UNIVERSIDAD COMPLUTENSE DE MADRID
FACULTAD DE MEDICINA
DEPARTAMENTO DE MEDICINA

TESIS DOCTORAL

Rendimiento cognitivo poblacional en enfermedad de parkinson y temblor esencial ¿Qué ocurre en ausencia de demencia?

MEMORIA PARA OPTAR AL GRADO DE DOCTOR

PRESENTADA POR

Álvaro Sánchez Ferro

DIRECTORES

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Madrid, 2018

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Félix Bermejo Pareja, Profesor emérito en CIBERNED, Catedrático Extraordinario en la Universidad Complutense de Madrid, y **Jesús Hernández Gallego**, Jefe de Sección del Departamento de Neurología del Hospital Universitario 12 de Octubre de Madrid y profesor de Neurología en la Universidad Complutense de Madrid.

INFORMAN QUE: el doctorando D. ÁLVARO SÁNCHEZ FERRO ha realizado, bajo su dirección y en el Departamento de Medicina y en el Hospital Universitario 12 de Octubre de la Comunidad de Madrid, un trabajo que lleva por título "Rendimiento Cognitivo Poblacional en Enfermedad de Parkinson y Temblor Esencial. ¿Qué Ocurre en Ausencia de Demencia?" y autorizan su presentación para optar al Grado de Doctor en Investigación en Ciencias Médico-Quirúrgicas.

Y para que así conste, expiden y firman el presente informe, en Madrid, Abril de 2017.

D. Félix Bermejo Pareja **D. Jesús Hernández Gallego**

19 de Noviembre de 2014, mi vuelta a casa

2 de Julio de 2016, mi pasado, mi presente y mi futuro

AGRADECIMIENTOS

Un trabajo como este representa una obra coral. Vaya por tanto mi gratitud a todas aquellas personas, compañeros, colegas, pacientes, familia y seres queridos, que han hecho posible el que esté hoy aquí escribiendo estas líneas.

La primera mención particular es obligada para con mis directores de tesis. A mi maestro Félix Bermejo Pareja le estaré siempre en deuda por haberme iniciado en este maravilloso mundo de la investigación y haberme abierto las puertas de su maravilloso estudio, NEDICES, que con tanto mimo y éxito diseñó. A mi otro maestro Jesús Hernández Gallego, le tengo y tendré ya siempre como amigo y ejemplo sempiterno de actitud vital y profesional.

También es necesario que exprese mi gratitud hacia todos mis compañeros de trabajo en el Hospital 12 de Octubre, en el Massachusetts General Hospital, en el Massachusetts Institute of Technology y ahora en HM-CINAC. Es injusto personalizar. Todos ellos me han enseñado de forma altruista y han hecho mis quehaceres profesionales infinitamente más llevaderos. No obstante, si que tengo que dedicarles unas palabras de cariño a Julián Benito-León que con su generosidad y brillantez me acompañó y acompaña desde mis inicios investigadores. Gracias a él, y al Dr. Bermejo, también he tenido la oportunidad de trabajar con dos maravillosos profesionales como son Elan. D. Louis y Alex J. Mitchell, my sincere gratitude to both of them. A Alberto Villarejo, ejemplo de persona, profesional y amigo íntegro y todoterreno, además de buen compañero de mesa. A José Antonio Molina por todo su cariño y apoyo. A Rocío Trincado, Verónica Puertas y Eva Carro que siempre han apoyado mis esfuerzos en estas lides. A Sara Moreno, la mejor "coR". A Fernando Sierra, cerebro privilegiado y camarada de fatigas durante la Río Hortega. A Isabel Barroeta, uno de mis mayores descubrimientos en Boston. A todos mis jefes pasados y presentes, Félix Bermejo nuevamente, Teresa Gómez Isla, Martha Gray y José Obeso.

Gracias por haber confiado en mi y haberme permitido contribuir a vuestras visiones.

Toca ahora dedicarle unas palabras a mis seres queridos. A ti Aníbal me hubiera encantado disfrutarte un poco más y que hubieras podido ser testigo de tantas cosas como me han ocurrido y ocurrirán. Sé que estarías orgulloso de este trabajo, como yo lo estoy de haber sido tu hijo. A mi abuela Teresa, sin duda uno de mis grandes amores, ejemplo de elegancia, rectitud y carisma. Te echo tremendamente de menos. A mis hermanos, Pablo y Susana. Me enorgullezco cada día de ser vuestro hermano y de acompañaros tanto en vuestros éxitos, como en vuestro periplo por la vida.

A todos mis amigos más cercanos, gracias por hacerme la vida más feliz: Manuel, Sandra, Sergio, Largo, Borja, Elena, Abel, Nacho, Antonio, Carlos, Hugo, Luis, Félix, Christian, Rosa, Edu, Álex, Jaime, Manolo, Iratxe, Ricardo y Melisse.

A ti Matuca, que tan orgullosa te sientes de habernos regalado la vida y los recursos para disfrutarla a cada instante. Madre no hay más que una y yo me siento tremendamente feliz de que tú seas la mía y que puedas ser testigo de este logro que también es tuyo.

A ti Laura, apuesta de presente, pasado y futuro. Ejemplo de sencillez, y naturalidad. Espero que tú y toda tu (nuestra) familia disfrutéis muchos años de este ya casi doctor a vuestro lado, yo lo haré al vuestro.

A los que se van, a los que vienen y
a los que vendrán

ABREVIATURAS

MDS	- Movement Disorder Society
WCST	- Wisconsin Card Selection Test
TMT	- Trail Making Test
FAB	- Frontal Assessment Battery
WAIS	- Wechsler Adult Intelligence Scale
BNT	- Boston Naming Test
CVLT	- California Verbal Learning Task
GDS	- Geriatric Depression Scale
MMSE	- Minimental State Examination
MoCA	- Montreal Cognitive Assessment Test
TOL	- Tower of London (Torre de Londres)
PRM	- Pattern Recognition Memory (parte de test CANTAB)
CANTAB	- Cambridge Neuropsychological Test Automated Battery
COWAT	- Controlled Oral Word Association Test
NART	- National Adult Reading Test
FCSRT	- Free and Cued Selective Reminding Test
BVMT	- Brief Visuospatial Memory Test
BJLOT	- Benton Judgment of Line Orientation
RBANS	- Repeatable Battery for the Assessment of Neuropsychological Status
LNS	- Letter Number Sequencing
LRKK2	- Leucin-Rich Repeat Kinase 2
PPMI	- Parkinson’s disease Progression Marker Initiative
HVLT-R	- Hopkins Verbal Learning Test Revised
UPDRS	- Unified Parkinson’s Disease Rating Scale
MAPT	- Microtubule Associated Protein Tau
COMT	- Catecol-O-Methyl-Transferasa

INDICE

RESUMEN

Introducción: La enfermedad de Parkinson y el temblor esencial son dos de las trastornos del movimiento más frecuentes. Sus manifestaciones fundamentales son motrices, pero también se han descrito alteraciones cognitivas. Existen pocos estudios poblacionales que las caractericen.

Objetivos: Evaluar las alteraciones cognitivas producidas por el temblor esencial y la enfermedad de Parkinson en las fases precoces de la enfermedad en un estudio poblacional en ausencia de demencia.

Métodos: Se analizaron los resultados del los test neuropsicológicos de los participantes del estudio NEDICES. Para ello se compararon sujetos con temblor esencial, enfermedad de Parkinson y controles sanos mediante test no paramétricos. Se ajustaron los resultados por potenciales variables confundidoras como son la edad y el nivel educativo.

Resultados: Los participantes con enfermedad de Parkinson y temblor esencial tuvieron un peor rendimiento cognitivo que los sujetos sanos. Los primeros mostraron un peor rendimiento en test de memoria y lenguaje. Los participantes con temblor esencial tuvieron una menor velocidad de procesamiento cognitivo. Evidenciamos una caída en el rendimiento cognitivo global medido por el test MMSE-37 en participantes en fases prediagnósticas del temblor esencial.

Conclusión: Se confirma la existencia de alteraciones precoces cognitivas en ambas enfermedades en ausencia de demencia. En nuestros hallazgos parece existir un perfil diferencial de las mismas y un gradiente de afectación mayor en los enfermos con Parkinson. La existencia de alteraciones en las fases preclínicas de sujetos con temblor esencial sugiere que se trate de una enfermedad neurodegenerativa.

ABSTRACT

Introduction: Parkinson's disease and essential tremor represent two of the most frequent movement disorders. Besides their motor manifestations, both entities can impair cognition. There are few population-based studies that characterize the cognitive status of participants with Parkinson's disease or essential tremor.

Aims: Understand the impact of Parkinson's disease and essential tremor on cognition in a population-based study of dementia-free participants.

Methods: We evaluated the neuropsychological performance of the participants enrolled in the NEDICES study. Three groups of subjects were compared using non-parametric techniques (i.e. Parkinson's disease, essential tremor and healthy participants). The results were further adjusted for potential confounder such as age or literacy.

Results: A poorer cognitive performance was found for the participant with Parkinson's disease and essential tremor. It was particularly evident for memory and language tests in the former and for cognitive processing speed in the later. There was a greater cognitive decline in the MMSE-37 test at follow up in the participants with essential tremor in the years before they were diagnosed.

Conclusion: We have confirmed a cognitive impairment in participants with Parkinson's disease and essential tremor in the absence of dementia. There was some overlap in the affected functions and, generally, there was a gradient of impairment, showing a poorer performance the people with Parkinson's. The existence of cognitive decline in the prediagnostic stage of essential tremor points towards a neurodegenerative etiology for this disease.

INTRODUCCIÓN

I. INTRODUCCIÓN

Los trastornos del movimiento constituyen un reto de gran importancia para el neurólogo, ya que muchos de ellos, de inicio clínico muy similar, van a tener una gran diferencia en el curso evolutivo. No existen biomarcadores fiables para detectarlos siendo su diagnóstico clínico. El diferenciarlos es fundamental por sus importantes repercusiones pronósticas y terapéuticas.

De estos trastornos del movimiento la enfermedad de Parkinson y el temblor esencial constituyen dos de las entidades más frecuentes en la rutina neurológica que afectan al movimiento (1,2). Ambas enfermedades se han definido tradicionalmente en torno a las manifestaciones motoras que producen (3). En el caso de la enfermedad de Parkinson, éstas se caracterizan fundamentalmente por la lentitud de movimiento, también llamada bradicinesia; la rigidez, o incremento de tono pasivo a la movilización articular; y el temblor. Este último se define por su aparición cuando la parte afectada está en reposo, y por tener una frecuencia típica de 4-6 Hz (3). En el temblor esencial existe una oscilación rítmica en las extremidades, que a diferencia de la enfermedad de Parkinson ocurre con la acción o al mantener una postura. Además, suele presentar una frecuencia de oscilación más rápida (4).

En fechas recientes, se ha empezado a delimitar una serie de características “no-motoras” y que exceden la visión tradicional antes expuesta (5). Sobre estos aspectos no motores pretendemos profundizar en este proyecto de investigación, particularmente en la repercusión que ambas enfermedades tienen en el funcionamiento cognitivo en sus fases iniciales, antes de que aparezca una demencia y a nivel de una población representativa de la población general, lo que se llama estudio poblacional.

I.i. Epidemiología del temblor esencial y de la enfermedad de Parkinson.

El temblor esencial es el trastorno de movimiento más frecuente (6). Diferentes estudios estiman que la prevalencia de la enfermedad se sitúa en torno al 0,4 – 3,9% de la población general (6,7) y la incidencia es 61,6 por 100.000 personas-año, aunque esta cifra proviene del estudio NEDICES que se restringe a población anciana. Su frecuencia de aparición va aumentando con los años, pero no es infrecuente que aparezca en la juventud (8). También es habitual el que tenga un componente familiar (7). En base a las cifras de población actuales (9) y la prevalencia de enfermedad referida, en España se estima que hay entre 185.872 y 1.812.256 personas con temblor esencial.

La enfermedad de Parkinson es la segunda entidad neurodegenerativa en frecuencia, sólo por detrás de la enfermedad de Alzheimer (1). Su prevalencia global para todos los rangos de edad es del 0,32% (10). Cada año se estima que 14 de cada 100.000 personas son diagnosticadas (1). Estos números se incrementan sustancialmente en personas mayores de 65 años, como describió el estudio NEDICES y en cuyos datos se ha basado esta tesis (11). En este grupo de edad se estima que 160 de cada 100.000 personas padecen Parkinson (12). Como dato adicional, la enfermedad de Parkinson es 1.5 veces más frecuente en varones (13). Con las cifras referenciadas, en España, se calcula que hay aproximadamente 148.697 personas afectadas por esta enfermedad.

I.ii. Fisiopatogenia del temblor esencial y la enfermedad de Parkinson

Aunque todavía no se conocen todos los aspectos que se relacionan con el desarrollo de estas enfermedades, existen una serie de factores asociados importantes que revisaremos a continuación para cada una de ellas.

I.ii.i. Temblor esencial

El temblor esencial no es una entidad homogénea. Esto se refleja en el elevado porcentaje de diagnósticos erróneos en el momento que los pacientes son revisados en centros de tercer nivel (hasta el 37%) (14). No obstante, cada vez parece más probable que se trate de una entidad asociada a neurodegeneración (15) y de hecho se han evidenciado alteraciones neuropatológicas específicas en tejido cerebral de pacientes afectos (4). Las regiones dónde se han constatado alteraciones han sido (i) el cerebelo con pérdida de células de Purkinje y (ii) el tronco del encéfalo con inclusiones similares a las encontradas en enfermos con Parkinson (16,17). No obstante, estos hallazgos no se han confirmado en todos los pacientes con temblor esencial (18).

Como factores causales de este proceso, el elemento que de forma más consistente se asocia al incremento de incidencia y prevalencia de la enfermedad es el envejecimiento (7). También es conocida su asociación familiar, habiéndose encontrado varios *loci* de susceptibilidad (19). Los factores ambientales han sido menos investigados y de forma particular sí se ha relacionado la existencia de temblor con ciertas sustancias con potencial neurotóxico como los alcaloides de la β-carbolina (20).

I.ii.ii. Enfermedad de Parkinson

Si bien existe un mayor conocimiento de los aspectos que condicionan la aparición de esta enfermedad, también existen innumerables cuestiones por dilucidar. La enfermedad de Parkinson se asocia a factores genéticos y ambientales que acaban produciendo un daño progresivo en sistema neuronales específicos (21). El sistema más comúnmente afectado, y directamente relacionado con las manifestaciones motoras de la enfermedad, es el sistema de los ganglios basales y en concreto el circuito que conecta la *Substantia Nigra* con el estriado (22). No obstante, la enfermedad tiene un carácter generalizado, afectando también a otras regiones del encéfalo e incluso del sistema nervioso periférico (23). Hay autores, y parece cada vez más probado, que propugnan una afectación progresiva y organizada de las diferentes estructuras cerebrales. El sistema de estadificación más aceptado es el propuesto por Braak y Braak (24). Asociado a este constructo está la presencia de síntomas que se relacionan directamente con el daño progresivo de las regiones afectadas (22). Se definen seis estadios, siendo los dos primeros asintomáticos y pudiendo detectarse solo la enfermedad en el tercer estadio, cuando ya hay implicación del mesencéfalo. Este estadiaje se ha hecho en estudios *post mortem* en base a la detección de una serie de proteínas que se acumulan en estas zonas del cerebro. La proteína fundamental es la alfa-sinucleina (25,26).

La causa que origina estos acúmulos de proteínas y los factores que condicionan su propagación son aún objeto de investigación. No obstante, también se han documentado diferentes mutaciones patogénicas *per se* con herencia mendeliana (27), también factores genéticos de susceptibilidad (28), y diferentes factores ambientales (29). Presumiblemente, todos ellos actúen de forma conjunta para que en un determinado momento se inicie la enfermedad que seguirá ya un curso progresivo e inexorable.

I.iii. Criterios diagnósticos actuales de enfermedad de Parkinson y temblor esencial

Tanto para el temblor esencial como para la enfermedad de Parkinson existen una serie de criterios formales que se usan a la hora de establecer el diagnóstico sobre todo en el contexto de estudios de investigación.

Los más frecuentemente utilizados para la enfermedad de Parkinson son los criterios del Banco de Cerebros de Londres (3) y que resumimos en la tabla 1. Recientemente la Movement Disorder Society (MDS) ha creado grupo de trabajo que los ha revisado, y es esperable que en un futuro cercano se empiecen a utilizar estos nuevos criterios (30). No obstante, aún no se han validado formalmente.

Respecto al temblor esencial unos de los criterios más comúnmente utilizados son los de la MDS y los de *Washington Heights-Inwood*, aunque al igual que para la enfermedad de Parkinson suelen reservarse para estudios de investigación. Estos criterios se han descrito en la tabla 2 (31).

Tabla 1. Criterios del Banco de Cerebros de Reino Unido para el diagnóstico de enfermedad de Parkinson idiopática (Adaptado de 3)

1er paso – Diagnóstico del síndrome parkinsoniano

- **Bradicinesia (lentitud en el inicio del movimiento voluntario con reducción progresiva de la velocidad y la amplitud del mismo tras una acción repetida).**
- **Además uno de los siguientes signos:**
  - **Rigidez muscular.**
  - **Temblor de reposo a 4-6 hercios.**
  - **Inestabilidad postural no debida a afectación visual, vestibular, cerebelosa o propioceptiva primaria.**

2º paso – Criterios de exclusión de enfermedad de Parkinson

- **Antecedente de ictus de repetición con una progresión escalonada de los signos parkinsonianos.**
- **Antecedente de traumatismos craneoencefálicos repetidos.**
- **Antecedente de encefalitis.**
- **Antecedente de crisis oculógiras.**
- **Tratamiento con neurolépticos al inicio de la sintomatología.**
- **Existencia de más de un familiar afecto.**
- **La enfermedad remite de forma sostenida.**
- **Afectación estrictamente unilateral después de tres años.**
- **Paresia supranuclear de la mirada.**
- **Signos cerebelosos.**
- **Afectación autonómica importante de forma precoz.**
- **Aparición de demencia de forma precoz con alteración en memoria, lenguaje y praxias.**
- **Signo de Babinski.**
- **Presencia de un tumor cerebral o hidrocefalia comunicante en un scanner cerebral.**
- **Respuesta negativa a una dosis suficiente de levodopa (una vez excluida malabsorción).**
- **Exposición a MPTP***

3er paso – Datos de apoyo positivos durante el seguimiento de la enfermedad

(Se requieren tres o más para el diagnóstico de enfermedad de Parkinson establecida)

- **Inicio unilateral.**
- **Presencia de temblor de reposo.**
- **Curso progresivo.**
- **Asimetría mantenida con predominio de la afectación en un lado del**

cuerpo

- **Respuesta excelente a levodopa (70 – 100%)**
- **Presencia de discinesias marcadas inducidas por levodopa.**
- **Respuesta a levodopa tras cinco o más años.**
- **Duración de la enfermedad diez o más años**

* MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

Tabla 2. Criterios diagnósticos de temblor esencial (Modificado de 31)

Criterios de la Sociedad de Trastornos de Movimiento

Criterios de Inclusión:
Temblor postural bilateral de manos y antebrazos, con o sin temblor cinético, visible y persistente.
Duración mayor de cinco años.

Criterios de exclusión:
Presencia de otros signos neurológicos (salvo signo de Froment).
Existencia de causas que puedan exacerbar el temblor fisiológico.
Consumo o abstinencia de sustancias que puedan producir temblor.
Traumatismo craneoencefálico en los 3 meses anteriores al inicio del temblor.
Evidencia de origen psicógeno.
Temblor de inicio súbito o rápido.

Criterios diagnósticos de temblor esencial del estudio genético de Washington Heights-Inwood

Temblor postural de grado +2 en al menos un brazo (puede existir además temblor cefálico, pero no es suficiente para el diagnóstico)
Temblor cinético de grado +2 al realizar al menos 4 actividades, o de grado +2 al realizar una y +3 al realizar otra. Estas actividades incluyen trasvasar agua a un vaso, usar una cuchara, beber de un vaso, realizar la maniobra dedo-nariz y dibujar una espiral.
Si el temblor afecta a la mano dominante, debe interferir, al menos, con una actividad de la vida diaria (comer, beber, escribir). Si el temblor no afecta a la mano dominante, este criterio es irrelevante.
Deben excluirse como causa del temblor el consumo de fármacos causantes de temblor y de alcohol, el hipertiroidismo y la distonía.
Ausencia de origen psicógeno (p. Ej, temblor abigarrado, inconsistente, que desaparece con la distracción del paciente).

Grados de temblor: 0: ausente; +1: de escasa amplitud (amplitud < 1 cm) o intermitente; +2: de moderada amplitud (1-2 cm); +3: de gran amplitud (> 2 cm), violento.

I.iv. Sintomatología del temblor esencial y la enfermedad de Parkinson

Al igual que la fisiopatogenia, la sintomatología de ambas entidades es variada y hasta se han descrito fenotipos específicos dentro de cada entidad.

