Universitat Autònoma de Barcelona

DISRUPCIÓN DE REDES NEURONALES EN EL DETERIORO COGNITIVO ASOCIADO A ENFERMEDADES QUE CURSAN CON TRASTORNOS DEL MOVIMIENTO

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DISRUPCIÓN DE REDES NEURONALES EN EL DETERIORO COGNITIVO ASOCIADO A ENFERMEDADES QUE CURSAN CON TRASTORNOS DEL MOVIMIENTO

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Abreviaturas y acrónimos

CEN	Central executive network
Cth	Cortical thickness
DBS	Disease Burden Score
DCL	Deterioro cognitivo leve
DMN	Default-mode network
EH	Enfermedad de Huntington
EP	Enfermedad de Parkinson
EP-DCL	Deterioro cognitivo leve asociado a la Enfermedad de Parkinson
EP-CN	Enfermedad de Parkinson con cognición normal
MDRS	Mattis Dementia Rating Scale
MMSE	Mini mental state examination
MoCA	Montreal Cognitive Assessment Scale
PD-CRS	Parkinson´s disease cognitive rating scale
RMf	Resonancia Magnética funcional
SN	Salience network
UHDRS	Unified Huntington´s disease Rating Scale
vcDFT	Variante conductual de la demencia Frontotemporal

VBM	Voxel-based morphometry

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RESUMEN

Las enfermedades que cursan con trastornos del movimiento presentan gran cantidad de alteraciones asociadas, tanto neuropsiquiátricas como cognitivas [1,2]. Todas ellas producen un gran impacto social, en forma de sufrimiento para los pacientes y sus familias, repercusión laboral y costes sanitarios directos e indirectos. Aunque parte de la sintomatología motora puede recibir tratamiento en algunas patologías como la Enfermedad de Parkinson (EP), los aspectos no motores no están tan bien atendidos y se encuentran presentes desde el inicio de la enfermedad. En el caso del deterioro cognitivo, su presentación suele ser más tardía y progresiva que los propios trastornos del movimiento, dando una ventana de oportunidad para su estudio y tratamiento antes de que los síntomas progresen. Adicionalmente, enfermedades genéticamente determinadas como la Enfermedad de Huntington (EH) extienden esta ventana de oportunidad a décadas antes de que se manifieste el primer síntoma motor.

Una de las barreras principales para lograr un diagnóstico precoz es la compresión de la fisiopatología. Procesos relativamente más sencillos, como la pérdida de velocidad y precisión del movimiento, son más fáciles de conceptualizar. Para ello disponemos de modelos como los circuitos de Alexander [3], que han sido fundamentales en nuestra comprensión de los trastornos del movimiento: gracias a esta descripción hemos podido entender el efecto farmacológico de la levodopa en el cerebro de los pacientes con Enfermedad de Parkinson, o desarrollar tratamientos de precisión como la estimulación cerebral profunda. En cambio, las funciones superiores (cognición, afecto) son mucho más difíciles de modelar. Gracias, entre otros, a la llegada a la neuroimagen funcional, estos procesos están siendo comprendidos cada vez más como una disfunción de circuitos o redes. Esto nos ha llevado a desplazarnos desde un paradigma localizacionista (una zona, una función) hacia una visión del cerebro como una serie de circuitos reverberantes y paralelos en los que la computación de cada función cognitiva se halla distribuida. A la manera de las complejas interacciones entre genes y proteínas, que han dado lugar al estudio del genoma y el proteoma, la neurología se mueve de forma creciente hacia el estudio del conectoma para describir los fenómenos más complejos.

En la enfermedad de Parkinson este abordaje ha permitido entender que grupos de regiones cerebrales, actuando como redes cognitivas a gran escala, se encuentran amenazados desde el inicio de la enfermedad. A pesar de que la neurodegeneración produce una marcada destrucción de tejido cerebral desde momentos tempranos, en forma de atrofia, existe la esperanza de que los cambios en la conectividad de estas redes puedan preceder a los

fenómenos más destructivos e identificar la aparición de complicaciones como el deterioro cognitivo. Estos hallazgos podrían hacerse extensivos a enfermedades genéticamente determinadas, como la Enfermedad de Huntington, en los que el periodo libre de síntomas puede comprender décadas. En el caso concreto del deterioro cognitivo, el estudio de los cambios funcionales en estas redes durante la fase motora o asintomática podría identificar rasgos de vulnerabilidad o mecanismos de compensación de relevancia para la prevención y tratamiento.

Por tanto, esta tesis pretende estudiar los cambios incipientes de las redes cognitivas en dos enfermedades que cursan con trastornos del movimiento, con la esperanza de arrojar luz sobre la estructura y funciones de estas redes en los estadíos iniciales de las enfermedades de Parkinson y Huntington respectivamente.

Nuestros objetivos fueron: 1. Entender los cambios incipientes en conectividad funcional en la Enfermedad de Parkinson, comparándolos con el grado de destrucción de tejido en forma de atrofia. Estudios previos habían demostrado que las regiones cerebrales correspondientes a las redes cognitivas frontoparietales se encontraban más activas que en personas sanas de la misma edad, sugiriendo la existencia de mecanismos de compensación. 2. Entender el papel que juega la evaluación clínica de los pacientes en la obtención de correlatos neuronales, dado que la red afectada y la intensidad de esta afectación pueden estar en relación con la presencia e intensidad de deterioro cognitivo leve. Los instrumentos utilizados para acreditar y evaluar esta presencia pueden ser determinantes para entender los efectos funcionales de la enfermedad de Parkinson sobre las redes cerebrales. 3. Entender cuál es el efecto del tratamiento dopaminérgico sobre el cambio funcional que se observa en las redes cognitivas en pacientes no dementes. Dado que los cambios observados en la literatura se localizaban en regiones con inervación dopaminérgica, y este neurotransmisor se suplementa desde el inicio de la enfermedad, estos cambios podrían constituir un artefacto y no un mecanismo de compensación en sí. 4. Entender los cambios funcionales que se producen en las redes cognitivas en la Enfermedad de Huntington. A pesar de ser una enfermedad con una sintomatología no motora prominente, la literatura de redes se ha centrado especialmente en los cambios en las redes motoras y existe un desconocimiento de los efectos de la enfermedad sobre las redes cognitivas, especialmente en la fase no motora.

Como resultados, esta tesis ha constatado los siguientes puntos:

1. Existe una disminución de la conectividad en las regiones frontoparietales, correspondientes a la red de relevancia (*salience network*), en los pacientes con parkinson y deterioro cognitivo leve cuando se compara con pacientes cognitivamente intactos. Esto se extiende a una alteración en la topografía de la red con una disminución del número de conexiones de nodos relevantes en los pacientes con deterioro cognitivo leve, lo que además se produce en ausencia de atrofia comparable en estas regiones.
2. Las herramientas de valoración neuropsicológica son relevantes a la hora de encontrar o no estos cambios incipientes. Existe una serie de cambios comunes a todas las escalas de evaluación cognitiva, pero a pesar de que existen varias escalas aceptadas para la valoración clínica, los correlatos de neuroimagen funcional no son iguales en todas ellas. Esto puede tener repercusiones a la hora de evaluar los cambios en las redes cognitivas.
3. Los pacientes con enfermedad de Parkinson sin demencia tienen un aumento de conectividad frontoparietal comparado con controles sanos, independientemente de si se les ha administrado medicación. No obstante, este componente cambia de forma dinámica con la administración de levodopa. Bajo tratamiento, los pacientes muestram una hiperconectividad en las regiones de la red de relevancia que se desplaza hacia las regiones de la red por defecto cuando no reciben medicación. De forma importante, esta respuesta es característica de los pacientes que convirtieron a demencia en un seguimiento a 10 años, con lo que la hiperconectividad funcional, lejos de constituir un mecanismo de compensación podría suponer un rasgo de vulnerabilidad.
4. Los pacientes con enfermedad de Huntington muestran cambios muy similares en sus redes cognitivas a otras enfermedades neurodegenerativas como la enfermedad de Parkinson, la enfermedad de Alzheimer o la demencia frontotemporal. Esto se traduce en una pérdida de conectividad funcional intrínseca en sus componentes y en una alteración de la arquitectura de la red, ambas correlacionadas con parámetros clínicos como la carga de enfermedad y puntuación cognitiva (*cogscore*). Estos cambios ya se encuentran presentes en la fase presintomática de la enfermedad, especialmente si se analiza el componente de conectividad funcional dinámica.

Como conclusión, se puede afirmar que las redes cognitivas de los pacientes con trastornos del movimiento sufren cambios relevantes desde las fases iniciales, en los que la cognición está relativamente preservada. Estos cambios son evidentes en la Enfermedad de Parkinson desde estadíos iniciales y ocurren incluso cuando descontamos los efectos de la medicación. Esta hiperconectividad funcional puede tener relevancia en la prevención y tratamiento del deterioro

cognitivo, especialmente considerando que su presencia podría condicionar la aparición de demencia a largo plazo. En el caso de la enfermedad de Huntington, los hallazgos apuntan también a una afectación precoz y clínicamente relevante de todas las redes cognitivas. Líneas futuras de investigación deben llevar a la aplicación de estas nociones fisiopatológicas a la resonancia individual de cada paciente, un horizonte que parecía técnicamente lejano, pero que se acerca cada vez más [4].

ABSTRACT

Diseases that present with movement disorders have a large number of associated alterations, both neuropsychiatric and cognitive [1]. All of them cause relevant social repercussions, in the form of suffering for patients and their families, labor disruptions and direct and indirect healthcare costs. Although part of the motor symptoms can be treated effectively in some pathologies such as Parkinson's disease (PD), non-motor aspects are not so well covered and are present from the onset of the disease. In the case of cognitive impairment, its presentation is usually later and more progressive than the movement disorders themselves, giving a window of opportunity for their study and treatment before the symptoms progress. Additionally, genetically determined diseases such as Huntington's disease (HD) extend this window of opportunity to decades before the first motor symptom manifests.

One of the main barriers to achieving an early diagnosis is the lack of understanding of the underlying pathophysiology. Relatively simpler processes, such as loss of speed and precision of movement, are easier to conceptualize. For this we have models such as the Alexander circuits [5], which have been fundamental in our understanding of movement disorders: thanks to this description we have been able to understand the pharmacological effect of levodopa on the brain of patients with Parkinson's disease, or develop precision treatments such as deep brain stimulation. In contrast, higher functions such as cognition or emotions are much more difficult to model. Thanks, among others, to the arrival of functional neuroimaging, these processes are increasingly being understood as a dysfunction of circuits or networks. This has led us to move from a localizationalist paradigm (one region, one function) towards a vision of the brain as a series of reverberating and parallel circuits in which the computation of each cognitive function is distributed. Like the complex interactions between genes and proteins, which have given rise to the study of the genome and the proteome, neurology is increasingly moving towards the study of the connectome to describe these most complex phenomena.

In Parkinson's disease, this approach has made it possible to understand that groups of brain regions, acting as large-scale cognitive networks, are threatened from the onset of the disease. Despite the fact that neurodegeneration produces a marked destruction of brain tissue from an early stage, in the form of atrophy, there is hope that changes in the connectivity of these networks may precede the most destructive phenomena and identify the appearance of complications such as cognitive impairment. These findings could be extended to genetically determined diseases, such as Huntington's disease, in which the symptom-free period can span

decades. In the specific case of cognitive impairment, the study of functional changes in these networks during the motor or asymptomatic phase could identify traits of vulnerability or compensation mechanisms of relevance for prevention and treatment.

Therefore, this thesis aims to study the incipient changes of the cognitive networks in two diseases that present with movement disorders, with the hope of shedding light on the structure and functions of these networks in the initial stages of Parkinson's and Huntington's diseases respectively.

Our objectives were: 1. To understand the incipient changes in functional connectivity in Parkinson's disease, comparing them with the degree of tissue destruction in the form of atrophy. Previous studies had shown that the brain regions corresponding to the frontoparietal cognitive networks were more active than in healthy people of the same age, suggesting the existence of compensation mechanisms. 2. To understand the role that the clinical evaluation of patients plays in obtaining neuronal correlates, since the affected network and the intensity of this affectation may be related to the presence and intensity of mild cognitive impairment. The instruments used to detect and evaluate this presence can be decisive in understanding the functional effects of Parkinson's disease on brain networks. 3. To understand the effect of dopaminergic treatment on the functional change observed in cognitive networks in non-demented patients. Given that the changes observed in the literature were located in regions with dopaminergic innervation, and this neurotransmitter is supplemented from the onset of the disease, these changes could constitute an artifact and not a compensation mechanism per se. 4. Understand the functional changes that occur in cognitive networks in Huntington's disease. Despite being a disease with prominent non-motor symptoms, the literature on networks has focused especially on changes in motor networks and there is a lack of knowledge of the effects of the disease on cognitive networks, especially in the non-motor phase.

As results, this thesis has confirmed the following points:

1. There is a decrease in connectivity in the frontoparietal regions, corresponding to the salience network, in patients with Parkinson's and mild cognitive impairment when compared to cognitively intact patients. This extends to an alteration in the topography of the network with a decrease in the number of relevant node connections in patients with mild cognitive impairment, which also occurs in the absence of comparable atrophy in these regions.

2. Neuropsychological assessment tools are relevant when it comes to finding these incipient changes. Although there are common findings across the several accepted scales, the correlates of structural and functional neuroimaging are not the same. This could have repercussions when evaluating changes in cognitive networks.

3. Patients with Parkinson's disease without dementia have increased frontoparietal connectivity compared to healthy controls, whether they are on medication or not, but this component changes dynamically with the administration of levodopa. Under treatment, patients show hyperconnectivity in the regions of the salience network that moves towards the regions of the default mode network when they do not receive medication. Importantly, this response is characteristic of patients who converted to dementia in a 10-year follow-up, so that functional hyperconnectivity, far from being a compensation mechanism, could represent a vulnerability trait.

4. Huntington's disease patients show very similar changes in their cognitive networks to other neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease or frontotemporal dementia. This translates into a loss of intrinsic functional connectivity in its components and an alteration of the architecture of the network, both correlated with clinical parameters such as disease burden and cognitive score. These changes are already present in the presymptomatic phase of the disease, especially if the dynamic functional connectivity component is taken into account.

As a conclusion, the cognitive networks of patients with movement disorders undergo relevant changes from the initial phases, in which cognition is relatively preserved. These changes are evident in Parkinson's disease from the initial stages and occur even when we discount the effects of the medication. This functional hyperconnectivity may have relevance in the prevention and treatment of cognitive impairment, especially considering that its presence could condition the appearance of dementia in the long term. In the case of Huntington's disease, the findings also point to an early and clinically relevant involvement of all cognitive networks. Future lines of research should lead to the application of these pathophysiological notions to the individual resonance of each patient, a horizon that seemed technically distant, but that is getting closer and closer [4].

1. INTRODUCCIÓN

1.1 Enfermedad de Parkinson

La EP es una enfermedad neurodegenerativa caracterizada por la afectación motora progresiva en forma de rigidez, bradicinesia (lentitud y torpeza del movimiento) y temblor [6]. Estos signos y síntomas vienen determinados por la afectación de los ganglios basales, un conjunto de estructuras de sustancia gris situados en la parte profunda del cerebro. La alteración patológica inicial es la pérdida de neuronas dopaminégicas en la *sustancia nigra* del mesencéfalo, que desencadenan un desequilibrio en los circuitos establecidos dentro de los ganglios basales. Esta pérdida inicial se va haciendo más generalizada a medida que la enfermedad progresa, con lo que la EP, restringida inicialmente a estructuras subcorticales, acaba afectando al cerebro de forma generalizada.

Por este último motivo, la EP no se restringe solamente a una afectación motora. Los síntomas no motores afectan a los pacientes desde estadios tempranos, siendo algunos, como la depresión, la apatía o los trastornos del sueño, previos a la detección de los síntomas motores en muchos casos. Sea cual sea el momento de su aparición, los síntomas no motores constituyen una de las causas fundamentales de pérdida de calidad de vida, costes sociales y sanitarios asociados a la EP. Lamentablemente, la existencia de tratamientos sintomáticos para los aspectos motores, como la levodopa -disponible desde los años 60 del siglo XX- o la estimulación cerebral profunda no suelen mejorar la sintomatología no motora en la misma medida. La EP continúa siendo una enfermedad de etiología desconocida en la que no existe un tratamiento curativo, pero los aspectos no motores de la misma siguen siendo comparativamente peor entendidos y tratados.

Esta tesis estudia la neurobiología de uno de los síntomas no motores más prevalentes y discapacitantes: el deterioro cognitivo y su evolución a demencia. Se estima que el 80% de los pacientes desarrollarán demencia a los 20 años del diagnóstico de la enfermedad [7]. La ausencia de tratamientos se deriva de la menor comprensión de los mecanismos subyacentes a la cognición y la memoria comparados con los que

estructuran el movimiento: no disponemos de una formulación tan precisa como la descrita por Alexander para los circuitos de los ganglios basales.

Además, en una enfermedad neurodegenerativa, es prioritario detectar los signos de disfunción cerebral antes de que produzcan síntomas discapacitantes, puesto que el sistema nervioso tiene una capacidad reducida o nula de regeneración una vez que el daño se ha establecido. Por tanto, la búsqueda de marcadores de daño precoz es fundamental para actuar de forma significativa en estos síntomas, y un paso previo clave es comprender cuáles son las estructuras más vulnerables en las fases iniciales.

1.2 Enfermedad de Huntington

La EH es una enfermedad neurodegenerativa genéticamente determinada por la expansión anormal de una repetición (CAG) en el gen *HTT* situado en el cromosoma 4 [8] . Los pacientes que presentan 40 o más repeticiones de este trinucleótido desarrollan la enfermedad. El debut clínico está marcado, como en la mayoría de enfermedades de este grupo, por los trastornos del movimiento en forma de corea, distonía o bradicinesia. De todas formas, y como ocurre en la EP, las alteraciones cognitivas y conductuales están presentes desde hasta 15 años antes de la aparición de los primeros síntomas motores [9]. En la EH se pueden detectar cambios cognitivos sutiles ya en las fases iniciales, y con la evolución de la enfermedad se puede objetivar la aparición de demencia en la mayor parte de los casos [10].

Al tratarse de una enfermedad genéticamente determinada, el interés de encontrar marcadores de disrupción sutil en el funcionamiento cerebral tiene interés tanto biológico como clínico. Por un lado, disponemos de una amplia ventana de oportunidad para entender la disrupción de las estructuras que soportan la cognición en lo que se denomina la parte pre-sintomática de la EH (Pre-EH), lo que no ocurre en otros trastornos que no tienen un origen genético. Por el otro, la aparición de tratamientos que mejoran la sintomatología o que aspiran a la curación de la enfermedad –como los recientes intentos por suprimir la huntingtina mutada mediante el uso de

oligonucleótidos antisentido [11]-, precisan de marcadores que sean lo suficientemente sensibles para detectar cambios en las fases presintomáticas de la enfermedad.

1.3 Neuropsicología en enfermedades que cursan con trastornos del movimiento: EP y EH

Como se ha mencionado previamente, tanto la EP como la EH muestran alteraciones cognitivas y neuropsiquiátricas desde el inicio de la enfermedad. Su detección y evaluación depende del uso adecuado de herramientas de valoración neuropsicológica, puesto que permiten diagnosticar, valorar la evolución y realizar un estadiaje de los pacientes. Además de la valoración clínica, estas herramientas son fundamentales en investigación para establecer las categorías sobre las que buscamos correlatos bioquímicos, neuroanatómicos o de función cerebral.

En la EP, aproximadamente el 30% de los pacientes diagnosticados *de novo* presentan quejas cognitivas subjetivas que no se aprecian en la exploración neuropsicológica y entorno a un 25% cumplen criterios de deterioro cognitivo leve (EP-DCL) [12]. Dado que el hecho patológico fundamental de la EP es la pérdida de inervación dopaminérgica, de forma clásica siempre se ha considerado que los circuitos frontoestriatales -fundamentalmente dopaminérgicos- son los más afectados por la enfermedad. Estas regiones soportan fundamentalmente procesos ejecutivos y por este motivo se ha considerado el deterioro cognitivo asociado a la EP como “frontal-disejecutivo”.

