MILD COGNITIVE IMPAIRMENT AND RESTING-STATE FUNCTIONAL CONNECTIVITY CHANGES IN PARKINSON’S DISEASE

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Objectives: Cognitive deficits are frequent in Parkinson’s disease (PD), and the presence of mild cognitive impairment (MCI) is known to increase dementia risk. Resting-state functional MRI (fMRI) can be used to detect interregional correlations in blood-oxygen-level dependent signal fluctuations, which have proven to be useful in the study of neurodegenerative diseases. We aimed to evaluate the presence and spatial distribution of resting-state functional connectivity changes associated with the presence of MCI in PD patients using fMRI.

Methods: Thirty-six healthy controls (HC) and 66 non-demented PD patients underwent resting-state fMRI. Subjects’ brain connectivity matrices were calculated after parcelation into 90 regions of interest. MCI was determined if Z scores for at least two tests in the three most-affected cognitive domains in PD (attention/executive, memory and visuospatial/visuoperceptual) fell below 1.5 points the expected score for age, sex and education. Results: Twenty-three (25%) PD patients fulfilled criteria for MCI. Compared with HC, PD patients had widespread reductions in interregional correlation strength. MCI patients had long-range connectivity reductions and shorter-range increases compared with HC. Comparisons between MCI and non-MCI patients, controlling for depression, medication and UPDRS-III, showed connectivity reductions in MCI patients mainly involving the frontal and occipital lobes.

Conclusions: Our findings show that the presence of MCI in PD is accompanied by long-range reductions in resting state functional connectivity, giving support to the potential of fMRI in detecting changes underlying cognitive deficits in this disease.

No conflict of interest.
EXPLORING THE GENETIC LANDSCAPE OF PARKINSON’S DISEASE – AN EXOME STUDY IN SARDINIA, A MEDITERRANEAN GENETIC ISOLATE

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Objectives: The etiologic landscape of Parkinson’s disease (PD) is complex. Rare, highly-penetrant mutations in different genes and common risk factors of small size-effects in several loci have been identified in patients with PD. We report the results of our genetic study on the etiology of PD in Sardinia.

Methods: We performed exome sequencing in 100 unrelated Sardinian PD patients. We first removed non-functional variants and we selected the novel SNPs shared by at least five unrelated PD patients, and absent in dbSNP129 and 1000Genomes databases. This approach yielded a total of 3,881 SNPs, that were then genotyped in 500 independent Sardinian individuals (242 PD and 258 controls) using a custom platform. Association of each variant with disease status was tested using Fisher’s exact test implemented in PLINK/SEQ.

Results: Out of 155 variants with p-value <0.5 and odds-ratio >3, thirty were confirmed by Sanger sequencing, and genotyped by TaqMan assays in 2,965 PD patients and 2,678 matched controls from southern Europe. No variants surpassed the required level of significance according to Bonferroni correction (p value <1.28 × 10−5). The lowest p value was 1.16 × 10−3 for a variant with final OR 2.8.
Conclusions: We identified a catalogue of interesting variants enriched in PD patients that might point to novel genetic determinants of PD with moderate/strong effect size. Our study suggests that, with regard to the inspected exome target region, the genetic bases of PD are highly heterogeneous.

No conflict of interest

- EXOME AND TARGETED SEQUENCING IDENTIFY A NEW GENE CAUSING ESSENTIAL TREMOR
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Objectives: Essential tremor (ET) is the most common movement disorder. To date, numerous genetic studies have failed to identify a common genetic cause for this condition. We aimed to identify new genes involved in the pathogenesis of ET by studying multiplex ET families.

Methods: We performed exome sequencing in an ET family in which the causative genetic variant segregated in an autosomal dominant fashion. We then performed targeted resequencing in a sample of 392 unrelated ET cases to identify additional mutations in the coding region of the identified gene. Finally, we performed transfection
experiments of two different mutant cDNAs in both HEK and oligodendrocyte precursor cells to evaluate the functional consequences of these mutations.

