Fundació La Marató de TV3
20th SYMPOSIUM
Neurodegenerative diseases

PREDICTION OF APATHY AND IMPULSE CONTROL DISORDERS IN PARKINSON'S DISEASE BASED ON THE FEEDBACK RELATED NEGATIVITY (FRN), A NEUROPHYSIOLOGICAL MARKER OF INCENTIVE PROCESSING

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1. Project abstract

Impulse control disorders and apathy are motivational disorders that frequently affect patients with Parkinson's disease. Impulse control disorders, which frequently lead to severe consequences to the patients and their families, are strongly linked to use of a type of Parkinson drugs, dopamine agonists. Avoiding this kind of medication in the cases with higher risk will probably blunt the incidence of this disorder. However, currently we are not able to identify patients at risk.

As well as the dysfunction that apathy generates in the patients and the suffering of their families, it usually heralds the development of dementia. Therefore, the identification of patients with high apathy risk may be useful to identify patients at risk of dementia.

Feedback-related negativity (FRN) is an evoked potential that mirrors the processing of gains and losses. This electric potential may differentiate patients at risk of each of these motivational disorders before they appear.

Objectives

- Main objective:

Assess the validity of feedback-related negativity (FRN) as a predictor of the development of apathy and impulse control disorders (ICD) in Parkinson's disease (PD).

- Secondary objectives

Develop predictive models of motivational disorders (ICD and apathy) in PD based FRN amplitude and other baseline variables.

Assess the difference in resting brain metabolism in patients presenting apathy, ICD and patients with no motivational disorders by means of 18F-FDG PET.

Design, proceedings and methods

One hundred PD patients with no motivational disorders will be assessed and followed up for two years. Electroencephalogram (EEG) signals will be recorded at baseline while the patients perform a gambling task. FRN amplitude will be calculated as the mean difference between the periods recorded after gains and after losses. Cognitive

performance, mood and genetic polymorphisms will be also assessed. During follow up motivational disorders will be screened every 6 months. Patients will be classified in three groups based on the results of the follow up: those with no motivational disorders, those with apathy and those with ICD. Finally, the usefulness of the FRN and the other basal markers as predictors of the development of apathy and ICD will be assessed.

2. Results

The recruitment and follow-up of the sample has been completed. In the ICD study, 120 patients were included, 10 were excluded because of previous ICD, 6 because of cognitive impairment precluding the proposed assessments. From those not excluded, 98 performed the EEG but 4 cases were excluded because of an insufficient number of events in one or more conditions of the task. Eighteen of the participants with valid records developed ICD during follow up. Patients who developed ICD do not differ from the others in age, sex, education, motor status (MDS UPDRS III) or impulsivity. Their ldopa equivalent daily dose was similar and dopamine agonists dose showed a trend toward significance with higher doses for patients who developed ICD ($p=0.06$). Mean FRN amplitude (as the difference between gains and losses) was 0.51mV in patients who did not develop ICD and 1.56mV in those who did ($p=0.013$).

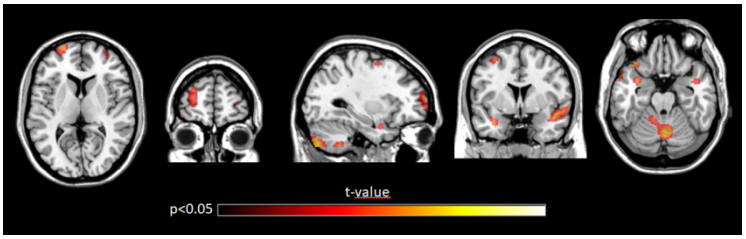
We developed a predictive model using established risk factors (age, dopamine agonists) besides the FRN. The FRN acts as an independent predictor ($p=0.017$). The area under the curve (AUC) of the associated ROC is 0.759. As a reference, the only model previously published has an AUC of 0.65 with only clinical data and 0.73 using genetic data.

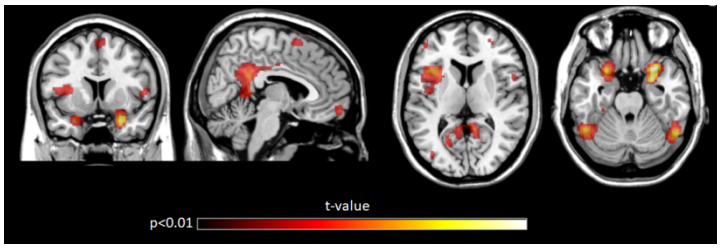
In the apathy study no patient was excluded because of previous apathy, therefore the sample is 114. The preliminary analysis did not show differences in FRN amplitude between patients who developed apathy and those who did not. Some data has not been analyzed yet.

Thirty-four participants performed a metabolic PET scan. At the time the scan was performed, 10 were apathetic, 9 had ICD and 15 had neither condition and acted as controls.

The ICD metabolic study showed ICD patients had a significant increase ($p<0.01$) in the posterior cingulate cortex, orbitofrontal, insula, medial prefrontal cortex, uncus amygdala and parietal and temporal areas. This result survives multiple comparisons.

Apathetic patients showed a metabolic decrease in fontal temporal and cerebellar areas ($p<0.05$).





3. Relevance and potential future implications

The FRN is a cognitive evoked potential which may be acquired easily when the adequate materials are available. The time taken to perform the gambling task is less than half hour and the required equipment is much more affordable than that required for neuroimaging. Besides, part of the equipment is usually available in hospital to perform EEG recording. Therefore the generalized acquisition of the FRN in PD patients is feasible as also, according to the developed model, is identifying patients at higher risk of ICD and adjusting their pharmacological treatment to control the risk. ICD being so strongly related to the use of dopamine agonists, the identification of patients at higher risk may blunt its incidence. Dopamine agonists, however, cannot be avoided on a general basis as this will lead to an unacceptable rise in motor complications of Parkinson's disease.

4. Generated bibliography

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