No obstante, los estudios en profundidad de todos los dominios cognitivos revelan que los pacientes con EP sufren cambios profundos en la memoria, lenguaje y especialmente función visuoespacial. La hipótesis del Síndrome Cognitivo dual [13] diferencia dos síndromes cognitivos en la EP: por un lado, el de un grupo de pacientes que muestra alteraciones en la planificación, memoria de trabajo y función ejecutiva, y por otro, el de otro conjunto de pacientes que muestra déficits tempranos en la función visuoespacial y fluencia semántica. El primer grupo suele mostrar una progresión lineal

dependiente de la gravedad de la enfermedad, mientras que el segundo, que presenta una disfunción cortical posterior más temprana, suele evolucionar a demencia. En general, la prevalencia de demencia en la EP se ha estimado en aproximadamente en 40% [14], y la prevalencia acumulada oscila entorno al 28% a los 5 años del diagnóstico, 48% a los 15 años y 83% a los 20 años [7]. Por tanto, la aparición y velocidad de progresión del deterioro cognitivo es altamente variable entre pacientes, y suele estar marcada por la aparición de déficits corticales posteriores.

Respecto a la EH, su perfil neuropsicológico ha sido descrito como el de una demencia fronto-subcortical, debido al predominio de los trastornos ejecutivos, atencionales y de velocidad de procesamiento [15]. No obstante, las alteraciones que van más alla de lo frontosubcortical son evidentes desde los inicios de la enfermedad y afectan a la integración visuomotora, la memoria episódica y autobiográfica y la producción y organización del lenguaje [16,17] El deterioro cognitivo es evidente y progresivo desde 15 años antes del comienzo de los síntomas motores y el desenlace final es la demencia en la gran mayoría de los casos [10]. Durante las fases iniciales es habitual que se reporten quejas subjetivas de memoria, sin que esto suponga un impacto claro sobre la funcionalidad. Aun así, se puede objetivar una disminución en la velocidad de procesamiento, el reconocimiento de emociones o el rendimiento en tareas de integración visuomotora [9,16]. A medida que la enfermedad progresa, la presencia de un síndrome disejecutivo se hace cada vez más evidente (comprendiendo un enlentecimiento psicomotor como síntoma más precoz, así como la disfunción ejecutiva y los trastornos de atención y memoria de trabajo), pero se ve acompañado con un deterioro de las funciones mnésicas, visuoconstructivas, del lenguaje y del procesamiento emocional y cognición social.

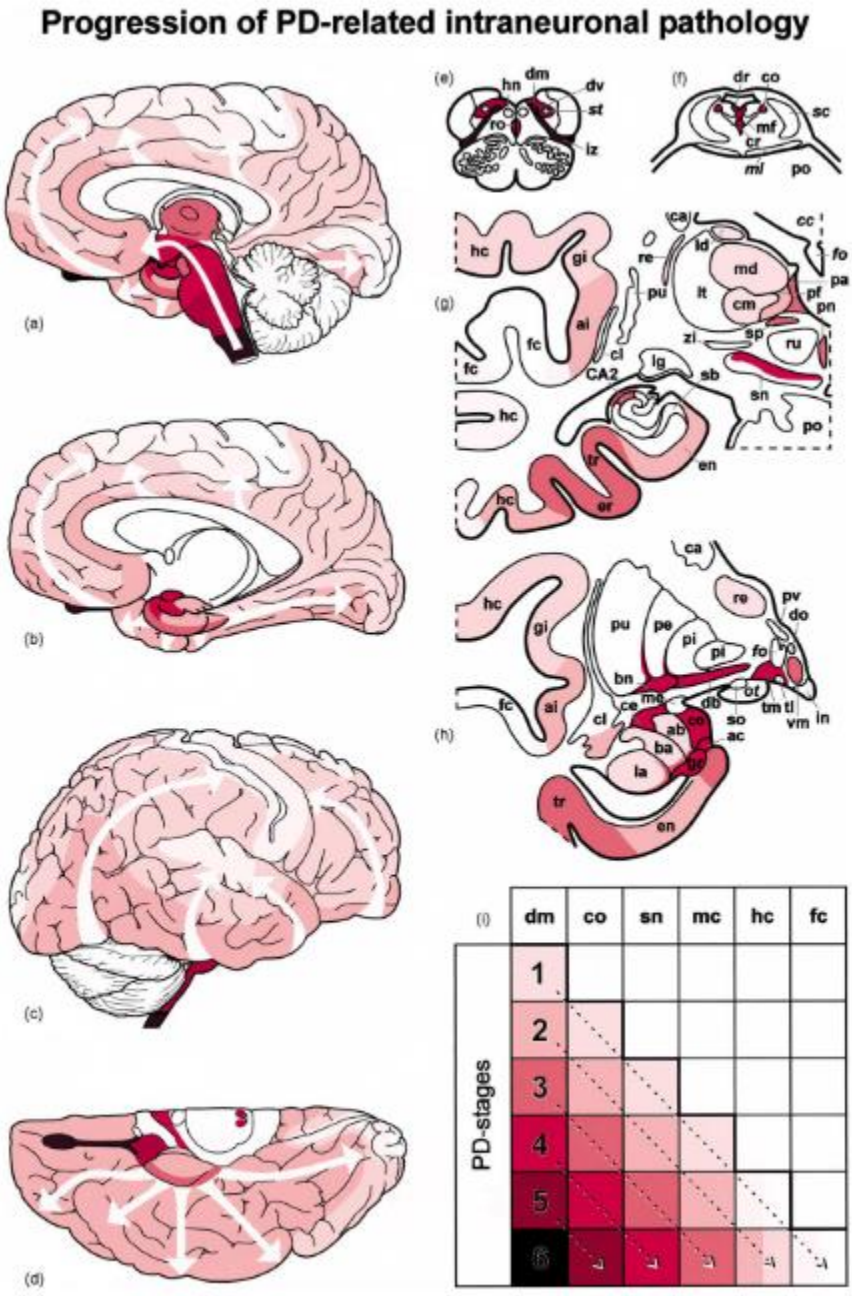
El complejo panorama neuropsicológico que ofrecen las dos enfermedades, con distintos fenotipos y velocidades de progresión, precisa de instrumentos de valoración específicos para cada enfermedad. En la EP, el uso inicial de herramientas empleadas en otras patologías, como el *Mini Mental State Examination* (MMSE) utilizado en la Enfermedad de Alzheimer, ha dado paso a la adopción de instrumentos validados específicamente para la EP, con distintos grados de complejidad. De esta manera, la

Movement Disorders Society (MDS) reconoce un nivel I de complejidad, diseñado para hacer cribaje del deterioro cognitivo, en el que los instrumentos son más sencillos y requieren menos tiempo de administración [18]. En esta categoría se encuadran escalas como la *Montreal Cognitive Assessment Scale* (MoCA), la *Mattis Dementia Rating Scale*, y la *Parkinson's Disease-Cognitive Rating Scale* (PD-CRS), todas ellas recomendadas por la MDS. Por otro lado se considera un nivel II de complejidad, en el que cada paciente es valorado empleando dos escalas de valoración neurpsicológica para cada uno de los cinco dominios cognitivos [19]. Éste método es el recomendado para la valoración clínica de los pacientes, aunque requiere evaluaciones más largas y personal clínico especializado, por lo que no puede realizarse en todos los centros. Desde el punto de vista científico, es una herramienta potente empleada en muchos estudios que buscan comprender la neurobiología de la EP [20,21], pero presenta algunas complicaciones, como las amplias combinaciones de pruebas que constituyen una evaluación adecuada, lo que genera problemas de clasificación de los pacientes. En lo relativo a la neuropsicología de la EH, la clasificación y estadiaje del deterioro cognitivo es un desafío. A diferencia de lo que ocurre en la EP, los instrumentos de psicometría más aceptados, como la MoCA, el MMSE o la puntuación cognitiva de la escala unificada para la EH (UHDRS-cogscore) carecen de puntos de corte para distinguir los estadíos iniciales de deterioro cognitivo leve, como sí ocurre en la EP.

1.4 Neurobiología de la EP y la EH

En la enfermedad de Parkinson la causa principal de la aparición de síntomas y signos clínicos es, como se ha mencionado previamente, la degeneración y muerte de las neuronas dopaminérgicas en la *sustancia nigra* del mesencéfalo. Éstas muestran una acumulación progresiva de inclusiones citoplasmáticas, denominadas cuerpos de Lewy, cuya característica es la presencia de la proteína presináptica alfa sinucleína (α-sin). De forma paralela a la destrucción de neuronas dopaminérgicas, los pacientes con EP muestran la aparición progresiva de patología relacionada con α-sin en regiones distribuidas por todo el córtex, siguiendo una progresión ascendente que incluye a los

núcleos de otros pares craneales, el tracto olfatorio, el córtex temporal anteromedial, las regiones asociativas y prefrontales y, finalmente, la participación de todo el córtex en los estadíos avanzados [22].



Progresión de la patología asociada a la enfermedad de Parkinson de acuerdo a los estadíos de Braak, mostrando la progresión desde el tronco del encéfalo hacia las regiones corticales (a) y las vías de progresión dentro del córtex (b,c,d). Adaptado de: Staging of brain pathology related to sporadic Parkinson's disease. Braak et al. Neurobiol Aging 2003.

Tradicionalmente, la extensión progresiva de la patología desde sus lugares primarios de aparición en el tronco del encéfalo hasta su aparición diseminada por todo el córtex se ha asociado a la progresión clínica de la enfermedad. No obstante, en el caso del deterioro cognitivo, esta progresión a estadíos histopatológicos más avanzados no se acompañó de progresión a demencia en un porcentaje significativo de los casos [23]. Esta divergencia entre la distribución anatómica de la enfermedad y su repercusión clínica continúa siendo uno de los aspectos pendientes de resolver en la EP. Esto probablemente se debe a la heterogeneidad de la patología subyacente; además de alfa sinucleína, las regiones afectadas en la EP muestran presencia de ovillos neurofibrilares, placas seniles y patología microvascular que contribuyen con certeza a la aparición de esta enfermedad. Finalmente, algunas condiciones genéticas, como la presencia de mutaciones en los genes de la propia alfa sinucleína (SNCA), el gen de la glucocerebrosidada (GBA) o la apolipoproteína E4 (APOE4) pueden conferir un mayor riesgo de progresión rápida de la enfermedad o de evolución a demencia. Por todos estos motivos, la investigación de los orígenes y evolución de los síntomas asociados a la EP, y especialmente en lo relativo a las funciones superiores-distribuidas por todo el córtex y difíciles de asignar a una zona concreta-, debe ir más allá de los criterios moleculares e histopatológicos.

En la Enfermedad de Huntington, la presencia de la proteína Huntingtina mutante (Mhtt) se ha asociado a una ganancia de función tóxica y, posiblemente, a cierta pérdida de función normal. El número de repeticiones del triplete CAG determina la aparición y gravedad de la enfermedad: esta se expresa con total seguridad a partir de las 40 repeticiones, mientras que aquellos que poseen entre 36 y 39 repeticiones presentan una penetrancia reducida y pueden estar afectos. Las cargas más altas, por encima de

las 55 repeticiones, se asocian con una expresión juvenil de la enfermedad, pero existe una variabilidad importante –de hasta 20 años- en la edad de inicio de la enfermedad entre personas que muestran el mismo número de repeticiones.

El papel fisiológico de la Htt es en general desconocido, aunque se relaciona con procesos de transporte vesicular, regulación génica y el neurodesarrollo en la etapa embrionaria [24]. Su acúmulo patológico, en cambio, causa la disfunción y muerte celular en poblaciones neuronales especialmente sensibles, destacando la población de neuronas espinosas medianas que abundan en los ganglios basales y ciertas regiones del córtex. Al igual que ocurre en la EP, otra serie de mecanismos moleculares intervienen más allá de la acción directa de la mHtt, destacando el papel cada vez más importante que se asigna a la proteína Tau. Esta proteína, codificada por el gen *MAPT* y asociada al funcionamiento de los microtúbulos intracelulares- relacionada por tanto con el transporte axonal, la plasticidad sináptica y el desarrollo de neuritas [25]-, se ha relacionado con una serie de enfermedades neurodegenerativas en las que tiene un papel central (Parálisis Supranuclear Progresiva, degeneración lobar frontotemporal, síndromes corticobasales) o en conjunto con otras proteínas (EP, Enfermedad de Alzheimer, etc)

Todos estos cambios neuropatológicos provocan una atrofia progresiva que es evidente desde 15 años antes del comienzo de los síntomas, comenzando por los ganglios basales [26]. La afectación implica sobre todo a la parte posterior del caudado, la región caudal del putamen, y, en general, una mayor afectación dorsal que ventral de todo el estriado. En cuanto a la repercusión cortical, la atrofia más precoz es la correspondiente al córtex occipital, seguida de las áreas de Brodmann 9, 46 y 10, correspondientes al córtex frontal y prefrontal.

Por tanto, en ambas enfermedades existen procesos moleculares y genéticos subyacentes que determinan una destrucción progresiva e inexorable de las estructuras profundas y corticales. La relación de estos cambios con la diferente velocidad de progresión de los síntomas y la aparición de complicaciones no motoras –cognitivas, neuropsiquiátricas-, es hoy en día uno de los principales retos a los que se enfrenta la neurología, tanto desde el punto de vista diagnóstico como terapéutico y de

seguimiento. Entender la progresión y difusión de esta patología requiere no sólo atender a las zonas histopatológicamente comprometidas –especialmente en los estadíos iniciales, cuando la prevención y el tratamiento pueden ser más eficaces-, sino un conocimiento más profundo de la organización de los sistemas neurológicos. En los últimos años estas investigaciones se han estructurado entorno a la definición y estudio de las denominadas redes cerebrales a gran escala, lo que ha permitido avanzar en el conocimiento de multitud de enfermedades neurodegenerativas, incluyendo la EH y la EP.

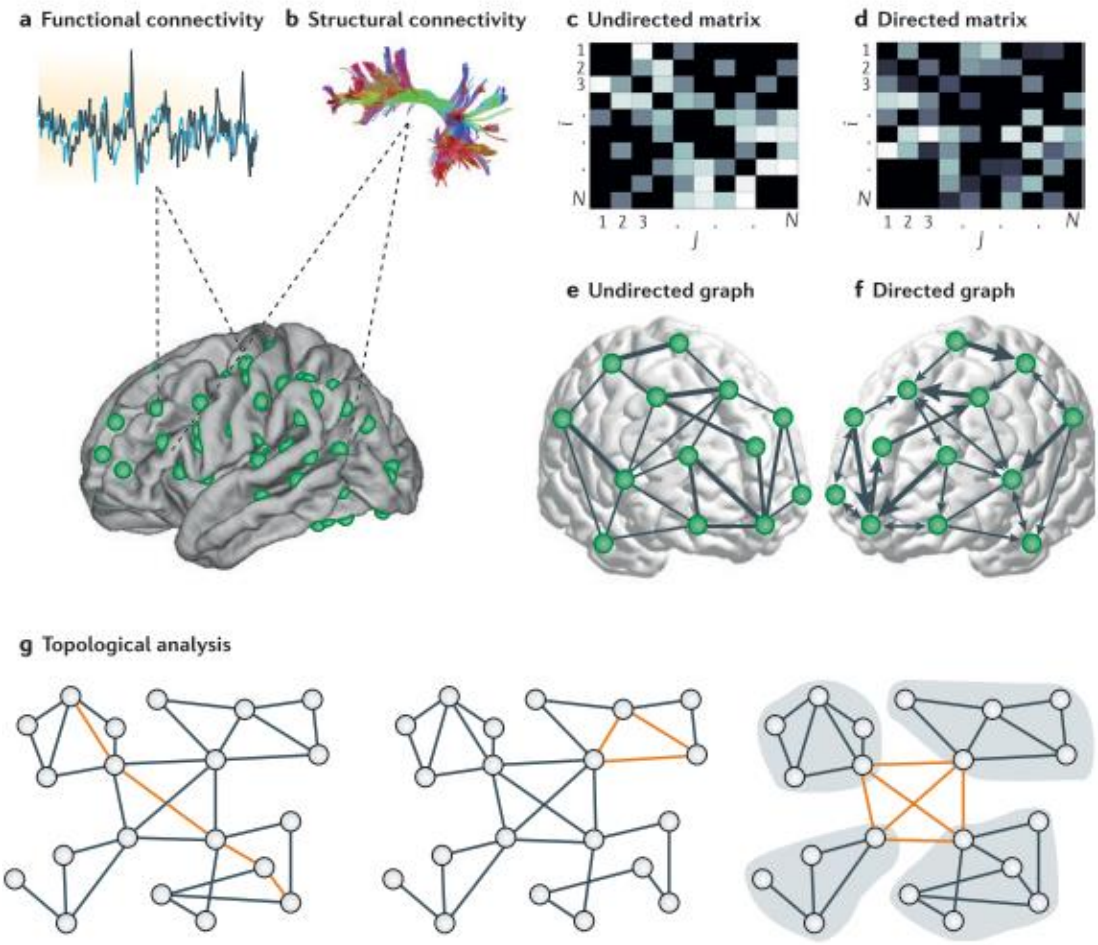
1.5 Estructura y función de las redes a gran escala en las enfermedades neurodegenerativas.

Desde los inicios de la neurología como disciplina uno de sus objetivos fundamentales ha sido lograr una correlación entre la topografía cerebral y las función del órgano. Los estudios iniciales de anatomistas durante los siglos XIX y XX condujeron a la adjudicación de funciones concretas a zonas del cerebro, como la localización de las funciones del lenguaje en la denominada área de Broca, o la identificación de las áreas motoras y premotoras que ejecutan y planifican el movimiento. Este conocimiento ha evolucionado considerablemente gracias al estudio de la anatomía lesional, y ha mejorado la práctica clínica en patologías como el ictus, la hemorragia cerebral o la patología traumática, donde la destrucción directa de regiones del cerebro se traduce en una sintomatología predecible.

No obstante, la utilidad topografía-síntoma ha sido mucho menos evidente en las enfermedades neurodegenerativas y limita especialmente la comprensión de fenómenos relacionados con las funciones superiores. Aunque son suficientemente conocidas las zonas preferentemente afectas en la EH y la EP, como se ha descrito en el apartado anterior, su relación directa con la sintomatología, gravedad y evolución de las mismas no es completamente satisfactoria. De forma creciente, este hecho se atribuye a que las funciones más complejas no dependen de la actividad de regiones concretas, sino de la capacidad del cerebro de actuar como un conjunto conectado. El

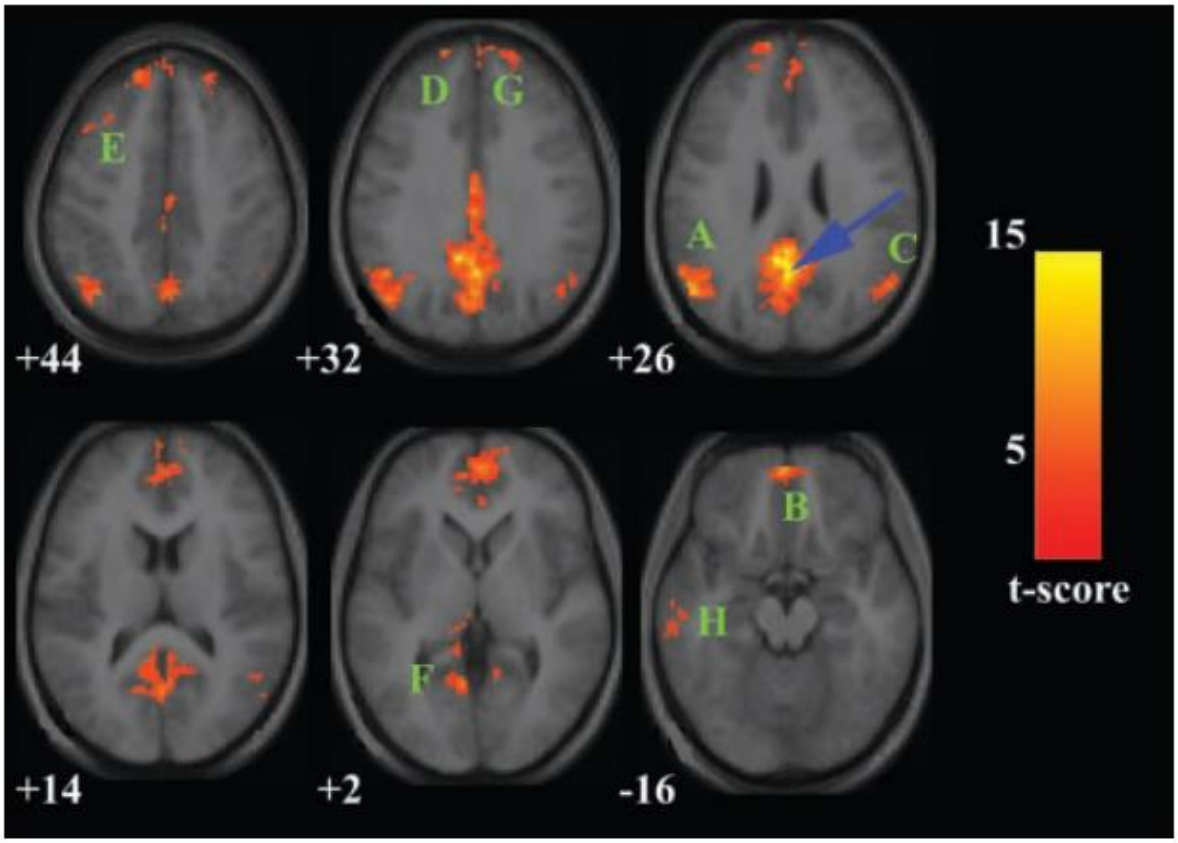
estudio de estas interconexiones ha dado lugar a la definición de redes, conjuntos de regiones cerebrales estrechamente interconectadas que cumplen un grupo de funciones determinadas.