**Results:** We first identified a missense mutation in TENM4 segregating in the ET family. In the targeted resequencing experiment we identified additional novel and damaging mutations in TENM4 in 18 of 392 (4.6%) unrelated ET cases. Following this analysis, we found two additional families in which two novel missense mutations were segregating with the disease phenotype. The transfection experiments of two different mutant TENM4 cDNAs showed a mislocalization of the corresponding mutant proteins and a reduced ability to form mono- and dimers for one of the mutants.

**Conclusions:** The genetic and functional data is corroborated by a knock-out mouse of Tenm4 displaying a clear and striking ET phenotype. The identification of TENM4, which is an important regulator of oligodendrocyte maturation, highlights the discovery of a major gene in the pathogenesis of ET.

No conflict of interest

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- **ROTIGOTINE IMPROVES SLEEP FRAGMENTATION IN PARKINSON’S DISEASE**

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**Objectives:** Sleep fragmentation (SF) is a frequent complaint in Parkinson’s disease (PD) that impacts on quality of life. In the RECOVER study rotigotine improved sleep quality, but no significant changes were observed in SF. These could be explained by a heterogeneous sample of patients with and without sleep problems. We aimed to assess the efficacy of rotigotine on SF in a sample of PD patients with subjective complaints of unsatisfactory nocturnal awakenings. Relationships between SF and the different aspects of sleep disturbance assessed by the Parkinson’s-Disease-Sleep-Scale-2 (PDSS-2), and the response of these aspects to rotigotine were explored.
Methods: Prospective, observational, multicentric study. Rotigotine effects on SF were assessed by change at 3 months in the item 3 (sleep maintenance) of the PDSS-2. A more specific questionnaire for SF was designed (PD-SFQ) to describe in more detail the phenomenology of SF, and the changes observed after rotigotine. The UPDRS-III and Geriatric-Depression-Scale (GDS) were administered to control for confounding factors.

Results: Sixty-two patients with SF were recruited (age 70 ± 7 years, disease duration 5.7 ± 4 years). Rotigotine onset (8.5 ± 3 mg/day) resulted in significant improvements of SF by the PDSS-2 ($p = 0.001$) and PD-SFQ ($p < 0.001$). Total PDSS-2 ($p < 0.001$) and UPDRS-III ($p = 0.01$) scores improved. No changes on the GDS ($p = 0.11$) appeared. Univariate and regression analyses showed improvements in SF to independently correlate with improvements in motor nocturnal symptoms ($p = 0.01$), restless legs symptoms ($p = 0.02$), and nocturia ($p = 0.04$).

Conclusions: Treatment with rotigotine was associated with significant improvement of sleep fragmentation, by amelioration of nocturnal motor symptoms, restless legs symptoms, and nocturia.

No conflict of interest.

- E-DUO STUDY: USE OF LEVODOPA-CARBIDOPA INTESTINAL GEL (LCIG) IN SPANISH PARKINSON’S DISEASE (PD) PATIENTS

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Objectives: Assess patient’s clinical characteristics, effectiveness and tolerability of LCIG in advanced PD in Spain.

Methods: PD patients treated with LCIG between January, 2006 and December, 2011 were included in this post-authorization, observational, retrospective, multi-centre study. Participant centers must have an experience of at least 5 LCIG patients. Data were collected from clinical examination and questionnaires performed in an actual scheduled visit and from the review of medical records.

Results: Of 185 PD patients treated with LCIG evaluated in 18 centers, 177 were finally included for analysis (figure 1). Socio-demographic and clinical characteristics are shown in table 1. Mean LCIG treatment duration was 2.58 ± 1.65 years (range from 0.01 to 7.26). Patients who continue on LCIG (n = 123) experienced a reduction in the percentage of daily ‘off-time’ (16.1 vs 47.6 before LCIG; $p < 0.0001$) and an increase in
the percentage of daily ‘ontime without disabling dyskinesia’ (55.5 vs 21.6 before LCIG; p < 0.0001), with no significant change in ‘on-time with disabling dyskinesia’. Improvements in different motor and non-motor symptoms are shown in figures 2 and 3. Complications related to system, gastrostomy and levodopa were 43.5%, 42.4% and 36.2%, respectively.

