777, 2019, IF 3,998, D1 prestige), Subsequently, this approach has been used as a pilot approach for comparison of brain MRI patterns in ICD patients with PD.

4. In an international collaborative study, we assessed the health-related quality of life (HRQoL) in Parkinson's disease in 3600 patients. Our study was the first large-scale study of the determinants of HRQL in an international sample. Notably, our team contributed 500 cases to the total sample. We were the largest contributor. These data suggest that ICD, as determined by the MDS-UPDRS scale, is a predictor of a lower HRQoL.
   (PARKINSONISM AND RELATED DISORDERS 52 pp. 83-89., 2018, IF 4,360, Q1 prestige).
5. Impulse control disorders (ICDs) in Parkinson's disease (PD) are increasingly being recognized as a clinically significant non-motor feature of PD that has the potential to affect quality of life. Magnetic resonance imaging (MRI)-detected white matter hyperintensities (WMHs) are common in PD and may be associated with both motor and certain non-motor symptoms. Given the limited number of non-motor features that have been studied in this context, our aim was to determine the potential association between the severity of WMHs and the severity of ICDs in Parkinson's disease. Data for this study were collected from Parkinson's disease patients treated at the University of Pécs. The patients underwent detailed neuropsychiatric assessment and high-resolution MRI1 as part of a comprehensive evaluation. All patients fulfilled the diagnostic criteria of the UK PD Society Brain Bank. They had no significant cognitive impairment or psychiatric problems. Of the 83 patients in this group, 13 were excluded before further analysis due to

conflicting ICD data (n=1), left handedness (n=1), insufficient imaging data (n=1) and suspected radiologically isolated syndrome (n=1): Radiologically isolated syndrome (n=1), presence of cortical, basal ganglia or pons lesions (n=5), cavernoma (n=1), developmental venous anomaly (n=2), marked skull thickening in combination with olfactory meningioma (n=1). The final sample included 70 subjects (48 male; mean age: 59.3 ± 10.1, range: 38-79 years). Supratentorial WMHs were also assessed by manual segmentation on the coronal FLAIR images using the 3D Slicer (4.10.2 r28257). Total volume and number of supratentorial WMHs were extracted for each subject using the fslstats tool in FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Fslutils). Fazekas scores and volume and number of supratentorial WMHs were also used to assess WMH severity. The modified Minnesota Impulsive Disorders Interview was used to evaluate ICDs. There was a significant interaction between age and severity of WMHs for ICDs. In our younger patients (<60.5 years), severity of WMHs was positively associated with ICDs (p=0.004, p=0.021, p<0.001, and p<0.001, respectively, for periventricular white matter and total Fazekas scores and for volume and number of WMHs). Our study supports the hypothesis that WMHs of presumed vascular origin may contribute to ICDs in PD. Our pilot study supports the hypothesis that WMHs of presumed vascular origin may be independently associated with the severity of ICDs in younger patients with PD, providing further evidence that ICDs are not a simple side effect of dopamine agonist therapy. Early detection of ICDs in Parkinson's disease may be particularly important because in many cases, ICDs are not clinically recognized until they have had a serious impact on patients' daily lives (especially on their personal, financial, or social status). Our results have the potential to improve early detection of ICDs in PD.



6. Our team evaluated the detectability of an early Parkinson's biomarker. The absence of nigral hyperintensity is a promising MR marker for Parkinson's disease, but the small size of this marker imposes limitations on its routine use. We compared MEDIC, segmented echo-planar (EPISEG), and fluid-attenuated inversion recovery (FLAIR) sequences, and MAG and susceptibility-weighted imaging (SWI) reconstructions of gradient-echo sequences for nigral hyperintensity imaging. Twenty-five healthy volunteers and twenty PD volunteers participated. The sensitivity to motion artifacts, the confidence of the radiologist in the interpretation, the rate of non-diagnostic scans, and the diagnostic accuracy were evaluated. EPISEG was less sensitive to motion artifacts than MEDIC, MAG, and SWI, whereas FLAIR was less sensitive to motion artifacts than MAG and SWI. The examiners were more confident with the use of EPISEG than with any of the other techniques,