El estudio de las redes ha estado vinculado de forma estrecha al desarrollo de la neuroimagen, especialmente funcional. Este hecho se debe a que el estudio de estas interconexiones debe hacerse *in vivo* y, por tanto, empleando técnicas mínimamente invasivas. Las secuencias de resonancia magnética funcional (RMf) permiten estudiar las fluctuaciones en el consumo de oxígeno de todas las regiones del cerebro, y detectar cuándo los patrones de esta utilización son similares entre dos o más de estas regiones [27]. Esta similitud es lo que permite definir a dos o más regiones como "conectadas", o integrantes de una red a gran escala. Inicialmente, estas dependencias se establecieron en conjunto con tareas motoras en un paradigma experimental: el golpeteo sostenido con un dedo producía una activación proporcional y fiable de la corteza motora y premotora [28].



Obtención de métricas de conectividad funcional a partir de las fluctuaciones de la señal dependiente de oxígeno (figura superior derecha) que se transforma en matrices de datos. De estas se pueden obtener datos de conectividad funcional y datos de topología de las redes empleando parámetros de teoría de grafos (figura inferior). Adaptado de: The connectomics of brain disorders. Fornito et al. Nature reviews neuroscience. 2015.

A continuación, en un estudio clave, Greicius y colaboradores analizaron las adquisiciones que se encontraban entre los bloques de tareas- sin actividad asociada, y por tanto, en reposo-, y descubrieron que el cerebro aparentemente inactivo presentaba una estructura coherente en el que una serie de regiones se mantenían conectadas “por defecto” [29].

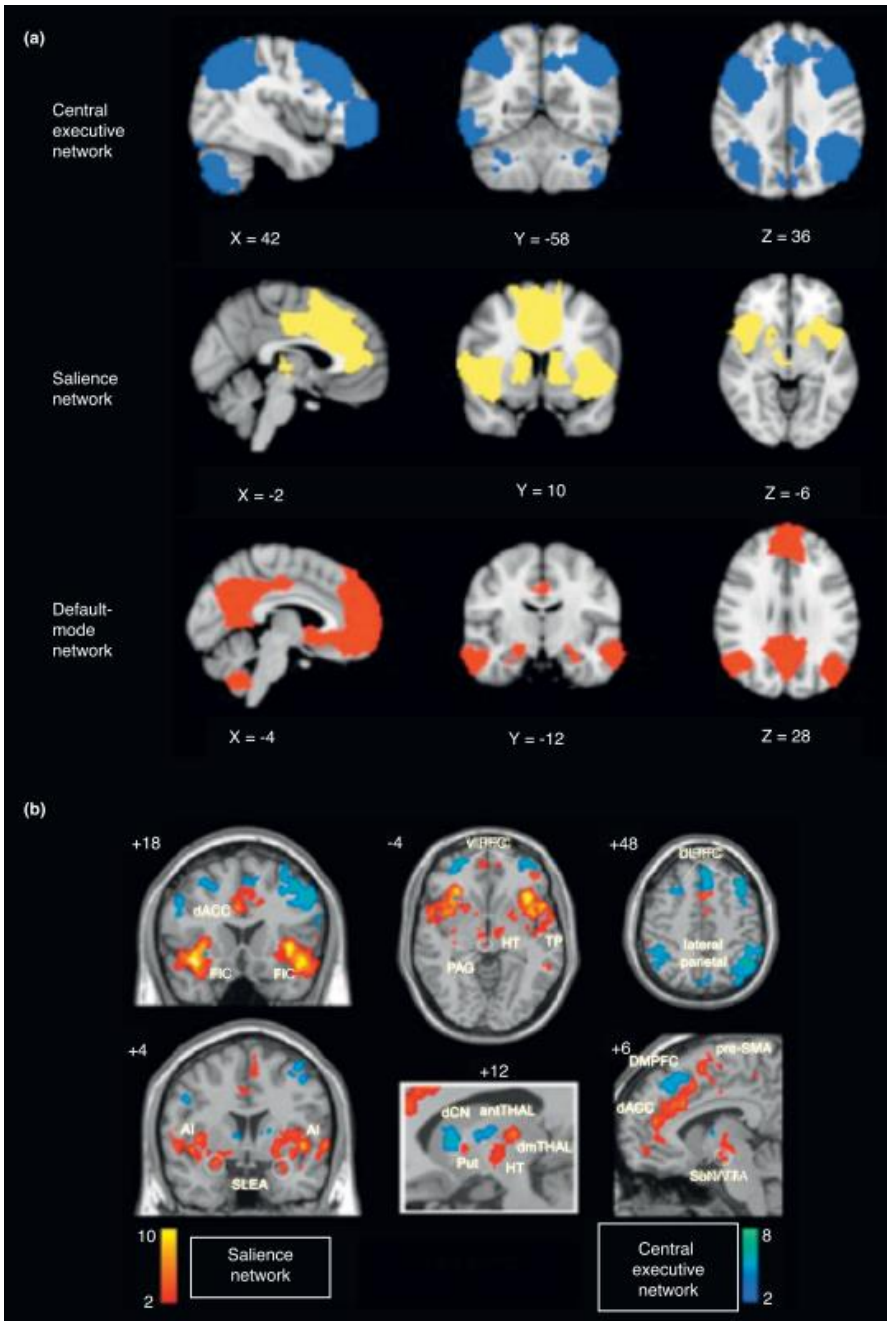


Mapa de conectividad que muestra, en rojo, las regiones interconectadas en situación de reposo, destacando el córtex prefrontal medial y el córtex cingulado posterior (flecha azul), ambas consideradas actualmente los nodos principales de la *default mode network*. Adaptado de: Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Greicius et al. PNAS, 2003.

Este descubrimiento dio el pistoletazo de salida a la descripción de redes “a gran escala”, que en muchos casos se relacionan con la cognición. Además de un conjunto de regiones activadas “por defecto”- que integran la conocida como *default mode network* (DMN), o red por defecto-, estudios subsiguientes mostraron que las regiones activadas durante los bloques de tareas no se restringían exclusivamente a las relativas al movimiento, sino que existían todo un conjunto que mostraba un incremento de

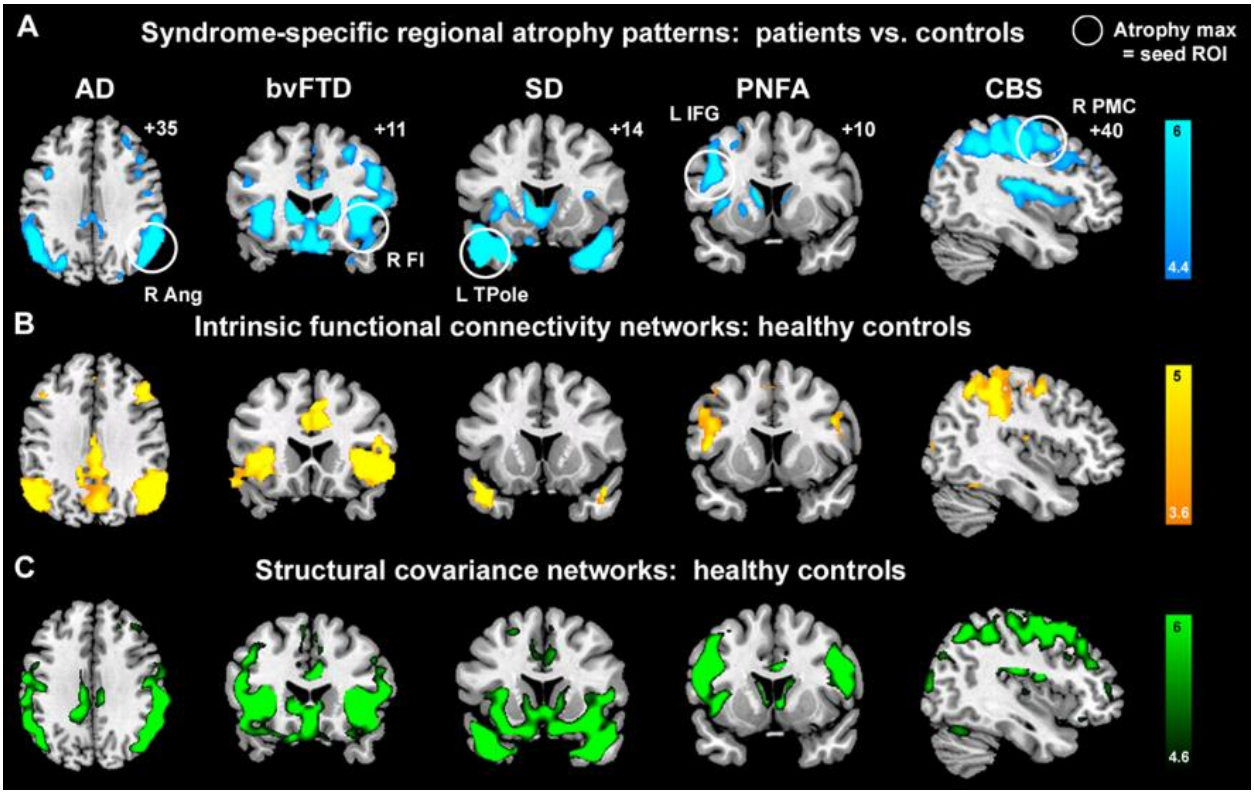
actividad en relación a tareas atencionales, de memoria de trabajo, etc. Este conjunto, denominado “tarea-positivo”, ha sido desgranado en una serie de estudios que ha identificado funciones atencionales, ejecutivas y de atribución de relevancia [30,31]. El cerebro queda por tanto organizado en una serie de circuitos a los que se atribuyen funciones muy diversas, y que tienen propiedades características de esta forma de organización: magnitud de la conectividad entre ellas, anticorrelaciones- la activación de una red implica la desactivación de otra-, o propiedades topográficas que emergen de la organización en redes y que pueden estudiarse mediante el análisis de teoría de grafos. Este mayor nivel de complejidad resulta más adecuado para estudiar las funciones cognitivas y ha resultado clave para entender algunas características de las enfermedades degenerativas.

Existen diversas maneras de organizar y denominar estas redes a gran escala, y la comunidad científica se encuentra lejos de haber alcanzado un consenso [32]. No obstante, ciertos modos de organización de estas redes han resultado más interesantes para desentrañar sus funciones, especialmente las cognitivas y conductuales. De esta manera, un modelo de tres redes (red por defecto, red central ejecutiva y red de relevancia) es particularmente interesante para estudiar tanto la cognición como la patología neuropsiquiátrica [33].



Las tres redes cognitivas nucleares según un modelo triple: por defecto (*default-mode network*), central ejecutiva (*central executive network*) y de relevancia (*salience network*). Adaptado de: Large-scale brain networks and psychopathology: a unifying triple network model. Vinod Menon, Trends in cognitive sicences, 2011.

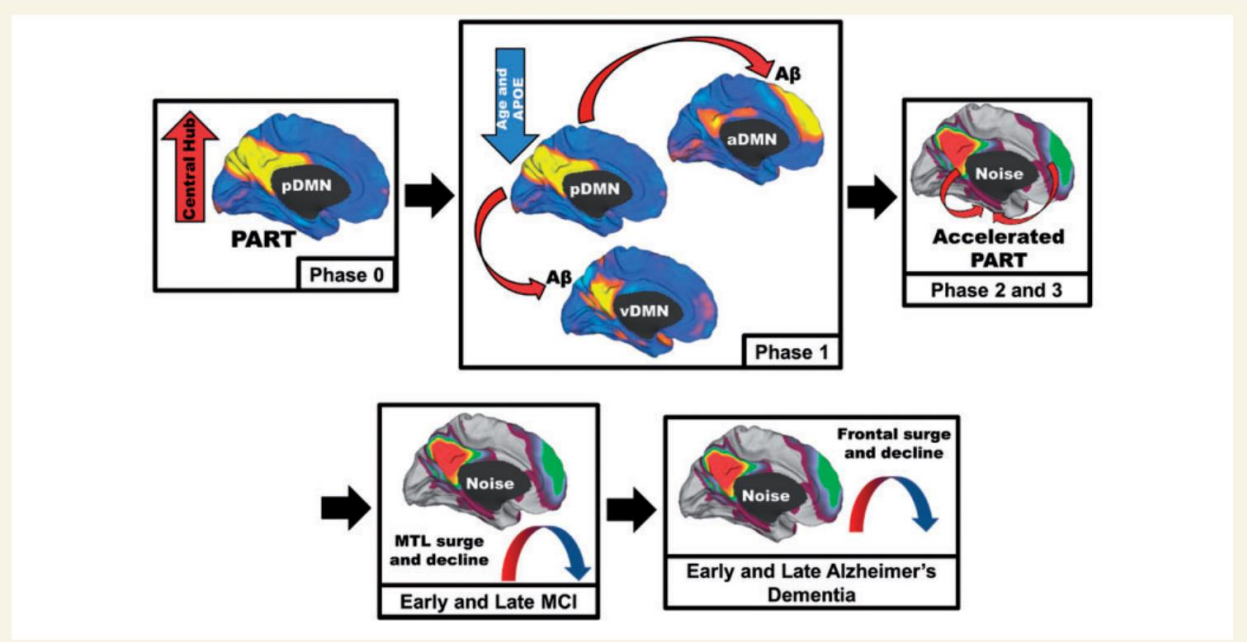
Más allá del punto de vista conceptual, este modelo de tres redes cognitivas ha sido particularmente relevante para el estudio de las enfermedades neurodegenerativas. En concreto, el trabajo de Seeley y colaboradores [34] ha conseguido conectar la sintomatología de los diversos síndromes neurodegenerativos con la afectación concreta de una red cognitiva a gran escala, lo que supone la primera prueba de que estas conexiones intrínsecas tienen repercusiones tangibles en la evolución de las enfermedades neurodegenerativas. De esta forma, la enfermedad de Alzheimer, caracterizada por un deterioro cognitivo de tipo mnésico, afecta principalmente a la red por defecto, que en controles sanos se relaciona con la memoria autobiográfica. Por el contrario, la variante conductual de la demencia frontotemporal (vcDFT) muestra una disminución de la conectividad intrínseca en la red de relevancia, que en sujetos sanos se relaciona con la monitorización del medio externo y la atribución de valor a los estímulos, ponderados en función del estado emocional y físico del sujeto. Estas funciones- similares a las descrita por Damasio en la teoría del marcador somático [35]-, se encuentran particularmente alteradas en la vcDFT.



Relación entre la afectación predominante de redes a gran escala y la presencia de enfermedades neurodegenerativas (de izquierda a derecha: Enfermedad de Alzheimer, variante conductual de la Demencia Frontotemporal, Demencia Semántica, Afasia Progresiva no Fluente, Síndrome Corticobasal). Adaptado de[36]: Neurodegenerative Diseases Target Large-Scale Human Brain Networks. Seeley et al. Neuron 2009.

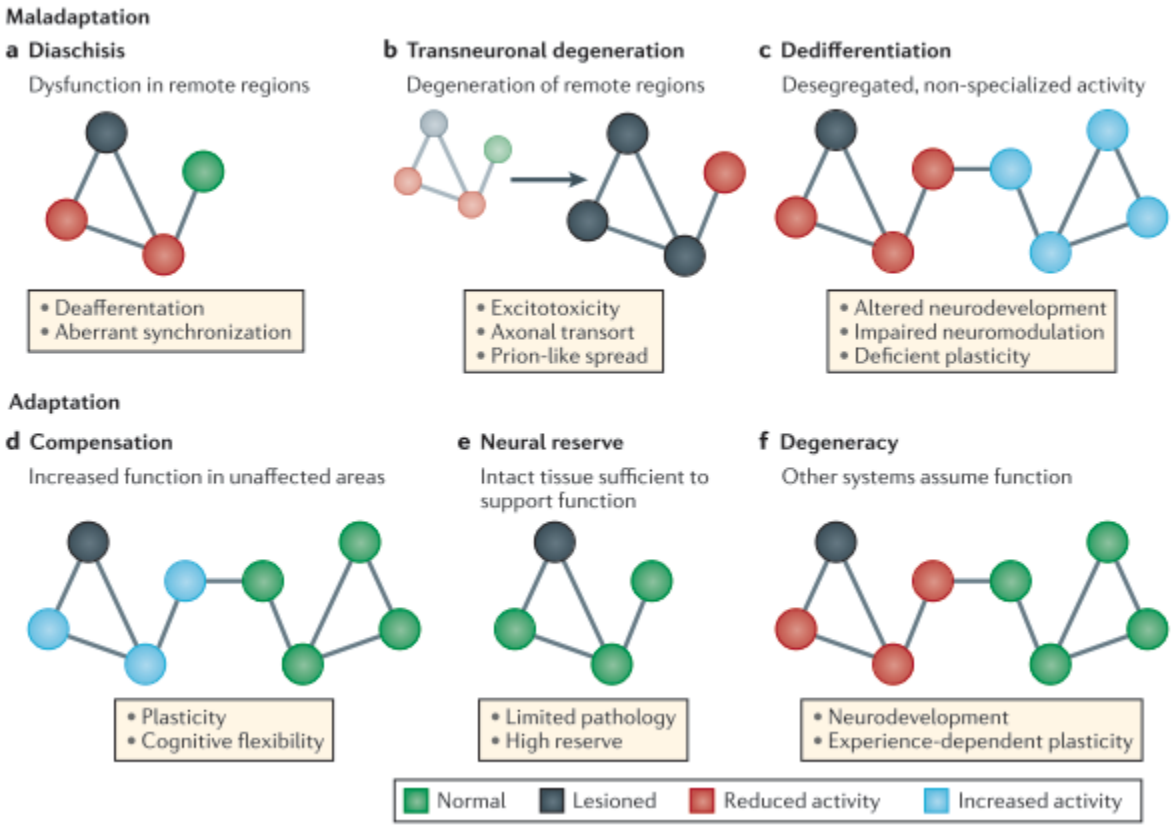
Además de establecer el vínculo entre enfermedad neurodegenerativa y red, otros trabajos han analizado cómo la interacción y composición de estas redes se altera en el transcurso de la enfermedad. Por ejemplo, el planteamiento de un dilema moral en pacientes con vcDFT muestra una alteración en la interacción de las redes de relevancia y por defecto: mientras que en un control sano, la red por defecto- esto es, la memoria autobiográfica del sujeto- influye de forma causal en la conectividad de la red de relevancia, los sujetos con vcDFT pierden esta modulación, lo que encaja con el

aplanamiento emocional característico de esta enfermedad [37]. Por otro lado, estudios de la progresión de la Enfermedad de Alzheimer muestran que el fracaso de la red por defecto sigue patrones muy similares a los del fallo en una red eléctrica, con la sobrecarga compensatoria de los módulos no afectados inicialmente dando paso a un declive generalizado cuando estos mecanismos de compensación se agotan [38]. Por tanto, estos conjuntos de regiones muestran propiedades emergentes, características de redes propias de otras disciplinas (como las redes sociales o las redes de telecomunicaciones) que capturan rasgos de la enfermedad difíciles de medir en un paradigma clásico.