Conclusions: LCIG improved motor symptoms with a safety profile similar to previous reports No conflict of interest.

- LRRK2 BINDS TO NEURONAL VESICLES THROUGH PROTEIN INTERACTIONS MEDIATED BY ITS C-TERMINAL WD40 DOMAIN

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Objectives: Mutations in Lucien-rich repeat kinase 2 gene (LRRK2) are associated with familial and sporadic Parkinson’s disease (PD). A sequence variant (G2385R) within the WD40 domain has been implicated as a risk factor for PD, but its physiological and pathological function has not been systematically addressed yet. In this study we analyzed functional and molecular features of the WD40 domain and we addressed the implication of the G2385R variant.

Methods: To investigate the protein-protein interactions conferred to LRRK2 by its WD40 C-terminal domain we performed GST pull downs coupled with Western-blot and LC-MS/MS analysis. To experimentally address the structural properties of the LRRK2 C-terminus and the impact of G2385R mutation, we analyzed by Transmission Electron Microscopy GST-fusion proteins encompassing LRRK2 WD40 wild type as
well as G2385R. Finally, we evaluated the role of LRRK2 WD40 domain in neuronal functions combining biochemical and imaging assays.

**Results:** Our results suggest that LRRK2 WD40 domain serves as a hub for protein interactions setting LRRK2 as part of a protein network involved in synaptic vesicle trafficking. Furthermore we showed that the G2385R mutation influences WD40 domain features in terms of folding and binding properties.

**Conclusions:** By establishing LRRK2 as a presynaptic scaffold protein, these data strongly support the idea that different protein-binding/scaffolding capabilities might underlie LRRK2-associated forms of PD.

No conflict of interest.

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**- ANALYSIS OF IN-AIR MOVEMENT IN HANDWRITING: A NOVEL MARKER FOR PARKINSON’S DISEASE**

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**Objectives:** Micrographia is a common feature of Parkinson’s disease (PD). Handwriting a text consists of on-surface and in-air movements. We used a digitizing tablet to assess both in-air and on-surface kinematic variables during the handwriting and studied the extent to which any set of the obtained measurements is useful in discriminating PD from HC.

**Methods:** In-air and on-surface kinematic variables during the handwriting of a sentence were assessed in 37 PD patients on medication and 38 age- and gender-matched healthy controls (HC) using a digitizing tablet. By applying feature selection algorithms and support vector machine learning methods we studied to which extent any set of the obtained measurements is useful in discriminating PD from HC.

**Results:** We demonstrated that assessing the in-air/ on-surface hand movements led to accurate classifications in 84% and 78% of subjects, respectively. Combining both modalities only improved the accuracy by 1% over the evaluation of in-air features alone.

**Conclusions:** Assessment of in-air movements during handwriting has a major impact on disease classification accuracy. Future studies should explore the sensitivity, specificity, and underlying pathophysiological mechanisms of this novel marker.
DEEP BRAIN STIMULATION OF SUB-THALAMIC NUCLEUS OF LUYS FOR ADVANCED PARKINSON DISEASE WITH OCTOPOLAR ELECTRODES: PROGRAMMING ELECTRICAL PARAMETERS GUIDED FOR A NEUROANATOMICAL 3D IMAGE SOFTWARE.