I.iv.i. Aspectos motores

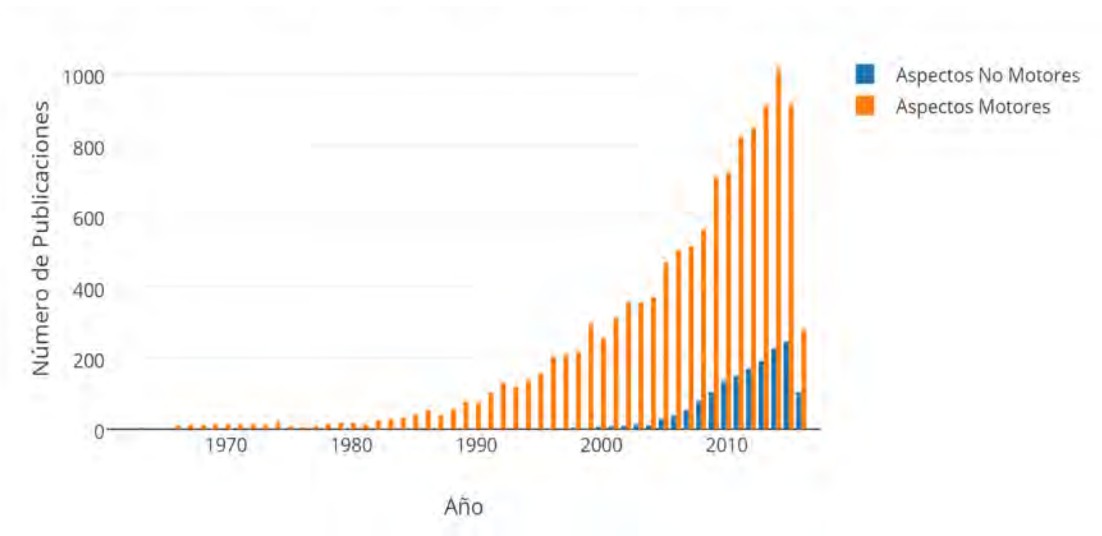
Como referíamos al inicio, la sintomatología cardinal tanto del temblor esencial como de la enfermedad de Parkinson es la denominada sintomatología motora. En el caso de la enfermedad de Parkinson los pacientes suelen debutar con lentitud de movimiento, típicamente en las extremidades superiores y/o rigidez, y temblor progresivos (3). A estos síntomas de inicio es habitual que se sumen otras manifestaciones como alteración de la marcha y de reflejos posturales. En un determinado punto empiezan a tener más fluctuaciones a lo largo del día en su estado motor, hasta condicionar serias limitaciones en la movilidad (29). Mención aparte merece el temblor, que característicamente ocurre en reposo y suele tener una frecuencia baja de 4-6 Hz (32).

El temblor esencial también tiene un carácter progresivo y suele manifestarse por un temblor de alta frecuencia, sobre todo en las extremidades superiores o región cefálica. Generalmente ocurren en la postura o con la acción aisladamente y con ciertas características diferenciales con la enfermedad de Parkinson (33). No obstante, a veces se han descrito casos con temblor también en reposo (34). Es raro que asocie otras manifestaciones motoras, aunque se ha mencionado también la posibilidad de cursar con alteraciones de coordinación por disfunción cerebelosa (35).

I.iv.ii. Manifestaciones no motoras en el temblor esencial y la enfermedad de Parkinson - aspectos generales

Recientemente, ha habido un cambio de paradigma en la definición de estas enfermedades. Desde una perspectiva puramente motora, cada vez se ha ido generando más evidencia de una afectación más generalizada con la presencia de otros síntomas y signos denominados no motores (5). En la figura 1 hemos utilizado el ejemplo de la enfermedad de Parkinson y las citas referenciadas en *PubMed* para aspectos motores y no motores. Además de la evidente disparidad en número de publicaciones, se puede ver que no es hasta el año 2000 cuando se empiezan a investigar estos aspectos denominados no motores.

Figura 1. Publicaciones referenciadas en PubMed sobre aspectos motores y no motores en la enfermedad de Parkinson



En la tabla 3 hemos presentado los síntomas y signos no motores más frecuentes en cada enfermedad. Parece por tanto evidente que los aspectos no motores de estas enfermedades son una parte importante de su espectro clínico y que están comparativamente menos estudiados que otras manifestaciones que tienen lugar en el curso clínico de estas patologías.

Tabla 3. Ejemplo de Manifestaciones No Motoras frecuentes en la Enfermedad de Parkinson y del Temblor Esencial

Enfermedad de Parkinson (36)	Temblor Esencial (37)
Clínica afectiva (ansiedad / depresión)	*Clínica afectiva (ansiedad / depresión)*
Pérdida de olfato	*Pérdida de olfato / Déficit audición*
Alteraciones de sueño	Alteraciones de sueño
Disautonomía (estreñimiento, etc.)	Alteraciones de personalidad
Síntomas sensitivos, dolor y fatiga	*Disfunción cognitiva*
Disfunción sexual o vesical	
Alteraciones neuropsiquiátricas	
Disfunción cognitiva	

El objetivo de la presente tesis es ampliar el conocimiento sobre estos aspectos no motores y en particular sobre las manifestaciones cognitivas en el temblor esencial y la enfermedad de Parkinson. Pretendemos caracterizar estos aspectos especialmente en las fases precoces de ambas enfermedades en ausencia de demencia y a nivel poblacional.

Para ello evaluaremos los resultados del rendimiento cognitivo de los sujetos que participaron en el estudio NEDICES. Un estudio de base poblacional de las principales enfermedades neurológicas y sus determinantes.

En la siguiente sección elaboraremos lo que se conoce hasta la fecha actual sobre este importante dominio “no motor”, que impacta dramáticamente la calidad de vida y el pronóstico del paciente. Sobre todo, cuando aparece su complicación más temible, el deterioro cognitivo o demencia. Reiteramos no obstante, que este trabajo se centra en entender estas manifestaciones en ausencia de demencia y a nivel poblacional.

Dado que la mayoría de la literatura previa se basa en el resultado de test neuropsicológicos, hemos elaborado una sección específica dónde se detalla de forma somera para que sirve cada test. En el caso de querer profundizar en las funciones evaluadas con cada test, remitimos al lector a esta sección. Pasamos ahora a detallar los estudios más relevantes para el propósito de este trabajo.

I.iv.iii. Cognición y temblor esencial

A la fecha de publicación de esta tesis, y según el conocimiento de los autores, no hay estudios poblacionales que investiguen las alteraciones cognitivas de personas con temblor esencial más allá de los resultados del estudio NEDICES. El resto de las evaluaciones existentes provienen de muestras hospitalarias. Es conocido que los estudios hospitalarios puede asociar sesgos de selección al no representar el espectro global de la enfermedad al evaluar los casos más avanzados, graves o con particularidades de manejo clínico (38).

En esta introducción revisaremos cuatro estudios que aunque no son poblacionales son de especial interés, al evaluar comparativamente las alteraciones cognitivas de personas afectadas con enfermedad de Parkinson y temblor esencial (39–42).

El primer estudio que describiremos es el de Gasparini et al. del año 2001, al ser el primero a nivel cronológico (41). Los autores evaluaron 15 sujetos con temblor esencial familiar, 15 sujetos con enfermedad de Parkinson, 15 controles sanos y 12 sujetos con formas mixtas de temblor esencial/enfermedad de Parkinson. Aplicaron una batería de test que incluyó: WCST, TMT, FAS, Torre de Londres y test de Stroop. Los autores encontraron alteraciones similares en sujetos con enfermedad de Parkinson y temblor esencial frente a controles sanos en el test de Stroop. Este test mide la capacidad de atención. También evidenciaron alteraciones en los enfermos de Parkinson en el test TMT que mide la velocidad de procesamiento cognitivo y en el test COWAT que mide la fluencia verbal fonética sobre todo dependiente de la función ejecutiva. En base a estos resultados, los autores hipotetizan que las alteraciones cognitivas que encuentran en sujetos con temblor esencial se deben a una disfunción fronto-subcortical. Además reflejan un gradiente de alteración con los sujetos con Parkinson más afectos que los temblores esenciales y estos más que los controles. Este último punto es crítico para este trabajo ya que es la base para una de nuestras hipótesis de estudio. Reseñar que los autores no excluyeron de forma sistemática la presencia de demencia.

El siguiente estudio por orden cronológico es el publicado por Lombardi et al en el mismo año (42). Este estudio incluyó una cifra similar de pacientes con 18 sujetos con temblor esencial y 18 pacientes con enfermedad de Parkinson. Además de los test WCST y COWAT que también evalúo el grupo anterior, los autores valoraron otra serie de dominios cognitivos con los test WAIS, BNT, Hooper, reconocimiento facial, dígitos, CVLT, y GDS. Hallaron una menor fluencia verbal en sujetos con temblor esencial y enfermedad de Parkinson frente a controles sanos. En los sujetos con Parkinson también objetivaron una alteración en los test WCST y CVLT, que miden memoria, y en el reconocimiento facial. Los autores vuelven a propugnar la existencia de un déficit fronto-subcortical en el temblor esencial.

Posteriormente, Frisina et al. (39) evaluaron 34 pacientes con temblor esencial y 26 pacientes con enfermedad de Parkinson. En este análisis se comparó el rendimiento en un test global de funcionamiento cognitivo como es el test Mini-mental (MMSE), y su correlación con un test de actividades instrumentales y con una escala motriz. Los autores no hacen una comparación directa en las funciones cognitivas, si no que establecen una correlación entre el rendimiento cognitivo de los pacientes con temblor y enfermedad de Parkinson y su actividad funcional/motriz. Cabe reseñar que la población estudiada era muy anciana y que al igual que en estudios previos no se excluyeron sujetos con demencia.

Más recientemente, Sengul et al. (40) comparan el rendimiento cognitivo de 37 pacientes con temblor esencial y 23 sujetos con enfermedad de Parkinson. Para ello usan el test de cribado cognitivo llamado MoCA y no encuentran diferencias significativas en los dos grupos.

Sintetizando esta información, parece probado que hay alteraciones cognitivas en pacientes con temblor esencial y que podrían ser compatible con un síndrome disejecutivo. El origen del mismo se ha relacionado con disfunción en circuitos cerebelosos y/o en el lóbulo frontal, aunque existen pocos estudios al respecto (43,44) Las alteraciones fundamentalmente encontradas afectan a la capacidad de atención y en la fluencia verbal. Existe cierto solapamiento con la enfermedad de Parkinson que revisaremos a continuación. Enfatizar nuevamente que estos estudios proceden de muestras hospitalarias, y en algunos casos de pacientes con enfermedad avanzada seleccionada para tratamiento quirúrgico, que no excluyen de forma sistemática la existencia de demencia y que incluyen un pequeño número de sujetos.

I.iv.iv. Cognición y enfermedad de Parkinson

En lo que respecta a la enfermedad de Parkinson en ausencia de demencia, si que hay un mayor número de estudios e incluso alguno poblacional. Revisaremos a continuación aquellos de mayor solidez metodológica y peso específico según la opinión de este autor. El orden también es cronológico y por tipo de estudio, cuando hay más de una publicación relacionada.

En el año 2004, Aarsland et al (45), evalúan prospectivamente 254 personas con enfermedad de Parkinson. Incluyeron dentro de su población de estudio sujetos con demencia asociada a la enfermedad. La prueba que utilizan es el test MMSE y encuentran una caída de un punto anual en aquellos sujetos para los que tienen seguimiento.

En ese mismo año se publica uno de los estudios más relevantes en la definición de las alteraciones cognitivas en fases precoces de la enfermedad de Parkinson (46). El estudio CamPaING (*Cambridgshire Parkinson's Incidence from GP to Neurologist*) incluye 201 casos de pacientes recientemente diagnosticados de enfermedad de Parkinson (N.B. los autores los clasifican como incidentes, pero en realidad son sujetos detectados dentro de los 25 meses anteriores a su inclusión en el estudio). Aplican una batería de pruebas neuropsicológicas más amplia que en la iniciativa anterior y que incluye el test MMSE, TOL, PRM, COWAT, NART y la fluencia semántica de animales. Los autores encuentran diferencias frente a valores normativos en tareas relacionadas con función frontoestriatal (TOL) en un 11% de los casos y en test que mide función mnésica relacionada con el lóbulo temporal (PRM) en un 8% de los sujetos. Ante estos hallazgos los autores hipotetizan un déficit fronto-ejecutivo en un subgrupo de sus pacientes y un déficit que denominan posterior en otro subgrupo de ellos.

Este mismo grupo publica en el año 2009 los datos de seguimiento a cinco años de 105 sujetos de esa cohorte (47). Específicamente se centran en investigar la fisiopatología de los déficits que comunicaron en su estudio basal, y evalúan la relación de los déficits fronto-ejecutivos y temporales con la actividad de la enzima COMT y con la actividad de gen MAPT respectivamente. Encuentran una relación entre el deterioro cognitivo y el gen MAPT que se relaciona con depósitos de proteína tau. La proteína tau tiene un conocido rol en la demencia del tipo Alzheimer y otras enfermedades neurodegenerativas (48). Sin embargo, los autores no encuentran una relación de la demencia con el enzima COMT y/o el déficit frontoejecutivo. Hipotetizan que éste último, que si se relaciona con COMT, sería una manifestación de la medicación y que sólo las alteraciones en MAPT son las que se asocian con el referido déficit de función posterior cerebral, con el envejecimiento y por tanto con el riesgo de demencia.

Como dato añadido a estos estudios, los mismos autores publican en el año 2013 datos de seguimiento a 10 años dónde evalúan a 49 sujetos de la cohorte original. En este análisis un 46% de los sujetos presenta demencia asociada a la enfermedad de Parkinson (49).

Volviendo al año 2009, Elgh et al. (50) comunican los datos de un estudio poblacional en Suecia sobre el rendimiento cognitivo de 88 sujetos con enfermedad de Parkinson en ausencia de demencia. La batería de test incluye las siguientes pruebas neuropsicológicas: FCSRT, BVMT. TMT, COWAT, BNT, BJLOT, WCST, Digit Span y memoria lógica. Encuentran alteraciones atencionales, de memoria episódica, de función ejecutiva y verbal en 18%, 14%, 13% y 13% de los sujetos respectivamente. En base a estos resultados, los autores proponen la existencia de un déficit prefrontal e y de hipocampo asociado a la enfermedad de Parkinson.

Schneider et al. (51) publican al año siguiente los resultados de las evaluaciones neuropsicológicas de los participantes en varios ensayos clínicos de futilidad (NET-PD), patrocinados por el instituto de Salud de EE.UU o NIH. Estos estudios aglutinan una muestra de 413 pacientes con Parkinson en fase precoz, e incluyen evaluaciones basales y a los 18 meses de seguimiento con los test FAB, RBANS y LNS. Sólo encuentran diferencias en las secuencias numéricas de letras (LNS), sin evidenciar un deterioro cognitivo en el tiempo. Concluyen que los test que emplearon no eran sensibles a los cambios cognitivos hipotéticamente presentes en su cohorte de sujetos, que tenía un alto nivel educativo y por tanto era más difícil encontrar diferencias.

Otro estudio relevante es el divulgado por Thaler et al. en el año 2012 (52). En él, los autores evalúan a una cohorte de 60 familiares de sujetos con Parkinson de origen genético, siendo 30 de ellos portadores de mutaciones en el gen de la LRKK2. Representa por tanto una de las iniciativas más grandes en las que se evalúan sujetos asintomáticos desde el punto de vista neurológico. Para ello usan un test de cribado cognitivo general como es el MoCA y también una tarea computarizada (mindstreams, Neurotrax Inc, NY) que mide diferentes funciones cognitivas. Encuentran en sujetos portadores alteraciones significativas (aunque en el rango de normalidad) en su funcionamiento ejecutivo.

Otro grupo constituido por Pedersen et al. es responsable del *Norwegian ParkWest project.* Mencionaremos dos de los trabajos reportados. El primero describe los resultados basales y de seguimiento a 3 años de una cohorte de 196 enfermos recientemente diagnosticados con enfermedad de Parkinson (53). Los datos de seguimiento incluyen 167 sujetos. Estudian diferentes funciones como la atención (test de Stroop), la memoria (CVLT), la fluencia semántica, y la percepción visuoespacial. Los autores encuentran alteraciones atencionales y en memoria verbal que predicen la conversión a demencia a los tres años. Recientemente, los autores han publicado los datos de seguimiento a 5 años en 150 sujetos de esta misma cohorte (54). Aunque en este estudio no comparan específicamente el rendimiento en las diferentes pruebas, si que reportan una cifra del 43,3% de sujetos con dos o más test alterados o lo que se denomina también como deterioro cognitivo ligero (MCI).

Finalmente, mencionaremos otras dos iniciativas que se han publicado en el año 2015. En la primera de ellas, el mismo grupo que estudió en 2009 a 88 sujetos, (55), publican ahora los resultados de los test neuropsicológicos de una cohorte nueva de 115 sujetos con enfermedad de Parkinson precoz. La batería utilizada incluye los siguientes test: FCSRT, BVMT BJLOT, digit span, TMT, BNT, COWAT, y WCST. Encuentran un 42,6% de los sujetos con MCI sobre todo con afectación de memoria episódica (FCSRT y BVMT), función visuoespacial (BJLOT), atención y flexibilidad mental (TMT) y en la fluencia semántica (animales).

Ese mismo año, Weintraub et al (56), estudian los resultados de la cohorte PPMI que incluye 423 sujetos con enfermedad de Parkinson y 196 controles sanos. Los test empleados fueron el HVLT-R, BJLOT, Symbol-digit modalities test, LNS y fluencia semántica (animales). Emplean tres definiciones operativas de MCI y encuentran porcentajes variables de sujetos. Con la definición más estándar, existe un 8,9% de los sujetos con dos o más test alterados. Encuentran alteraciones en la memoria en la gran mayoría de ellos (89,2%) y alteraciones ejecutivas, atencionales y en velocidad de procesamiento en una 10,8%.

En resumen, existen varios estudios previos a esta tesis en los que se ha documentado la existencia de alteraciones neuropsicológicas en las fases precoces de la enfermedad de Parkinson e incluso en lo que se conoce como fases preclínica de la enfermedad antes de que se haya establecido el diagnóstico (52). Además de los déficits fronto-ejecutivos/atencionales que suelen verse cuando el sujeto tiene demencia, también se han objetivado alteraciones en funciones que antiguamente se asociaban más al desarrollo de enfermedad de Alzheimer, como son los alteraciones mnésicas y en la fluencia verbal (57). Si bien esta última puede tener un componente ejecutivo (58).

I.v. Evaluación de la sintomatología cognitiva en enfermedad de Parkinson y temblor esencial

Como hemos visto en el apartado anterior, existen una multitud de test que se pueden emplear para evaluar la función cognitiva. Para facilitar la compresión de la literatura previa y de los resultados de este proyecto de investigación, hemos detallado aquí las funciones más frecuentemente evaluadas y los diferentes test que se han utilizado tanto por otros autores como por nosotros para ello. Esta descripción no pretende ser exhaustiva.

I.v.i. Test de *cribado* o de rendimiento cognitivo global

En este apartado describiremos tres test fundamentalmente.

MMSE: Este test fue descrito por Folstein et al. en el año 1975 (59). Se ha adaptado al Español por Lobo et al (60). Evalúa diferentes dominios cognitivos de forma grosera como son la memoria, atención y cálculo, orientación, lenguaje y capacidad visuoespacial. Su puntuación va de 0 a 30 puntos.

MMSE-37: Esta versión es una adaptación del test MMSE y es la que se ha utilizado en el estudio NEDICES. De forma adicional añade una tarea atencional más, una orden visual y una tarea de construcción consistente en copiar dos círculos solapados (61). Su puntuación va de 0-37 puntos.

MoCA: Este test también es un test de cribado poblacional y a diferencia de los anteriores incluye alguna tarea ejecutiva y visuoespacial adicional También mide orientación, lenguaje y memoria y se puntúa de 0-30 (62). Se muestra algo superior respecto a los test anteriores para el cribado de deterioro cognitivo en poblaciones afectadas por enfermedad de Parkinson (63).

I.v.ii. Test específicos

En la tabla 4 hemos incluidos los principales test específicos mencionados en este trabajo con la función que evalúan, las áreas principales del cerebro involucradas, el rango de puntuación y su referencia.

En el apartado de métodos específico de cada artículo se describirán los test empleado en mayor detalle y remitimos al lector a cada sección específica.

I.vi. Relevancia práctica de este trabajo

Queremos finalizar esta introducción resaltando la importancia o consecuencias prácticas de este trabajo. Esta radica en ampliar el conocimiento de las manifestaciones de ambas enfermedades, servir este conocimiento como base para avanzar en su fisiopatología , y también poder entender el riesgo de los sujetos que las padecen de desarrollar demencia, una complicación con un impacto evidente en la morbimortalidad de estos enfermos.