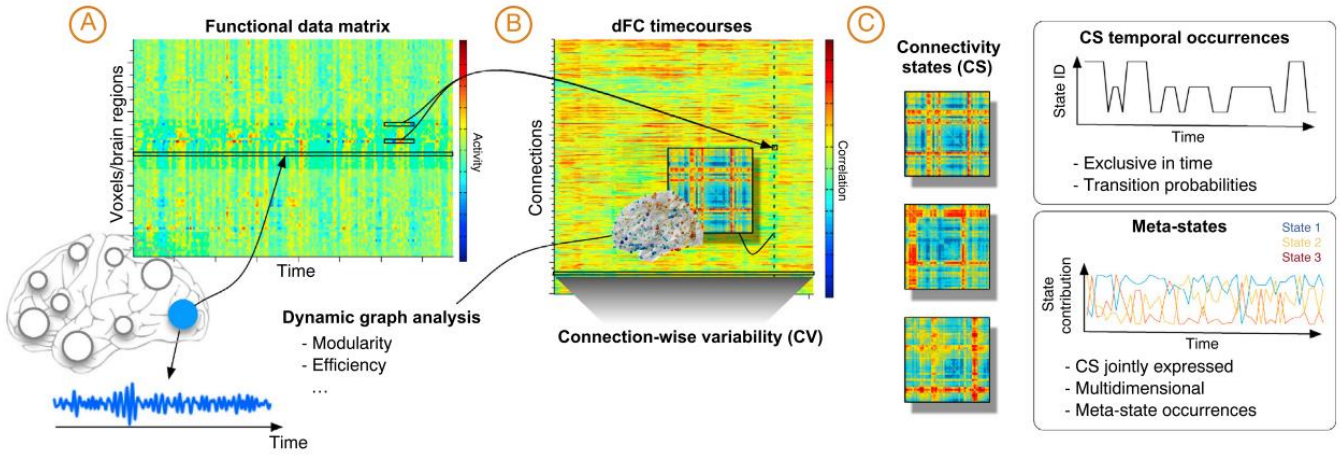
Declive progresivo de la red por defecto en la Enfermedad de Alzheimer: tras un incremento inicial de la conectividad se produce un agotamiento y declive generalizado que coincide con las fases más avanzadas de la demencia. Fuente: Cascading network failure across the Alzheimer's disease spectrum. Jones et al. Brain 2016.

Finalmente, el desarrollo de nuevas técnicas más allá de la conectividad funcional clásica permite refinar el estudio de estas señales. Como ya se ha mencionado, la concepción del cerebro como una red conectada permite emplear conceptos de la disciplina matemática conocida como teoría de grafos [36]. Mediante este análisis, las regiones cerebrales se convierten en nodos de una red que tienen propiedades topológicas como, por ejemplo, la centralidad, que explica la importancia de ese nodo en la transmisión eficiente de información a lo largo de la red.



Utilidad del análisis de teoría de grafos para definir propiedades emergentes de las redes cerebrales, más allá de la conectividad funcional clásica. Las ilustraciones muestran la aproximación a fenómenos clásicos de la neurología como la diasquisis, compensación o reserva neuronal. Adaptado de: The connectomics of brain disorders. Fornito et al. Nature reviews neuroscience. 2015.

De forma adicional, cada vez cobra más importancia el estudio de la dinámica de las redes a gran escala. Mientras la RMf clásica promedia la adquisición de señales durante toda la sesión del sujeto, obteniendo una imagen global de la conectividad de estas, la RMf dinámica aspira a capturar estos parámetros de conectividad en breves momentos del tiempo (lo que se conoce como “ventanas”) para intentar capturar las interacciones dinámicas entre ellas. Se espera que este tipo de análisis pueda ofrecer una visión más cercana a la conectividad cambiante que caracteriza a las redes cerebrales, y multitud de estudios están empezando a aplicarlo en enfermedades degenerativas, incluida la EP[39].



Obtención de datos de conectividad funcional dinámica mediante la metodología de ventana deslizante. Se obtienen secuencias de tiempo correspondientes a cada región del cerebro y posteriormente se resumen estas relaciones dinámicas en “estados de conectividad”. Fuente: Tapping into Multi-Faceted Human Behavior and Psychopathology Using Fmri Brain Dynamics. Bolton et al. Trends in neurosciences 2020.

1.6 Alteración de las redes cognitivas a gran escala en la EP.

Dado el predominio de la clínica motora, el estudio de las redes a gran escala en la EP se ha centrado especialmente en las alteraciones de las redes somatomotoras. En estos estudios se ha encontrado una previsible disrupción en la conectividad intrínseca de los ganglios basales, que diferencia controles sanos de pacientes con EP con gran sensibilidad y especificidad [40]. Otros estudios, en cambio, registran un patrón de incremento de la conectividad que involucra a los ganglios basales, cortex cingulado anterior y área motora suplementaria [41]. La interpretación de estos resultados es compleja, puesto que los pacientes con EP reciben medicación dopaminérgica que puede alterar sustancialmente la conectividad de estos circuitos, un hecho que no está contemplado en el diseño de la mayoría de estos estudios [42].

En lo referido a redes cognitivas, el triple modelo de cognición descrito en el punto anterior ha sido evaluado de forma exhaustiva. Un estudio de Tessitore y colaboradores mostró una menor actividad de la DMN en pacientes con EP y cognición normal (EP-CN) comparados con controles, y sin una evidencia de pérdida de materia gris asociada [43]. En los pacientes con EP y deterioro cognitivo leve (DCL), la pérdida de conectividad intrínseca en la DMN se ha asociado con el declive cognitivo [44]. Por otro lado, el declive en la disponibilidad de receptores dopaminérgicos en la red de relevancia (SN) se relacionó con déficits mnésicos y ejecutivos en una pequeña muestra de pacientes con EP-DCL [45]. Otro de los aspectos propios de la teoría de redes –sus interacciones, en forma de acoplamiento o anticorrelación-, también ha sido estudiado en la EP, con el hallazgo de que una menor anticorrelación entre SN y DMN se asocia con déficits atencionales, motores, visuales y ejecutivos [46].

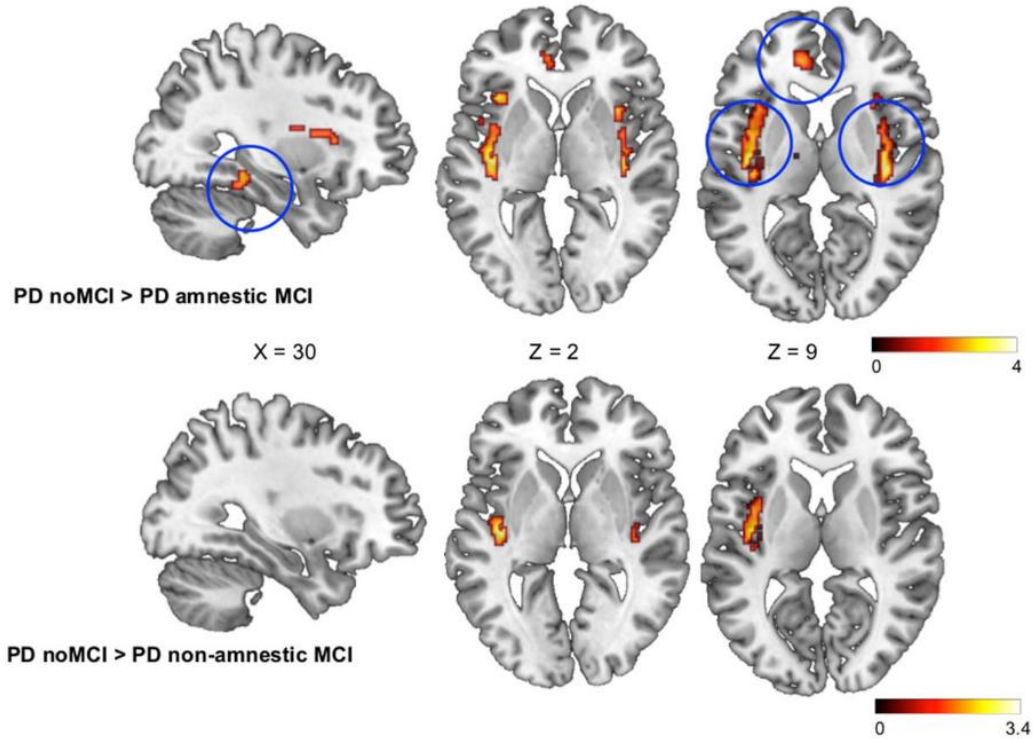
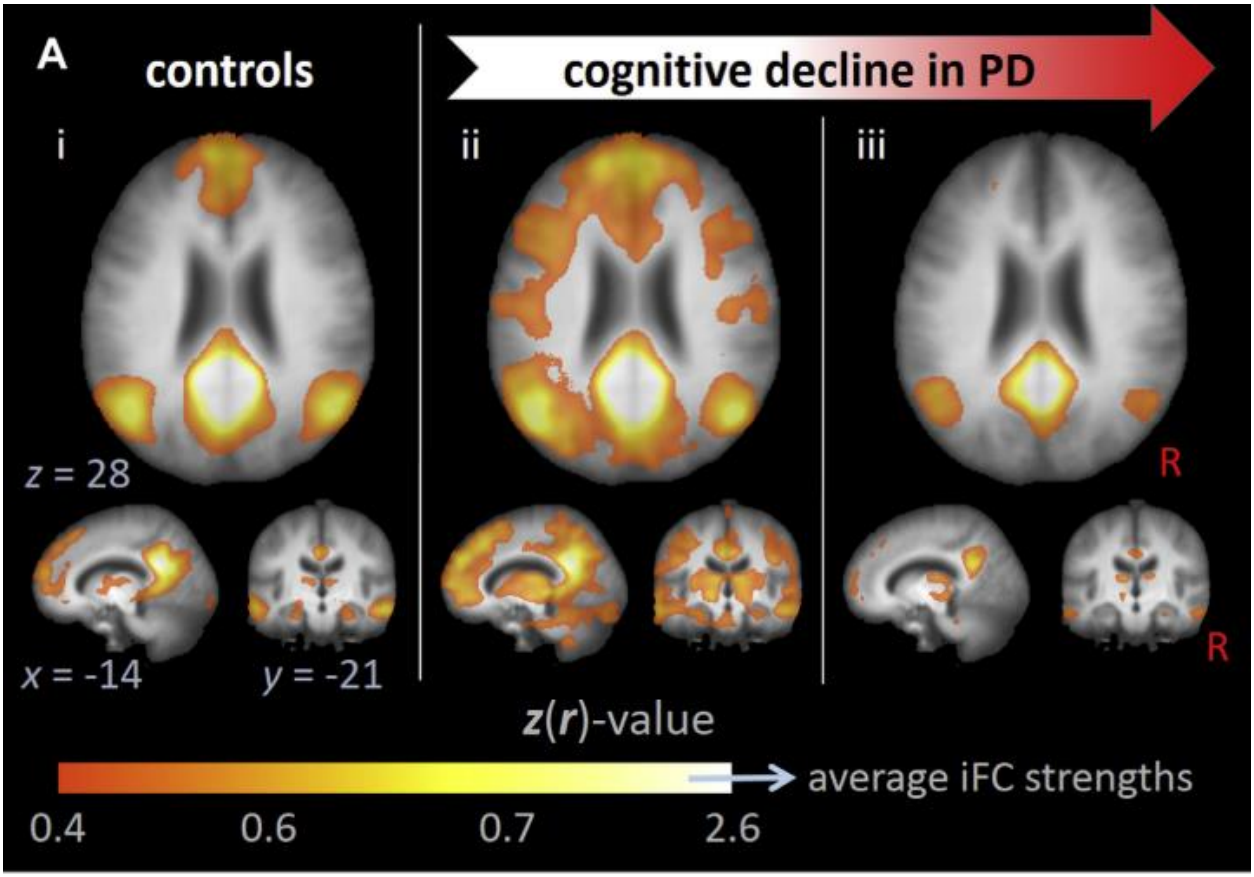


FIGURE 1: Statistical parametric maps of regions of reduced D2 receptor availability in Parkinson disease (PD) with amnestic mild cognitive impairment (MCI; top) and nonamnestic MCI (bottom) compared to PD patients with no MCI (cognitively normal). Blue circles (top) indicate regions of the salience network (bilateral insula and left anterior cingulate cortex), as well as the right parahippocampal gyrus. Color scales represent T value.

Mapas de distribución de receptores dopaminérgicos en grupos de pacientes con EP-DCL vs EP-CN: el primer grupo mostró una disminución de la disponibilidad de receptores en áreas clave de *salience network,* como el córtex insular. Fuente: Salience Network and Parahippocampal Dopamine Dysfunction in Memory-Impaired Parkinson Disease. Christopher et al. Annals of Neurology 2014.

No obstante, todos estos hallazgos han ido especialmente orientados a constatar los cambios asociados al declive cognitivo. Una de las perspectivas más interesantes de los modelos de redes es la posibilidad de realizar un análisis de los mecanismos que ocurren antes de que el daño estructural tenga lugar, de forma similar al modelo de "fallo en cascada" propuesto para la enfermedad de Alzheimer. Esta noción permitiría buscar mecanismos de compensación o rasgos de vulnerabilidad en las redes cognitivas antes de que se produzca el fracaso y comiencen los síntomas. Esto es especialmente relevante en el caso de la EP, dado que existe un largo periodo en el que el deterioro cognitivo está ausente o solamente se observan signos mínimos. En

cambio, enfermedades neurodegenerativas como la EA o la vcDFT debutan con sintomatología cognitiva, en un momento en el que es presumible que exista daño funcional y estructural en estas redes a gran escala. Esta premisa se intuye en trabajos como el de Gorges y colaboradores en el que los autores observaron un incremento de conectividad en las redes frontoparietales en pacientes con EP-CN comparados con sujetos sanos de su misma edad, un fenómeno que declinaba y finalmente desaparecía con la instauración progresiva del deterioro cognitivo y la demencia [47]. Esta hiperconectividad podría localizarse topográficamente en los territorios dependientes de SN, inervados por la vía mesocórtico-límbica, que se encuentra relativamente respetada en los inicios de la enfermedad [48]. Junto con esto, el hecho de que el declive de los receptores dopaminérgicos se asocie con el inicio del EP-DCL podría llevar a pensar en un fenómeno de compensación de estas redes en los estadíos iniciales del DCL, merced a su inervación dopaminérgica relativamente preservada. Por tanto, el análisis de fenómenos iniciales, con una evaluación detallada de la fenomenología neuropsicológica y una descripción de la arquitectura y disrupción de las redes cognitivas, puede ser una de las contribuciones más interesantes del estudio de las redes a gran escala en la EP. También queda pendiente analizar en este contexto cuál es el papel de la medicación dopaminérgica y las modificaciones que puede inducir en estos fenómenos precoces de hiperconectividad.



Evolución de la conectividad funcional en los pacientes cognitivamente intactos comparados con controles sanos, en fases iniciales (centro) y en fase de demencia (derecha). La imagen del centro muestra una mayor conectividad frontoparietal bilateral, mientras que en la fase de demencia no sólo desaparece ésta, sino que también es menor en otras regiones frontales y posteriores. Fuente: "To rise and to fall: functional connectivity in cognitively normal and cognitively impaired patients with Parkinson's disease". Gorges et al. Neurobiol Dis, 2014.

1.7 Alteración de las redes cognitivas a gran escala en la EH.

El estudio de las redes a gran escala ha recibido comparativamente menos atención que en la EP, y de forma similar, se ha centrado en la evaluación de las redes visuomotoras. En éstas es donde se han encontrado mayores diferencias, evidenciando que la gravedad de la sintomatología motora se correlaciona con una menor conectividad funcional en el córtex somatomotor ([49,50], y que déficits en el reconocimiento visual y velocidad motora pueden asociarse con una menor conectividad en redes visuales.

En cambio, los hallazgos relativos a las redes cognitivas son más escasos. En una reciente revisión [51], los cambios en redes cognitivas ocupan una pequeña proporción respecto a los encontrados en otras redes a gran escala. Los resultados obtenidos conciernen a la DMN y exclusivamente en población sintomática [52], mientras que sólo se pudo apreciar un aumento de conectividad en DMN en población presintomática en resonancia magnética asociada a tareas [53]. Las redes ejecutivas mostraron una disociación entre una menor conectividad posterior [50] y una hiperconectividad frontoparietal [54], pero los resultados se restringieron a la población sintomática. Más sorprendente es la absoluta falta de resultados en lo concerniente a la SN, remarcada en esta revisión, y especialmente llamativa dado que la EH presenta una afectación prominente de la atribución de relevancia, como se puede observar en la prevalencia de apatía, la irritabilidad y otros trastornos psicóticos desde el comienzo de la enfermedad [2]

Por tanto, existe una falta de estudios que describan en detalle las alteraciones de las redes cognitivas a gran escala en pacientes sintomáticos y presintomáticos. Uno de los motivos que puede llevar a esta falta de resultados es la ausencia de estudios dirigidos a estudiar las redes cognitivas, usando parcelaciones a tal efecto; la magnitud de los cambios en otras redes y sistemas, principalmente motores y visuales, puede oscurecer cambios relevantes en las redes ejecutivas o de relevancia. Además, es preciso abordar el estudio de estas redes con una perspectiva amplia, que incluya los parámetros clásicos de conectividad funcional pero que también adopte en el mismo

estudio un análisis topológico empleando teoría de grafos. Finalmente, ningún estudio hasta la fecha ha abordado el estudio de la conectividad funcional dinámica, lo que podría implicar la detección de cambios más sutiles, especialmente relevantes en las fases presintomáticas.

2. HIPÓTESIS Y OBJETIVOS

2.1 Hipótesis general

Los pacientes con enfermedades que cursan con trastornos del movimiento presentan alteraciones tempranas y definidas de las redes cognitivas a gran escala, que se relacionan con el desarrollo y progreso del deterioro cognitivo asociado a estas enfermedades.

2.2 Hipótesis específicas

1. En la EP existe un incremento de conectividad en los pacientes con cognición normal o deterioro cognitivo leve, que se traduce en alteraciones en las propiedades de redes frontoparietales, especialmente la red de relevancia.

2. La valoración de estas alteraciones precoces en la EP depende de la clasificación clínica que se emplee para agrupar a estos pacientes en EP-CN o EP-DCL, y de la administración de medicación dopaminérgica.

3. En la EH se pueden observar alteraciones en todas las redes cognitivas a gran escala desde las fases pre-manifiestas de la enfermedad, y estos cambios están relacionados con las puntuaciones clínicas relativas a la progresión de la enfermedad y el deterioro cognitivo.

3. OBJETIVOS

3.1. Objetivo principal

Analizar la estructura y función de las redes cognitivas a gran escala en pacientes sin demencia diagnosticados de trastornos del movimiento y su relación con el diagnóstico y progresión del deterioro cognitivo.

3.2. Objetivos secundarios

1. Analizar la existencia de un posible fenómeno de compensación en estadíos iniciales de la EP correspondiente a una hiperconectividad frontoparietal de la red de relevancia.
2. Analizar el papel del tratamiento sustitutivo dopaminérgico en los desequilibrios entre las redes cognitivas a gran escala en la EP.
3. Analizar la estructura y funciones de las redes cognitivas a gran escala en la EH y el papel de los cambios en conectividad funcional dinámica.

4. COMPENDIO DE PUBLICACIONES

4.1. Artículo 1

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RESEARCH ARTICLE

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A divergent breakdown of neurocognitive networks in Parkinson's Disease mild cognitive impairment

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Abstract

Cognitive decline is a major disabling feature in Parkinson's disease (PD). Multimodal imaging studies have shown functional disruption in neurocognitive networks related to cognitive impairment. However, it remains unknown whether these changes are related to gray matter loss, or whether they outline network vulnerability in the early stages of cognitive impairment. In this work, we intended to assess functional connectivity and graph theoretical measures and their relation to gray matter loss in Parkinson's disease with mild cognitive impairment (PD-MCI). We recruited 53 Parkinson's disease patients and classified them for cognitive impairment using Level-1 Movement Disorders Society-Task Force Criteria. Voxel-based morphometry, functional connectivity and graph theoretical measures were obtained on a 3-Tesla MRI scanner. Loss of gray matter was observed in the default mode network (bilateral precuneus), without a corresponding disruption of functional or graph theoretical properties. However, functional and graph theoretical changes appeared in salience network nodes, without evidence of gray matter loss. Global cognition and executive scores showed a correlation with node degree in the right anterior insula. We also found a correlation between visuospatial scores and right supramarginal gyrus node degree. Our findings highlight the loss of functional connectivity and topological features without structural damage in salience network regions in PD-MCI. They also underline the importance of multimodal hubs in the transition to mild cognitive impairment. This functional disruption in the absence of gray matter atrophy suggests that the salience network is a key vulnerable system at the onset of mild cognitive impairment in PD.

