W-86
The Impact of Non-Motor Symptoms on Diagnostic Delay in Parkinson's Disease

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Background: Parkinson's disease (PD) is characterized by a wide range of motor and non-motor symptoms. Broader biological definitions of PD are discussed and receive increasing attention, going beyond the current motor-centered PD definition. The heterogeneity of non-motor PD symptoms poses a challenge for early and accurate diagnosis of PD.
Objectives: The main objective of this study is to evaluate systematically whether non-motor symptoms affect the timing of PD diagnosis. This is accomplished by modeling disease progression in large-scale longitudinal data.
Question: The project aims to determine whether specific non-motor symptoms of people with PD systematically delay or hasten the diagnosis compared to the typical time point of PD diagnosis.
Methods: This study utilized data from three large PD cohorts and analyzed it through a latent time joint mixed-effects model (LTJMM). This approach allows an alignment of disease trajectories of individual people with PD on a common disease time scale, and subsequently the determination of whether diagnoses were made earlier or later than the cohort's average diagnosis time. Initial clinical symptoms at the typical diagnosis time were estimated using several mixed-effects models, depending on the scales of the outcomes. Non-motor scores were grouped into 12 distinct non-motor domains and pooled estimates were calculated across all three cohorts using three-level meta-analyses with random effects. P-values were corrected for multiple testing using Benjamini-Hochberg procedure.
Results: The analysis included 1,124 individuals diagnosed with PD. Several non-motor symptoms were found to contribute to a diagnosis later than the average: anxiety (p=0.0043), autonomic dysfunction (p=0.0019), depression (p=0.0004), fatigue (p=0.012), pain (p=0.0085), sleep disturbances (p=0.0043), and a higher overall burden of non-motor symptoms (p=0.0006, Fig. 1). In contrast, impulsivity (p=0.12), REM sleep behavior disorder (p=0.28), apathy (p=0.32), hyposmia (p=0.79), and hallucinations (p=0.09) did not impact diagnostic delay.

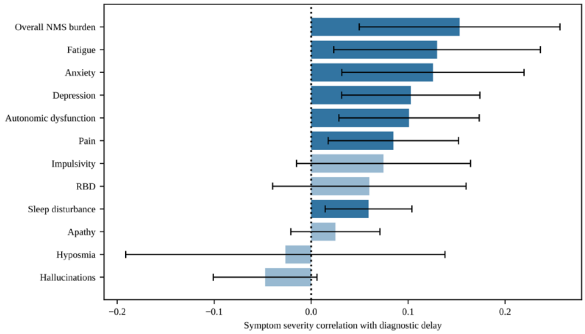

Figure 1: Association of non-motor symptoms with diagnostic delay. Pooled estimates from the three cohorts are shown. Abbreviations: RBD: REM sleep behavior disorder.

Conclusions: Through statistical modeling of initial clinical presentations of people with PD and a model-based estimation of diagnostic delay, the study successfully identified several non-motor symptoms that impact the timing of PD diagnosis without requiring direct clinical observations at the point of typical diagnosis. These findings support a biological conceptualization of PD that considers early non-motor symptoms, highlighting the need for diagnostic criteria that reflect the whole disease's heterogeneity.

W-92
Transcranial magnetic stimulation and new generation deep brain stimulation devices – a combined ex vivo and computational study

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Background: Given the potential of applying transcranial magnetic stimulation (TMS) in patients implanted with deep brain stimulation (DBS) for studying corticospinal and intracortical excitability, there is an increased need for assessing the safety of this combination.
Objectives: We aimed to assess the electromagnetic interactions between TMS and DBS systems in various DBS lead configurations and TMS coil positions.
Question: Does applying TMS on DBS patients induce currents in the lead that might exceed the manufacturer's safety limits, thereby posing a risk to patient safety?
Methods: We applied a combined *ex vivo* and *in silico* approach to investigate the safety of combining TMS with one of the most common DBS systems, namely Boston Scientific segmented electrodes. For the *ex vivo* approach, TMS pulses were delivered over the DBS electrode and lead extension using a Magstim 200 magnetic stimulator with a 70mm figure-of-eight-coil, and an intensity of 100% maximum stimulator output (MSO). TMS-induced currents in the DBS lead were measured during alternating lead configuration (forming no loops, one loop, two loops) and different positions of the TMS coil (with the coil's center directly over the central point of the DBS lead loop, off-center to the right, and off-center to the left). The TMS-DBS scenario with the highest risk (highest induced current) was chosen for a follow-up *in silico* simulation with similar experimental parameters performed on a personalized head model of a DBS patient using the SIM4Life software.[1]
Integrating electromagnetic properties of all head tissues as well as TMS/DBS, we employed a magneto-static vector potential solver to simulate the electromagnetic interactions between the TMS coil and DBS leads (focusing on loops), followed by a magneto quasi-static approach to analyse the dynamically induced current in the DBS loops within a realistic framework and a multi-tissued head model. Detailed profiles of the lead's electromagnetic exposure along with distributions of TMS-induced currents within and outside the loops were acquired and analysed.
Results: In the *ex vivo* experiments, TMS-induced currents in DBS leads exhibited a range from 16 to 165 mA, influenced by variations in TMS coil positioning and the number of lead extension loops. Notably, the maximum current was observed in the scenario where the TMS coil was placed off-center and DBS lead formed two loops. By simulating this specific setup in a personalized head model with anatomical and topographical details, the induced current peaked at 11.46 mA in the DBS loops, approaching the safety threshold of 12 mA specified by the manufacturer.