Tabla 4. Test neuropsicológicos de uso común para evaluar el temblor esencial y la enfermedad de Parkinson. Clasificación basada en el tipo de función cognitiva

Test	***Referencia***
Batería neuropsicológica	
RBANS	(64)
Funciones atencionales y ejecutivas	
WCST	(65)
TMT Parte A, Parte B	(66)
FAB	(67)
TOL	(68)
Digit Span	(69)
LNS (WAIS-III)	(70)
Test de Stroop	(71)
Symbol-Digit Modalities	(72)
Memoria	
CVLT	(73)
PRM	(74)
FCSRT	(75)
BVMT	(76)
Memoria Lógica	(77)
Láminas SEN	(61)
HVLT-R	(78)
Lenguaje	
BNT	(79)
Fluencia – Frutas	(80)
Fluencia – Animales	(80)
COWAT	(81)
Capacidad visuo-espacial	
BJLOT	(82)

HIPÓTESIS y OBJETIVOS

II. HIPÓTESIS Y OBJETIVOS

II.i. Hipótesis

- Existen alteraciones cognitivas en la enfermedad de Parkinson y el temblor esencial, en ausencia de demencia, a nivel poblacional.

- El gradiente de alteraciones esperables será mayor para la enfermedad de Parkinson, seguida del temblor esencial en comparación a controles sanos.

- Existe un solapamiento en las funciones cognitivas afectadas, pero es esperable que haya déficits específicos de cada entidad.

- Las alteraciones cognitivas representan manifestaciones precoces de la enfermedad que incluso acontecen en las fases preclínicas de ambas entidades.

II.ii. Objetivos

- Describir las alteraciones cognitivas que ocurren en la enfermedad de Parkinson y en el temblor esencial en ausencia de demencia y a nivel poblacional.

- Comparar el rendimiento cognitivo de la enfermedad de Parkinson frente al temblor esencial y viceversa en ausencia de demencia y en un contexto poblacional.

- Evaluar, en lo posible, el momento de aparición de las alteraciones cognitivas a través de la caracterización del rendimiento cognitivo en las fases preclínicas de la enfermedad

MÉTODOS

III. MÉTODOS

La metodología del estudio NEDICES ha sido ampliamente descrita en artículos previos (61,83–86). En esta sección nos limitaremos a resumir aquellos aspectos básicos que ayudan a entender este proyecto. También remitimos al lector a la sección de métodos de cada articulo incluido en esta monografía en la sección de resultados. Muchos de los aspectos metodológicos están recogidos en ellos (87–89).

III.i. Población y protocolo del estudio

Todas las investigaciones se hicieron sobre los participantes del estudio NEDICES, una encuesta poblacional acerca de la prevalencia, incidencia y principales determinantes de las condiciones neurológicas de una población anciana (≥ 65 años) de tres áreas del centro de España (84,90).

El estudio se aprobó por el Comité de Ética del Hospital 12 de Octubre y los participantes fueron evaluados en dos periodos de tiempo diferente. La evaluación basal ocurrió en los años 1994/1995 y la evaluación de seguimiento en los años 1997/1998. En estas evaluaciones se recogió información médica y sociodemográfica de cada participante (61). Además, se hizo una evaluación motora específica mediante las escalas UPDRS (91) y Hoehn-Yahr (92) y una evaluación específica del temblor (93).

III.ii. Criterios diagnósticos de temblor esencial y enfermedad de Parkinson y definiciones de enfermedad.

Para el diagnóstico de enfermedad de Parkinson, el cuestionario del estudio constó de tres preguntas específicas (existencia de un diagnóstico previo, temblor o bradicinesia). Aquellos que respondieron de forma positiva a una o más preguntas fueron evaluados en persona por un neurólogo. Éste estableció el diagnóstico de enfermedad de Parkinson cuando objetivó dos signos cardinales de la enfermedad (bradicinesia, temblor, rigidez o alteraciones posturales) y no encontró rasgos atípicos (94).

En el caso del temblor esencial, se preguntó en el cuestionario si el participante había tenido alguna vez temblor en las manos o extremidades inferiores que durara varios días. Aquellos que contestaron de forma positiva, al igual que en el ejemplo anterior, fueron evaluados por un neurólogo. Se estableció el diagnóstico de temblor esencial ante la presencia de temblor de acción en la cabeza, extremidades o voz sin otra causa atribuible. Además, el temblor debía ser de carácter gradual y o bien (i) haber ocurrido desde hace un año o más (ii) o haberse acompañado de una historia familiar (95).

Para cada enfermedad se definió además como caso prevalente a aquel que ya presentaba la condición en el estudio basal (1994-1995). Aquellos casos que no presentaban la enfermedad en el estudio basal, pero que la presentaron en el seguimiento se catalogaron como incidentes (87).

Para el diagnóstico de demencia se emplearon los criterios DSM (93).

III.iii. Evaluación Neuropsicológica

En las dos evaluaciones del estudio se hizo un cribado cognitivo global con el test *MMSE-37* además de con un test de funcionalidad (FAQ-Pfeffer) (96,97). Los resultados del test *MMSE-37* se dividieron a su vez por subdominios relacionados con orientación, memoria, atención, lenguaje y construcción visuo-espacial) (87).

De forma complementaria en la visita de seguimiento se aplicó una batería neurospicológica con los siguientes test:

- Velocidad de procesamiento psicomotriz con el TMT parte A (98).
- Fluencia verbal semántica: los participaron nombraron el máximo número posible de frutas y verduras en 60 segundos respectivamente (80,99).
- Memoria: Se evalúo con el test de los seis objetos (memoria de reconocimiento) y con memoria narrativa basada en el recuerdo de la historia del test de Wechsler (77).

III.iv. Selección final de participantes

De los 5278 participantes iniciales se seleccionaron aquellos con seguimiento y con los resultados de las pruebas neuropsicológicas evaluadas en cada subestudio. En el estudio comparativo entre temblor esencial y Parkinson, la muestra final comprendió 46 sujetos con enfermedad de Parkinson, 180 sujetos con temblor y 2212 participantes sanos (89).

En la evaluación del test MMSE-37 en la fase preclínica de la enfermedad de Parkinson se compararon un total de 2487 sujetos. Treinta y siete de ellos tenían enfermedad de Parkinson prevalente, 21 fueron evaluados antes del diagnóstico y estaban por tanto en la fase preclínica de la enfermedad. Para este estudio se compararon 2429 controles (87).

Finalmente, en el estudio que también caracterizó la caída en test MMSE-37, pero en sujetos con temblor esencial, la muestra final incluyó 2375 participantes de los cuales 137 tenían temblor esencial prevalente, 56 estaban en fase preclínica del temblor y se evaluaron 2184 controles para esta comparación (88).

Asociado a cada estudio hay un diagrama explicativo del flujo de evaluaciones y la selección de las muestras finales de participantes.

III.v. Análisis estadístico

De forma sucinta se hizo en primer lugar para cada estudio una comparación de las variables sociodemográficas. El objeto de la misma fue evidenciar desajustes en las poblaciones de estudio en potenciales variables confundidoras de la hipótesis de estudio. Ante la no normalidad estadística de los estudios neuropsicológicos, se realizaron análisis no paramétricos comparativos de las variables de interés. Posteriormente, se ajustó con modelos multivariantes para ajustar por los potenciales confundidores encontrados en el primer análisis. Adicionalmente se realizaron análisis estratificados para descartar nuevamente efectos espurios de otras variables que pueden confundir los resultados de los estudios neuropsicológicos (prestando especial atención al nivel educativo y edad de los participantes). Para estos análisis se utilizaron los paquetes estadísticos SPSS y R (100).

RESULTADOS

IV.RESULTADOS

Accepted: 9 February 2017

DOI: 10.1111/ane.12752

ORIGINAL ARTICLE

WILEY Acta Neurologica Scandinavica

Cognition in non-demented Parkinson's disease vs essential tremor: A population-based study

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Funding information
The Spanish Health Research Agency and the Spanish Office of Science and Technology supported NEDICES. Dr. Alvaro Sanchez-Ferro has received funding from Consejería de Educación, Juventud y Deporte of Comunidad de Madrid, and the People Programme (Marie Curie Actions) of the European Union's Seventh Framework Programme (FP7/2007-2013) under REA grant agreement n° 291820. Dr. Sánchez-Ferro has also been supported by the Madrid-MIT M+Vision Consortium (Comunidad de Madrid). Dr. Benito-León is supported by the National Institutes of Health, Bethesda, MD, USA (NINDS #R01 NS39422), the Commission of the European Union (grant ICT-2011-287739, NeuroTREMOR), and the Spanish Health Research Agency (grant FIS PI12/01602). Dr. Louis has received research support from the National Institutes of Health: NINDS #R01 NS042859 (principal investigator), NINDS #R01 NS39422 (principal investigator), NINDS #R01 NS086736 (principal investigator), NINDS #R01 NS073872 (principal investigator), NINDS #R01 NS085136 (principal investigator), and NINDS #R01 NS088257 (principal investigator). Dr. Bermejo-Pareja is supported by NINDS #R01 NS39422 from the National Institutes of Health, Bethesda, MD, USA, and from the Commission of the European Union (grant ICT-2011-287739, NeuroTREMOR)

Objectives: Patients with Parkinson's disease (PD) and essential tremor (ET) have a higher risk of cognitive impairment than age-matched controls. Only a few small studies (11-18 subjects per group) have directly compared the cognitive profile of these conditions. Our aim was to compare the cognitive profile of patients with these two conditions to each other and to healthy individuals in a population-based study of non-demented participants.

Materials and methods: This investigation was part of the NEDICES study, a survey of the elderly in which 2438 dementia-free participants underwent a short neuropsychological battery. We used nonparametric techniques to evaluate whether there are differences and/or a gradient of impairment across the groups (PD, ET, and controls). Also, we performed a head-to-head comparison of ET and PD, adjusting for age and education.

Results: Patients with PD (N=46) and ET (N=180) had poorer cognition than controls (N=2212). An impaired gradient of performance was evident. PD scored lower than ET, and then each of these lower than controls, in memory (*P*<.05) and verbal fluency (*P*<.001) tasks. When we compared PD and ET, the former had lower scores in verbal fluency (*P*<.05), whereas the later had a poorer cognitive processing speed (*P*<.05).

Conclusions: This large population-based study demonstrates that both conditions influence cognitive performance, that a continuum exists from normal controls to ET to PD (most severe), and that although deficits are in many of the same cognitive domains, the affected cognitive domains do not overlap completely.

KEYWORDS
epidemiology, movement disorders, neurobehavioral manifestations, neuropsychological profile, neuropsychology

1 | INTRODUCTION

Patients with Parkinson's disease (PD) and essential tremor (ET) have a higher risk of cognitive impairment than healthy individuals who are matched by age and education.[1,2] Their pattern of dysfunction has traditionally been labeled as that of a fronto-subcortical type.[3] Deficits in areas such as attention,[4,5] verbal fluency,[2,5] and memory[6] may be noted even at early stages of both conditions.[2,7] In PD, this impairment has been linked with degeneration of cortical association areas.[8] In ET, the neuropathological correlates of cognitive impairment have not been completely elucidated.[9]

While considerable efforts are being made to fully characterize and better understand the non-motor features of ET and PD, the two most common tremor disorders,[10-12] only three studies have directly compared the cognitive profile of these two disorders, and each of these had small sample sizes (11-18 patients in each group).[6,13,14] Furthermore, two of the studies[6,13] enrolled surgical patients, a highly selected group whose cognitive deficits are likely to differ from (ie, be less marked than) those of the average patient. All three studies assessed patients who self-selected for treatment (ie, patients attending clinics) rather than those sampled directly from the population. Clinic patients often differ phenotypically from those in the population. Finally, patients with both ET and PD may have Alzheimer's disease (AD) and other forms of dementia, and none of the studies explicitly removed these from the sample to obtain a less-confounded and cleaner picture of cognition. Hence, there is a need for more comprehensive study.

In this population-based study of non-demented participants, we performed a head-to-head comparison of the cognitive profile of 180 individuals with ET and 46 with PD, comparing them to 2212 healthy aged controls. Our four a priori hypotheses were that (i) both conditions affect cognitive performance relative to that of controls, even in the absence of a clinical diagnosis of dementia, (ii) a continuum exists in this performance from normal controls to ET to PD (most severe), (iii) the deficits in ET and PD are in many of the same cognitive domains; however, (iv) the affected cognitive domains do not overlap completely, and there are demonstrable differences between ET and PD.

2 | MATERIAL AND METHODS

2.1 | Study population

This investigation was part of the Neurologic Disorders in Central Spain (NEDICES), a population-based survey of the prevalence, incidence, and determinants of major elderly-associated conditions. Detailed accounts of the background, study population, and methods of the survey have been reported.[15-17]

2.2 | Standard protocol approvals, registrations, and patient consents

All procedures were approved by the ethical standards committees on human experimentation at "12 de Octubre" Hospital (Madrid). Written (signed) informed consent was obtained from all enrollees.

2.3 | Study evaluation

Detailed accounts of the study assessments have been published.[16,18,19] Face-to-face evaluations were performed at baseline (1994-1995) and at one follow-up (1997-1998). The face-to-face interview included data collection on demographics, current medications (including medications with central nervous system [CNS] effects), medical conditions (eg, diabetes mellitus, hypertension, and heart disease), lifestyle habits, and the presence of depressive symptoms (the question, "do you suffer from depression?"). As described,[18] a neurological examination was performed, comprising a general neurological examination, a tremor examination, and the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS)[20] and the Hoehn-Yahr scale.[21]

2.4 | Diagnostic criteria for PD and ET

Diagnostic criteria for ET,[18] PD,[19] and dementia[1] have been described elsewhere. For the diagnosis of PD, the study questionnaire had three questions to screen for parkinsonism (ie, previous diagnosis of PD, presence of tremor, and presence of bradykinesia). Persons who screened positive (ie, they responded positively to ≥1 of these three questions) for PD underwent a general neurological examination and the motor portion of the UPDRS.[20] Parkinsonism was diagnosed when at least two cardinal signs (resting tremor, rigidity, bradykinesia, and impaired gait/postural reflexes) were present. PD was diagnosed in patients without secondary causes of parkinsonism or atypical features.[19] A Hoehn and Yahr stage was assigned to each case.[21]

The evaluation of tremor and diagnosis of ET involved a screening question in the questionnaire ("have you ever had tremor of the head, hands, or legs that has lasted longer than several days?") with 68.6% sensitivity.[22] The same examination as in PD was performed. It also included an assessment of postural and kinetic tremors (sustained bilateral arm extension, bilateral finger-nose-finger maneuver, drawing Archimedes spirals) and UPDRS.[20] Participants were diagnosed with ET if they had an action tremor of the head, limbs, or voice without any other recognizable cause. Second, the tremor had to be of gradual onset (ie, slow and progressive) and (i) present for at least 1 year or (ii) accompanied by a family history of the same disorder (at least one reportedly affected first-degree relative). In addition, on an Archimedes spiral, tremor severity had to be moderate or greater (rating >2 according to the Washington Heights-Inwood Genetic Study of ET Rating Scale).[23] Participants with tremor related to alcohol withdrawal, hyperthyroidism, anxiety, PD, antidopaminergic drug intake, lithium therapy, or other known causes of tremor were not considered to have ET. If ET was diagnosed, the age of onset of tremor was elicited.[22]

2.5 | Neuropsychological tests

During the follow-up evaluation (1997-1998), all participants underwent a short neuropsychological evaluation.[24,25] The tests used were as follows:

1. Global cognitive performance: This was assessed with an expanded, 37-item version of the Mini-Mental State Examination (37-MMSE) that ranged from 0 to 37.[26,27]
2. Psychomotor or cognitive processing speed: This was assessed with the Trail Making Test part A.[28] Here, we report the number of errors while performing the task.
3. Verbal fluency: For semantic fluency, participants were asked to name as many different animals and fruits as they could within 60 seconds.[29]
4. Memory: This was evaluated with the following tests: a) six-object test[24,30](naming test): This was the ability to recall six objects 5 minutes later [range 0 (greater cognitive impairment) to 6]). b) Story recall: The "story recall" task was derived from the Wechsler Memory Scale-Rev. and measured memory (delayed logical memory) for aurally presented contextual material. The total number of words recalled was summed (range 0 [greater cognitive impairment] to 6).[31]
5. Premorbid intelligence: This was evaluated with the "Word Accentuation" Test. This test assesses the accentuation of 30 infrequently used Spanish words written without the accent marks (range 0 [greater impairment] to 30).[32]

2.6 | Final selection of participants

Of the 5278 participants who were enrolled at baseline, 672 were lost to follow-up (112 declined and 560 were unreachable) and 790 died before they were contacted the second time. Of the remaining 3816, we excluded 921 with missing neuropsychological information and 457 subjects with stroke or dementia. The final sample (N=2438) included patients with PD (N=46) and ET (N=180), as well as the remaining healthy controls (N=2212) (Figure 1). This sample was similar to the initial 3816 individuals in terms of sex (1403 [57.4%] vs 2231 [58.5%] women, chi-square=0.47, P=.489), but on average was 0.9 years younger (75.6±5.7 vs 76.5±6.4 years, P<.001) and included a lower percentage of illiterate subjects (238 [10.0%] vs 489 [12.9%], chi-square=11.50, P<.001).

2.7 | Statistical analyses

Statistical analyses where performed using R.[33] Significance was accepted at the 5% level (two-sided). Neuropsychological tests scores were not normally distributed (Kolmogorov-Smirnov tests for all items, P<.001). Therefore, although mean and median values were reported, differences across groups and cognitive domains were assessed with a Kruskal-Wallis test correcting for post hoc multiple comparisons. The chi-square test was used to analyze categorical variables. We used the Jonckheere-Terpstra test, a nonparametric method, to detect a trend (gradient) of performance in the neuropsychological results. In addition, we computed adjusted T scores for each test.[34] To do this, healthy participants were divided in twelve groups by age in tertiles (≤68 *years*, from 69 to 74 years, and ≥75 *years*), and educational category (illiterate, can write and read, primary studies, secondary studies, or higher). Then, with the mean and standard deviation of their respective healthy control group, the T score was calculated for each patient with PD and ET. With these adjusted T scores, we compared

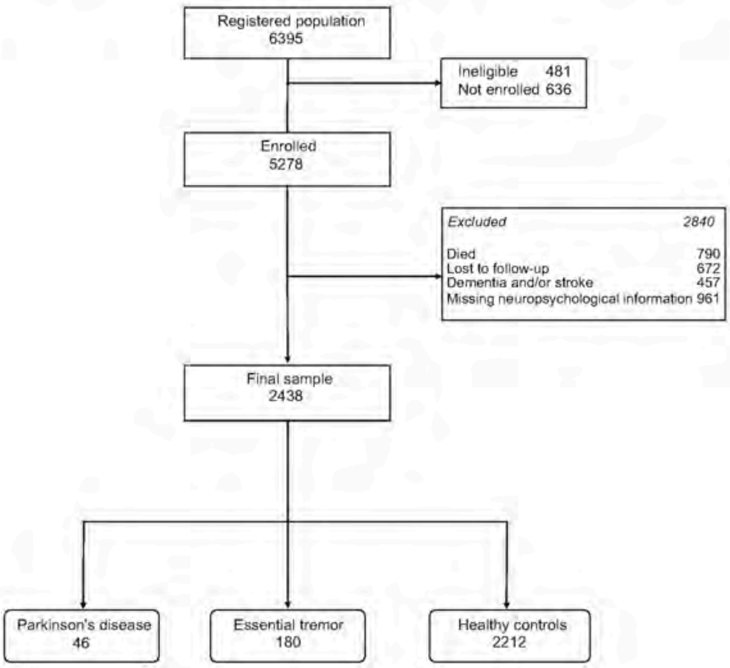

FIGURE 1 Flowchart of the study

the performance of the ET and PD groups in the different cognitive domains avoiding for the confounding effects of age and education. The cutoff for normality was defined as one (T score<40) or two standard (T score<30) deviations from the reference values.[34]

To further adjust for confounding, a series of nonparametric stratified analyses was performed. The purpose of these tests was to understand the magnitude and directionality of the effect of these confounders on the cognitive tests results rather than their significance (ie, if PD or ET scored lower than the controls across the different strata). The strata were defined by age in tertiles (≤*68 years*; from 69 to 74 years and ≥*75 years*), gender (male vs female), education (illiterate, can write and read, primary studies, secondary studies, or higher), presence of depressive symptoms (no vs yes), and medications with CNS effects (no vs yes). In addition, we double-checked the results of the stratified results in the younger and more educated subjects. We performed a final subanalysis to define the influence of the age of onset (≥65 years) on the cognitive performance of the patients with ET. The purpose was to evaluate whether there was a different cognitive phenotype of those with an older onset.[35]

3 | RESULTS

3.1 | Demographic features

The final sample included 46 patients with PD, 180 patients with ET, and 2212 healthy controls (Table 1). The groups differed in terms of age, sex, educational level, intake of medications with CNS effects, and depressive symptoms. The patients had mean disease duration of 5.3 [4.0]±5.1 years (PD) and 10.4 [6.0]±12.2 years (ET). In the PD group, 29 [63.0%] had unilateral disease (stage I) or bilateral disease without axial symptoms (stage II), based on the Hoehn-Yahr scale.