and MEDIC was superior to FLAIR. The percentage of non-diagnostic scans was lower for EPISEG than for other sequences. The best diagnostic performance was achieved with EPISEG (sensitivity = 65 %, specificity = 96 %). Using EPISEG, the absence of nigral hyperintensity in Parkinson's disease was associated with a higher Hoehn-Yahr stage and a higher MDS-UPDRS II + III stage. Hyperintensity may be intact in the very early stages of Parkinson's disease. The promising properties of EPISEG may help to translate nigral hyperintensity imaging into daily clinical practice.
SCIENTIFIC REPORTS 11: (1) 1179, 2021, IF: 4.379, Q1 Prestige

7. As planned, 1000 patients with Parkinson's disease (612 men, mean age 64.2 years) were screened for impulse control disorders. In detailed neuropsychological examinations, we found symptoms of impulsive behavior in 376 cases. However, the psychiatric diagnosis of impulse control disorder, based on DSM-5 criteria, was confirmed in only 102 cases (either pre-existing or current impulse control disorder, lifetime prevalence: 10.2%). A small proportion of ICD patients (n=29) had symptoms of only one type of disorder (compulsive and uncontrollable eating 8, shopping compulsions 5, compulsive gambling 8, compulsive sexuality 4 and excessive use of dopaminergic medication 4), while the majority of patients had two (n=52) or more than two (n=21) explored compulsive behaviors. Our clinical results confirm that impulsivity is observed in a significant proportion (37.6%) of patients with PD, but only in about 10% of them a diagnosis of ICD can be made. Our study is the first large-scale cohort study to assess the lifetime prevalence of ICD patients in the East-Central European PD population.

Other results helped by the SNN125143 research funding:

8. Our team was the first who demonstrated clinimetrically that composite scores based on the Movement Disorders Society Sponsored Unified Parkinsons's Disease Rating Scale (MDS-UPDRS) are feasible. Since the publication of the Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale (MDS-UPDRS), numerous studies have utilized it as an either primary or secondary outcome in clinical trials. This comprehensive scale is composed of four different sections, Parts I and II: Non-Motor and Motor Experiences of Daily Living, Part III: Motor Examination, and Part IV: Motor Complications. Extensive clinimetric evaluations revealed that the factor structure of the MDS-UPDRS was most parsimonious and valid when the individual Parts were considered as assessing independent domains. Consequently, the inventors of the scale unambiguously declared that each part of the MDS-UPDRS should be interpreted individually and the development of composite or total scores is not advised. however, in clinical practice, the composite scores (e.g. total score) are frequently used as either primary or secondary output measures. In the present study, we evaluated the feasibility of the commonly utilized composite scores as possible outcome variables and subsequently determined their Minimal Clinically Important Difference (MCID) threshold values.
(MOVEMENT DISORDERS 33: 5 pp. 835-839., 2018, IF 8,22, D1 prestige)
9. Our team was the first to determine the minimal clinically important difference for the historic parts of the Unified Dyskinesia Rating Scale. Motor complications represent an important clinical problem in the treatment of Parkinson's disease (PD). The Motor Complications Part of the Movement Disorder Society-sponsored Unified Parkinson's Disease Rating Scale (MDS-UPDRS Part IV) and the Unified Dyskinesia Rating Scale (UDysRS) are among the most reliable instruments to evaluate these problems. The minimal clinically important difference thresholds are the smallest changes in the outcome measures that are clinically meaningful. Our study aimed to calculate the minimal clinically important difference thresholds for the MDS-UPDRS Part IV and the historic parts of the UDysRS.
(PARKINSONISM AND RELATED DISORDERS 58: pp. 79-82., 2019, IF 4,360, Q1 prestige)
10. Our team was the first who determined the minimal clinically important difference threshold values for tremors. These estimates are highly important for judging the clinical relevance of various treatment options.
MOVEMENT DISORDERS 34: (5) pp. 759-760., 2019, IF 8,697, D1 prestige)
11. Our team was the first who determined the minimal clinically important difference threshold values for dystonia. These estimates are highly important for judging the clinical relevance of various treatment options.
MOVEMENT DISORDERS 35: (7) pp. 1218-1223., 2020, IF 10,338, D1 prestige)