KEYWORDS
default mode network, functional neuroimaging, Parkinson's disease, salience network

Frederic Sampedro and Juan Marín-Lahoz authors contributed equally in this work.

1 | INTRODUCTION

Progressive cognitive impairment is a major challenge in Parkinson's disease (PD). Mild cognitive impairment in PD (PD-MCI) is considered a transitional state between normal cognition (PD-NC) and Parkinson's disease dementia (PDD) and is considered an independent risk factor for dementia (Aarsland & Kurz, 2010). Research on PD-MCI has progressed substantially since the Movement Disorder Society-Task Force (MDS-TF) defined consensus criteria for PD-MCI (Litvan et al., 2012). However, predicting which PD-MCI patients will develop dementia based on neuropsychological testing alone has proven ellusive, and objective biomarkers that allow early diagnosis and progression tracking of cognitive deterioration in PD are needed.

A neural networks perspective (Gratwicke, Jahanshahi, & Foltynie, 2015) could be useful to bridge the gap between pathophysiology and clinical phenotypes. The concept of large-scale brain networks provides a scaffold of connected brain areas serving specific cognitive functions (Menon, 2011). The dysfunction of these large-scale brain networks could identify subjects at risk of dementia before local structural changes appear (Tessitore et al., 2012). Analysis of resting-state via functional MRI (fMRI) is one of the most promising tools in this neural networks perspective. Work by Seeley, Crawford, Zhou, Miller, and Greicius (2009) has shown that neural networks, defined on an fMRI basis, are targeted by particular neurodegenerative diseases (Seeley et al., 2009). This link between neurodegenerative diseases and cognitive function has been further developed into a triple model of cognition (Menon, 2011), comprising the default mode network (DMN), the salience network (SN), and the central executive network (CEN).

The DMN was the first to be described (Greicius, Krasnow, Reiss, & Menon, 2003), corresponding to regions of the medial prefrontal cortex, posterior cingulate, precuneus and lateral an medial prefrontal cortices. It is thought to be responsible of mental processes during resting state, such as self-reflection and screening of internal thoughts. The CEN, composed by areas of the dorsolateral prefrontal cortex and the posterior parietal cortex, is instrumental in cognitive-demanding processes and goal-directed behaviour. Switching between self-directed and stimulus-driven processes is achieved via SN, which is anchored in the insular and anterior cingulate cortices (Seeley et al., 2007). This network serves as a fulcrum that pivots between default and central executive activities.

Some neurodegenerative diseases show characteristic disruptions in these cognitive networks: Alzheimer´s disease (AD) shows reduced DMN connectivity, coherent with a predominant amnestic presentation, whereas frontotemporal dementia shows a predominant SN disruption that is congruent with the diminished social-emotional function (Zhou et al., 2010). Furthermore, some aspects of the clinical phenotype can be adscribed to disruptions of network interaction, such as the impaired moral reasoning in frontotemporal dementia, explained by Chiong et al. (2013) as a loss of SN influence over the DMN during a moral reasoning task.

These three networks have also shown changes related to cognition in PD. A study by Tessitore et al. (2012) in PD-NC shows decreased DMN activity compared to healthy controls, without evidence of gray matter loss on its territories. In PD-MCI, loss of intra-DMN connectivity has been correlated with cognitive decline (Sala-Llonch, Baggio, Valldeoriola, & Compta, 2015). On the other hand, SN has been linked to nonmotor aspects of PD, given its integrative role of executive, sensorimotor and salience processing (Christopher, Koshimori, Lang, Criaud, & Strafella, 2014). In PD-MCI, loss of D2 dopaminergic receptors in SN territories has been correlated with executive and memory deficits in a small sample of PD-MCI patients (Christopher et al., 2015). The interaction between these large-scale networks has also been probed, showing that changes in network anticorrelations between the SN and the DMN correlate with widespread deficits in attentional, motor, visual, and executive functions (Peraza et al., 2015). However, studies aimed to identify vulnerable traits in these networks at the onset of PD-MCI are still lacking. The decline of SN connectivity in patients who develop PD-MCI and PDD could be a potential marker of cognitive impairment in the early stages of PD. Thus, the characterization and analysis of these early changes in connectivity could be useful for the early detection of PD-MCI. Moreover, early identification of patients at risk for dementia could be key to more accurately selecting participants for clinical trials assessing disease-modifying treatments.

The goal of this study was to analyze early changes in relevant hubs of neurocognitive networks in PD-MCI, using a multimodal approach in a sample of nondemented PD patients. We analyzed (a) functional connectivity and anticorrelations through a region of interest (ROI) analysis of the three neurocognitive networks; (b) graph theory metrics to explore the topological properties of key nodes in these networks; and (c) structural parameters via voxel-based morphometry (VBM) in the regions that showed functional and topological changes. Our main hypotheses were (a) alterations in SN connectivity are key to early detection of PD-MCI; (b) loss of normal anticorrelation patterns between large scale neural networks characterizes PD-MCI; and (c) changes found in functional connectivity cannot be explained by the loss of gray matter volume (GMV).

2 | METHODS

2.1 | Participants

We prospectively recruited 57 patients with idiopathic PD who attended the Movement Disorders Outpatient Unit and who were willing to participate in this study. Inclusion criteria were diagnosis of PD according to the United Kingdom PD Society Brain (Hughes, Daniel, Kilford, & Lees, 1992) and exclusion criteria were (a) presence of dementia, according to the Movement Disorders Society Criteria (Emre et al., 2007); Hoehn & Yahr scale > III; (b) presence of any other significant psychiatric, neurological or unstable systemic comorbidities; (c) pathological MRI findings beyond mild white matter hyperintensities, or not compatible with PD in FLAIR sequence; and (d) presence of head motion or other MRI artifacts. Two patients were excluded because of dementia, and two were excluded after reviewing MRI images for quality control. Patients included in the study were assessed by a multidisciplinary team of neurologists,

neuropsychologists and nurses. All patients were taking a combination of antiparkinsonian drugs. Medication was not changed for this study and all assesments (clinical, neuropsychological, and MRI acquisition) were performed with the patients in the "on" state.

All patients provided written informed consent according to the Declaration of Helsinki. The study was approved by the Ethics Comitee for Clinical Research at the Hospital de la Santa Creu i Sant Pau.

2.2 | Cognitive assessment

For the diagnosis of PD-MCI, we employed the Level-1 Task Force criteria, which provide an assessment of global cognition and precise cut-off scores for PD-MCI. A cut-off score of 83 points or less for the total PD-CRS score has been shown to provide high sensitivity and specificity for the diagnosis of PD-MCI (Fernández de Bobadilla et al., 2013). Compared to Level-2 criteria, a clear cut-off score using a properly validated test of global cognitive function in PD populations is less influenced by the various neuropsychological tasks used by different research groups. We also administered a comprehensive neuropsychological battery that included two neuropsychological tests per cognition domain. These tests were used to identify subtypes of PD-MCI, outline their potential neural correlates, and to explore the link between graph theoretical parameters and cognitive subdomains. Attention and working memory were assessed using the Digit Span Forward and Trail Making Test-A; executive dysfunction was measured using the Trail Making Test-B and phonemic fluency; visuospatial function was determined by the Rey–Osterrieth complex figure (ROCFT) and the Visual Object and Space Perception Battery (VOSP; number location); language function was evaluated using the Boston Naming Test and Token Test; and memory function was assessed using the Free and Cued Selective Reminding Test (FCSRTR) and ROCFT.

2.3 | MRI acquisition

MRI scans were acquired in a 3-Tesla Philips Achieva station. T1-weigthed images were acquired using a specific axial T13D-MPRAGE MRI (TR/TE 500/50 ms, flip angle = 8°, field of view (FOV) 23 cm, with in-plane resolution of 256 × 256 and 1 mm slice thickness). Resting-state BOLD images during 12 min were also obtained. (TR = 2000 ms, FOV 240 mm, voxel size 3 mm, TE = 30 ms, flip angle 78°).

2.4 | Voxel-based morphometry

GMV imaging data were obtained from T1-weighted images using a VBM approach in SPM12. The processing pipeline method is described in detail in our previous work (Martinez-Horta et al., 2016). Briefly, the original T1-MRI images were segmented to obtain their corresponding gray matter tissue probability maps. These maps were then spatially normalized into MNI space using DARTEL. Isotropic smoothing (FWHM = 8 mm) was then applied.

The GMV images were individually smoothed and entered into a voxelwise, second-level, two-sample *t*-test between PD-NC and PD-MCI patient groups to determine GMV differences. This statistical model included age, sex, UPDRS-III, and total intracranial volume as covariates of no interest. Results were considered significant using $p < 0.05$ false discovery rate (FDR) corrected and a minimum extent of 100 contiguous voxels.

2.5 | Functional connectivity analysis

Functional connectivity was analyzed using CONN v14p software and its standard processing pipeline (described in depth in (Whitfield-Gabrieli & Nieto-Castanon, 2012)).

The set of functional brain networks described in (Shirer, Ryali, Rykhlevskaia, Menon, & Greicius, 2012) and available at https://findlab.stanford.edu/functional_ROIs.html was introduced in CONN to explore connectivity changes within these regions in our sample. In particular, we focused on the DMN, SN, and CEN ROI. A detailed depiction of each ROI is provided in Figure S7.

A ROI-to-ROI analysis between the network components was performed from the *Z*-score connectivity matrices of each subject. Both intragroup (PD-NC, PD-MCI) and intergroup (PD-NC vs. PD-MCI) connectivity patterns were studied and compared; using age, sex and UPDRS-III as nuisance covariates. Significance was set at $p < 0.05$ corrected for multiple comparisons (FDR).

2.6 | Graph theoretical analysis

Graph theoretical measures were computed and compared across groups using a connectivity cost threshold of 0.15, which in our sample represented the best combination of global and local efficiency, and thus, of small-worldness. The adjacency matrices were built using both one- and two-way edge thresholds to account for the possible effects of negative correlations. We analyzed the seven parameters offered by Conn toolbox (global efficiency, local efficiency, betweenness centrality, average path length, clustering coefficient, cost, and node degree). Age, sex, and UPDRS-III were used as covariates of no interest within all group analyses. Results were considered significant at $p < 0.05$ FDR-corrected.

We also extracted the values of node degree for each patient, and wherever significant differences were found between cognition groups, these measures were entered into a correlation analysis alongside parameters of global cognition (PD-CRS) or the appropiate neuropsychological measures related to that node (for instance, anterior insulae-executive function). With these parameters, we ran a correlation analysis of the whole PD sample using SPSS software and Microsoft Excel for visual plotting.

3 | RESULTS

3.1 | Clinic and sociodemographic data

Fifty-three patients with early-to-mid stages of PD were included (age 68.4 ± 7 years; disease duration 6.4 ± 3 years, UPDRS III 23.5 ± 9). Thirty-four patients were classified as PD-NC and nineteen as PD-MCI. Groups did not differ in terms of education, disease duration,

TABLE 1 Clinical and sociodemographical data of patients according to cognition status based on level-I criteria

	Cognitive status		
	PD-NC	PD-MCI	p value
N	34	19	
Age, year	65.8 ± 6.7	73 ± 4.5	<0.01
Sex, % men	69% 24/34	52% male, 10/19	0.11
PD onset, year	6.4 ± 3	6.3 ± 3.2	0.9
Education, year	13 ± 4.3	11 ± 4.61	0.07
Laterality, % left	47% left	42% left	0.8
PD-CRS total score	98.8 ± 10	72.7 ± 7	<0.01
UPDRS III	22.6 ± 8.8	29 ± 7	<0.01
H&Y	1.9 ± 0.7	2 ± 1.01	0.57
LEDD	681 ± 363	597 ± 237	0.31

Note. Clinical and sociodemographical data according to neuropsychological testing.
Abbreviations: H&Y, Hoehn and Yahr rating scale; LEDD, Levodopa equivalent daily dose; PD-CRS, Parkinson's disease cognitive rating scale; PD-MCI, Parkinson's disease mild cognitive impairment; PD-NC, Parkinson's disease normal cognition; UPDRS III, unified Parkinson's disease rating scale.

disease severity, or levodopa equivalent daily dose (LEDD), but showed differences in age, sex, and UPDRS III score. These parameters were therefore introduced as covariates in the analyses between the two groups. Regarding cognitive subdomains, the 19 PD-MCI patients were classified as multiple-domain according to Level-2 criteria (see Table 1). Thus, we could not describe the imaging findings for specific PD-MCI subtypes (such as disexecutive-predominant PD-MCI vs. visuospatially predominant PD-MCI).

3.2 | VBM results

With the restrictive criteria controlled for FDR, PD-MCI patients showed significantly less gray matter in the bilateral precuneus and the posterior cingulate cortex than PD-NC patients (Figure 1). No increases in gray matter were observed in the PD-MCI group compared to PD-NC.

3.3 | Functional connectivity: ROI to ROI intrinsic connectivity

We tested connection strength and node relevance for each network in both PD-MCI and PD-NC groups. We then analyzed SN connectivity. In PD-NC patients, SN showed the highest coherence between the left anterior insula (AI) and right AI (T = 18.3). Other statistically significant relations were found between the two supramarginal (Sm) gyrii (T = 17.14). In PD-MCI patients, the strongest connectivity was observed between the right and left mid-frontal cortices

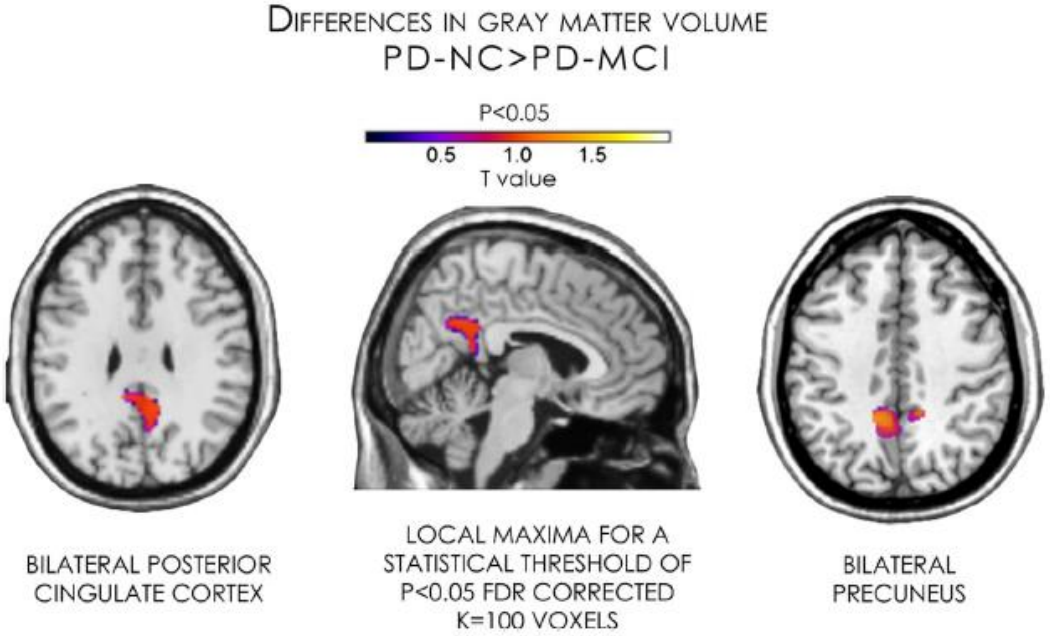

FIGURE 1 Voxel-based morphometry showing decreases in gray matter volume in PD-MCI compared to PD-NC patients, according to the PD-CRS dassification (for a statistical threshold of $p < 0.05$ corrected for multiple comparisons). The main areas of volume reduction are located in the bilateral precuneus and the posterior cingulate cortex. Abbreviations: PD-CRS, Parkinson's disease cognitive rating scale; PD-MCI: Parkinson's disease mild cognitive impairment; PD-NC, Parkinson's disease normal cognition [Color figure can be viewed at wileyonlinelibrary.com]

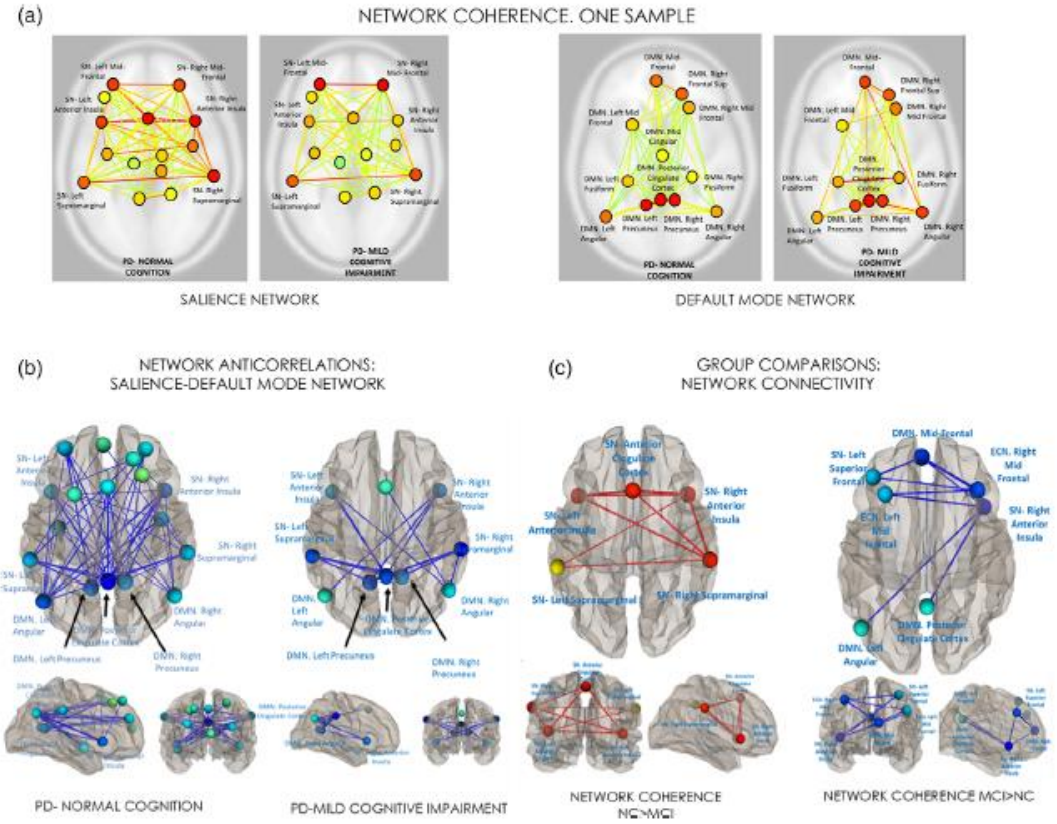

FIGURE 2 Summary of functional connectivity results. All tests shown met a $p < 0.05$ FDR-corrected threshold. (a) One sample t-test comparison of salience and default mode networks across PD cognition showed less connection strength in key SN nodes in PD-MCI patients. (b) Anticorrelations between salience and default mode networks showed a reduction in quantity and strength. (c) Group comparison, showing greater connectivity of SN in PD-NC, and increased connectivity of SN and DMN in PD-MCI. Abbreviations: DMN, default-mode network; PD-MCI, Parkinson's disease mild cognitive impairment; PD-NC: Parkinson's disease normal cognition; SN: salience network [Color figure can be viewed at wileyonlinelibrary.com]

(T = 13.74), while connectivity between the two insulae (T = 8.3) and the two supramarginal gyrii (T = 10.3) decreased.

The DMN showed a less stark contrast between cognitive states. In PD-NC patients, strong connections bound posterior elements of the DMN, such as both precuneus (T = 27.36) and those with posterior cingulate cortex (PCC, T = 19.4). In PD-MCI, similar connections remained between left and right precuneus (T = 16.7), and between bilateral precuneus and PCC (T = 13.3). Thus, though decreases in network connectivity were also apparent in the DMN, the overall network structure (i.e, which nodes were the most connected) remained similar. The depiction of SN and DMN connectivity is shown in Figure 2a. A more detailed connectivity table is provided in Figures S1 and S2.