3.2 | Cognitive performance—ET and PD vs controls (hypothesis 1)

Essential tremor and Parkinson's disease patients performed significantly more poorly than controls in several tests and in global cognition (Table 2; Fig. S1). When the patients with PD and ET were compared with the controls, the mean raw difference for the global cognition test (ie, the MMSE-37) was −2.3 points and −1.6 points, respectively. The six-object and the story delayed recall test scores were −0.7 and −0.8 points significantly worse in the patients with PD than the controls. In the verbal fluency tasks, there was a greater than one-point difference for both the animal- and fruit-naming tests between the PD group and the controls. Finally, the patients with ET erred one point more than the controls in the cognitive processing speed task, the Trail Making Test part A, although the significance was lost in the post hoc comparison. In analyses that stratified by age in tertiles, gender, prior education, presence of depressive symptoms, and CNS drug intake, the group differences observed in the primary analyses persisted (data not shown).

3.3 | Cognitive performance—trend analyses (hypothesis 2)

Based on the Jonckheere-Terpstra test (Table 2), a significant trend was detected: The patients with PD scored less well than the patients with ET, and these scored less well than the controls. This trend was evident for global cognition ($P<.001$), both memory tasks ($P<.05$), and the fruit-naming test ($P<.001$). The only test in which patients with ET performed more poorly than patients with PD and controls was cognitive speed processing, in which patients with ET showed a nonsignificant trend of increased number of errors ($P=.071$). Again, these

TABLE 1 Demographic and baseline features of the participants (N=2438)

	Parkinson's disease [PD] (N=46)	Essential Tremor [ET] (N=180)	Healthy Controls [CNT] (N=2212)	Significance test* Post hoc *comparison*
Age (years)	78.1 [77.5]±5.5	76.2 [75.5]±5.7	75.4 [74.5]±5.7	**P<.001** PD>CNT
Sex (female)	17 (37.0)	107 (59.4)	1279 (57.8)	**P=.016** PD<CNT; PD<ET
Education				
Illiterate	9 (19.6)	31 (17.2)	198 (9.0)	**P=.006** (Illiterate percentage) PD>CNT; ET>CNT
Can write and read	18 (39.1)	73 (40.6)	942 (42.6)	
Primary studies	17 (37.0)	52 (28.9)	743 (33.6)	
Secondary or higher	2 (4.3)	24 (13.3)	328 (14.8)	
Medications with CNS effects (yes)[a]	18 (39.1)	67 (37.2)	431 (19.5)	**P<.001** PD>CNT; ET>CNT
Answered yes to the question "do you suffer from depression?"	16 (34.8)	75 (41.7)	476 (21.5)	**P<.001** ET>CNT

Quantitative data as mean [median]±standard deviation for continuous variables or frequencies (percentages) for categorical variables; significant results are in bold.

*Kruskal-Wallis and chi-square tests adjusted for post hoc pairwise comparisons.

[a]Medications potentially influencing cognitive performance (anxiolytics, stimulants, antipsychotics, antidepressants, antihistamines, antihypertensive agents, or antiepileptic drugs).

TABLE 2 Neuropsychological performance of the NEDICES participants grouped by diagnostic category (N=2438)

	Parkinson's disease [PD] (N=46)	Essential tremor [ET] (N=180)	Healthy controls [CNT] (N=2212)	Significance test* Post hoc comparison	Trend analysis *Jonckheere-Terpstra test*
Global cognition *37-Mini-Mental State Examination*	27.8 [28.5]±6.0	28.5 [29.0]±5.2	30.1 [31.0]±4.8	**P<.001** *PD<CNT; ET<CNT*	**P<.001**
Memory *Six-object test delayed recall*	3.4 [4.0]±1.7	3.9 [4.0]±1.7	4.1 [4.0]±1.5	**P=.005** *PD<CNT*	**P=.011**
Memory *Story delayed recall*	2.9 [3.0]±2.2	3.5 [4.0]±2.1	3.7 [4.0]±2.0	**P=.007** *PD<CNT*	**P=.007**
Verbal fluency *Number animals in 1′*	12.0 [11.0]±5.6	13.5 [13.0]±4.7	13.4 [13.0]±4.4	**P=.020** *PD<CNT; PD<ET*	P=.200
Verbal fluency *Number fruits in 1′*	9.3 [8.5]±3.2	9.9 [10.0]±3.1	10.5 [10.0]±3.0	**P=.001** *PD<CNT*	**P=.001**
Cognitive speed processing** *Trail Making Test errors*	1.7 [0.0]±4.1	2.8 [0.0]±5.7	1.8 [0.0]±4.4	**P=.047** Post hoc comparison N.S	P=.071
Premorbid intelligence** *Word Accentuation Test*	13.8 [15.0]±8.2	15.6 [16.0]±9.1	16.4 [16.0]±8.7	P=.226	P=.160

Data as mean [Median]±standard deviation for continuous variables or frequencies (percentages) for categorical variables; significant results are in bold; N.S=non-significant.

*Kruskal-Wallis test adjusted for post hoc pairwise comparisons.

**N=2171 for Trail Making Test part A time (PD=34; ET=148; controls=1989), N=2161 for Trail Making Test part A errors (PD=35; ET=144; controls=1982), and N=1823 for the Word Accentuation Test (PD=33; ET=133; controls=1657).

relationships continued in stratified analyses that considered the same variables as in hypothesis 1 (data not shown).

3.4 | Cognitive profile—ET vs PD (hypotheses 3 and 4)

The head-to-head comparison of the ET and PD patients is detailed in Table 3. The calculated T scores were consistently lower in the patients with PD, except for the cognitive processing speed task, but they only reached significance in the lower number of animals that the PD individuals named (*P*=.05). With respect to the percentage of patients with abnormal results, defined by a T score below forty, in all tests there were subjects who could be considered impaired. In the animal-naming test, 12 patients with PD (26.1%) scored abnormally in comparison with 25 ET patients (13.9%) (*P*=.07). When all of the cognitive tests were considered, there were 26 PD (56.5%) and 82 ET (45.6%) patients with at least one abnormal domain. By domain, there were 19 PD (41.3%) and 59 ET (32.8%) patients with a poorer performance in memory tasks, 16 PD (34.8%) and 41 ET (30.0%) with abnormal language functioning and 2 PD (5.7%) vs 18 ET (12.5%) patients showing more errors in the cognitive speed-processing task. None of these differences reached significance.

When we excluded the illiterate and older (third tertile, ie, ≥75 years) patients (N=78 ET and 13 PD), the difference in language performance of the two groups was significant (*P*=.02) with seven PD (53.8%) vs 15 ET (16.7%) scoring in the abnormal range. The other domains' differences remained similar and did not reach significance.

3.5 | Age of tremor onset and its influence on the cognitive performance of ET

When we stratified patients with ET by age of tremor onset, 58 (32.2%) had their onset prior to age 65 years and 122 (67.8%) had an onset ≥65 years. The two groups differed in terms of their median current age (71.5 vs 75.5 years, respectively; *P*<.05). Their neuropsychological performance was similar in all tests, with only the one exception of the animal-naming task (*P*<.05). When we computed the adjusted T scores by age and educational attainment, this difference was no longer significant (*P*=.10).

4 | DISCUSSION

In this study, we characterized the cognitive performance of a population-based sample of 46 patients with PD, 180 patients with ET, and 2212 healthy controls. Our goal was to test four a priori hypotheses about the cognitive profile of PD and ET patients relative to that of controls and relative to one another.

Our first a priori hypothesis was that both ET and PD would have poorer cognitive performance relative to that of controls, even in the absence of a clinical diagnosis of dementia. Our results confirm this hypothesis by demonstrating the existence of significant differences in an important percentage of patients with each of these movement disorders when they were compared with healthy individuals. These results support those previously reported by Lombardi et al. in a small sample of 18 patients with ET and 18 patients with PD, although that study did not enroll healthy controls; rather, data from enrolled ET and PD patients were compared to published normative data.[6]

TABLE 3 Comparison of the different cognitive domains ("T scores") in the Parkinson's disease (N=46) and essential tremor (N=180) participants

	Parkinson's disease (PD)	Essential Tremor (ET)	Significance test*	PD vs ET cases with a T score<40 (%)	PD vs ET cases with a T score<30 (%)
Global cognition *37-Mini-Mental State Examination*	48.1 [50.8]±10.5	48.4 [50.4]±9.93	P=.922	15 (32.6) vs 44 (24.6)	2 (4.3) vs 8 (4.5)
Memory *Six-object test delayed recall*	46.3 [47.5]±10.9	48.7 [51.4]±11.3	P=.115	12 (26.1) vs 36 (20.0)	5 (10.9) vs 18 (10.0)
Memory *Story delayed recall*	47.3 [49.4]±10.8	49.3 [53.0]±10.8	P=.279	15 (32.6) vs 43 (23.9)	2 (4.3) vs 13 (7.2)
Verbal fluency *Number animals in 1*	48.6 [46.5]±12.8	51.4 [51.4]±11.0	P=.050	12 (26.1) vs 25 (13.9)	1 (2.2) vs 0 (0.0)
Verbal fluency *Number fruits in 1*	47.8 [43.9]±10.3	49.3 [48.2]±10.8	P=.209	8 (17.4) vs 28 (15.6)	1 (2.2) vs 3 (1.7)
Cognitive speed processing[a] *Trail Making Test errors*	50.9 [54.1]±9.4	47.8 [53.8]±14.3	P=.100	2 (5.7) vs 17 (11.8)	1 (2.2) vs 10 (6.9)

Quantitative data as mean [median]±standard deviation.
*Mann-Whitney test.
[a]Trail Making Test part A; PD=35; ET=145; A T score of 40 or 30 represents, respectively, one or two standard deviations from the normal values of their age and schooling group.

Our second a priori hypothesis was that a gradient of neuropsychological performance would exist between PD, ET, and healthy controls, with the former being the most affected. This continuum was demonstrated by the raw and stratified trend analyses we performed in language and memory domains. Gasparini et al., in a clinic-based study, previously suggested the likely presence of such a continuum of impairment. They studied 15 patients with PD, 15 ET patients with familial history of ET, 15 ET patients with a familial history of PD, and 15 controls. Their research highlighted an altered performance in attentional tasks for both ET and PD groups, but with the PD group showing broader deficits.[13] A more recent study of surgical patients by Benge et al.,[14] which validated an executive scale in a sample of deep brain stimulation candidates, included 15 patients with PD and 11 patients with ET. The patients with PD performed more poorly that the patients with ET in this scale.[14] Most prior studies enrolled and assessed patients with PD or patients with ET, but not both. None of these studies were population-based or specifically ruled out AD and other dementia subtypes.

The third and fourth hypotheses suggested an overlap of the affected cognitive domains in ET and PD, yet not a complete overlap. In the study of Lombardi et al., the ET group performed more poorly in verbal fluency tests, whereas the patients with PD also had poorer performance in visuospatial, memory, and attentional tasks.[6] Moreover, Gasparini et al. reported an altered performance in some attentional tasks for both ET and PD, but with the patients with PD performing less well in some verbal fluency and executive tasks.[13] In our cohort, in the trend analyses, the PD participants performed less well than the patients with ET, and both groups performed less well than the controls, in tests measuring global cognition, memory, and verbal fluency. These results confirm the existence of an overlap of affected domains.[36] Nonetheless, when the intensity and the percentage of subjects with an impaired function in a specific domain were compared, the two groups showed differences. In this head-to-head comparison, patients with ET consistently scored less well than the patients with PD in cognitive processing speed, although this result was marginally significant in the trend analyses. This fact could be related to greater cerebellar involvement of the ET cases[37,38] as, in our opinion, tremor itself could not justify an increased number of errors.[38] Nonetheless, this last point will have to be confirmed in future studies, as it is fairly hypothetical. On the other hand, our results differ from those of Lombardi et al[6] as the PD, and not the ET, had a significantly poorer performance in verbal fluency. This is in agreement with what Gasparini et al.[13] and larger epidemiological studies.[39] Overall, the differences noted for some of the tests were modest when compared with previous studies.[39] The largest difference was noted for the six-object test in the patients with PD and patients with ET.

These NEDICES study results highlight the current view that PD and ET patients have on non-motor cognitive features even when there are no signs of dementia.[7,12] The PD sample mainly included mild cases (63% cases had a Hoehn-Yahr stage ≤2), and hence, a cortical neuropathological involvement, according to Braak staging, seemed unlikely. Considering the five-year mean disease duration, the chance of misdiagnosing PD with dementia with Lewy bodies also seems improbable.[40]

In the current sample of ET and PD patients, we observed certain domains to be affected. It is worthwhile noting that there may be some overlap with what may be found in other neurodegenerative conditions. For example, during the preclinical stage of Alzheimer's disease, selective impairment of memory function may be observed.[41] In preclinical stages of frontotemporal dementia, executive and language deficits have been reported.[42]

Regarding the clinical consequences of our findings, various reports have evidenced that subtle cognitive deficits, even in the absence of dementia, can impact the quality of life, predict "loss of independence," and impair activities of daily living in these frequent movement disorders.[43-46] Nonetheless, the clinical and prognostic implications of these deficits will have to be studied further.

Recently, it has been proposed that late onset of tremor (ie, ≥65 years) could represent a different clinical entity than earlier onset ET.[35] With this in mind, we performed a subanalysis, stratifying patients with ET by age of onset. The neuropsychological performance of the two groups was similar in all tests. Based on our data, there does not seem to be a distinct cognitive phenotype in participants with younger tremor onset (ie, <65 years) compared with later tremor onset (ie, ≥65 years); however, additional studies are needed before firm conclusions may be reached.

Our study has several limitations. First, we had to exclude a large proportion of subjects because of lost to follow-up, missing neuropsychological data, and other attrition issues. The excluded subjects were slightly older and had a slightly higher percentage of illiterates than those who were included. The potential bias introduced would most likely have been toward a poorer performance among those who were excluded. In addition, the NEDICES study only included participants aged 65 years or older. Therefore, these analyses will have to be replicated in younger subjects. Second, the number of tests we could include was limited because the evaluation was part of a larger epidemiological study. It would have been interesting to characterize additional domains (eg, visuospatial function). Another important limitation of our study is the lack of additional time-point evaluations, from which the evolution of these cognitive phenotypes could have been addressed. Certainly, future efforts should include additional follow-up visits to confirm and expand our results. Moreover, our evaluation of depression was limited, and we may have underascertained depression, resulting in residual confounding. Nevertheless, a validation study showed a high level of agreement between the data generated from the screening question we used and a more detailed in-person psychiatric assessment, suggesting that such residual confounding is likely to have been low.[47] Further, we could not completely rule out confounding effects of other covariates. Because of the non-normality of the neuropsychological data, our approach to minimize the effect of these confounders in the tests' scores was to perform stratified analyses, evaluate T scores adjusted by age and education, and also reproduce some of the analyses in younger subjects with a higher educational category.

We believe that our conclusions are important for the definition and characterization of the cognitive aspects of ET and PD. We have confirmed that PD and ET impair cognitive performance, even in the absence of dementia, and that a continuum of severity exists between the two conditions, with PD showing a greater impact than ET. Also, there is some overlap in the type of impairment that they produce, but with disease-specific features, such as the predominant effect in verbal fluency of PD and in cognitive processing speed of ET. The last aspect should be further investigated to elucidate the mechanisms and structural correlates producing these diverse early cognitive effects. Besides their pathophysiological implications, these data could have added value in the differential diagnosis, prognosis, and management of these frequent movement disorders.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Carmen Gasca for her suggestions to improve this publication. The authors gratefully acknowledge the vital help of the other members of the NEDICES Study Group: Additional information about collaborators of the NEDICES study can be found on the Web (http://www.ciberned.es/estudio-nedices).

CONFLICT OF INTEREST

ASF, JBL, EDL, IC, JHG, VPM, and FBP report no disclosures.

AUTHOR CONTRIBUTIONS

ASF collaborated in the conception, organization, and execution of the research project; the statistical analysis design; and the writing of the manuscript first draft and the review and critique of the manuscript. JBL collaborated in the conception, organization, and execution of the research project; the statistical analysis design; and the review and critique of the manuscript. EDL collaborated in the conception, organization, and execution of the research project; the statistical analysis design; and the review and critique of the manuscript. IC collaborated in the conception, organization, and execution of the research project; the interpretation of the results; and the review and critique of the manuscript. JHG collaborated in the conception of the research project and the review and critique of the manuscript. VPM collaborated in the interpretation of the results and the review and critique of the manuscript. FBP collaborated in the conception, organization, and execution of the research project; the statistical analysis design; and the review and critique of the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Sánchez-Ferro Á, Benito-León J, Louis ED, et al. Cognition in non-demented Parkinson's disease vs essential tremor: A population-based study. *Acta Neurol Scand*. 2017;00:1-8. https://doi.org/10.1111/ane.12752

RESEARCH ARTICLE

Rate of Cognitive Decline in Premotor Parkinson's Disease: A Prospective Study (NEDICES)

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ABSTRACT: Previous research has documented cognitive impairment in the early stages of Parkinson's disease (PD). It is not known when this decline starts or if decline progresses at an accelerated rate during the premotor period of the disorder. In this population-based prospective study of older people (≥65 years) from the Neurological Disorders in Central Spain (NEDICES) cohort, we compared the rates of cognitive decline in 3 groups: (1) non-PD elderly controls; (2) prevalent PD patients (those diagnosed with the disease at baseline, 1994–95); and (3) premotor PD subjects (those diagnosed with the disease at follow up, 1997–98, but not at baseline). A 37-item version of the Mini–Mental State Examination (37-MMSE) was administered in the 2 visits of the study. From 2487 participants (age, 72.8 ± 6.0 years), including 2429 controls, we recruited 21 premotor PD cases, and 37 prevalent PD cases. At baseline, the mean 37-MMSE score was 28.5 ± 4.7 in prevalent cases, 28.1 ± 4.6 in premotor cases, and 29.9 ± 5.0 in controls (P = .046). During the 3-year follow-up period, there was a significant score decline of 2.4 ± 4.6 points in prevalent cases versus 0.2 ± 4.1 points in premotor cases and 0.3 ± 4.0 points in controls (Kruskal-Wallis test, P = .03). In the NEDICES cohort, cognitive test scores of prevalent PD cases declined at a rate above and beyond that observed in premotor PD cases and in controls. The rate of cognitive decline in premotor PD and controls was similar. Our data suggest that a decline in global cognitive function does not occur in premotor PD. © 2012 *Movement* Disorder Society

Key Words: cognitive function; elderly; epidemiology; Parkinson's disease; premotor symptoms; population-based study

Cognitive dysfunction is a common and disabling feature among Parkinson's disease (PD) patients.[1] Traditionally, it has been linked to the late stage of the disorder, although recent evidence suggests it also may appear early in the evolution of PD.[2–6] Most of these data came from clinical series, which are prone to recruitment bias.[3,4] Population-based studies that prospectively assess if cognitive dysfunction appears in early PD are rare.[2,5,7] Furthermore, in those studies, patients were referred by practitioners or ascertained through medical records linkage[2,5,7]; therefore, they may have excluded patients who do not seek medical advice In addition, sampling patients with more severe forms of the disease may have influenced their findings. In the population-based Neurological Disorders in Central Spain (NEDICES) study, all participants

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Funding agencies: The Spanish Health Research Agency and the Spanish Office of Science and Technology supported NEDICES.

Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

Received: 4 February 2012; **Revised:** 2 July 2012; **Accepted:** 17 July 2012
Published online 12 December 2012 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.25148

were assessed for PD irrespective of their medical care.[8–12] Of the patients with PD, 28.4% had not been diagnosed prior to the start of the study and would not have been recruited if we had relied exclusively on practitioner referrals.[11] We recently reported that cognitive dysfunction is not typically a premotor feature of subjects who subsequently develop PD in NEDICES.[13] However, it is not known whether cognitive decline progresses in premotor PD cases at a faster rate than in elders without this disease.

To our knowledge and based on those preliminary analyses, we have conducted the first population-based longitudinal study in which all participants were assessed for PD regardless of their medical care, documenting changes in global cognitive function prospectively over time, comparing prevalent PD cases (ie, diagnosed with PD at baseline) with premotor PD cases (diagnosed with incident PD at follow-up) as well as controls without this disease (not diagnosed with PD at baseline or at follow-up). We hypothesized that the cognitive deficits in PD would not be static but would deteriorate, mainly in prevalent PD cases, and that this deterioration would occur at a rate above and beyond that observed in premotor PD cases and similarly aged controls. To address this question, we utilized data from the NEDICES, in which PD cases (including premotor PD cases) and controls were prospectively evaluated 2 times separated by approximately 3 years.

