

ADIS

Early Diagnosis of Alzheimer's Disease by Immune Profiling of Cytotoxic Lymphocytes and Recording of Sleep Disturbances

Poster number: 20

Poster presenter: Sophia Krix

Aims, research questions and working hypothesis

Sleep-awake alterations, such as nighttime awakenings, nocturnal wandering, and excessive daytime sleepiness, are common symptoms in Alzheimer's Disease (AD), which might happen early in the disease course and are associated with more rapid decline and caregiver burden. The early degeneration of the arousal system, specially affecting the brainstem nucleus locus coeruleus, leads to dysregulation of the noradrenergic system. The depletion of noradrenaline, a neurotransmitter with neuroprotective effects, mediates both sleep-wake dysregulation and neuroinflammatory pathways contributing to disease progression. Furthermore, sleep disturbances themselves increase systemic inflammation. Inflammation is a well-known driver of AD pathogenesis and thus understanding of mechanisms linking cognitive impairment, sleep disturbances and inflammation could facilitate earlier diagnosis of the disease. In this regard, aims of ADIS include a) to explore the potential of digital sleep monitoring for early diagnosis, b) to investigate the correlation between digitally assessed sleep perturbances and immune biomarkers, and c) to explore new blood-based candidate biomarkers based on insights of the role of peripheral cytotoxic lymphocytes in AD.

Means/methods implemented by the consortium

A remote actigraphy device (Motionwatch 8) was used for sleep monitoring of individuals with mild cognitive impairment (n=25) and mild dementia (n=25) due to Alzheimer's and healthy controls (n=25) for 10 days. Raw actigraphy data as well as aggregated sleep features were analysed with machine learning methods (Random Forest, XGBoost, Logistic Regression, LSTM) for predicting the diagnostic status of the individuals. Model predictions were investigated with post-hoc explainability methods (Integrated Gradients, SHAP values) to identify the most important sleep phases and sleep measures. We compared the sleep-monitoring device to traditional sleep questionnaires (PSQI, ESS) to test the benefit of digital sleep monitoring.

What are the outcomes of the project?

We evaluated a sleep-monitoring device for the detection of cognitive impairment at early and progressed stages of the disease. Our results show that machine learning models based on actigraphy data with additional demographic information can identify patients with mild cognitive impairment equally well as traditional sleep questionnaires, and outperform when comparing healthy controls with individuals at a prodromal stage.

Significance and impact of the work on the field

A passive sleep-monitoring device offers a low-cost, scalable, easily accessible and non-invasive solution, which is applicable at home. Such technologies could support general practitioners to decide, which people should preferably be referred to a neurologist for more precise (differential) diagnosis.

Next steps and future challenges

We will analyze the correlation of immune biomarkers with the predicted probability of a cognitive impairment. Moreover and in a separate workstream, we will investigate single cell RNA sequencing data derived from peripheral blood mononuclear cells regarding the potential to detect the disease in an early stage. Main challenges include the delayed delivery of data due to delays in the lab experiments.

CONTROL-PD

Control estimation modulated by subjective medication status in Parkinson's disease

Poster number: 21

Poster presenter: Filip Grill

Aims, research questions and working hypothesis

Depression is highly prevalent in Parkinson's disease (PD), suggesting that the dopaminergic deficits characteristic of PD extend beyond motor dysfunction and also impact psychiatric symptoms. A growing body of research points to aberrant dopamine signaling as a factor impairing the ability to learn statistical regularities in the environment. Building on this, we hypothesize that dopamine plays a crucial role in estimating the controllability of the environment, a key environmental statistic fundamental to the learned helplessness model of depression. The primary research question concerns whether dopamine signaling affect the estimation of environmental controllability in individuals with PD.

Means/methods implemented by the consortium

To investigate this, we conducted an online study with 90 individuals diagnosed with PD, all of whom performed a task designed to assess their ability to estimate the controllability of their environment. Prior to completing the task, participants were asked to self-report how medicated they felt on their dopaminergic treatment, providing an index of their current dopaminergic state. Data was collected and analyzed to assess interactions between environmental controllability and dopamine signaling.

What are the outcomes of the project?

Preliminary analyses suggest an interaction between perceived controllability of the environment and dopaminergic function. Specifically, participants demonstrated differences in performance depending on the objective controllability of the task environment, with dopamine levels appearing to modulate this relationship such that overmedicated patients are better at estimating the environment as controllable when the environment *is* controllable. These findings suggest a potential link between dopamine and the estimation of control in PD.

Significance and impact of the work on the field

This work has significant implications for understanding the broader role of dopamine in cognitive processes beyond motor control, particularly in how individuals with PD perceive and interact with their environment. The results may offer insights into the mechanisms underlying psychiatric symptoms like depression in PD and provide a potential avenue for refining therapeutic approaches that target not just motor symptoms but also cognitive aspects of the disease

Next steps and future challenges

We are continuously collecting more data on this task from cohorts involved in the CONTROL-PD consortium. Further research is required to confirm these preliminary findings and explore the underlying neural mechanisms in more detail: to identify the specific mechanism being modulated by dopamine a computational model needs to be fit to the data. Future work should incorporate neuroimaging techniques to identify brain regions being modulated by dopamine during environmental controllability estimation. A key challenge moving forward will be determining how different levels of dopamine modulation—through medication or disease progression—affect cognitive and psychiatric states in PD.