CEN followed a similar functional pattern, with mild differences between cognition states. The strongest connections in both PD-NC and PD-MCI groups were found between mid-frontal cortices and ipsilateral angular gyrii.

3.4 | Functional connectivity: Differences between cognition groups

Network intrinsic connectivity provides an initial overview of the changes between groups, but to properly outline differences in cognitive networks between PD-NC and PD-MCI patients, we followed the same criteria for ROI selection and entered our data in a two-sample t-test. Results are shown in Figure 2c. Details of individual connections are available in Figure S3.

Network coherence analysis showed greater connectivity between the two anterior insulae, anterior cingulate cortex and right supramarginal gyrus in PD-NC patients than in PD-MCI patients. PD-MCI patients showed greater functional coupling between hubs of normally anticorrelated DMN and SN-CEN hubs: while an increased connectivity was observed between the right anterior insula (SN) and both the posterior cingulate cortex (DMN) and left angular cortex (DMN), no connectivity differences within DMN hubs were found between groups.

Interestingly, when GMV of the precuneus was introduced as a nuisance covariate in order to explore the link between structural and functional findings, no differences in intrinsic SN connectivity could be established between the two groups (Figure S8). However, introducing the LEDD did not result in significant changes in the group comparisons (Figures S10 and S11).

3.5 | Functional connectivity: Anticorrelations

In the anticorrelation analysis, ROIs pertaining to both SN and DMN were chosen for comparisons using a one-tailed, one-sample t-test in both cognition groups. Results are shown in Figure 2b, and connectivity measures are shown in Figure S4.

In PD-NC patients, main anticorrelations appeared between right AI and PCC ($T = -9.8$), and between right AI and left angular gyrus ($T = -7.6$). Thus, anticorrelated regions in the PD-NC group featured a more anterior insular cluster and a posterior DMN-related group of nodes structured around PCC, precuneus, and left angular cortex. In PD-MCI patients, however, the volume and intensity of these anticorrelations were drastically reduced, and though a posterior, DMN-centered cluster persisted, few anticorrelations between these hubs and insular SN survived the statistical threshold.

3.6 | Graph theoretical analysis

As described in Section 2, we analyzed seven graph theory parameters: global efficiency, local efficiency, betweenness centrality, average path length, clustering coefficient, cost, and node degree. Figure 3 shows the results of NC > MCI contrasts.

In keeping with previous connectivity results, the main findings in GT measures were found in SN hubs. Both anterior insulae and both supramarginal gyrii showed a greater node degree and cost in PD-NC patients than in PD-MCI patients. Local efficiency was also higher in the right anterior insula in the PD-NC group. No differences were found in

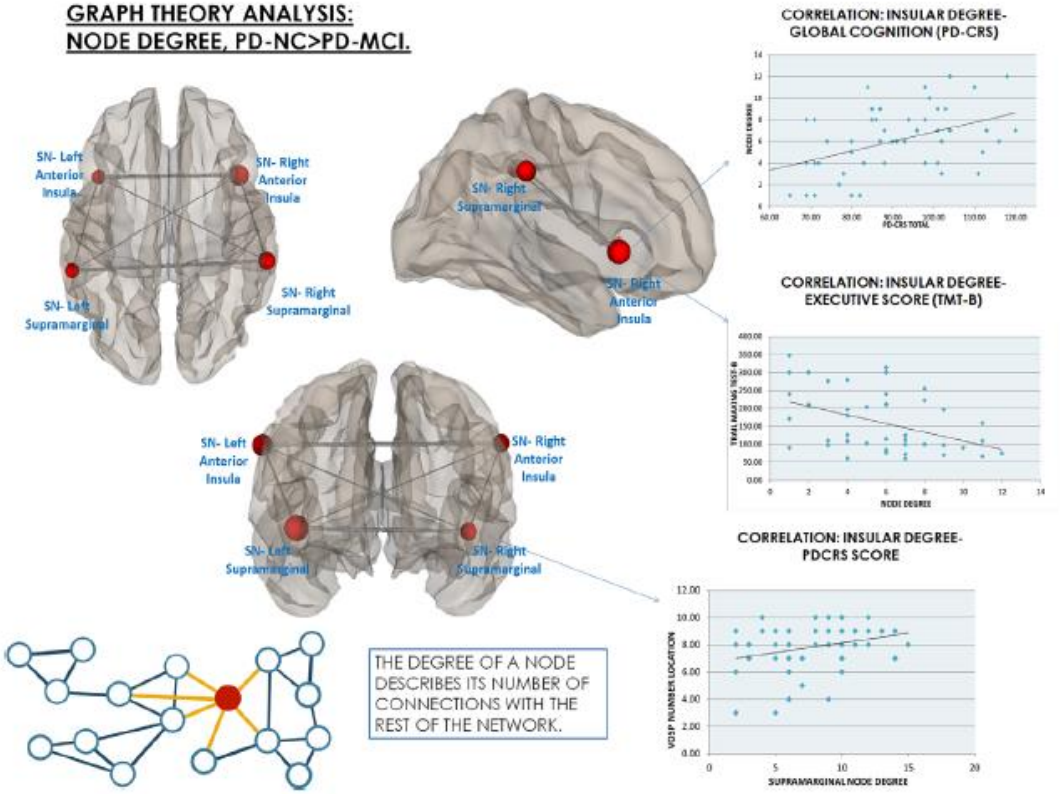

FIGURE 3 Summary of graph theory findings. In direct contrasts between PD-NC and PD-MCI patients, node degree was higher in the anterior insulae and supramarginal gyrii in the PD-NC group ($p < 0.05$, FDR-corrected). Global cognition (PD-CRS) and executive scores were correlated with node degree in the right anterior insula. Visuospatial function (VOSP number location) was correlated with node degree in the right supramarginal gyrus. Abbreviations: PD-CRS, Parkinson's disease cognitive rating scale; PD-MCI, Parkinson's disease mild cognitive impairment; PD-NC, Parkinson's disease normal cognition; VOSP, visual object and space perception battery [Color figure can be viewed at wileyonlinelibrary.com]

the remaining parameters analyzed for this statistical threshold. Connectivity values for node degree can be found in Figure S5.

GT analysis showed changes in node degree of key hubs pertaining to the SN. These regions were also identified as connectivity hubs in the FC analysis. We therefore tried to explore the clinical significance of node degree values by correlating them with neuropsychological performance (Figure 3). We chose relevant nodes from the previous analysis (right anterior insula, right supramarginal gyrus) and selected tests for global cognition (total PD-CRS score), executive function (Trail Making Test B) and visuospatial skills (VOSP number location). We found a positive correlation between global PD-CRS score and right AI node degree ($r = 0.456$, $p = 0.001$). Regarding executive and visuospatial functions, node degree in right AI correlated with TMT-B ($r = -0.447$, $p = 0.001$), and VOSP number location correlated with node degree in the right supramarginal cortex ($r = 0.305$, $p = 0.02$).

4 | DISCUSSION

In the present work we aimed to identify the features that characterize early disruption of cognitive networks in PD-MCI. First, we found that loss of GMV was restricted to DMN nodes, consistent with previous literature (Mak et al., 2015; Weintraub et al., 2012). Second, we observed intrinsic coupling, anticorrelations, and topological properties of core SN nodes to be specifically lower in PD-MCI patients than in PD-NC patients. Third, changes in topological properties—such as node degree—in SN hubs correlated with impairment in global cognitive function, executive, and visuospatial tasks.

Interestingly, we uncovered divergent trends in structural and functional disruptions of cognitive networks in PD-MCI patients. While functional changes appeared in SN hubs in the absence of gray matter loss, DMN showed reductions of GMV in the precuneus and posterior cingular cortex, with no functional or topological differences (Figure 4). These findings could have two interpretations. On the one hand, decreased functional connectivity in the SN and the loss of gray matter in the precuneus of the DMN could be independent phenomena that reflect the different rate of deterioration of structural and functional features of brain networks. This would be the most inmediate conclusion, since loss of gray matter and functional connectivity decline do not overlap in any of these large-scale networks. However, given the lack of functional connectivity differences between PD-NC and PD-MCI, when the tests are controlled by the GMV of the precuneus (Figure S8), these two phenomena might seem to be linked in PD-MCI. When GMV in the precuneus declines, so does connectivity in the PD-MCI group, but when volume loss is regressed out, the intrinsic connectivity of the SN is not statistically different between groups. This strengthens the notion that

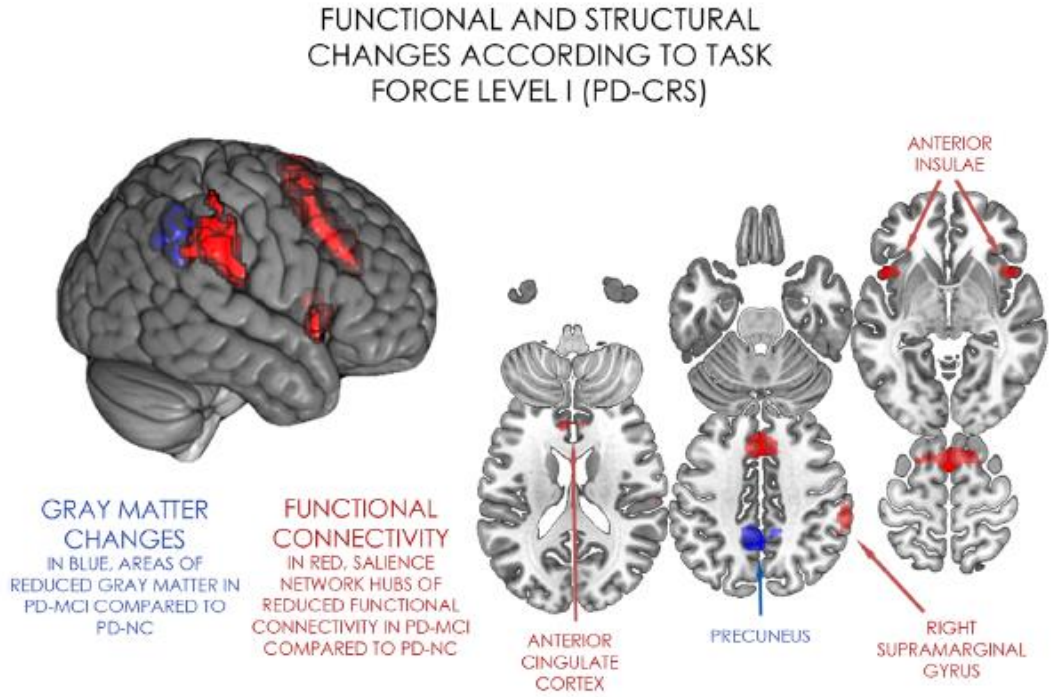

FIGURE 4 A summary of functional, topological, and structural findings of this study. The functional changes in the hub of the SN are shown in red in the insular, anterior cingulate and supramarginal cortices. Decreases in gray matter volume in the precuneus are outlined in blue. Abbreviation. SN, salience network [Color figure can be viewed at wileyonlinelibrary.com]

functional connectivity changes could be driven by structural changes in other large-scale networks. It is perhaps explained by absence of changes in connectivity between salience and DMNs in the PD-MCI > PD-NC contrast. This increased connectivity between antagonical networks, which reflects the loss of anticorrelations in PD-MCI, remains similar regardless of GMV in the precuneus (Figure S9).

Furthermore, this study attempted to establish a link between the initial neuropsychological features of PD-MCI and network disruption in these early stages of cognitive impairment. According to the dual syndrome hypothesis (Kehagia, Barker, & Robbins, 2012; Pagonabarraga et al., 2008), the addition of posterior cortical dysfunctions over a progressive dysexecutive syndrome—the consequence of gradual dopamine denervation, cholinergic deficits, and cortical atrophy—appears to be the neuropsychological hallmark leading to dementia. Accordingly, although PD-MCI patients in our sample mainly showed impairment in executive functions, signs of network dysfunction were widespread, involving networks encompassing both prefrontal and posterior cortical structures. Functional connectivity decay, aberrant network syncronization, and loss of properties such as nodal degree affected both executive and visuospatial hubs of the SN. These findings are in accordance with previous data (Christopher et al., 2014) indicating that loss of dopamine not only affects fronto-striatal loops, but also leads to extensive changes in the SN, especially at the level of the anterior insula and connected areas such as the supramarginal gyrus. Thus, disruptions in networks subserving posterior cortical functions can be found in PD-MCI, even when they are not clinically evident, as subdomain analyses showed no impairment in visuospatial or mnesic performance.

As a first step in this work, we conducted a VBM analysis to detect areas of gray matter loss in PD-MCI. These regions showing reduced gray matter correspond to the main hubs of the DMN, namely, the posterior cingulate cortex and precuneus. Previous studies comparing PD-NC and PD-MCI have found a pattern of reduced gray matter in precuneus, PCC and perihippocampal gray matter (Mak et al., 2015; Weintraub et al., 2012) or no significant differences (Melzer et al., 2012). Cortical thinning studies also show changes in cuneus, fusiform, and temporal cortices (Pagonabarraga et al., 2013; Segura et al., 2014). However, studies in PD cognition show that structures of the DMN, such as medial temporal and inferior parietal cortices, exhibit functional changes well before gray matter loss appears (Sala-Llonch et al., 2015). The study by Tessitore et al. (2012) showed a similar phenomenom, where PD-NC patients showed functional disruption of the DMN without proportional gray matter loss in this network; interestingly, in their final remarks the authors suggest that frontoparietal networks could play a role in maintaining normal cognition in PD-NC patients. In our sample, DMN regions showed reduced gray matter in PD-MCI patients, but there were no differences in functional connectivity compared to PD-NC patients. This is in contrast with SN regions, which showed a marked alteration in connectivity and GT parameters without evidence of structural changes. Thus, decreases observed in SN functional connectivity cannot be explained as a result of gray matter loss. In summary, DMN disruption without gray matter loss could be a feature of PD-NC, and a similar process of disrupted connectivity but preserved SN gray matter could mark the transition to PD-MCI.

According to our data, then, SN dysfunction appears as an intrinsic feature of mild cognitive impairment in PD. Previous knowledge points towards a buffering role of SN in the initial stages of cognitive decline: core processing regions of SN receive dopaminergic input from the mesocortical pathway, which originates in the ventral tegmental area (VTA). Studies comparing the dorsal and ventral dopaminergic pathways showed that, in the early stages of PD, the VTA is relatively spared compared to the sustantia nigra pars compacta (Javoy-Agid, Taquet, Ploska, Cherif-Zahar, & Ruberg, 1981), constituting a surplus of dopaminergic inervation for the insular cortex. When this source is finally exhausted, signaled by a decrease in D2 receptors, cognitive decline occurs (Christopher et al., 2015). Besides preferential innervation, the pivotal role of the insular cortex in SN also lies in its multiple connections with sensorimotor, emotional (hippocampus, amygdala, orbitofrontal cortex), and executive hubs (Christopher et al., 2014; Menon & Uddin, 2010). Through these connections, the insula allows the SN to select salient stimuli and dynamically direct the interplay of other large scale networks (Nomi et al., 2016). We found that these functions are impaired in the transition to PD-MCI: network coherence is diminished, anticorrelations with DMN are lost, and the degree of key nodes is lowered. These measures could represent a link between neuropsychological decline and network disruption. Furthermore, the dysexecutive syndrome observed in our PD-MCI patients, perhaps emerging from impaired SN switching, could be hiding the incipient failure of large scale systems.

Besides the interplay between large scale networks, hubs identified in GT analysis underlined the relevance of both the anterior insulae and supramarginal gyrii. The latter has been linked to awareness of space through integration of visual, propioceptive and vestibular information (Kheradmand, Lasker, & Zee, 2015). Both regions, therefore, are able to integrate multimodal information, the versatility of which might be useful when other network hubs start to fall apart. Indeed, the succesive failure of different networks in each stage of the disease—DMN in PD-NC, SN in PD-MCI—seems to follow a model of cascading network failure, as recently proposed for DMN in AD (Jones et al., 2015). In this framework, the first affected are the posterior components of DMN, which shift processing burden to frontal, unaffected regions of the network. As disease progresses and amyloid starts to accumulate, the disintegration of the vulnerable posterior hubs propagates through the network, causing a collapse similar to a cascading failure in a power grid. In PD, DMN hubs could also be the first to show disruptions in early, cognitively-unimpaired patients, but as disease progresses, it is the disruption in SN hubs which seem to signal the onset of PD-MCI.

Defining the "early-failing" regional hubs for each neurodegenerative syndrome could be fruitful in the early detection of cognitive impairment. Based on our findings, the anterior insulae and supramarginal gyrii appear to be two such hubs in PD. Both regions show marked decreases in connectivity in PD-MCI, and we were able to link the loss of node degree with diminished executive and visuospatial

cognitive scores. As we move from the localizationist paradigms onto a networks perspective, one of the stepping stones is the fact that large scale networks are differently targeted by neurodegenerative syndromes (Seeley et al., 2009). In fact, the clinical manifestations that give each entity its features (such as memory loss in Alzheimer´s, or the dysexecutive syndrome in PD) probably stem from the networks that are initially perturbed. It seems logical, thus, that we continue our biomarker quest by probing those regions that might be "first responders" when large-scale networks begin to unravel.

We acknowledge some limitations of our study. First, the sample size limits the scope of our findings. Second, the lack of an age-matched healthy cohort dampens possible claims of network compensation in PD-NC patients, which merits further studies. However, we believe the main results of this study pertain to the specific interface between PD-NC and PD-MCI, and thus offer new insights into this stage of PD. Third, all scans were performed in the "on" state, therefore some of the results might be influenced by treatment regime; however, daily equivalent levodopa dose was not significantly different between the cognitive groups, and including this parameter as a nuisance covariate did not result in meaningful differences. Finally, the cross sectional nature of this study makes further longitudinal studies desirable in order to test the accuracy of our findings. On the other hand, our results are coherent with previous knowledge in connectomic literature, both in PD and in other neurodegenerative diseases, and they show a substantial agreement between diverse modalities of neuroimaging and neuropsychological assessment, using standard neuroimaging pipelines and stringent, FDR-corrected analyses.

In summary, the present findings indicate that multimodal assessment captures divergent phenomena affecting cognitive networks at the onset of PD-MCI. Atrophy in DMN nodes is not mirrored by functional disruption, while early decline in global cognition, executive and visuospatial performance can be linked to functional disruption centered in SN hubs.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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4.2. Artículo 2

Aracil-Bolaños I, Sampedro F, Marín-Lahoz J, et al. Tipping the scales: how clinical assessment shapes the neural correlates of Parkinson's disease mild cognitive impairment. Brain Imaging Behav. 2021

Aracil-Bolaños I, Sampedro F, Marín-Lahoz J, et al. Tipping the scales: how clinical assessment shapes the neural correlates of Parkinson's disease mild cognitive impairment. Brain Imaging Behav. 2021

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4.3. Artículo 3

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RESEARCH ARTICLE

WILEY

The impact of dopaminergic treatment over cognitive networks in Parkinson's disease: Stemming the tide?

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Abstract

Dopamine-replacing therapies are an effective treatment for the motor aspects of Parkinson's disease. However, its precise effect over the cognitive resting-state networks is not clear; whether dopaminergic treatment normalizes their functional connectivity-as in other networks- and the links with cognitive decline are presently unknown. We recruited 35 nondemented PD patients and 16 age-matched controls. Clinical and neuropsychological assessments were performed at baseline, and conversion to dementia was assessed in a 10 year follow-up. Structural and functional brain imaging were acquired in both the ON and practical OFF conditions. We assessed functional connectivity in both medication states compared to healthy controls, connectivity differences within participants related to the ON/OFF condition, and baseline connectivity of PD participants that converted to dementia compared to those who did not convert. PD participants showed and increased frontoparietal connectivity compared to controls: a pattern of higher connectivity between salience (SN) and default-mode (DMN) networks both in the ON and OFF states. Within PD patients, this higher SN-DMN connectivity characterized the participants in the ON state, while within-DMN connectivity prevailed in the OFF state. Interestingly, participants who converted to dementia also showed higher SN-DMN connectivity in their baseline ON scans compared to nonconverters. To conclude, PD patients showed higher frontoparietal connectivity in cognitive networks compared to healthy controls, irrespective of medication status, but dopaminergic treatment specifically promoted SN-DM hyperconnectivity.