Patients and Methods

Study Population

Data for these analyses were derived from the NEDICES study. Detailed accounts of the study population and sampling methods have been published.[8–12,14–20] Institutional ethics approval and written informed consent from participants at the time of enrollment were obtained.

Evaluation

The study population was composed of elderly subjects ≥ 65 years old living in 3 well-defined geographical areas in central Spain (Las Margaritas, Lista, and Arévalo). Face-to-face interviews included data collection on demographics, current medications, medical conditions, lifestyle habits, and the presence of depressive symptoms or use of antidepressant medications, a marker that may be less prone to recall bias than the screening question.[21] As described,[11,12] neurological examinations were performed when PD was diagnosed.[22] Albeit not specifically designed for PD, the 37-item Mini–Mental State Examination (37-MMSE) was administered to evaluate global cognitive performance of the cohort.[19,20,23–26] It included all the standard MMSE items as well as 3 additional items: (1) an attention task, that is, "Say 1, 3, 5, 7, 9 backwards"; (2) a visual order, that is, a man raising his arms; and (3) a simple construction task, that is, copying 2 overlapping circles.[12,19,23–26] In addition to the global score, different cognitive domain tasks were grouped in subscores (10 points for orientation, 6 points for memory, 10 points for attention, 9 points for the different language tasks, and 2 points for construction).

Screening methods and diagnostic criteria used for PD[11,12] dementia,[19,20] essential tremor,[15] and stroke[17,18] have been described elsewhere.

All subjects who fulfilled the criteria for PD at both baseline (1994–95) and follow-up (1997–98) evaluations were considered prevalent PD. Premotor PD were defined as those subjects who were free of PD at the first wave but who developed PD during follow-up.

When parkinsonism and dementia occurred simultaneously at the time of diagnosis, the subject was not diagnosed with PD. We relied only on routine clinical diagnosis, not employing an exact time span to differentiate PD from other synucleinopathies (criteria for dementia with Lewy bodies were proposed just after the NEDICES study was designed).[27]

Final Selection of Participants

Of the 5278 participants who were evaluated at baseline, we excluded 727 with prevalent dementia or other prevalent neurological conditions such as stroke and essential tremor, known to be associated with cognitive changes and dementia.[24,25,28,29] This was because our aim was to assess changes in cognitive scores among neurologically unimpaired persons. We excluded an additional 1001 participants because they declined or had incomplete follow-up assessments, died, or were unreachable. We also excluded the 1063 participants without complete 37-MMSE at both assessments (Fig. 1). These were primarily the participants who were unavailable for face-to-face interviews (ie, they were evaluated by mailed questionnaires). The final sample of 2487 was similar to the base sample of 5278 participants in sex (1422 [57.2%] vs 3040 [57.6%] were women; $\chi^2 = 0.12$, $P = .73$) and drugs prescribed with potential effects on the central nervous system such as anticonvulsants like primidone, anxiolytics, and antihistamines (363 [14.6%] vs 806 [15.3%]; $\chi^2 = 0.60$, $P = .438$), but were more educated (265 [10.7%] vs 711 [13.6%] illiterate; $\chi^2 = 13.36$, $P = .004$) and, on average, 1.5 years younger (72.8 ± 6.0 years [median, 72 years] vs 74.3 ±7.0 years [median, 73 years]; Mann–Whitney test, $P < .001$).

Statistical Analyses

Analyses were performed in SPSS (version 20.0). None of the continuous variables was normally distributed (Kolmogorov–Smirnov, $P < .001$), even after log-transformation. Therefore, scores on baseline

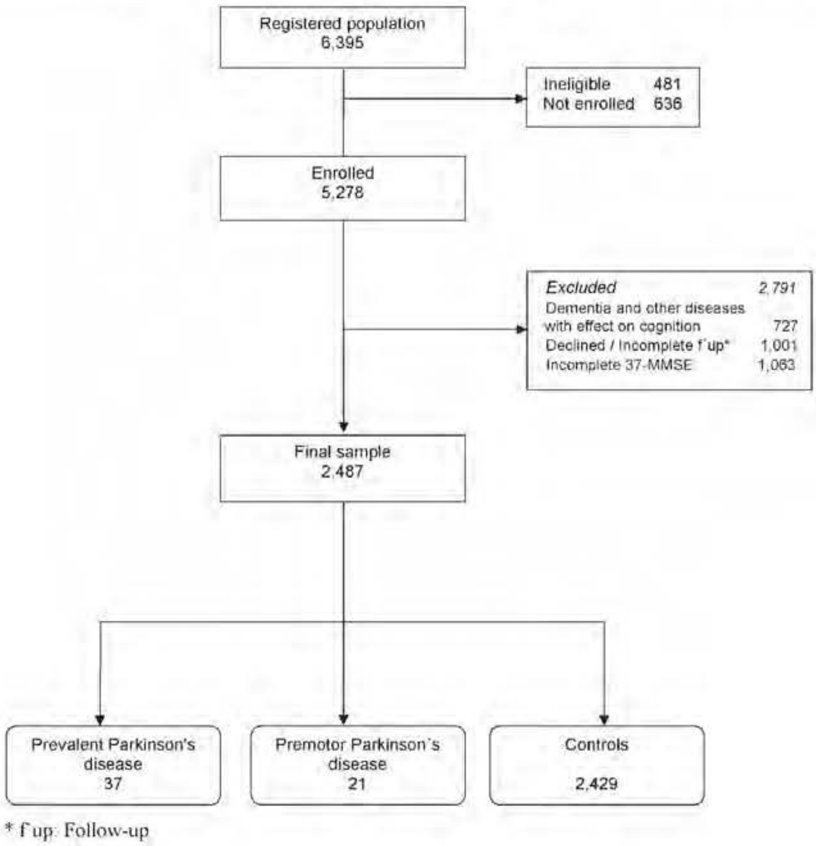

FIG. 1. Flowchart of the study.

characteristics were compared using a nonparametric approach including Kruskal–Wallis tests, Mann–Whitney tests, and Spearman's rho (r_S). Linear regression analyses were not possible because the change in 37-MMSE was also not normally distributed. Therefore, to initially assess the effects of possible confounders, the main factors that could affect cognition (age, sex, educational level, presence/absence of depressive symptoms or use of antidepressant medication, use of medications with central nervous system effects, and geographical area) were categorized, performing stratified analyses to compare the change in 37-MMSE score in these strata. Because of the loss of power in these analyses, *P* values were not reported; rather, the aim was to determine whether the magnitude of the case–control difference persisted after stratification.

In additional analyses, we divided the participants into 2 groups based on their change in 37-MMSE. Those who declined $\geq$ 4 points were considered the decline group, and the no-decline group comprised all subjects who exhibited a decline $\leq$ 3 points between the 2 evaluations. We compared the proportions of participants in each group. This choice of cutoffs was based on previous reports of change in the MMSE in PD and healthy elderly subjects.[30,31] Thus, in a population-based Norwegian study, the mean annual decline on the MMSE for PD patients was 1 point (for a 3.4-year follow-up, a 3.4-point decline would be expected). Furthermore, in a longitudinal population-based Swedish study, a decline $\geq$ 4 points in the MMSE during a 3-year follow-up had a sensitivity of 83% and a specificity of 80% for a diagnosis of dementia.[30] Taking these study data together, we decided to use this 4-point change as a clinically relevant threshold.[30,31] In ancillary sensitivity analyses, we also considered alternate cut-off points (3 and 5). In addition, multivariate logistic regression analyses were performed, thereby allowing us to assess potential confounding variables for a second time. In these models, the dependent variable was the 37-MMSE "decline" variable (reference, no decline), and the independent variable was case–control status (reference, control group).

TABLE 1. Main baseline demographic and clinical variables

	Controls (n = 2429)	Premotor PD (n = 21)	Prevalent PD (n = 37)	P value
Age (y)	72.7 (71.0) ± 6.0	76.0 (76.0) ± 6.5	75.2 (74.0) ± 5.0	< .001
Sex (female)	1387 (57.1)	12 (57.1)	23 (62.2)	.83
Geographical area				.12
Las Margaritas3	673 (27.7%)	8 (38.1%)	6 (16.2%)	
Lista	785 (32.3%)	5 (23.8%)	9 (24.3%)	
Arévalo	971 (40%)	8 (38.1%)	22 (16.2%)	
Educational level				.34
Illiterate	254 (10.5%)	3 (14.3%)	8 (21.6%)	
Can read and write	999 (41.1%)	9 (42.9%)	12 (32.4%)	
Primary studies	824 (33.9%)	7 (33.3%)	14 (37.8%)	
≥ Secondary studies	352 (14.5%)	2 (9.5%)	3 (8.1%)	
Current smoker[a]	289 (11.9%)	1 (4.8%)	3 (8.1%)	.47
Current ethanol consumption[a]	859 (35.4%)	6 (28.6%)	9 (24.3%)	.30
Diabetes mellitus[a]	380 (15.7%)	5 (23.8%)	6 (16.7%)	.59
Hypertension[a]	1032 (42.6%)	9 (42.9%)	19 (52.8%)	.47
Depressive symptoms or antidepressant use[a]	564 (23.4%)	5 (25.0%)	15 (40.5%)	.051
Medications with central nervous system effects	347 (14.3%)	4 (19.0%)	12 (32.4%)	.007

Mean ± standard deviation (median) or frequency (%) are reported.
The Kruskal–Wallis test was used for comparisons of age, and the χ^2 test for proportions.
[a]Data on some participants were missing

Results

The final sample, 2487 participants (mean age ± standard deviation, 72.8 ± 6.0 years), comprised 37 patients with prevalent PD, 21 individuals with premotor PD, and 2429 controls. The mean follow-up was 3.4 (median, 3.3) ± 0.5 years, which was similar in all groups (Kruskal–Wallis test, P = .753). The PD cases (prevalent/premotor) were older than controls (Table 1). A higher proportion of prevalent PD cases were taking medications with central nervous system effects, but in other respects, cases and controls were similar (Table 1). The groups differed with respect to the proportion of patients with depressive symptoms or antidepressant medication use (χ^2 test, P = .051), with that difference derived from the prevalent PD versus control comparison (χ^2 test, P = .015) rather than the premotor PD versus control comparison (χ^2 test, P = .795).

At baseline, the mean 37-MMSE was 28.5 ± 4.7 (median, 29) in prevalent PD cases versus 28.1 ± 4.6 (median, 28) in premotor PD cases and 29.9 ± 5.0 (median, 31) in controls (Kruskal-Wallis, P = 0.046), with marginally significant differences in the premotor PD–versus–control comparison (Mann–Whitney test, P = .08) and the prevalent PD–versus–control comparison (Mann–Whitney test, P = .07). During the 3-year follow-up period, the 37-MMSE declined by 2.4 ± 4.6 points in prevalent PD cases (median, 1 point) versus 0.2 ± 4.1 points in premotor PD cases (median, −1 point) versus 0.3 ± 4.0 points in controls (median, 0 points)—Kruskal–Wallis, P = .03 (see Table 2). There were significant differences between prevalent PD cases and controls in the decline of 37-MMSE (Mann–Whitney test, P = .008). However, there were no differences between premotor PD cases and controls in the decline of 37-MMSE (Mann–Whitney test, P = .684).

In our controls, we examined whether baseline 37-MMSE scores were associated with potential confounding variables. The 37-MMSE was correlated with age (r_S = −0.268, P < .001), sex (mean ± SD [median], 29.7 ± 4.9 [30] in men vs 30.0 ±4.9 [31] in women; Mann–Whitney test, P = .06), educational category (r_S = 0.401, P < .001), geographical area (mean ± SD [median], 28.6 ± 5.2 [29] in Las Margaritas vs 32.0 ± 4.2 [33] in Lista and 29.0 ± 4.8 [29] in Arévalo; Kruskal–Wallis test, P < .001), subjective depressive symptoms or antidepressant use (28.8 ±5.0 [29] in those who responded "yes" vs 30.2 ±4.9 [31] in those who responded "no"; Mann–Whitney test, P < .001). The 37-MMSE was marginally correlated with medications that could affect cognition (mean ± SD [median], 29.4 ± 5.3 [30] in those taking a medication vs 30.0 ± 4.9 [31] in those who do not take a medication; Mann–Whitney test, P = .10).

In stratified analyses, in nearly all strata, the decline in 37-MMSE score in prevalent PD cases was severalfold higher than the decline in scores in premotor PD cases and controls (Table 2).

In 12 participants (0.5%), the 37-MMSE changed by more than 15 points; when these outliers were excluded, the results were similar (the 37-MMSE declined by 2.0 ± 4.0 points [median, 1 point] in prevalent PD cases vs 0.2 ±4.1 points cases [median, −1 point] in premotor PD vs 0.2 ± 3.7 [median, 0 points] in controls (Kruskal–Wallis test, P = .04).

TABLE 2. Decline in 37-MMSE score during follow-up

	Controls (n = 2429)	Premotor PD cases (n = 21)	Prevalent PD cases (n = 37)
All participants	0.3 [0.0] ± 4.0	0.2 [−1.0] ± 4.1	2.4 [1.0] ± 4.6
Age strata			
Tertile 1 (≤68)	0.1 [0.0] ± 3.8 (66.6 ± 1.1)	−2.3 [−4.0] ± 2.9 (67.0 ± 1.0)	9.0 [9.0] ± NA (68.0 ± NA)
Tertile 2 (69–75)	0.1 [0.0] ± 3.7 (71.7 ± 2.0)	1.0 [1.0] ± 3.8 (71.7± 2.1)	1.7 [0.0] ± 4.4 (71.7 ± 2.0)
Tertile 3 (≥76)	0.3 [0.0] ± 4.1 (80.8 ± 3.9)	0.4 [−1.0] ± 4.5 (81.1 ± 3.8)	3.0 [2.0] ± 4.7 (80.0 ± 3.1)
Sex strata			
Male	0.2 [0.0] ± 4.0	1.5 [2.0] ± 4.0	1.6 [1.0] ± 3.2
Female	0.3 [0.0] ± 3.9	−0.8 [−2.0] ± 3.9	2.9 [2.0] ± 5.3
Educational level strata			
Illiterate	0.0 [0.0] ± 4.4	0.0 [2.0] ± 4.3	3.4 [3.5] ± 2.3
Can read and write	0.3 [0.0] ± 4.0	1.4 [2.0] ± 4.7	1.6 [1.5] ± 3.7
Primary studies	0.1 [0.0] ± 3.6	−1.7 [−2.0] ± 2.1	1.6 [0.0] ± 5.2
≥Secondary studies	0.6 [0.0] ± 4.3	1.5 [1.5] ± 6.4	7.0 [5.0] ± 8.2
Depressive symptoms or antidepressant use strata			
Yes	0.3 [0.0] ± 4.0	0.8 [−2.0] ± 5.8	3.7 [4.0] ± 4.7
No	0.3 [0.0] ± 4.0	0.2 [1.0] ± 3.6	1.5 [1.0] ± 4.4
Medications with central nervous system effects strata			
Yes	0.5 [0.0] ± 3.8	1.8 [2.0] ± 6.2	3.1 [3.0] ± 5.3
No	0.3 [0.0] ± 4.0	−0.2 [−1.0] ± 3.5	2.1 [1.0] ± 4.3
Geographical area strata			
Las Margaritas	0.4 [0.0] ± 4.0	0.5 [0.0] ± 5.0	1.8 [3.5] ± 3.9
Lista	0.2 [0.0] ± 4.0	−0.2 [−2.0] ± 3.0	3.7 [0.0] ± 6.8
Arévalo	0.4 [0.0] ± 4.0	0.1 [0.0] ± 4.1	2.1 [1.0] ± 3.8

Mean [median] ± standard deviation and frequency (%) are reported. Negative values indicate baseline 37-MMSE score was lower than 37-MMSE score at follow-up (ie, improvement in score). All positive values indicate a decline in score (ie, baseline 37-MMSE > follow-up 37-MMSE). NA, not applicable (there is only 1 patient in this group; therefore standard deviation could not be obtained). In each age stratum, the numbers in parentheses indicate the mean ± standard deviation age of participants in that stratum; these values demonstrate that cases were similar in age to controls within the 3 age strata.

We also assessed the decline per unit time (ie, the rate of cognitive decline). The rate of cognitive decline was 0.1 ± 1.2 (median, 0) points/year for controls, 0.0 ± 1.2 (median, −0.3) points/year for premotor PD cases, and 0.7 ± 1.5 (median, 0.3) points/year for prevalent PD cases (Kruskal–Wallis test, $P = .03$). There was a significant difference between prevalent PD cases and controls in the rate of cognitive decline (Mann–Whitney test, $P = .012$). However, there was no difference between premotor PD cases and controls in the rate of cognitive decline (Mann–Whitney test, $P = .632$).

When the participants were stratified into "decline" versus "no-decline" groups, a significant difference was found ($\chi^2 = 10.57$, $P = .005$), with prevalent PD cases including a relatively high proportion of patients who declined ≥4 points (37.8%), compared with the control and PD premotor groups (17.3% and 19.0%, respectively). In a logistic regression model, prevalent PD cases were 2.9 times more likely than controls to have a "decline" in 37-MMSE (OR, 2.9; 95% confidence interval [CI], 1.5–5.7; $P = .002$). However, the odds of "decline" in 37-MMSE were similar in premotor PD cases and controls (OR, 1.1; 95% CI, 0.4–3.3; $P = .836$). To further assess the potential confounding effects of age, sex, geographical area, educational level, depressive symptoms or antidepressant use, and medications with central nervous system effects, we adjusted for these in a logistic regression model, and prevalent PD cases were 2.6 times more likely to decline than controls (OR, 2.6; 95% CI, 1.3–5.1; $P = .007$). Likewise, the odds of "decline" in 37-MMSE were similar in premotor PD cases and controls (adjusted OR, 1.0; 95% CI, 0.3–3.0; $P = .996$). In additional sensitivity analyses, we also considered alternate cut-off points from ≥4 points. If those who declined ≥5 points were considered the "decline group," then prevalent PD cases were 3 times more likely to decline than controls (adjusted OR, 3.0; 95% CI, 1.4–6.1; $P = .003$). Likewise, the odds of "decline" in 37-MMSE were similar in premotor PD cases and controls (adjusted OR, 1.0; 95% CI, 0.3–3.5; $P = .987$). When those who declined ≥3 points were considered the decline group, results were similar. Prevalent PD cases were 1.9 times more likely to decline than controls (adjusted OR, 1.9; 95% CI, 0.9–3.6; $P = .07$). Likewise, the odds of "decline" in 37-MMSE were similar in premotor PD cases and controls (adjusted OR, 1.1; 95% CI, 0.4–3.0; $P = .784$.

The 37-MMSE divided into subscores was compared across cases and controls. A significant mean decline was found for the orientation (1.2 points, $P = .001$) and language (0.6 points, $P = .012$) domains (Table 3).

TABLE 3. Decline in 37-MMSE subscores during follow-up

	Controls (n = 2429)	Premotor PD cases (= 21)	Prevalent PD cases (= 37)	P value
Orientation (10 points)	0.3 (0.0) ± 1.3	0.5 (0.0) ± 1.1	1.2 (1.0) ± 2.0	.001
Immediate recall (3 points)	0.0 (0.0) ± 0.4	0.0 (0.0) ± 0.0	−0.1 (0.0) ± 0.2	.43
Attention and calculation (10 points)	−0.1 (0.0) ± 2.6	0.0 (0.0) ± 2.8	0.4 (0.0) ± 2.8	.53
Delayed recall (3 points)	0.1 (0.0) ± 1.2	−0.2 (0.0) ± 1.2	0.3 (0.0) ± 1.2	.29
Language (9 points)	0.0 (0.0) ± 1.3	−0.3 (0.0) ± 1.5	0.6 (0.0) ± 1.1	.012
Copying (2 points)	0.1 (0.0) ± 0.7	0.3 (0.0) ± 0.6	0.1 (0.0) ± 0.9	.16

Mean (median) ± SD are reported. All the positive values indicate a decline in the MMSE score.
The Kruskal–Wallis test was used for comparisons of data.

Prevalent PD cases had a lower median 37-MMSE score than did controls at baseline, suggesting that some of them may already have had mild cognitive impairment. In an additional analysis, we excluded all prevalent PD cases with baseline 37-MMSE scores below the mean baseline 37-MMSE score of controls (ie, scores < 30). In these analyses, the 37-MMSE declined by 3.8 ± 5.3 points (median, 1.5 points) in the 18 prevalent PD cases versus 0.2 ± 4.1 points (median, −1 point) in premotor PD cases versus 0.3 ± 4.0 points (median, 0 points) in controls (Kruskal–Wallis, $P = .02$).

