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Aims, research questions and working hypothesis

Frontotemporal dementia (FTD) and dementia with Lewy bodies (DLB) show overlapping symptoms and clinical features with other types of dementia, especially in the early phases. Differential diagnostics is very challenging and, so far, no disease-modifying therapies or specific and cost-effective early biomarkers for these neurodegenerative diseases exist. Thus, sensitive and specific tools allowing accurate diagnosis are essential for choosing correct symptomatic medication and recruitment of early-stage patients to clinical trials. SynaDeg hypothesizes that synaptic changes represent the earliest pathological alterations indicating neurodegeneration in FTD and DLB. FTD patients regardless of their genetic background present alterations in the glutamatergic and GABAergic systems, whereas DLB patients show mixed neurotransmitter disturbances. We postulate that it is possible to identify disease-specific synaptic alterations and measurable physiological disturbances that can be feasibly implemented to clinical practice for improved early diagnostics of FTD and DLB.

SynaDeg specifically aims to: **1) Identify early physiological and synaptic changes**, which will aid in the improvement of the early diagnosis of FTD and DLB. These include changes in behaviour and autonomic function (*e.g.*, gastrointestinal complaints, heart rate variation, sleep, physical and social activity) and alterations in neurotransmitter system function as assessed by non-invasive transcranial magnetic stimulation; **2) Discover new cerebrospinal fluid and blood-based biomarkers indicating synaptic dysfunction**; **3) Characterize specific pathological and functional alterations and their molecular mechanisms underlying synaptic dysfunction** in brain samples and induced pluripotent stem cell (iPSC)-derived neurons from genetic and sporadic FTD and DLB patients; **4) Strengthen collaboration between research community and patient organizations (POs)** to promote efficient dissemination of SynaDeg results to scientific community, health care professionals, and lay audience, to establish ethical and best practices for patient recruitment, and to share knowledge on disease management in health service systems.

Means/methods implemented by the consortium

SynaDeg research efforts jointly promote discovery of new predictive and prognostic biomarkers and personalized treatment targets to combat neurodegeneration in FTD and DLB. SynaDeg activities take place in five interconnected, parallel work packages. This includes a collection of prospective cohorts (WP1) to assess and validate new early diagnostic tools and their relationship to the newly identified biomarkers and to access new samples for biomarker and mechanistic studies (WP2 and 3). WP4 and 5 involve dissemination and communication as well as management and coordination of SynaDeg activities in collaboration with patient organizations, respectively.

What are the outcomes of the project?

All the data yielded so far from the different scientific WPs in the SynaDeg project validate its initial idea that specific synaptic deficits and disturbances are present in FTD and DLB patients and suggest that we can identify underlying mechanisms, potential early biomarkers, and clinical symptoms and signs associating with synaptic disturbances in these diseases.

Significance and impact of the work on the field

SynaDeg endeavours are expected to clarify disease mechanisms and yield new disease-specific fluid biomarkers, therapeutic targets, and non-invasive clinical and physiological assessment tools to aid early identification and treatment of FTD and DLB patients.

Next steps and future challenges

The integrative data analyses to reveal correlations between the clinical and physiological symptoms are ongoing. We hope that the results of these analyses can be eventually exploited in the clinical practice to improve FTD and DLB early diagnostics and disease monitoring. We have also identified specific molecular-level changes that associate with the synaptic alterations in the iPSC-neurons, which may represent new biomarker or therapeutic targets. Some of these targets will be studied in more detail in the next steps. The clinical and preclinical research activities and collaboration among the consortium are expected to extend beyond the SynaDeg project.