12. Our team was the first to clinimetrically compare the clinical usability of different tremor scales. These data are highly important for planning clinical trials.
    JOURNAL OF PARKINSONS DISEASE 10: (1) pp. 275-282., 2020, IF 5,568, D1 prestige)
13. Our team determined the impact of trimetazidine on the severity of symptoms and the health-related quality of life of patients with PD. A consecutive series of 42 patients with PD using trimetazidine underwent detailed neurological and neuropsychological assessments at baseline and three months after the discontinuation of trimetazidine. Clinically relevant improvements were achieved with discontinuation of trimetazidine. Discontinuation of trimetazidin results in clinically relevant improvements in Parkinsonian symptoms.
    SCIENTIFIC REPORTS 10: (1) 10050, 2020, IF: 4.379, Q1 Prestige
14. Trimetazidine (TMZ), an antianginal drug, can worsen the symptoms of movement disorders, therefore, the European Medicines Agency (EMA) recommended avoiding the use of this drug in PD. We investigated the impact of this recommendation on the observed trend of TMZ use in PD in Hungary from 2010 to 2016 by conducting a nationwide, retrospective study of health administrative data of human subjects. Interrupted time series analyses were performed to explore changes in user trends after the EMA recommendations. We found that TMZ use in PD decreased by 6.56% in each six-month interval after the EMA intervention. TMZ discontinuation was the highest immediately after the intervention, however, its rate slowed down subsequently. The rate of new TMZ prescriptions did not reduce significantly, therefore, the decreased overall use was mainly attributable to the increased rate of discontinuation only. The main indications for TMZ use were circulatory system disorders, especially angina pectoris, however, off-label utilization was also considerable (40%). The EMA recommendations on TMZ use seem to be only moderately effective in Hungary.
    ENEURO 8: (3) ENEURO.0452-20.2021, 2021, IF: 4,081, Prestige Q1
15. Our team has also shown that intensive long-term physical activity can improve the symptoms of Parkinson's disease and may slow the disease progression.
    MEDICINE AND SCIENCE IN SPORTS AND EXERCISE 51: (2) pp. 237-245., 2019, IF 4.029, D1 prestige)
16. Our team was the first to study the discriminative capabilities of the Addenbrooke Cognitive Examination version III for detecting mild and major neurocognitive disorders in PD. Parkinson's disease (PD) is the second most common neurodegenerative disorder characterized by numerous motor and non-motor symptoms. Neurocognitive disorders (NCD) are one of the most troublesome problems and their diagnosis is often challenging. We compared the sensitivity and specificity of several versions of Addenbrooke Cognitive Examination (ACE-I, ACE-III, Mini-ACE) on 552 subjects with PD.
    (BEHAVIOURAL NEUROLOGY 2018 p. 5932028 Paper: 5932028 , 9 p. 2018, IF: 1,908, Q2 prestige)
17. Our team was the first who demonstrated that the newly developed Parkinson's Disease Composite Scale is clinically useful for detecting changes associated with levodopa treatment.
    PARKINSONS DISEASE 2019: 1412984, 2019, IF 1,758, Q2 prestige)
18. The ^{123}I-FP-CIT dopamine transporter SPECT imaging is a sensitive method to assess functional dopaminergic neuron terminals in the striatum. The method has also been available in Hungary for years. There are two main indications: (i) to help differentiate essential tremor from clinically uncertain Parkinsonism, including patients with early symptoms, and (ii) to help differentiate dementia with Lewy bodies from Alzheimer's disease. This paper aims to review ^{123}I-FP-CIT SPECT imaging based on international data/guidelines and our own experiences, thereby assisting nuclear medicine practitioners and neurologists.
    IDEGGYOGYASZATI SZEMLE / CLINICAL NEUROSCIENCE 72: (11-12) pp. 381-388., 2019, IF 0,337)
19. Our team was the first who proposed and clinically confirmed that the 123I-FP-CIT dopamine transporter SPECT imaging can reliably differentiate Parkinson's disease from trimetazidine-induced parkinsonism.
    PARKINSONISM AND RELATED DISORDERS 62: pp. 117-121., 2019, IF 3,926, Q1 prestige)
20. We compared the precision of the 1.5 Tesla and 3.0 Tesla MRI imaging for targeting subthalamic nuclei during stereotactic surgeries. Deep brain stimulation (DBS) involves placing electrodes within specific deep brain nuclei. For movement disorders, the most common indications are tremors, Parkinson's disease, and dystonias
    IDEGGYOGYASZATI SZEMLE / CLINICAL NEUROSCIENCE 2018;71(11–12):405–410, IF: 0,113.
21. COVID-19 has made providing in-person care difficult. In most countries, including Hungary, telemedicine has partly served as a resolution for this issue. To explore the effects of COVID-19 on neurological care, the