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Objectives: The effectiveness of DBS-STN depends on adequate targeting in the STN nucleus. The post operative establishment of optimal electrophysiological parameters is a difficult goal after electrodes implantation. To show the results of DBS-STN in two PD patients with octopolar electrodes and a Neuroanatomical 3D guide for optimizing the electrical parameter after DBS-STN

Methods:
1. Two PD patients underwent DBS-STN
2. Octopolar electrodes in both STN nuclei
3. Cranial MRI and CT for planning STN target
4. Cranial CT one week post surgery fusion images
5. Neuroanatomical 3D software guide
6. Scales: UPDRS, Chaudari Non motor symptoms, motor fluctuations diaries and videos

Results: Both patients showed an excellent response after DBS-STN compared to basal scales with improvement of: UPDRS scale (70% and 85% o ), Motor fluctuations (90% and 95%), Non motor fluctuation scale improvement 85% and 94%. The Octopolar electrodes allowed the distributing of the current along the STN nucleus so the motor and non-motor symptoms showed an important improvement compared to empirical setting.

Conclusions: The neuroanatomical 3D software guide and the octopolar electrodes can help to optimize the clinical result after DBS-STN in PD patients due to more possibilities to establish an adequate setting of electrophysiological parameters

References:
- CORTICAL ATROPHY IN PARKINSON’S DISEASE WITH AND WITHOUT MILD COGNITIVE IMPAIRMENT

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Objectives: Cognitive deficits are frequent manifestations of Parkinson’s disease (PD), and the presence of mild cognitive impairment (MCI) is known to increase the risk of subsequent dementia. Our aim was to evaluate the presence of cortical degeneration as measured by cortical thinning according with the presence of MCI in PD patients using structural MRI.

Methods: Thirty-four healthy controls (HC) and 90 non-demented PD patients received high-resolution structural MRI scans. MCI was determined if Z scores for at least two tests in the three most-affected cognitive domains in PD (attention/ executive, memory and visuospatial/visuoperceptual) fell below 1.5 points the expected score for age, sex and education. FreeSurfer was used to assess cortical thickness and perform group comparisons.

Results: Forty patients (44%) of PD patients were classified as having MCI. Group comparisons, correcting for age and education, revealed that, compared with controls, PD patients showed cortical thinning in posterior, predominantly parieto-temporal regions. Compared with non-MCI patients, MCI patients had reduced thickness in frontal and occipital areas. Global mean cortical thickness was significantly reduced in the collapsed PD patient group and in the MCI PD subgroup compared with HC.

Conclusions: Our findings show that PD is accompanied by global cortical atrophy that predominates in posterior regions and, in patients with cognitive impairment, also involves frontal areas.

No conflict of interest.
DETECTING COGNITIVE DEFICITS WITH NO MANIFEST SYMPTOMS: THE USEFULNESS OF COGNITIVE PROCESSING SPEED IN EARLY STAGES.

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Objective: The aim of this communication is introducing the importance of the inclusion of cognitive processing speed (CPS) in neuropsychological assessments for MCI, PD or AD as the slowdown of the CPS is present in multiple diseases of the CNS among which we can include cognitive impairments of diverse aethologies. In the assessment of cognitive domains we usually use time-controlled neuropsychological tasks. These timings are often considered for the final conclusions of the overall cognitive status of the patients. However, we do not take into consideration that maybe only the CPS is slowed and there’s no affectionation in the other cognitive domains but only slowed capacity of the system.

Methods: To enhance those assessments some tests have been recently developed and adapted in order to be able to differentiate among the cognitive difficulties presented over evaluation on everyday clinical practice. We will be presenting several studies that have been conducted to quantitatively evaluate the slowing of CPS in different stages of aging and cognitive impairment, including MCI and early stages of AD and PD.

Results: Decreased speed of processing has been found to contribute to compromised functional status. We will be presenting some guidelines again which an individual could be assessed; the ability to assess separately the different cognitive areas and the CPS can be of great help to assess and monitor the evolution of different conditions.

Conclusions: CPS should be considered in everyday assessments as maybe some conditions attributed to specific diseases are only the reflect of the slowness in CPS due to the aging process.

No conflict of interest.