In a final analysis, we included rather than excluded all participants with prevalent dementia. In these analyses, the 37-MMSE declined by 0.4 ± 4.1 points (median, 0 points) in the sample, including 2.3 ± 4.6 points (median, 0 points) in the prevalent PD cases versus 0.2 ± 4.1 points (median, 1 point) in the premotor PD cases versus 0.4 ± 4.1 points (median, −1 point) in the controls (Kruskal–Wallis test, $P = .048$).

Discussion

In recent publications, subtle neuropsychological impairment has been found in early PD cases.[6] It has been suggested[2,5,7] that these differences also occurred in incident cases, although the definition of "incident" was not uniform across the studies. In the current research, we have demonstrated that cognitive test scores in prevalent PD declined at a rate above and beyond the rate observed in both premotor PD and control groups (among whom the rates of progression were similar). This observation is in agreement with some of our prior results,[13] suggesting that overt, clinically significant cognitive dysfunction rarely occurs in the very early premotor phase of PD. This is not necessarily inconsistent with the observation that some impairment may appear a few years after the motor manifestations of PD are evident, as we also previously found.[6]

In this study, there was a significant decline of 2.4 points (0.7 points/year) in the 37-MMSE scores of the prevalent PD cases, which is similar to that reported in the Rogaland (Norway) population-based survey.[7] An interesting finding is that the subscores most affected were orientation and language. Both have been related to fronto-subcortical dysfunction. Language impairment has been linked to phonemic/executive tasks but also to cortical ones.[2,32] Although it is not possible to further refine the analysis because of the limited value of the 37-MMSE, the decline of language scores in the prevalent group but not in the premotor group suggests other coexisting factors, perhaps not dopaminergic in nature. In fact in several studies, an Alzheimer's-type pathology has been found in some subjects with PD dementia, and this cannot be discounted as possible in the NEDICES cohort.[33]

This study had several limitations. First, the 37-MMSE is a relatively abbreviated screening tool for dementia and not specifically designed for PD. The use of more detailed neuropsychological test batteries would enable future investigators to study these changes in greater detail. Nevertheless, even with this relatively simple, abbreviated tool, we were able to establish clear case–control differences. Second, the 37-MMSE was administered at 2 times; use of additional times would allow assessment of the extent to which the case–control difference continued beyond the 3-year time window. Third, there were some baseline differences with potential confounding effects.[34] However, we controlled this source of bias with stratified analyses and logistic regression. Fourth, attrition rates were considerable. Many subjects were lost to follow up. This could have biased the studied sample toward the less impaired cases, as can be inferred by our comparison, with the selected having decreased age and literacy. Nevertheless, if we had included these hypothetically more affected cases, they would have been in the prevalent/control group rather than in the premotor group, so the differences could have been even more evident. Fifth, the sample size was limited. We could not conduct intragroup analyses to see if some patients on the premotor group had a different behavior compared with others. Finally, although we performed analyses in which we adjusted for depressive symptoms, our evaluation of depression was limited, and we may have underascertained depression, resulting in residual confounding. Nevertheless, a validation study showed a high level of agreement between the data generated from the screening question we used and a more detailed in-person psychiatric assessment, suggesting that such residual confounding is likely to have been low.[21]

This study also had several strengths. First, the study was population based, allowing us to assess a group of patients with relatively mild PD unselected for medical treatment or surgery. Second, the assessments were conducted prospectively in a standardized manner. Third, cases were compared with a large sample size of several thousand controls. Fourth, we were able to adjust for the potential confounding effects of a number of important factors. Fifth, we followed the patients for a considerable time (mean time, 3.4 years). This issue is of importance in a disease like PD, where some diagnostic uncertainty exists, particularly in initial cases, with a broad differential diagnosis including dementia with Lewy bodies.[35,36] Finally, although we acknowledge that there is no standard definition of what premotor PD is, we have used a strategy based on 2 prospective assessments that can be valuable for epidemiological studies when other proposed means (ie, evaluation of premotor symptoms, DaTSCAN imaging, or substantia nigra ultrasound) are difficult to apply or have not yet been validated.

In conclusion, premotor PD cases do not appear to be significantly different from controls in terms of global cognitive performance. Further studies are required to confirm this hypothesis, expressly with premotor prospective data and eventually with a pathological/biomarker correlate. ■

Acknowledgments: Additional information about collaborators and detailed funding of the NEDICES study can be found on the Web (http://www.ciberned.es/estudio-nedices).

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Rate of cognitive decline during the premotor phase of essential tremor

A prospective study

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ABSTRACT

Objective: To characterize the rate of cognitive decline during the premotor phase of essential tremor (ET) in comparison to prevalent ET cases and controls.

Methods: In this population-based, prospective study of people aged 65 years and older (Neurological Disorders in Central Spain), a 37-item version of the Mini-Mental State Examination was administered at 2 visits (baseline and follow-up, approximately 3 years later). We compared the rate of cognitive decline in 3 groups: prevalent ET cases (i.e., participants diagnosed with ET at baseline and at follow-up), "premotor" ET cases (i.e., participants diagnosed with incident ET at follow-up, but not at baseline), and controls (i.e., participants not diagnosed with ET at baseline or follow-up).

Results: The 2,375 participants included 135 prevalent ET cases, 56 premotor ET cases, and 2,184 controls. During the follow-up period of 3.4 ± 0.5 years (mean ± SD), the 37-item version of the Mini-Mental State Examination declined by 0.7 ± 3.3 points (0.2 ± 1.0 points/year) in prevalent ET cases, 1.1 ± 3.5 points (0.3 ± 1.0 points/year) in premotor ET cases, and 0.1 ± 3.9 points (0.0 ± 1.2 points/year) in controls ($p = 0.014$). The difference between premotor ET cases and controls was significant ($p = 0.046$), as was the difference between prevalent ET cases and controls ($p = 0.027$).

Conclusions: In this prospective cohort, cognitive test scores in premotor and prevalent ET cases declined at a faster rate than in elders without this disease. A decline in global cognitive function may occur in a premotor phase of ET. *Neurology*® **2013;81:60-66**

GLOSSARY

CI = confidence interval; **DSM-IV** = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; **ET** = essential tremor; **37-MMSE** = 37-item Mini-Mental State Examination; **NEDICES** = Neurological Disorders in Central Spain; **OR** = odds ratio.

Mild cognitive deficits have been reported to occur in patients with essential tremor (ET) in many independent studies,[1–8] including a population-based study of largely treatment-naive ET patients (Neurological Disorders in Central Spain [NEDICES] study).[8] These studies suggest that a frontosubcortical-type dysfunction occurs in some patients with ET.[9–14] In the NEDICES study, lower cognitive test scores were associated with more reported functional difficulty, indicating a clinical-functional correlate.[15] The NEDICES study provided evidence that cognitive deficits in ET are not static, and appear to be progressing at a faster rate than in elders without this disease.[16] There could be a "premotor" stage of ET, as there is in other adult-onset and late-life motor disorders. However, population-based studies that prospectively assess whether cognitive dysfunction appears in premotor ET (i.e., those subjects who were free of ET at baseline but who developed ET during the follow-up) have not been conducted.

We hypothesized that the cognitive deficits in premotor and prevalent ET would not be static, but would deteriorate, and that this deterioration would occur at a rate above that observed in similarly aged controls. Using data from the NEDICES study, we evaluated ET

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

cases (participants diagnosed with ET at baseline and at follow-up), "premotor" ET cases (participants diagnosed with incident ET at follow-up, but not at baseline), and controls (participants not diagnosed with ET at baseline or follow-up) at 2 time points separated by approximately 3 years.

METHODS **Study population.** We derived the data for these analyses from the NEDICES study.[17–28] We have previously published details regarding the study population and sampling methods.[17–28] The study population was composed of subjects aged 65 years and older living in 3 well-defined geographical areas in central Spain (Las Margaritas, Lista, and Arévalo).

Standard protocol approvals, registrations, and patient consents. Investigators obtained ethics approval from the Human Research Ethics Committee of the University Hospitals 12 de Octubre and La Princesa (Madrid). All enrollees signed written informed consent.

Evaluation. Each participant received either a face-to-face evaluation (at baseline, 1994–1995, and at follow-up, 1997–1998) or a questionnaire (mailed to participants who were unavailable for face-to-face interviews). During the face-to-face interview, we collected data on demographics, current medications, medical conditions, depressive symptoms (the question, "Do you suffer from depression?"), and lifestyle. The interview included one screening question for ET ("Have you ever suffered from tremor of the head, hands, or legs that has lasted longer than several days?").[23,26] This question was a Spanish adaptation of that used by the Italian Longitudinal Study on Aging Working Group.[29] To assess the performance of this screening question, we selected and contacted a random sample of approximately 4% of those who had screened negative.[17] Of 205 subjects who were contacted, we successfully scheduled 183 for a neurologic examination by a senior neurologist who routinely evaluates patients with movement disorders (J. Olazarán [see http://www.ciberned.es/estudio-nedices]) as described.[25,26] The diagnostic criteria for ET were similar to those used in the Sicilian study[30] (see below), and none (0%) of the 183 subjects were diagnosed with ET.[17]

Subjects who screened positive for ET underwent a neurologic examination,[23–26] which comprised a general neurologic examination and the motor portion of the Unified Parkinson's Disease Rating Scale.[31] During this examination, we asked participants to perform manual tasks to assess postural and kinetic tremors. For subjects who could not be examined, we obtained medical records from general practitioners, from in-patient hospitalizations, and from neurologic specialists (if they had visited one). In addition, we reviewed death certificate diagnoses for each screened subject who had died before neurologic examination.

Diagnostic criteria for ET were similar to those used in the Sicilian study.[30] The first criterion was action tremor of the head, limbs, or voice without any other recognizable cause. Second, the tremor had to be of gradual onset (i.e., slow and progressive) and 1) present for at least 1 year, or 2) accompanied by a family history of the same disorder (at least one reportedly affected first-degree relative). Third, on an Archimedes spiral, tremor severity had to be moderate or greater (rating ≥2 according to the Washington Heights–Inwood Genetic Study of ET Rating Scale).[32] Subjects with tremor related to Parkinson disease, medications, or other known causes of tremor were not diagnosed with ET. We diagnosed Parkinson disease and other forms of parkinsonism when at least 2 cardinal signs were present on the Unified Parkinson's Disease Rating Scale.[31] The diagnosis of dementia was made by consensus of 2 neurologists, who applied the *DSM-IV* criteria.[27,28]

We administered a 37-item Mini-Mental State Examination (37-MMSE) to evaluate global cognitive performance in the cohort.[8,27,28,35–37] The 37-MMSE included all of the standard MMSE items as well as 3 additional items: 1) an attention task, i.e., "say 1, 3, 5, 7, 9 backward"; 2) a visual order, i.e., a man raising his arms; and 3) a simple construction task, i.e., copying 2 overlapping circles.[8,27,28,35–37] We grouped cognitive domain tasks into several subscores (orientation [0–10 points], memory [0–6 points], attention and calculation [0–10 points], language tasks [0–9 points], and construction/copying [0–2 points]).[8,27,28,35–37]

Final selection of participants. Of the 5,278 participants evaluated at baseline, we excluded 2,903 with incomplete data, dementia, or other neurodegenerative conditions (figure).

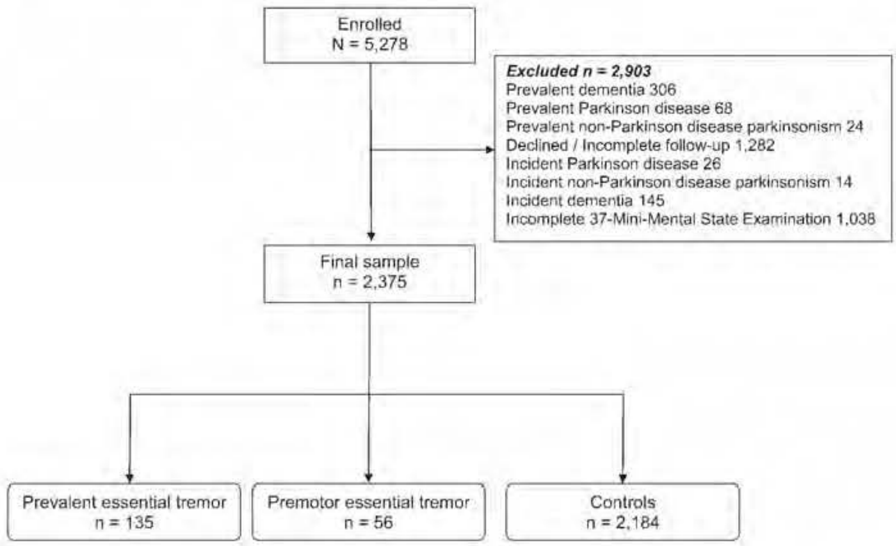
The final sample of 2,375 participants included 135 cases of prevalent ET, 56 premotor ET cases, and 2,184 controls (figure). The final sample of 2,375 participants was similar to the excluded 2,903 participants in terms of sex (1,346 [56.7%] vs 1,694 [58.4%] women, $\chi^2 = 1.51$, $p = 0.22$), but they were more educated (242 [10.2%] vs 469 [16.4%] illiterate, $\chi^2 = 45.2$, $p < 0.001$) and, on average, 3.4 years younger (72.4 ± 5.8 vs 75.8 ± 7.4 years, $t = -18.1$, $p < 0.001$).

Statistical analyses. We performed analyses in SPSS version 20.0 (IBM Corp., Armonk, NY). None of the continuous variables were normally distributed (Kolmogorov-Smirnov, $p < 0.001$), even after log-transformation. Therefore, we compared baseline characteristic scores using a nonparametric approach including Kruskal-Wallis tests, Mann-Whitney tests, and Spearman ρ (r_s). Linear regression analyses were not possible because the change in 37-MMSE score was also not normally distributed. Therefore, to initially assess the effects of possible confounders, we divided the main factors that could affect cognition (age, sex, educational level, presence/absence of depressive symptoms or use of antidepressant medication, use of medications with CNS effects, and geographical area) into categories, and we performed stratified analyses to compare the change in the 37-MMSE score across groups in each stratum. Because of the loss of power in these analyses, we did not report p values; rather, the aim was to determine whether the magnitude of the case-control difference persisted after stratification.

In additional analyses, we divided change in 37-MMSE score into tertiles (lower tertile ≥2-point improvement in score, upper tertile ≥2-point decline in score), comparing cases and controls regarding their distribution within these tertiles (χ^2 test). In addition, we performed multivariate logistic regression analyses, thereby allowing us to assess, for a second time, the same confounders. In these models, the dependent variable was the upper tertile of 37-MMSE score change (reference = lower tertile) and the main independent variable was case-control status.

RESULTS The final sample of 2,375 participants (mean ± SD age = 72.4 ± 5.8 years) comprised 135 prevalent ET cases, 56 premotor ET cases, and 2,184 controls. The mean follow-up was 3.4 ± 0.5 years (median = 3.3 years), which was similar in all groups (Kruskal-Wallis test, $p = 0.253$). Premotor and ET cases were marginally older than controls (table 1), and a higher proportion of premotor and ET cases were illiterate and lived in Las Margaritas, a predominantly working-class area (table 1). In addition, a higher proportion of ET cases was taking medications with CNS

Figure **Flow chart of the study**



effects and reported more depressive symptoms than controls, but in other respects, cases and controls were similar (table 1). The baseline 37-MMSE score was lowest in prevalent ET cases and highest in controls (table 1), with significant differences in the prevalent ET cases vs controls comparison (Mann-Whitney test, $p = 0.020$), but not in the premotor ET cases vs controls comparison (Mann-Whitney test, $p = 0.33$).

Table 1 **Main baseline demographic and clinical variables**[a]

	Controls (n = 2,184)	Premotor ET (n = 56)	Prevalent ET (n = 135)	p Value
Age, y	72.4 (71.0) ± 5.8	73.0 (72.0) ± 5.7	73.6 (72.0) ± 6.3	0.062
Sex, male	950 (43.5)	24 (42.9)	55 (40.7)	0.82
Geographical area				
Lista (professional area)	708 (32.4)	11 (19.6)	30 (22.2)	0.007
Arévalo (rural area)	860 (39.4)	22 (39.3)	53 (39.3)	
Las Margaritas (working-class area)	616 (28.2)	23 (41.1)	52 (38.5)	
Educational level				
Illiterate	210 (9.6)	8 (14.3)	24 (17.8)	0.023
Can read and write	911 (41.7)	23 (41.1)	61 (45.2)	
Primary studies	738 (33.8)	15 (26.8)	37 (27.4)	
≥Secondary studies	325 (14.9)	10 (17.9)	13 (9.6)	
Current smoker[b]	256 (11.7)	4 (7.1)	16 (11.9)	0.57
Current alcohol consumption[b]	794 (36.4)	20 (35.7)	47 (34.8)	0.93
Diabetes mellitus[b]	349 (16.1)	10 (17.9)	25 (18.7)	0.70
Hypertension[b]	1,082 (49.6)	34 (61.8)	71 (52.6)	0.17
Depressive symptoms or antidepressant use[b]	496 (22.8)	21 (38.9)	56 (41.5)	<0.001
Medications with CNS effects	307 (14.1)	11 (19.6)	40 (29.6)	<0.001
Baseline 37-MMSE score	30.1 (31.0) ± 4.8	29.5 (30.0) ± 5.0	28.8 (30.0) ± 5.7	0.045

Abbreviations: ET = essential tremor; 37-MMSE = 37-item Mini-Mental State Examination.
[a] Mean (median) ± SD or frequency (%) are reported. Kruskal-Wallis test was used for comparisons of age, and Fisher exact p test or χ^2 test was used for proportions.
[b] Data on some participants were missing.

During the 3-year follow-up period, the 37-MMSE declined by 0.7 ± 3.3 points in prevalent ET cases (median = 1 point), 1.1 ± 3.5 points in premotor ET cases (median = 1 point), and 0.1 ± 3.9 points in controls (median = 0 points) (Kruskal-Wallis test, $p = 0.014$) (table 2). The difference between prevalent ET cases and controls was significant (Mann-Whitney test, $p = 0.027$); similarly, the difference between premotor ET cases and controls was significant (Mann-Whitney test, $p = 0.046$); however, the difference between premotor ET cases and prevalent ET cases was not significant (Mann-Whitney test, $p = 0.563$).

In controls, we examined whether baseline 37-MMSE scores were associated with potential confounding variables. The 37-MMSE was correlated with age ($r_S = -0.227$, $p < 0.001$), educational category ($r_S = 0.396$, $p < 0.001$), geographical area (mean ± SD [median] = 29.0 ± 4.9 [30] in Las Margaritas vs 32.2 ± 4.0 [33] in Lista and 29.3 ± 4.8 [30] in Arévalo; Kruskal-Wallis test, $p < 0.001$), subjective depressive symptoms or antidepressant use (29.2 ± 4.8 [29] in those who responded "yes" vs 30.5 ± 4.7 [31] in those who responded "no"; Mann-Whitney test, $p < 0.001$), and sex 31.6 ± 4.5 [33] in men vs 29.1 ± 4.7 [29] in women; Mann-Whitney test, $p < 0.001$). However, the baseline 37-MMSE was not correlated with medications that could affect cognition (mean ± SD [median] = 29.9 ± 4.9 [31] in those taking a medication vs 30.2 ± 4.8 [31] in those not taking a medication; Mann-Whitney test, $p = 0.44$).

In stratified analyses, in nearly all strata, the decline in 37-MMSE score in both premotor and prevalent ET cases was higher than the decline in scores in controls (table 2), indicating that these variables were not likely to be a source of confounding.

Table 2 Decline in 37-MMSE score across clinical strata during the 3.4-year mean follow-up period[a]

	2,184 Controls	56 Premotor ET cases	135 Prevalent ET cases
All participants	0.1 [0.0] ± 3.9	1.1 [1.0] ± 3.5	0.7 [1.0] ± 3.3
Age strata[b]			
Tertile 1, ≤68 y	0.0 [0.0] ± 3.9 (66.6 ± 1.1)	2.0 [1.5] ± 3.6 (66.9 ± 1.0)	0.8 [1.0] ± 3.1 (66.5 ± 0.9)
Tertile 2, 69–73 y	0.1 [0.0] ± 3.6 (70.8 ± 1.4)	0.5 [0.0] ± 3.3 (71.3 ± 1.6)	0.5 [1.0] ± 2.6 (70.8 ± 1.3)
Tertile 3, ≥74 y	0.2 [0.0] ± 4.1 (78.9 ± 4.2)	0.9 [1.0] ± 3.6 (79.3 ± 3.7)	0.8 [1.0] ± 3.8 (79.6 ± 4.0)
Sex			
Male	0.2 [0.0] ± 4.1	0.6 [1.0] ± 2.9	0.8 [1.0] ± 3.1
Female	0.0 [0.0] ± 3.6	1.4 [1.0] ± 3.8	0.6 [0.0] ± 3.4
Educational level			
Illiterate	−0.3 [−1.0] ± 4.4	3.7 [3.0] ± 2.7	−0.6 [−1.0] ± 3.1
Can read and write	0.0 [0.0] ± 3.8	1.7 [2.0] ± 4.1	1.1 [1.0] ± 3.6
Primary studies	0.2 [0.0] ± 3.7	−1.0 [−1.0] ± 1.9	0.8 [0.0] ± 2.8
≥Secondary studies	0.5 [0.0] ± 4.1	0.6 [1.0] ± 2.5	0.7 [1.0] ± 2.5
Depressive symptoms or antidepressant use			
Yes	0.0 [0.0] ± 4.0	1.2 [1.0] ± 3.7	0.7 [0.0] ± 3.2
No	0.1 [0.0] ± 3.8	0.9 [1.0] ± 3.1	0.6 [1.0] ± 3.0
Medications with CNS effects			
Yes	0.4 [0.0] ± 4.0	−0.2 [1.0] ± 3.5	1.2 [1.0] ± 3.4
No	0.1 [0.0] ± 3.9	1.4 [1.0] ± 3.4	0.5 [1.0] ± 3.2
Geographical area			
Las Margaritas	0.0 [0.0] ± 3.8	1.7 [1.0] ± 3.5	0.8 [1.0] ± 3.3
Lista	0.0 [0.0] ± 3.9	0.1 [0.0] ± 3.1	0.3 [0.0] ± 3.0
Arévalo	0.3 [0.0] ± 3.9	0.9 [0.0] ± 3.7	0.8 [1.0] ± 3.5

Abbreviations: ET = essential tremor; 37-MMSE = 37-item Mini-Mental State Examination.