knowledge of neurology specialists on telemedicine, and the present state of telecare in Hungary, with a special focus on Parkinson's disease. Between July and October 2021, a nationwide online survey was conducted among actively practicing Hungarian neurology specialists who were managing patients with Parkinson's disease. A total of 104 neurologists were surveyed. All levels of care were evaluated in both publicly funded and private healthcare. Both time weekly spent on outpatient specialty consultation and the number of patients with Parkinson's disease seen weekly significantly decreased in public healthcare, while remained almost unchanged in private care ($p<0.001$). Higher portion of patients were able to receive in-person care in private care (78.8% vs. 90.8%, $p<0.001$). In telecare, prescribing medicines has already been performed by the most (n=103, 99%). Electronic messages were the most widely known telemedicine tools (n=98, 94.2%), while phone call has already been used by most neurologists (n=95, 91.3%). Video-based consultation has been more widely used in private care (30.1% vs. 15.5%, $p=0.001$). Teleprocedures were considered most suitable for monitoring progression and symptoms of Parkinson's disease and evaluating the need for adjustments to antiparkinsonian pharmacotherapy. COVID-19 has had a major impact on the care of patients with Parkinson's disease in Hungary. Telemedicine has mitigated these detrimental effects; however, further developments could make it an even more reliable component of care. IDEGGYOGYASZATI SZEMLE / CLINICAL NEUROSCIENCE 75: (7-8) pp. 265-273., 2022, IF: 0,708.

22. Directional deep brain stimulation, which can reduce the side effects of treatment, has been developed in recent years. Several pilot studies have shown that the directional stimulation can provide a wider therapeutic window and a lower therapeutic current strength as compared to the omnidirectional stimulation.
23. To test the hypothesis that directional stimulation may be associated with a greater reduction in total daily antiparkinsonian medication (ApMed) compared to omnidirectional stimulation, we conducted a single-center, open-label, prospective, registry-based, comparative study. Fifty-two patients who received directional stimulation and fifty-seven subjects who received omnidirectional bilateral subthalamic deep brain stimulation (STN-DBS) were enrolled in the study. Preoperatively and 12 months postoperatively, the dose of different ApMed, the number of tablets used daily, the severity of motor and non-motor symptoms using the MDS-UPDRS, and the health-related quality of life (HRQoL) using the 39-item Parkinson's Disease Questionnaire (PDQ-39) were assessed. In terms of changes in levodopa equivalent daily dose, directional STN DBS resulted in a 13% greater reduction in total daily dose of ApMed. The main contributor to this difference was the 10.3% greater reduction in levodopa dose. The number of different types of ApMed was also reduced to a greater extent with directional stimulation. The improvement in the severity of motor and non-motor symptoms was comparable, but we found a 15.8% greater improvement in global HRQoL in patients with directional stimulation according to changes in the summary index of the PDQ-39. Based on our data, directional programming can further increase the reduction in the total daily dose of ApMed after STN-DBS. In addition, directional stimulation may have additional beneficial effects on global HRQoL. NEUROMODULATION, 2023, IF 3.025