KEYWORDS
cognitive networks, dopamine, functional MRI, Parkinson's disease

1 | INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease characterized by the progressive loss of nigrostriatal dopaminergic neurons. Its clinical hallmarks are the onset of tremor, rigidity, and bradykinesia (Postuma et al., 2015). Given the progressive loss of dopaminergic terminals and the efficacy of dopamine-replacing therapies (DRTs) on motor symptoms, levodopa has been the mainstay of PD treatment over the past 50 years. However, some nonmotor aspects are not as well addressed by dopaminergic treatments. Chief among them is progressive cognitive impairment and dementia, which affects a majority of PD patients over the disease course (Hely, Reid, Adena, Halliday, & Morris, 2008). PD patients show dysexecutive symptoms from the onset of the disease, but the progressive emergence of posterior cortical disruptions heralds the slide into cognitive impairment (González-Redondo et al., 2014; Mak et al., 2015; Pagonabarraga & Kulisevsky, 2012). The neural correlates of these early stages have been defined in structural terms: frontal areas exhibit reduced cortical thickness in PD patients compared to healthy controls (HCs), with patients with mild cognitive impairment (PD-MCI) showing additional losses of gray matter in temporo-parietal regions (Pagonabarraga, Soriano-mas, & Llebaria, 2014; Segura et al., 2014). However, we still lack patterns of cognitive network disruption that predate cognitive decline, and structural imaging is not likely to provide them (Lanskey et al., 2018).

Using functional MRI, PD-MCI has been linked to altered functional connectivity and graph theoretical metrics in diverse studies (Baggio et al., 2015; Sala-Ilonch, Baggio, Valldeoriola, & Compta, 2015), and distinct subtypes of cognitive impairment can be outlined using these parameters (Lopes et al., 2016). More recently, metrics of dynamic functional connectivity have been adopted to study changes in time-dependent components of brain networks, identifying distinct connectivity states related to cognition (Fiorenzato et al., 2019), and links of network dynamics to visuospatial memory (Engels, Vlaar, McCoy, Scherder, & Douw, 2018). Interestingly, the relative increase of frontoparietal functional connectivity in nondemented PD patients, compared to HCs, might point toward compensation or vulnerability features in at-risk patients (Gorges et al., 2015). These features are distinct at a network level in normal cognition (PD-NC), and seem to wane in the PD-MCI patients (Aracil-Bolaños et al., 2019), disrupting the functional integrity of frontoparietal networks in the absence of gray matter loss (Amboni et al., 2015). Thus, the investigation of early disruptions could provide network signatures of future decline in patients who show no overt clinical signs of cognitive impairment.

These mechanisms might be affected by dopaminergic treatment and therefore the role of DRT has to be accounted for. Studies that jointly analyze functional MRI and quantitative levels of dopamine via FP-CIT have shown that dopamine-dependent functional networks comprise motor and cerebellar regions, but also frontoparietal cognitive networks have links to cortical hubs such as the posterior cingulate cortex (Baik et al., 2014). However, while many excellent studies have approached the effects of dopamine depletion on brain topology (Shine et al., 2019), few have employed ON–OFF paradigms to explore resting-state cognitive networks. A comprehensive review on the role of dopaminergic treatment over functional MRI concluded that the DRT tends to normalize the aberrant connectivity present in the OFF state (Tahmasian et al., 2015), but its effect on cognitive large-scale networks is not well-known. While older studies have focused on the acute effects of dopaminergic treatment over the dorsal and ventral connections of the striatum (Macdonald & Monchi, 2011), a perspective that encompasses the diversity of cognitive networks, beyond frontostriatal loops, is still lacking.

To sum up, no study to date has assessed the differences which levodopa causes on large-scale cognitive networks, such as the default, salience or central executive networks. Furthermore, it is unclear whether these changes might constitute an adaptive mechanism or, on the contrary, could represent a vulnerability trait regarding long term conversion to dementia. Thus, in the present study we explored the role of dopaminergic treatment over cognitive networks by recruiting a group of nondemented PD participants and age-matched HCs, taking into account dopaminergic treatment by acquiring functional MRI (fMRI) images both in the ON and the OFF conditions. We followed-up a subgroup of participants and evaluated long-term conversion to dementia in order to assess the clinical relevance of network connectivity differences.

2 | METHODS

2.1 | Participants

Forty participants with idiopathic PD regularly attending our Movement Disorders Outparticipant Unit and 16 age-matched HCs who were willing to participate in this study were prospectively recruited. Inclusion criteria was the diagnosis of PD according to the United Kingdom PD Society Brain Bank (Hughes, Daniel, Kilford, & Lees, 1992) and exclusion criteria were: (a) presence of dementia according to MDS-PDD Criteria (Emre et al., 2007) and Parkinson's Disease Cognitive Rating Scale (PD-CRS) total score <64 (de Bobadilla et al., 2013); Hoehn & Yahr scale >III; (b) presence of any other significant psychiatric, neurological, or unstable systemic comorbidities; (c) pathological MRI findings beyond mild white matter hyperintensities; (d) presence of head motion or other MRI artifacts; and (e) inability to tolerate MRI acquisition in the OFF state. Four participants were excluded due to image quality-checking and one participant because of dementia. All participants provided written informed consent according to the Declaration of Helsinki. The study was approved by the Ethics Committee for Clinical Research at the Hospital de la Santa Creu i Sant Pau, Barcelona.

2.2 | Clinical assessment

Participants were assessed using a battery of clinical and neuropsychological tests. All participants were clinically assessed at baseline,

together with the MRI acquisition, and a subset of participants who completed follow up were assessed for conversion to dementia in a 10-year follow-up (2008–2018 period). Motor status was assessed using the Unified Parkinson's disease rating scale part III (UPDRS-III). Anxiety and depression were evaluated using the Hospital Anxiety and Depression Scale (HADS). At time of inclusion, global cognitive status was addressed using the Parkinson's disease cognitive rating scale (PD-CRS) and the Clinical Dementia Rating (CDR). The PD-CRS comprises nine subtests that assess immediate verbal memory, naming, sustained attention, working memory, unprompted drawing of a clock, copy of a clock, delayed free recall, alternating verbal fluency, and action verbal fluency. The PD-CRS provides a total score ranging from 0 to 134; cutoff scores <64 and <82 were previously proven to be reliable for the screening of dementia and PD-MCI, respectively (de Bobadilla et al., 2013; Pagonabarraga et al., 2008; Pagonabarraga, Corcuera-solano, Vives-gilabert, Llebaria, & Garcı, 2013). The CDR was used as gold standard for cognitive status in several studies, including the validation study of the PD-CRS (Pagonabarraga et al., 2008). This instrument assesses cognitive and functional performance in six areas: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care (Hughes, Berg, Danziger, Coben, & Martin, 1982). A CDR of 0 indicates no cognitive deficits, 0.5 indicates very mild cognitive impairment, and 1–3 indicate mild to severe cognitive impairment. As per inclusion criteria, all participants were free of cognitive impairment in the range of dementia and thus, had a PD-CRS total score >64 and a CDR <1.

All participants were assessed in the practical OFF and ON conditions. For the ON acquisitions, and by virtue of being in a fluctuating stage of the disease, all participants were scanned after they took their levodopa dose in the OFF state in the morning and their best ON was achieved. For the OFF-state acquisitions, participants observed a strict 12 hr practical OFF period, and they were examined by a trained neurologist prior to the acquisition to ensure that the scans were reflecting a true OFF state.

At follow-up, the CDR was chosen to determine the global cognitive status of participants. Those with a CDR <1 were considered nondemented, whereas those with CDR equal or above 1 were considered as with major cognitive impairment in the range of dementia.

2.3 | MRI acquisition and preprocessing

MRI acquisition was performed on a 1.5 Tesla Signa Excite system (General Electric, Milwaukee, WI) station scanner. A high-resolution T1-weighted anatomical image was obtained for each participant using a three-dimensional fast spoiled gradient inversion-recovery prepared sequence with 130 contiguous slices (TR, 11.8 ms; TE, 4.2 ms; flip angle, 15°; field of view, 30 cm; 256 × 256 pixel matrix; slice thickness, 1.2 mm).

Resting-state BOLD images during 6 min were obtained using a functional MRI sequence consisting of gradient recalled acquisition in the steady state (TR = 2,000 ms, TE = 50 ms, flip angle 90°, 64 × 64 pixel matrix, FOV 240 mm, in-plane voxel size 3.75 × 3.75 mm, slice thickness 4 mm), both in the ON and practical OFF conditions (12 hr withdrawal of dopaminergic medications prior to MRI acquisition).

2.4 | Cortical thickness analysis

A standard cortical thickness pipeline was applied. Cortical thickness analysis was performed using the FreeSurfer 6.0 software package (https://surfer.nmr.mgh.harvard.edu/). The specific methods used for cortical reconstruction of T1-MRI brain images have been described in detail elsewhere (Fischl & Dale, 2000). Briefly, optimized surface deformation models following intensity gradients accurately identify white matter and gray matter boundaries in the cerebral cortex, from which cortical thickness is computed at each vertex of the resulting surface. Finally, the resulting cortical surfaces were normalized to average space and smoothed using a Gaussian kernel of 10 mm FWHH.

2.5 | Functional connectivity analysis

Functional imaging preprocessing was performed using CONN v20 software and its standard processing pipeline, described in depth in (Whitfield-Gabrieli & Nieto-Castanon, 2012). Briefly, functional scans were first slice-timing corrected, realigned, and spatially normalized to the Montreal Neurological Institute (MNI) space using co-registration with the associated anatomical data. Then, resting-state images were submitted to CONN's standard denoising pipeline, which combines two steps: linear regression of potential confounding effects and temporal band-pass filtering. For the first step, factors that are identified as potential confounding effects to the estimated BOLD signal are estimated and removed separately for each voxel and for each participant and functional run/session using Ordinary Least Squares regression to project each BOLD signal timeseries to the sub-space orthogonal to all potential confounding effects. Potential confounding effects used in CONN's default denoising pipeline implement an anatomical component-based noise correction procedure (aCompCor), and include: (a) Noise components from cerebral white matter and cerebrospinal áreas: potential confounding effects are defined from the observed BOLD signal within each of two anatomically-defined noise areas computed by applying a one-voxel binary erosion step to the masks of voxels with values above 50% in white matter and CSF posterior probability maps. Within each area five potential noise components are estimated: (a) the first computed as the average BOLD signal, and the next four computed as the first components in a Principal Component Analysis of the covariance within the subspace orthogonal to the average BOLD signal and all other potential confounding effects. (b) Estimated participant-motion parameters: a total of 12 potential noise components are defined from the estimated participant-motion parameters in order to minimize motion related BOLD variability: three translation and three rotation parameters plus their associated first-order derivatives. (c) Identified outlier scans or scrubbing: a variable number of noise components (one for each identified outlier scan during the outlier identification preprocessing step)

are used as potential confounding effects to remove any influence of these outlier scans on the BOLD signal. Potential outlier scans are identified from the observed global BOLD signal and the amount of participant-motion in the scanner. Acquisitions with framewise displacement above 0.9 mm or global BOLD signal changes above 5 *SD* are flagged as potential outliers. Framewise displacement is computed at each timepoint by considering a 140 × 180 × 115 mm bounding box around the brain and estimating the largest displacement among six control points placed at the center of this bounding-box faces. Global BOLD signal change is computed at each timepoint as the change in average BOLD signal within SPM's global-mean mask scaled to standard deviation units. (d) Constant and first-order linear session effects, and constant task effects, if applicable.

Then, the obtained data were filtered using a band-pass filter in the range of 0.01–0.1 Hz in order to focus on slow-frequency fluctuations while minimizing the influence of physiological, head-motion, and other noise sources. Filtering is implemented using a discrete cosine transform windowing operation to minimize border effects, and performed after regression to avoid any frequency mismatch in the nuisance regression procedure.

The entire matrix of ROI-to-ROI functional connectivity values (using the bivariate correlation measure) was computed for each participant using the set of functional brain networks described in our previous work (Aracil-Bolaños et al., 2019) and available at https://findlab.stanford.edu/functional_ROIs.html. In particular, we focused on 43 regions of interest (ROIs) located in the default-mode (DMN), salience (SN), and Central Executive (CEN) networks, and also performed analyses on the 11 ROIs pertaining to the sensorimotor network. This parcellation scheme has been useful to delineate the network-phenotype link in neurodegenerative disease (Seeley, Crawford, Zhou, Miller, & Greicius, 2009), allowing for a defined triple network psychopathological model (Menon, 2011) that is useful in diseases that show cognitive and affective symptoms, such as PD. Furthermore, this triple network model has been useful in the study of neurodegenerative conditions that span diverse clinical presentations, such as frontotemporal dementia (Chiong et al., 2013) or Alzheimer's disease (Zhou et al., 2010). In PD, dopaminergic dysfunction in the salience network has been linked to cognitive decline (Christopher et al., 2015), and altered connectivity between salience and default-mode networks has also been associated with cognitive impairment in PD (Peraza et al., 2017) Therefore, this parcellation can be considered suitable for the study of the interaction between neurodegenerative disorders, large-scale cognitive networks and clinical phenomena.

A ROI-to-ROI analysis between all the network components was performed from the Z-score connectivity matrices of each participant. Both intragroup (PD-ON vs. PD-OFF) and intergroup (PD-ON/OFF vs. Controls)) connectivity patterns were studied and compared. A full description of the cognitive ROI location is provided in Table S3.

2.6 | Statistical analyses

For the cortical thickness analysis, a vertexwise generalized linear model was set to compare both nondemented PD participants with HC, and also to compare PD participants who converted to dementia with respect to those who did not. Only clusters surviving *p*-value <.05 after multiple comparison correction by permutation-testing with 10,000 permutations were considered significant.

For the functional connectivity comparisons, we performed two-sample *T*-tests (PD-ON vs. controls, PD-OFF vs. controls, PD-converters vs. PD nonconverters) and a paired T-test (PD-ON vs. PD-OFF) to compare the groups; age, sex, and other demographics were used as covariates of no interest whenever differences were found across groups: sex in PD versus control analyses, and age and PD-CRS in dementia converters versus nonconverters (see Tables 1 and S1). Finally, in the subset of participants that completed the 10 year follow-up and had both ON and OFF scans we performed a mixed ANOVA interaction analysis considering both within-participant conditions (medication status) and between group conditions (converter vs. nonconverter).

In ROI-to-ROI rsfMRI connectivity analyses there is a need to control Type I errors as the number of comparisons between ROI connections can exceed the thousands. Conservative approaches like the Holm–Bonferroni correction might however result in too conservative estimations, given that the number of tests grows quadratically with the number of nodes, resulting in *p*-values lower than .00001 for a standard network of 90 nodes and a family-wise data error of $\alpha = .05$ (Zalesky, Cocchi, Fornito, Murray, & Bullmore, 2012). This has led to the development of techniques such as Network-Based Statistics (NBS) or Spatial Pairwise Clustering (SPC) that aim to control Type I errors by clustering connections and applying permutation testing to ascribe a family-wise error (FWE) corrected *p*-value to each cluster. SPC shows lower sensibility but higher specificity and a finer resolution compared to NBS. Thus, we have used SPC to identify relevant clusters in each of the contrasts of interest; each cluster is

TABLE 1 Clinical and sociodemographic data of the study sample

Group	Participants	Controls	*p*-value
N	35	16	N/A
Age, years	65 ± 9	66.8 ± 7.8	.45
Sex, % men	74%, 26/35	50%, 8/16	.06
PD onset, years	7.3 ± 4.5	N/A	N/A
Education, years	10 ± 5	10 ± 4.8	.99
MDS UPDRS III	20 ± 7.1 (ON) 25 ± 10.2 (OFF)	N/A	N/A
Hoehn & Yahr	1.9 ± 0.3 (ON) 2.2 ± 0.6 (OFF)	N/A	N/A
LEDD	807 ± 447	N/A	N/A
PD-CRS score	88 ± 15	N/A	N/A
HADS score (ON)	5 ± 3.3	N/A	N/A
STAI score (ON)	35 ± 14	N/A	N/A
Fluctuating participants	14/35	N/A	N/A

Abbreviations: HADS, Hospital Anxiety and depression scale; LEDD, Levodopa equivalent daily dose; PD, Parkinson disease; PD-CRS, Parkinson's disease cognitive rating scale; STAI, State-trait anxiety inventory; UPDRS, Unified Parkinson's Disease Rating Scale.

characterized by its mass—sum of *F*- or *T*-squared statistics over all connections within each cluster—and then compared to a distribution of expected cluster mass values under the null hypothesis using permutation testing (10.000 permutations) and a *p*-value <.05. Finally, a multiple comparison correction using a stringent FWE correction with a *p*-value <.05 is applied at the cluster level (unless specified as uncorrected).

3 | RESULTS

3.1 | Clinical and sociodemographic data

Thirty-five participants in the mid stages of PD (age 65 ± 9 years; disease duration 7.3 ± 4.5 years, MDS-UPDRS III 23.5 ± 9) and 16 HCs (age 66.8 ± 7.8 years) were included. PD participants showed no clinically relevant depression (HADS-D 5 ± 3.3); anxiety as measured by the STAI showed that some participants cleared the commonly accepted threshold of 44 points (STAI 35 ± 14 in the ON state) but none showed HADS-A scores above 11 points. All the participants had simple, predictable motor fluctuations according to their medical records, and upon evaluation, 14 participants were classified as fluctuating according to MDS-UPDRS (Part 4.3 ≥1) (Table 1). No participants featured clinically meaningful dyskinesias. MRI scans were obtained for all controls and PD participants in the ON state, while 24 participants had scans acquired both in the ON and OFF states within a time period of 7 days; LEDD remained thus constant between ON and OFF acquisitions. Sociodemographic and clinical characteristics of participants with no MRI in the OFF state did not differ significantly from participants with MRI in the ON and OFF states. Regarding quality control of functional scans, PD-ON, PD-OFF, and controls had no significant differences in framewise displacement (controls 0.082, PD-ON 0.106, PD-OFF 0.108, One-way ANOVA $p = .44$).

Twenty-five PD patients were evaluated after 10 years of follow-up. Ten participants were lost to follow-up: five participants did not have enough clinical data to ascertain conversion to dementia, two chose to continue follow-up in other hospitals, two had disabling neurological events (a debilitating stroke and an intracranial hemorrhage during a deep brain stimulation procedure) and one died shortly after study completion of non-neurological causes. However, the excluded group did not differ significantly in age (68 vs. 64 years in excluded participants, $p = .12$), UPDRS (23 vs. 20 points in excluded participants, $p = .29$) or LEDD (743 vs. 832 mg in excluded participants, $p = .60$). Of the 25 participants that completed follow-up, thirteen (52%) were classified as converters according to CDR. Both groups were comparable in disease duration, educational level, UPDRS-III, and LEDD, but converters at baseline were older ($p = .02$) and had lower PD-CRS scores ($p = .03$, Table S1). A subset of these participants ($N = 17$, with seven dementia converters) had MRI both in the ON and OFF conditions. Both groups were comparable in disease duration, educational level, UPDRS-III, LEDD, and PD-CRS, but converters were older at baseline ($p = .049$) (see Table S2).

3.2 | Cortical thickness

In the structural imaging comparison, nondemented PD participants showed cortical thinning in regions of the right superior frontal cortex compared with controls (Figure S1). Controls did not show any reductions in cortical thickness compared to the PD group. Analyzing the baseline scans of the PD group that completed a 10-year follow-up, PD participant that developed dementia (PDD) did not show any cortical thinning compared to PD participants who did not develop dementia. Furthermore, using the cortical thickness of the right superior frontal gyrus as a covariate of no interest when comparing PD and control groups we found similar functional connectivity results (see Figure S1). A regression analysis between the cortical thickness of this cluster and the functional connectivity of the PD group showed a trend associating frontal cortical thickness with fronto-parietal connectivity, but did not survive multiple comparison testing (not shown).

3.3 | Functional connectivity differences between PD and HC in the ON state

PD patients showed higher connectivity than HCs in two clusters when using a parcellation that included both cognitive and sensorimotor ROIs (Figure 1).

The first cluster (mass = 410, *pval* = .006) connected the sensorimotor elements of the parcellation—including both precentral regions and the supplementary motor area—with both frontal and posterior regions of the DMN, including the precuneus, posterior cingulate cortex, and bilateral angular cortex. Some elements of the SN, including the mid cingulate gyrus and the SN regions of the precuneus, were also involved. These connections were not present in HCs, which furthermore showed no increased connectivity compared to PD patients.