[a] Mean [median] ± SD (mean ± SD) are reported. Negative values indicate that the baseline 37-MMSE score was lower than the 37-MMSE score at follow-up (i.e., improvement in score). All positive values indicate a decline in score (i.e., baseline 37-MMSE > follow-up 37-MMSE).

[b] In each age stratum, the numbers in parentheses indicate the mean ± SD age of participants in that stratum; these values demonstrate that cases had similar ages to controls within the 3 age strata.

We also assessed the cognitive decline per unit time (i.e., the rate of cognitive decline). The rate of cognitive decline was 0.0 ± 1.2 (median = 0.0) points/year for controls, 0.3 ± 1.0 (median = 0.3) points/year for premotor ET cases, and 0.2 ± 1.0 (median = 0.2) points/year for prevalent ET cases (Kruskal-Wallis test, $p = 0.014$). The difference between premotor ET cases and controls was significant (Mann-Whitney test, $p = 0.039$), as was the difference between prevalent ET cases and controls (Mann-Whitney test, $p = 0.033$); however, the difference between prevalent ET cases and premotor ET cases was not significant (Mann-Whitney test, $p = 0.460$).

Change in 37-MMSE score was stratified into tertiles: 50 (37.0%) prevalent ET cases, 24 (42.9%) premotor ET, and 691 (31.6%) controls were in the upper tertile; 29 (21.5%) prevalent ET, 11 (19.6%) premotor ET, and 686 (31.4%) controls were in the lower tertile ($\chi^2 = 10.21$, $p = 0.037$). In a logistic regression model, prevalent ET cases were 1.71 times more likely than controls to have a change in 37-MMSE score in the upper vs lower tertile (odds ratio [OR] = 1.71, 95% confidence interval [CI] = 1.07–2.74, $p = 0.025$), and premotor ET cases were 2.17 times more likely than controls to have a change in 37-MMSE score in the upper vs lower tertile (OR = 2.17, 95% CI = 1.05–4.46, $p = 0.036$). We further assessed the possible confounding effects of age, sex, geographical area, educational level, depressive symptoms or antidepressant use, and medications with CNS effects in a multivariate logistic regression model. In this model, prevalent ET cases were 1.67 times more likely than controls to have a change in 37-MMSE score in the upper vs lower tertile ($OR_{prevalent\ ET} = 1.67$, 95% CI = 1.04–2.69, $p = 0.035$), and premotor ET cases were 2.38 times more likely than controls to have a change in 37-MMSE score in the upper vs lower tertile ($OR_{premotor\ ET} = 2.38$, 95% CI = 1.12–5.03, $p = 0.023$). Finally, we conducted a sensitivity analysis in which we only included confounders that were significant at a p value <0.005 (i.e., depressive symptoms or antidepressant use and medications with CNS effects), and the results were similar ($OR_{prevalent\ ET} = 1.68$, 95% CI = 1.04–2.69, $p = 0.033$; and $OR_{premotor\ ET} = 2.38$, 95% CI = 1.13–5.02, $p = 0.023$).

We compared changes in 37-MMSE subscores in cases and controls (table 3). Given the issue of multiple comparisons, we performed a Bonferroni correction and set the p value at 0.0083. None of the differences were significant, although there were several trends (for language, $p = 0.15$, and for construction/copying, $p = 0.05$).

Prevalent and premotor ET cases had lower median 37-MMSE scores than controls at baseline, suggesting that some of them may already have had mild cognitive deficits. In an additional analysis, we excluded all prevalent and premotor ET cases with baseline 37-MMSE scores that were below the mean baseline 37-MMSE score of controls (i.e., scores <31). In these analyses, the 37-MMSE declined by 1.3 ± 2.9 points (median = 1.0) in the 65 prevalent ET cases, 1.3 ± 3.3 points in the 27 premotor ET cases (median = 1.0 points), and 0.1 ± 3.9 points in the 2,184 controls (median = 0 points) (Kruskal-Wallis, $p = 0.003$).

Finally, we conducted sensitivity analyses to confirm the robustness of our findings. First, we excluded 31 premotor ET cases because these individuals had not been examined in person by a neurologist at baseline. The 37-MMSE declined by 0.7 ± 3.3 points (median = 1) in prevalent ET cases, 1.7 ± 3.6 points (median = 1) in the remaining 25 premotor ET cases, and 0.1 ± 3.9 points (median = 0) in controls ($p = 0.010$). The difference between these premotor ET cases and controls remained significant ($p = 0.033$), as was the difference between prevalent ET cases and controls ($p = 0.027$). Second, baseline handwriting samples from the 31 premotor ET cases and 31 age-matched controls were blindly reviewed by one of the authors (E.D.L.) and rated using Bain and Findley's 10-point scale.[38] None of the cases and

Table 3 Decline in 37-MMSE subscores during the 3.4-year mean follow-up period[a]

	2,184 Controls	56 Premotor ET cases	135 Prevalent ET cases	p Value
Orientation, 10 points	0.2 (0.0) ± 1.2	0.4 (0.0) ± 1.3	0.2 (0.0) ± 1.5	0.61
Immediate recall, 3 points	0.0 (0.0) ± 0.4	0.0 (0.0) ± 0.0	0.0 (0.0) ± 0.2	0.89
Attention and calculation, 10 points	0.2 (0.0) ± 2.6	0.0 (0.0) ± 2.2	0.2 (0.0) ± 2.3	0.22
Delayed recall, 3 points	0.1 (0.0) ± 1.2	0.3 (0.0) ± 1.2	0.0 (0.0) ± 1.3	0.36
Language, 9 points	0.0 (0.0) ± 1.2	0.2 (0.0) ± 1.3	0.2 (0.0) ± 1.2	0.15
Construction/copying, 2 points	0.0 (0.0) ± 0.7	0.2 (0.0) ± 0.7	0.2 (0.0) ± 0.8	0.05

Abbreviations: ET = essential tremor; 37-MMSE = 37-item Mini-Mental State Examination.
[a] Mean (median) ± SD are reported. All positive values indicate a decline in the MMSE score. Kruskal-Wallis test was used for comparisons of data. Given the issue of multiple comparisons, we performed a Bonferroni correction and set the p value at 0.0083.

controls had tremor that was in the ET range (all had Bain and Findley[38] handwriting tremor scores ≤ 1, which are within the range of normal).[38] Furthermore, each of the 31 was reinterviewed during the follow-up evaluation to establish that the onset of his or her tremor had been after the baseline assessment.

DISCUSSION In the current prospective study of community-dwelling elders without dementia, we demonstrated that baseline cognitive test scores were lower in premotor ET cases than controls; moreover, during the 3-year follow-up period, these scores declined at a rate that was significantly faster in premotor ET cases than controls.

Premotor ET cases on average experienced a 1.1-point reduction in the 37-MMSE over 3 years. Although this reduction was significantly greater than that seen in controls, in absolute terms, it was a modest change.

For many years, ET was viewed as a monosymptomatic condition, characterized only by a kinetic arm tremor, but over the last 10 years, a plethora of previously unrecognized motor and nonmotor problems have emerged.[39] A recent paradigm presents ET as a more complex clinical entity.[39] Furthermore, the current and prior data focus on the possibility that nonmotor symptoms could precede the onset of classic motor manifestations. For example, in prospective analyses of the NEDICES study, baseline self-reported depression was associated with increased risk of incident ET.[40] These prospective data suggest that the mood disorder in ET may be more than a secondary response to disease manifestations; this mood disorder may be a primary feature of the underlying disease. When these nonmotor problems present early and precede motor symptoms, we cautiously suggest that this should perhaps be regarded as evidence of premotor ET. Additional studies of such a premotor phase of ET are needed, particularly as they may be important for our understanding of when and where ET begins and how it evolves in these initial stages.

This study had limitations. First, we used a 2-phase procedure to screen for ET. Therefore, it is likely that some premotor cases were not properly diagnosed with ET at baseline because they screened negatively. However, in a prior pilot study, none (0%) of the 183 participants who had screened negatively for any of the neurologic disorders tested in the NEDICES study were diagnosed with ET,[17] indicating that use of the screening question was likely to yield few false negatives. Furthermore, we conducted additional analyses in which we excluded 31 premotor cases that were not evaluated at baseline on direct examination and found similar results. Second, the 37-MMSE is a relatively abbreviated screening tool for dementia. The use of more detailed neuropsychological test batteries would enable future investigators to study these changes in greater detail. A final limitation of the study was that there were no available data on tremor severity. Hence, we were not able to comment on any relationships between tremor severity, or change in tremor severity, and change in cognitive scores.

This study also had several strengths. First, the study was population-based, allowing us to assess a group of patients with relatively mild ET unselected for medical treatment or surgery. Second, we conducted the assessments prospectively in a standardized manner. Third, we compared cases with a large sample of several thousand controls. Fourth, we adjusted for the potential confounding effects of a number of important factors.

Using a prospective, population-based design, we demonstrated that cognitive test scores in "premotor" ET cases declined at an accelerated rate compared with controls. This study provides further evidence that cognitive deficits in ET are not static. Further studies are required to confirm these results, expressly with premotor prospective data and eventually with a pathologic/biomarker correlate.

AUTHOR CONTRIBUTIONS

J. Benito-León and E.D. Louis collaborated in the conception, organization, and execution of the research project, the statistical analysis design, the writing of the manuscript first draft, and the review and critique of the manuscript. Á. Sánchez-Ferro and F. Bermejo-Pareja collaborated in the conception, organization, and execution of the research project, and the review and critique of the manuscript.

STUDY FUNDING

Additional information about collaborators and detailed funding of the NEDICES study can be found on the Web (http://www.ciberned.es/estudio-nedices). The Spanish Health Research Agency and the Spanish Office of Science and Technology supported the NEDICES study. Drs. Benito-León and Bermejo-Pareja are supported by grant R01 NS039422 from the NIH, Bethesda, MD. Dr. Sánchez-Ferro is supported by a grant "Contrato de Investigación Río Hortega" from Instituto de Salud Carlos III, Spain. Dr. Elan D. Louis has received research support from the NIH, Bethesda, MD: National Institute of Neurological Disorders and Stroke grants R01 NS042859 (principal investigator), R01 NS39422 (principal investigator), T32 NS07153-24 (principal investigator), R01 NS073872 (principal investigator), R21 NS077094 (coinvestigator), and R01 NS36630 (coinvestigator). Dr. Louis has also received research support from the Parkinson's Disease Foundation (principal investigator).

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received January 14, 2013. Accepted in final form March 13, 2013.

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DISCUSIÓN

V. DISCUSIÓN

Empezábamos esta tesis doctoral preguntándonos qué ocurre en la cognición de los sujetos con enfermedad de Parkinson y temblor esencial cuando no existe demencia. Después de los tres trabajos presentados, podemos afirmar que en ambas entidades existen diferencias en el rendimiento cognitivo respecto a controles sanos. Discutiremos en mayor detalle cada hallazgo específico a lo largo de esta disertación, pero cabe aquí sintetizar las principales aportaciones de esta tesis.

En primer lugar, hemos confirmado que, incluso en ausencia de demencia, existe una alteración en las funciones cognitivas relacionadas con el lenguaje y la memoria de los enfermos de Parkinson y en la velocidad de procesamiento cognitivo en los sujetos con temblor esencial (89). En estos últimos, y como aporte fundamental al ser nuestro estudio el único a nivel poblacional en temblor, encontramos también diferencias con los controles sanos. Al igual que ocurrió con los aspectos no motores de la enfermedad de Parkinson (figura 1), parece que la visión del temblor esencial se va ampliando. Es esperable que en un futuro cercano dilucidemos otras alteraciones no motoras de esta entidad (37).

Se debe destacar que observamos un gradiente entre las dos entidades y algo de solapamiento en las funciones afectadas (89). Este hallazgo está en acuerdo con otros estudios dónde se ha visto que ambas entidades comparten elementos comunes. Cabe sugerir que en un subgrupo de pacientes estemos ante mecanismos etiopatogénicos similares (101). Este trabajo redunda en las conclusiones presentadas por otros miembros de nuestro grupo investigador que apoyan que el temblor esencial “benigno” no lo sea tanto. Parece por tanto cada vez más plausible que pueda subyacer en un origen degenerativo en esta entidad (15).

Como elemento final de esta síntesis, antes de profundizar en cada apartado específico, hemos confirmado la hipótesis de que las alteraciones cognitivas pueden ser precoces e incluso anteceder al diagnóstico clínico en sujetos con temblor y no así en los enfermos con Parkinson (87, 88). Para este último ejemplo, como se menciona en el editorial anexo por dos expertos en el área (102) cabe pensar que el resultado no sea nulo, si no inconcluyente al no ser sensible el test utilizado para detectar las alteraciones precoces de ese subgrupo de pacientes (87).

Es por tanto justo enfatizar que ambas entidades, enfermedad de Parkinson y temblor esencial, incluso cuando no existe demencia, repercuten precozmente en el funcionamiento cognitivo de las personas afectadas.

Como fortalezas del estudio NEDICES queremos destacar su base de estudio poblacional. Es conocido que los estudios de carácter poblacional representan mejor que las observaciones de casos hospitalarios el espectro de enfermedad, al no seleccionar a los sujetos y por tanto abarcar todo el espectro de la enfermedad (38). Esto nos da confianza a la hora de extrapolar nuestros hallazgos al conjunto de enfermos con Parkinson y con temblor esencial.

De forma adicional, el amplio número de sujetos estudiados, con una gran muestra asociada de sujetos sanos, ha sido crítico para complementar iniciativas previas. Esto es más manifiesto en el campo del temblor esencial, dónde casi todos los estudios existentes se restringían a un escaso número de casos (39–42).

Otra ventaja del estudio NEDICES es que pudimos excluir de forma sistemática los sujetos con demencia para estos análisis. Hecho que nos permite tener confianza en que las alteraciones precoces que estudiamos no se ven enmascaradas por sujetos con mayor afectación cognitiva, y que pudieran distorsionar el comportamiento de los grupos estudiados.

Queremos llamar la atención sobre la definición de casos incidentes. Con la excepción del estudio presentado por Thaler et al. (52), en nuestra opinión no hay iniciativas con muestras de sujetos amplias que estudien las manifestaciones cognitivas en las fases preclínicas o prodrómicas de ambas entidades, entendiendo estas por la fase que antecede al diagnóstico en la que el sujeto aún no ha expresado la enfermedad (103). Es bien conocido para el ejemplo de la enfermedad de Parkinson, y no lo es para el caso del temblor esencial, que hay una larga fase preclínica que puede preceder al diagnóstico incluso en 10 años (104). A nuestro entender, el estudio NEDICES representa el único estudio poblacional que ha evaluado a los sujetos en esta fase preclínica. Esto nos permite concebir aspectos desconocidos de la fisiopatología de la enfermedad y en concreto en el caso del temblor esencial apoyar el origen degenerativo que mencionábamos (15).

Si hemos aludido a nuestras fortalezas, también tendremos que explicar nuestras debilidades. El estudio NEDICES, por las fechas en las que fue diseñado, incluyó una batería de evaluación neuropsicológica limitada. Este hecho es más relevante si cabe para el estudio basal, o primer corte, de 1994/1995, dónde sólo recogimos el test de cribado global MMSE-37. Hubiera sido deseable tener una caracterización más amplia de la población del estudio y es este un aspecto que habrá que resolver en futuras iniciativas (102). No obstante, como decíamos anteriormente, la ausencia de iniciativas similares en el apartado de la fase preclínica, a pesar de que nuestros datos estén basados en un test de cribado muy general, nos permite acercarnos a una realidad antes desconocida.

Otra limitación reseñable es la ausencia de más cortes temporales en el seguimiento, ya que las alteraciones cognitivas pueden ser dinámicas y hay sujetos que pueden evolucionar hacia un mayor deterioro o incluso mejorar cognitivamente. Varias de las iniciativas mencionadas en la introducción, han incluido más cortes temporales (49). Esto ha permitido a otros autores entender la evolución desde el punto de vista cognitivo de los sujetos estudiados y es algo que hubiera sido deseable para el estudio NEDICES. Es interesante reseñar que con nuestra población se han llevado a cabo varios estudios censales con datos de mortalidad (105). Estos estudios han paliado la falta de perspectiva evolutiva y han permitido estimar el impacto futuro de las alteraciones referidas. Como posible trabajo tras esta tesis, podría plantearse evaluar la mortalidad de los diferentes sujetos que muestran un rendimiento cognitivo inferior a la norma, especialmente en las fases preclínicas.

Como aludiremos posteriormente, algunas de las diferencias encontradas fueron de pequeña magnitud (tamaño de efecto basado en estadístico d de Cohen menor de 0,4). Esto hace que al hilo del punto anterior, desconozcamos las implicaciones pronósticas de nuestros hallazgos y será por tanto necesario evaluar datos prospectivos de indicadores de mortalidad o similares para confirmar que estas alteraciones tienen una importancia clínica.

Finalmente en el apartado de limitaciones, mencionar que hubo un porcentaje elevado de participantes que no pudieron estudiarse en el seguimiento. Estas pérdidas de sujetos son conocidas y asumidas en estudios poblacionales. En el caso particular que nos ocupa no pensamos que haya afectado a nuestras conclusiones ya que los sujetos que no se siguieron fueron generalmente más ancianos, con menor nivel cultural y con mayor comorbilidad (87–89). Estos sujetos es esperable que tengan un peor rendimiento cognitivo y por tanto hubieran favorecido nuestras hipótesis *a priori*.

A continuación discutiremos una a una las hipótesis del estudio en relación a los resultados obtenidos y a la literatura previa.

V.i. Hipótesis 1. Existen alteraciones cognitivas en la enfermedad de Parkinson y el temblor esencial, en ausencia de demencia, a nivel poblacional.

Nuestros resultados corroboran la existencia de alteraciones cognitivas en ambas enfermedades. En nuestro trabajo más reciente publicado en Acta Neurologica Scandinavica (89) objetivamos que, prácticamente, los pacientes con ambas enfermedades puntuaron 2 puntos menos en el test de cribado global (MMSE-37) respecto a los controles sanos. También encontramos una diferencia significativa en los sujetos con enfermedad de Parkinson al recordar un ítem menos en las tareas de memoria evaluadas y decir una palabra menos que los controles sanos en las tareas de fluencia verbal semántica. Con una significación marginal, pero evidente, hallamos que los sujetos que tenían temblor esencial cometían un error de media más que los controles en el test de velocidad de procesamiento psicomotriz TMT-A.. Nuestros hallazgos se reafirman con los resultados de los otros dos estudios reportados en esta tesis y en los que se objetivaron caídas medias en la puntuación del test Minimental de 0,7 y 2,4 puntos respectivamente para los sujetos con temblor esencial y con enfermedad de Parkinson prevalente en ausencia de demencia (87,88).

La confirmación de esta hipótesis ratifica los resultados de los diferentes trabajos mencionados en la introducción. Como evidencia discordante, mencionar únicamente el sub-estudio NET-PD que evalúo la cognición de los participantes de varios ensayos clínicos de futilidad y en el que no encontraron alteraciones evidentes en los enfermos con Parkinson. Los autores atribuyeron este resultado no concluyente a que los test seleccionados no fueron los más idóneos para detectar alteraciones cognitivas (106). De esta manera, afianzan el concepto de que existen alteraciones cognitivas latentes en ambas entidades en ausencia de demencia. Para enfatizar la importancia de estos hallazgos, nuestro trabajo ha sido comentado en un reciente editorial de la prestigiosa revista *Nature Reviews Neurology* (107).

V.ii. Hipótesis 2. El gradiente de alteraciones esperables será mayor para la enfermedad de Parkinson, seguida del temblor esencial en comparación a controles sanos.

A pesar de que en ambos grupos de enfermos se excluyó la presencia de demencia/deterioro cognitivo relevante específicamente, dado que el grado de gravedad clínica y la presencia de demencia son más marcados en la enfermedad de Parkinson, anticipamos que las alteraciones que encontraríamos en este estudio serían más evidentes en estos enfermos.

Esta hipótesis también se confirmó en el estudio comparativo entre ambas entidades, en las que consistentemente, y con la excepción del test TMT, encontramos una tendencia significativa a mostrar puntuaciones más bajas los enfermos con Parkinson ($P < 0.05$ en el test de Jonckheere-Terpstra).

Como hallazgo interesante, este hecho no se ha confirmado para las fases preclínicas de la enfermedad dónde los sujetos con temblor esencial preclínico mostraron una caída significativa en su rendimiento cognitivo global (test MMSE-37), al contrario que los sujetos con enfermedad de Parkinson preclínica. Las razones para ello no están claras actualmente pudiendo explicarse de forma especulativa por la diferente sensibilidad del test MMSE-37 a detectar alteraciones en estos dos grupos de pacientes. Será interesante en un futuro evaluar con baterías neuropsicológicas más amplias si estas diferencias persisten y/o por el contrario se confirma también una mayor afectación de los sujetos con enfermedad de Parkinson en las fases pre-diagnósticas.

Respecto a la comparación con la literatura previa, únicamente el estudio de Gasparini et al. (41) encuentra un gradiente de afectación entre ambas entidades. Parece por tanto plausible que a nivel de importancia, las alteraciones cognitivas de la enfermedad de Parkinson, incluso en ausencia de deterioro cognitivo, sigan siendo de mayor calado que las del temblor esencial. Estos hallazgos habrán de ser confirmados en estudios futuros.

V.iii. Hipótesis 3. Existe un solapamiento en las funciones cognitivas afectadas, pero es esperable que haya déficits específicos en cada entidad.

Al haber un solapamiento en muchas de las características clínicas y factores condicionantes entre ambas entidades, nuestra predicción a priori fue que también habría un cierto solapamiento en las funciones cognitivas alteradas. El gradiente de alteración que encontramos y que describíamos anteriormente, apoya esta hipótesis nuevamente. La salvedad es que en los pacientes con enfermedad de Parkinson se vio una alteración mayor en funciones de lenguaje y memoria frente al temblor esencial, dónde hubo una tendencia marginal a tener una menor velocidad de procesamiento cognitivo (89).

Estos resultados refrendan los reportados por el grupo de Cambridge en el estudio CampaIGN y confirman la existencia de alteraciones que sugieren el daño en estructuras posteriores (temporo-parietales) del cerebro, que se relacionarían con la memoria y el lenguaje (47). Varios de los estudios descritos en la introducción han encontrado también alteraciones en estas funciones cognitivas. Todo ello apunta a que a nivel fisiopatológico sean estas las zonas probablemente involucradas en el ulterior desarrollo de demencia y mediante su detección permitirían identificar alteraciones precoces en un hipotético caso futuro de que se desarrollen terapias específicas para estas manifestaciones cognitivas.

Paralelamente, será interesante evaluar mediante estudios de imagen avanzados y también mediante estudios prospectivos de sujetos con déficits en las funciones reseñadas de lenguaje y memoria. Esto servirá para entender los mecanismos que condicionan el desarrollo de demencia en la enfermedad de Parkinson. Por todo ello, no resulta posible con los datos actuales determinar las bases neurobiológicas de estos cambios. Es pertinente también estudiar si éstos están relacionados con patología tipo Alzheimer, que pueden asociarse al desarrollo de enfermedad de Parkinson (108), o alternativamente, y de forma más probable, a una sinucleinopatía latente en regiones corticales cerebrales (109), lo que resultaría llamativo ya que sin haber expresión clínica de un deterioro cognitivo hubiera alteraciones neocorticales. Este hallazgo daría pie a cuestionar el modelo propuesto por Braak y Braak dónde la afectación esperada sería más secuencial y por tanto tardía (24). Confiamos que en un futuro cercano, con el advenimiento de marcadores moleculares de las diferentes proteínas implicadas (proteína tau, α-sinucleina y β-amiloide), sea posible entender las bases neurobiológicas de estas alteraciones cognitivas.

El caso del temblor esencial es aún más misterioso al no haber una teoría fundada de su origen. Estudios recientes han demostrado alteraciones cerebelosas y en los circuitos fronto-cerebelosos (110). Cabe especular que estos hallazgos fueran los responsables de la alteración en la velocidad de procesamiento que hemos encontrado en estos pacientes.

No pensamos que las alteraciones motrices que tienen los sujetos con temblor esencial justifiquen nuestros hallazgos, ni tampoco la coexistencia con otras patologías asociadas al envejecimiento. Al hilo de este último punto, algunos autores han querido diferenciar las formas de temblor presentes en la senectud de las formas juveniles de temblor, sugiriendo que las primeras pudieran tener otras causas asociadas como son cambios tipo Alzheimer (111). En la cohorte NEDICES no hemos objetivado diferencias en función de la edad de inicio del temblor (antes o después de los 65 años). Por tanto, no parece que esto explique nuestros resultados (89).

Creemos necesario que se avance en el conocimiento de la neuropatología del temblor esencial, para poder establecer relaciones causales entre nuestras observaciones y una disfunción cerebelosa o de otro tipo.

Con humildad debemos también reconocer que las alteraciones encontradas han sido de escasa magnitud (tamaños de efectos pequeños en base al estadístico d de Cohen), por lo que también habrá que comprender las implicaciones a nivel clínico y pronóstico de nuestros hallazgos.

V.iv. Hipótesis 4. Las alteraciones cognitivas representan manifestaciones precoces de la enfermedad que incluso acontecen en las fases preclínicas de ambas entidades.

Como aportación novedosa de nuestros estudios, que de hecho ha motivado uno de los editoriales anexos (102), hemos podido estudiar las alteraciones cognitivas que acontecen en las fases preclínicas (antes de que se haya establecido el diagnóstico), tanto de participantes con temblor esencial como de sujetos con enfermedad de Parkinson.

Este es un área de creciente importancia, ya que se baraja que la identificación precoz de las entidades asociadas a neurodegeneración, podría facilitar el que se desarrollaran tratamientos modificadores de enfermedad (103). Esto es especialmente patente para la enfermedad de Parkinson, dónde diferentes estudios han confirmado que en el momento del diagnóstico la pérdida neuronal estriatal es superior al 50% para algunos grupos neuronales (112).

Caracterizar por tanto estas fases preclínicas es una de las prioridades actuales de diferentes actores claves del sector (113,114). En nuestro estudio, en el caso de la enfermedad de Parkinson, no hemos podido detectar diferencias en el rendimiento evolutivo cognitivo respecto a controles sanos (87). Como describíamos anteriormente, pensamos que esto se debe a la ausencia de test sensibles que puedan detectar alteraciones sutiles en el protocolo del estudio NEDICES. Sirva como justificación que el estudio se diseñó mucho tiempo antes de que el conocimiento en esta área se desarrollará (61). No obstante, cabe también la posibilidad de que en las fases preclínicas no hubiera manifestaciones cognitivas. Este hecho parece contradecirse por estudios previos, como el ya mencionado de Thaler et al. en el que se objetivaron alteraciones cognitivas en una cohorte amplia de portadores asintomáticos de mutaciones en el gen de LRKK2 (52).

En el caso del temblor esencial, y de forma pionera, hemos investigado también si existen alteraciones previas al diagnóstico (88). Este hecho se ha demostrado a través del rendimiento menor en el test MMSE-37 en sujetos con temblor esencial que se diagnosticaron en el segundo corte del estudio, y que también se evaluaron antes de desarrollar la enfermedad. Enfatizar aquí que en un análisis de la estrategia seguida para detectar los casos, la posibilidad de que los sujetos hubieran sido erróneamente clasificados como sanos a pesar de haber tenido temblor es desdeñable. En un análisis de 183 participantes con un test de cribado negativo en la evaluación basal de NEDICES, ninguno de ellos presentaba temblor al ser evaluados por un neurólogo. Dato que confirma la ausencia de falsos negativos con esta estrategia (115).

Nuestros hallazgos apoyan el que realmente el temblor esencial pueda, al menos en algunos casos, tener un origen degenerativo y que siga un patrón similar a enfermedades como el Parkinson y el Alzheimer en relación a esta fase pre-sintomática (15). Este área es de especial interés, teniendo en cuenta que el temblor es una enfermedad mucho más prevalente que el Parkinson y dónde también se podrían investigar mecanismos que modificaran el curso de la enfermedad para después ser trasladadas a otras entidades neurodegenerativas (como son la propia enfermedad de Parkinson y la enfermedad de Alzheimer).

V.v.Hipótesis alternativas futuras

Decía el premio Nobel de Medicina del año 1937 Albert von Szent-Györgyi Nagyrápolt “Descubrir significa mirar a lo mismo y pensar algo diferente“. Aplicando este axioma, nos proponemos en esta sección sugerir planteamientos alternativos que expliquen nuestros hallazgos y los descritos en la introducción.

Por un lado empezaremos con la base anatómica de las alteraciones encontradas. Se han atribuido todas las manifestaciones cerebrales posteriores en la enfermedad de Parkinson a patología eminentemente cortical (47). Nuestro primer planteamiento alternativo es que esto no sea así, y que puedan relacionarse estos déficit con las alteraciones que ocurren de forma muy marcada y selectiva a nivel estriatal (116,117). Es conocida la relación del estriado ventral con el hipocampo, la corteza temporal y el lóbulo órbito-frontal (117). Cabe hipotetizar que los sujetos con afectación del estriado ventral tengan una mayor predisposición al desarrollo del deterioro cognitivo. Esto relacionaría los déficits posteriores con un déficit estriatal. Podríamos hablar así hablar de un síndrome “fronto-témporo-parieto-estriatal” asociado al daño en esta última estructura cerebral. Esto es fácilmente objetivable con estudios de imagen en los que se puede comparar la integridad de esta región en sujetos con MCI frente a participantes sanos y será fruto de análisis posteriores a esta tesis.

A nivel etiológico cabría también especular con una causa independiente del depósito de alfa-sinucleina en los fenotipos que asocian clínica cognitiva. Es sabido que las denominadas demencias fronto-temporales pueden asociar mutaciones en el gen MAPT y que pueden cursar con déficits mnésicos y del lenguaje (118). También es conocido la existencia de un fenotipo motor en muchas de ellas. Desde el punto de vista neuropatológico se han documentado depósitos concomitantes de proteína *tau* en cerebros de personas con demencia asociada a enfermedad de

Parkinson (108). Lo mismo cabe decir de la enfermedad de Alzheimer, dónde se ha objetivado la existencia de déficits motores, donde a veces hay coexistencia con la enfermedad de Parkinson y también se han documentado casos con neuropatologías mixtas (108).

Cabe por tanto sugerir que los modelos reduccionistas discutidos al principio no sean del todo generalizables y que dependiendo de (i) las proteínas acumuladas, (ii) las zonas dónde estas proteínas se depositen, se enferme de una forma u otra. Esto cambiaría radicalmente las estrategias terapéuticas para abordar estas enfermedades ya que se precisarían de terapias que evitaran estos depósitos proteicos en general y no específicamente para una proteína concreta. Al igual que en el ejemplo anterior, será interesante ver el resultado de más estudios neuropatológicos y de imagen (idealmente con marcadores moleculares) para entender las complejas interacciones entre todos estos factores.

V.vi. Impacto de esta tesis e implicaciones futuras

Empezábamos este trabajo con una pregunta y, como suele ocurrir en la ciencia, salimos con muchas más. Este trabajo ha servido, en nuestra opinión, para avanzar en el conocimiento de las alteraciones cognitivas en la enfermedad de Parkinson y en el temblor esencial y dar pie a estudiar nuevas cuestiones que facilitarán el entendimiento de estas enfermedades.

La principal relevancia de nuestros resultados es el entender qué esta causando las manifestaciones de estas misteriosas entidades. Este es el paso necesario para poder desarrollar tratamientos efectivos, que ofrezcan soluciones a nuestros pacientes y que no nos afamen a los neurólogos solo como brillantes semiólogos, pero con poco impacto en el curso de las enfermedades que manejamos.

Además de las deseadas implicaciones terapéuticas, anticipamos también implicaciones a nivel pronóstico. El caracterizar estas alteraciones es capital para entender qué sujetos desarrollarán una demencia posteriormente y por tanto que puedan beneficiarse de estrategias terapéuticas diferenciales.

Adicionalmente, este estudio puede tener consecuencias diagnósticas, al permitir detectar elementos diferenciales entre dos entidades, la enfermedad de Parkinson y el temblor esencial, que en ocasiones son difícilmente distinguibles. Sería interesante evaluar test específicos que exploten las diferencias encontradas en este trabajo para poder apoyar el proceso diagnóstico en casos complejos.

Esperamos que el conocimiento generado también pueda transferirse a otras enfermedades neurodegenerativas y que nuestro pequeño grano de arena ayude a cimentar la búsqueda de tratamientos efectivos que paren el proceso de muerte neuronal tanto en el cerebro envejecido como en el joven.

CONCLUSIONES

VI. CONCLUSIONES

- En una muestra poblacional, hemos confirmado que la enfermedad de Parkinson y el temblor esencial alteran el funcionamiento cognitivo incluso en ausencia de demencia.

- El patrón de afectación de ambas enfermedades tiene ciertas similitudes. No obstante, en nuestros resultados la enfermedad de Parkinson afecta de forma predominante la fluencia semántica y la memoria en concordancia con estudios previos. El temblor esencial altera la velocidad de procesamiento cognitivo, hallazgo que deberá ser confirmado en estudios posteriores.

- Pueden existir alteraciones cognitivas pre-diagnósticas en el temblor esencial, sugiriendo un perfil similar a otras enfermedades neurodegenerativas.

- Las bases etiopatogénicas de estas alteraciones no están aún definidas y son necesarios estudios que avancen en los mecanismos etiológicos de las mismas.

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VII. REFERENCIAS

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VIII. ANEXOS

VIII.i. EDITORIALES SOBRE LOS ARTÍCULOS

EDITORIAL

Many Roads Lead to Parkinson's Disease

Bernard Ravina, MD, MS,[1]* and Dag Aarsland, MD, PhD[2,3,4]

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Defining the clinical period immediately preceding the onset of motor symptoms, or premotor Parkinson's disease (PD), is an important research priority that could affect the detection and treatment of PD. Several clinical signs, such as hyposmia, REM behavior disorder (RBD), and constipation, may be early disease manifestations that reflect underlying alpha-synuclein pathology as well as predict subsequent onset of motor manifestations. There is variable evidence supporting the predictive value of these potential premotor signs for the development of motor signs consistent with PD.[1] Recent studies have shown cognitive deficits in patients with incident PD, raising the question of whether or not subtle cognitive impairment may predate overt motor manifestations.[2–4]

In this issue of *Movement* Disorders, Sanchez-Ferro et al. address the rate of cognitive decline in subjects who were subsequently diagnosed with PD.[5] Sanchez-Ferro et al. used the prospectively assessed, population-based Neurological Disorders in Central Spain (NEDICES) cohort to address this question. The NEDICES cohort studied 5,278 subjects 65 years of age and over and average of 3.4 years. Subjects were assessed at baseline and 3.4 years later using the 37-item Mini–Mental State Examination (MMSE) at both time points. After excluding subjects with baseline dementia, comorbid neurological disorders, and incomplete information, 2,487 were used in the analyses. Thirty-seven subjects diagnosed with PD at both time points were considered prevalent cases, and 21 diagnosed only at follow-up were considered incident cases; the preceding baseline was regarded as their premotor period. The remaining 2,429 participants were treated as controls. During the 3-year follow-up, the prevalent PD group progressed at a significantly faster rate on the 37-item MMSE (2.4 ± 4.6) than the premotor (0.2 ± 4.1) or healthy control (0.3 ± 4.0) groups. Stratified analyses to address potential confounders of baseline age, education level, and depressive symptoms suggest a consistent pattern of faster cognitive decline in prevalent cases, although cells may become sparse in specific strata yielding unstable estimates. These findings confirm the rate of cognitive decline in prevalent PD reported on previously, although little information is provided to understand the duration or severity of PD in these cases. The main findings suggest that global cognitive decline, as detected by the 37-item MMSE, may not be an antecedent of motor PD.

Studies such as this one that prospectively assesses potential premotor manifestations preceding the traditional diagnosis of PD will be critical for defining the premotor period. There are important limitations of this study that the investigators address, including potential confounders, infrequent follow-up, and extensive loss to follow-up. Perhaps the chief limitation is the use of the 37-item MMSE as the screening test. The 37-item test consists of the standard Folstein MMSE, plus 5 points for backward repetition of 5 digits, 1 point for imitating the picture of a person with raised arms, and 1 point for copying overlapping circles. The sensitivity of this test to early impairments is not well established. The observed decline in prevalent PD cases shows some sensitivity to cognitive decline. Although a more-focused battery may yet detect differences in premotor cohorts, as compared to controls, this study suggests that clinically significant cognitive decline is unlikely in the premotor period.

The anatomical substrate of some suspected premotor signs, such as constipation, olfactory impairment, and RBD, is distinct from the dopaminergic loss that is most closely associated with motor signs. The

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Relevant conflicts of interest/financial disclosures: Bernard Ravina is an employee of Biogen Idec. Dag Aarsland has received honoraria from Lundbeck, Novartis, DiaGenic, Glaxo SmithKline, GE Healthcare, served on an advisory board for DiaGenic, and received research support from Novartis, Merck Serono, Lundbeck, and GE Healthcare.
Author Roles: Dr. Ravina drafted the manuscript; both Drs. Aarsland and Ravina revised the manuscript.

Full financial disclosures and author roles may be found in the online version of this article.

Received: 13 November 2012; **Accepted:** 15 November 2012
Published online 24 January 2012 in Wiley Online Library (wileyonlinelibrary.com).
DOI: 10.1002/mds.25325

Nature Reviews Neurology | Published online 24 Mar 2017; doi:10.1038/nrneurol.2017.40

MOVEMENT DISORDERS

Comparison of cognitive impairment in Parkinson disease and essential tremor

A gradient of global cognitive impairment exists between healthy controls, patients with essential tremor and patients with Parkinson disease (PD), according to a new study. Performance in multiple domains revealed overlapping but distinct patterns of impairment in the two disorders.

Cognitive impairment often accompanies PD and essential tremor, and the impairments are similar — they usually affect attention, verbal fluency and memory. Direct comparisons between the impairments in the two conditions have so far been limited to just three small studies in which patients with dementia were not excluded. In their new study, Álvaro Sánchez-Ferro and colleagues aimed to address the limitations of the previous populations.

"This project was part of a large population-based study called Neurologic Disorders in Central Spain (NEDICES), and we investigated cognitive deficits in people affected by essential tremor and PD in the absence of dementia," explains Sánchez-Ferro. "We compared the two diseases to gain further insight into the impairment that exists at the early stages of these disorders."

The study included 180 patients with essential tremor, 46 with PD, and 2,212 healthy controls. Participants had taken tests of global cognitive performance, cognitive processing speed, verbal fluency, memory and premorbid intelligence, and the researchers used nonparametric tests to compare the scores.

The analysis revealed that patients with essential tremor and patients with PD were cognitively impaired relative to healthy controls, and that the global impairment was more severe in PD than in essential tremor, indicating a gradient of impairment. A head-to-head comparison of performance in the two conditions showed that this trend held true in tests of memory and verbal fluency, although the differences were not significant. By contrast, patients with essential tremor consistently performed worse than patients with PD on tests of cognitive processing speed, indicating distinct patterns of impairment in the two conditions.

> "the global impairment was more severe in PD than in essential tremor"

"To adjust for confounding effects, we performed a series of subanalyses that gave us enough confidence to attribute our findings to the diseases and not to factors such as age or literacy," states Sánchez-Ferro.

The results require confirmation in further studies, but Sánchez-Ferro says that, if replicated, the findings will help us to understand the pathophysiology of essential tremor and PD and will highlight the fact that the symptoms of essential tremor are not restricted to motor function.

"The findings could also pave the way to develop novel methods to differentiate these two disorders, which can have substantial overlap," concludes Sánchez-Ferro.

Ian Fyfe

ORIGINAL ARTICLE Sánchez-Ferro, Á. *et al.* Cognition in non-demented Parkinson's disease versus essential tremor: a population-based study. *Acta Neurol. Scand.* http://dx.doi.org/10.1111/ane.12752 (2017)

FURTHER READING Aarsland, D. *et al.* Cognitive decline in Parkinson disease. *Nat. Rev. Neurol.* http://dx.doi.org/10.1038/nrneurol.2017.27 (2017)

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