The second cluster with higher connectivity in nondemented PD featured cognitive hubs of the SN and the DMN (mass = 379, $p = .009$). Higher connectivity was found among frontal nodes of both networks—featuring superior and mid frontal cortices both of SN and DMN—, but also spanning antero-posterior connections of the bilateral precuneus and posterior cingulate cortex with both insular cortices and supramarginal gyrii. Again, there was no increased connectivity for HCs in any of these areas.

Finally, this increased connectivity of the frontoparietal nodes in the PD-ON group was also correlated with higher PD-CRS scores in a group of frontoparietal regions, headlined by SN nodes such as the cingulate, superior frontal and supramarginal gyrii, which showed higher connectivity with frontal and angular nodes of the DMN (mass 182, $p = .02$; see Figure S2).

3.4 | Functional connectivity differences between PD and HC in the OFF state

In the OFF state, PD participants featured higher connectivity than HCs between sensory-motor regions of the cortex and cognitive hubs

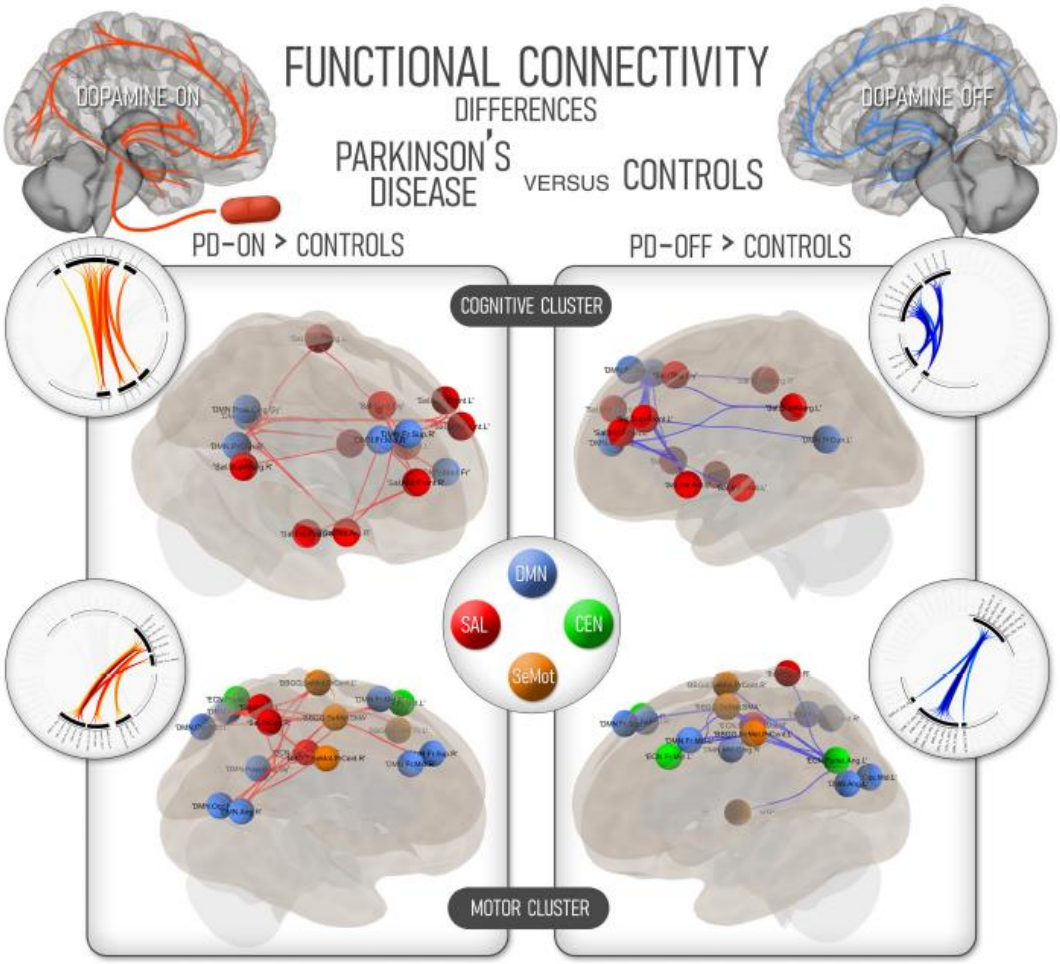

FIGURE 1 Differences in functional connectivity between nondemented Parkinson's disease participants and healthy, age-matched controls. The three large-scale cognitive networks are considered on the upper renders (labeled "cognitive cluster"), while the changes in the three cognitive networks plus the sensorimotor network are showcased in the lower renders. On the left part of the image, regions with higher functional connectivity in the Parkinson's disease participants in the ON state are highlighted. Regions with higher connectivity compared to controls in the OFF state are shown in the right part of the image. The color code corresponding to the four large-scale networks is shown in the central ring. CEN, central executive network; DMN, default-mode network; SAL, salience network; SeMot, sensorimotor network; PD, Parkinson's disease

of the DMN (mass = 333, $p = .008$), both containing similar components to the ON state. Assessing cognitive regions, PD participants also showed higher intrinsic connectivity between SN and DMN components without medication (mass = 252, pval = .02). This contrast showed a similar structure to the ON state but included fewer posterior cortical hubs of the DMN, with posterior cingulate and right precuneus not present in this comparison. No instances of higher connectivity were found in HCs (Figure 1).

3.5 | Functional connectivity differences within nondemented PD: ON–OFF comparisons

Performing within-participant comparisons in the ON and OFF states, PD participants showed a reconfiguration of cognitive networks under medication (Figure 2).

In the ON state, PD participants featured a cluster of connections between SN nodes and predominantly posterior DMN nodes

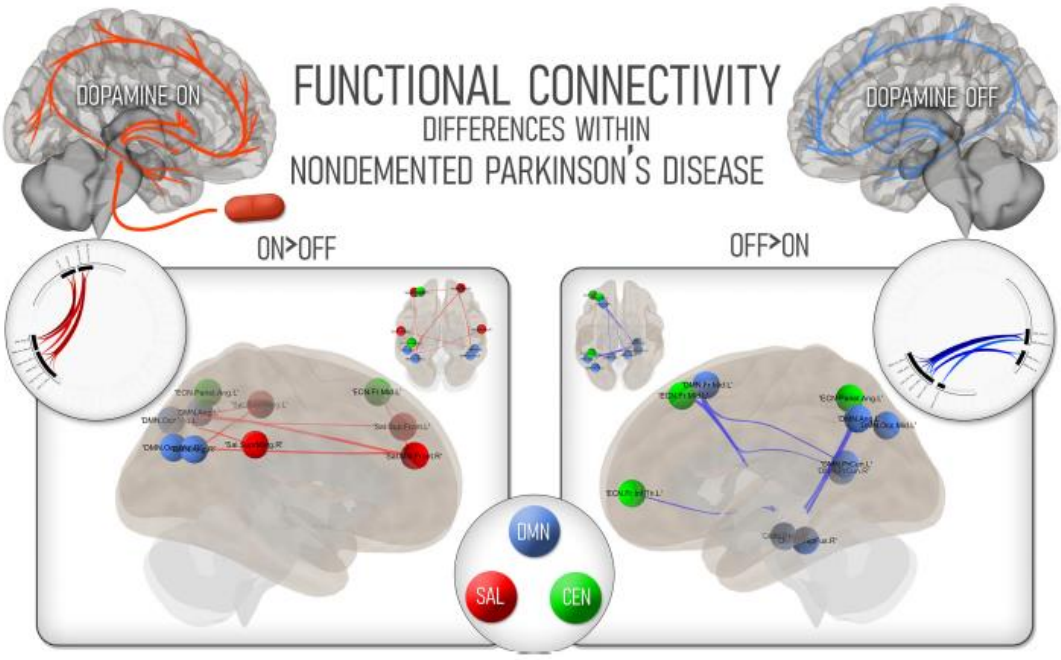

FIGURE 2 Changes within nondemented Parkinson's disease participants according to medication status. On the left, regions which showed higher connectivity in PD participants in the ON state; on the right, regions showing higher connectivity in the OFF state. The color code corresponding to the three large-scale cognitive networks is shown in the central ring. CEN, central executive network; DMN, default-mode network; PD, Parkinson's disease; SAL, salience network

(mass = 141.46, $p = .04$). These connections included the bilateral supramarginal gyrii and frontal cortices of the SN and bilateral mid occipital and angular cortices on the DMN.

In the OFF state, the relevant cluster showed enhanced connectivity of key hubs of the DMN with other DMN and CEN nodes (mass = 142, $p = 0.04$). Of note, the bilateral precuneus showed higher connectivity with occipital, frontal and angular cortices of the same network, with higher connectivity also present in the right fusiform and parahippocampal nodes of the DMN.

3.6 | Functional connectivity differences in converters to dementia

Participants that converted to dementia in a 10-year follow-up showed distinct connectivity patterns compared to nonconverters in their baseline ON scans.

Dementia converters featured a cluster of connections that captured the higher connectivity between key SN and DMN hubs (mass = 268, $p = .01$) This higher connectivity was found specifically between the insular cortices and cingulate gyrus of the SN and the posterior cingulate cortex of the DMN, together with increased connectivity in other relevant regions such as the angular and occipital nodes of the DMN (Figure 3). Given the disparity in cognitive scores at baseline, we used the PD-CRS score as a covariate of no interest in the analysis, and still found a cluster of increased connectivity across SN and DMN nodes (mass = 126, $p = .009$ uncorrected) No clusters featuring higher connectivity in nonconverters were found in this analysis.

Finally, we performed an exploratory analysis—given the small sample size (seven participants) in the group of patients who converted to dementia—within the subset of participants that had both long-term follow-up and baseline scans in the ON and OFF conditions (Figure 3). The participants that converted to dementia showed, in the ON condition, higher connectivity between SN components, mainly within the insular cortex, also featuring the participation of the bilateral supramarginal gyri (mass = 98, $p = .008$ uncorrected). No differences were found in the OFF condition for any of the groups, nor were instances of higher connectivity found in the nonconverter group.

4 | DISCUSSION

In this work, we have explored how cognitive networks in nondemented PD are shaped by dopaminergic treatment, both compared to age-matched HCs and contrasting patients in the ON and OFF states.

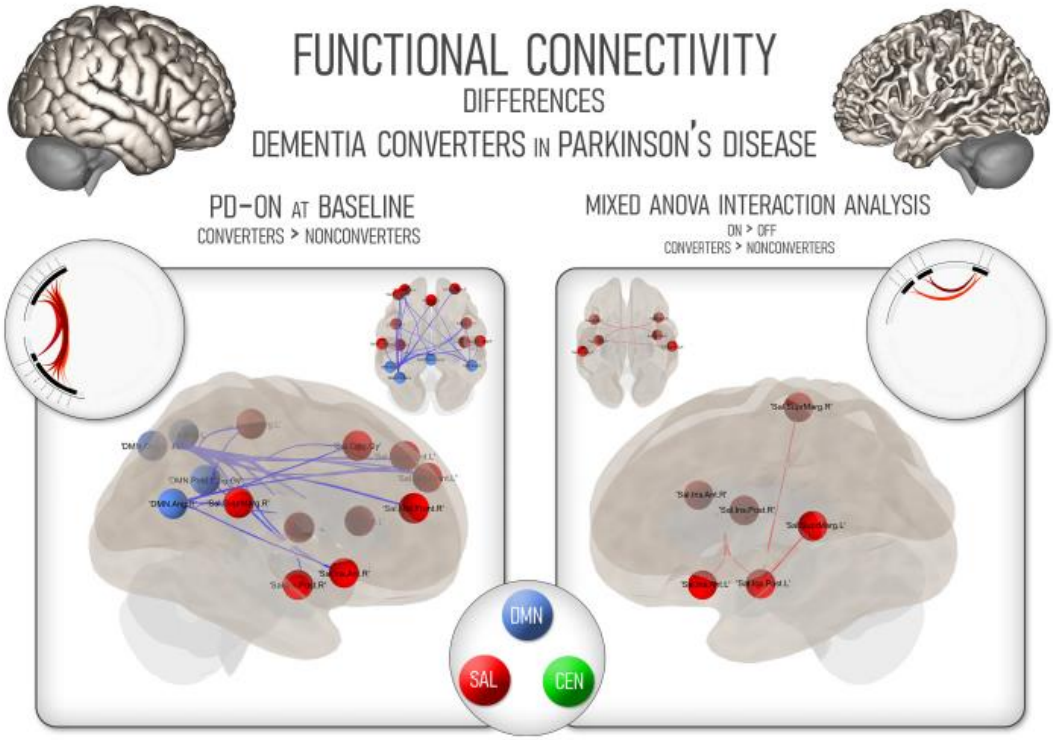

FIGURE 3 Cognitive network changes in Parkinson's disease participants in a 10-year follow-up. On the left, changes in functional connectivity comparing converters to nonconverters using baseline scans in the ON state. On the right, mixed interaction analysis according to both conversion to dementia and medication state. CEN, central executive network; DMN, default-mode network; PD, Parkinson's disease; SAL, salience network

We first conducted a cortical thickness study to frame our functional results. We found scarce differences between PD participants and age-matched controls, mainly centered around the right superior frontal gyrus. While contrasting with previous studies (Mak et al., 2015), a recent longitudinal showed that the rate of cortical thinning of PD patients and healthy, age-matched controls is indeed very similar after age 60 (Gorges et al., 2020). Therefore, structural changes in our cohort would be hardly sufficient to explain the differences in resting-state cognitive networks, and using cortical thickness both as a covariate of no interest or as a regressor in functional connectivity analyses did not yield any significant results.

On the functional analysis, our first goal was to determine whether PD patients showed differences in cognitive network connectivity compared to HCs, and whether these differences were dependent on medication. In broad terms, our results showed that nondemented PD participants feature higher frontoparietal cognitive network connectivity, irrespective of medication status. These differences included two main sources of higher functional connectivity. The first was the higher connectivity compared to controls found between sensorimotor regions, such as the supplementary motor cortex and precentral gyrii, and a wide range of predominantly DMN nodes. The second was the higher connectivity between SN and DMN hubs in PD participants. These differences were similar overall in the ON and OFF conditions, although the ON state featured more widespread interactions between normally anticorrelated hubs, such as the insular cortices in the SN and the posterior cingulate/precuneus of the DMN. These differences could be interpreted as a decrease of normal anticorrelations between these large-scale cognitive networks within the PD group, a feature that has been previously reported in PD (Aracil-Bolaños et al., 2019; Peraza et al., 2017). With this knowledge, previous reports of higher frontoparietal connectivity in nondemented PD patients (Gorges et al., 2015)—which waned as patients slid into cognitive decline—, can be adscribed to cognitive networks and cannot be explained merely as an effect of dopaminergic medication.

Our second goal with this study was to ascertain which effect DRTs exerted over cognitive networks when comparing the ON and OFF states in PD participants. As previously mentioned, it is widely accepted that dopaminergic treatment normalizes functional connectivity in brain networks (Tahmasian et al., 2015). This could have

implications when interpreting connectivity differences in nondemented PD, since the aforementioned higher frontoparietal connectivity could be an artifact introduced by the dopaminergic treatment. In our sample, PD participants in the ON state showed clear increases in SN-DMN connectivity, whereas in the OFF state, a cluster of predominantly DMN connections was more prevalent. Consequently, DRT was associated with lower posterior-DMN connectivity, at the same time that frontoparietal cognitive networks showed higher functional connectivity. Therefore, the effect of DRT on cognitive networks does not seem to merely "normalize" connectivity, especially in the systems that have a stronger dopaminergic component, such as the SN. Instead, DRT seems to promote network configurations that dampen anticorrelations and reduce within-DMN connectivity The link between dopaminergic pathways and the SN has been explored in a recent study (McCutcheon et al., 2019), in which higher intrinsic SN functional connectivity was related to higher dopaminergic synthesis in the mesocorticolimbic pathway, measured using 18-Fluorodopa. It is likely that DRT plays a similar role in PD patients, enhancing the connectivity of SN nodes with strong mesocorticolimbic input, such as the anterior insula, and depressing the functional connectivity of the anticorrelated posterior DMN hubs.

The extent to which these differences might contribute to cognitive decline is presently unknown. Previous studies show that the decline in dopamine receptor availability in the anterior insula has been linked to the onset of cognitive decline in PD (Christopher et al., 2015). The more immediate explanation would be that the increases in connectivity observed in SN nodes could constitute a compensation mechanism that delays cognitive decline. In this line, a recent study showed an association of preserved cognition with increased functional connectivity within subnetworks of the cingulate cortex—a key SN node—in PD patients, concurrent with deteriorated structural covariance in this regions (Zhou et al., 2020). We did indeed find that PD-ON participants showed a positive correlation between higher frontoparietal functional connectivity and higher PD-CRS scores at baseline. However, while hyperconnectivity can be considered a compensation mechanism (Hillary et al., 2015), studies in different neurological diseases show that this might not always be the case. In Alzheimer's disease, Apolipoprotein E4 carriers, who have an increased genetic risk of neurodegeneration, show increased coherence of the DMN during working memory tasks (Filippini et al., 2009). It has been shown that higher functional connectivity implies increasing metabolic costs as measured by 18-FDG uptake (Tomasi, Wang, & Volkow, 2013). In our sample, the analysis of baseline scans in the ON state showed that the participants who converted to dementia featured higher functional connectivity between SN-DMN nodes while under medication, compared to those who staved off cognitive decline. We also analyzed a subset of participants, which had data regarding conversion to dementia and both ON and OFF scans. Although these results should be interpreted with caution and considered as exploratory, when conversion to dementia and medication state were both factored in, higher connectivity within the SN was found to be a feature of PD patients that converted to dementia. These preliminary results suggest that rather than a compensation mechanism, this network reconfiguration under DRT could constitute a vulnerability trait in nondemented PD.

This study has some limitations. First, not all participants were scanned both in the ON and OFF states, given the intrinsic difficulties of dopamine withdrawal. Second, sample size limits the scope and statistical power of our findings, and we acknowledge that the control group was age but not sex-matched. Third, cognitive assessment was not performed conforming to Level-II criteria, though the administered Level-I scale is a Movement Disorders Society endorsed tool (Skorvanek et al., 2018) and has shown very good accuracy compared to Gold-Standard criteria (de Bobadilla et al., 2013). Strengths of this study include the multimodal approach, using both cortical thickness and functional connectivity, the standardized methodology and neuroimaging pipeline (Aracil-Bolaños et al., 2019; Whitfield-Gabrieli & Nieto-Castanon, 2012) and the stringent statistical thresholds applied throughout the analysis.

To sum up, this study shows that dopaminergic therapies shape the functional connectivity of cognitive networks in nondemented PD patients, enhancing the link between normally-anticorrelated SN and DMN. These differences in functional connectivity appear in regions with relatively preserved mesocorticolimbic input, such as the insular regions of the SN, and merit further investigations regarding their relevance in the progression of cognitive decline in PD.

DISCLOSURES

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AUTHOR CONTRIBUTIONS

Ignacio Aracil-Bolaños contributed to conception, organization, and execution of the research project; designed and executed the imaging and statistical analyses and wrote the first draft. **Frederic Sampedro** contributed to execution of the research project, assisted in statistical and imaging analyses, and provided review and critique of the manuscript. **Jesus Pujol** contributed to conception, organization, and execution of the research project and provided review and critique of the

manuscript. **Carles Soriano-Mas** contributed to conception, organization, and execution of the research project and provided review and critique of the manuscript. **José María Gónzalez-de-Echávarri** contributed to statistical and imaging analyses and provided review and critique of the manuscript. **Jaime Kulisevsky** contributed to conception, organization, and execution of the research project and provided review and critique of the manuscript. **Javier Pagonabarraga** contributed to conception, organization, and execution of the research project and provided review and critique of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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4.4. Artículo 4

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RESEARCH ARTICLE

Structure and Dynamics of Large-Scale Cognitive Networks in Huntington's Disease

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ABSTRACT: Background: Huntington's disease is a neurodegenerative disorder characterized by clinical alterations in the motor, behavioral, and cognitive domains. However, the structure and disruptions to large-scale brain cognitive networks have not yet been established.
Objective: We aimed to profile changes in large-scale cognitive networks in premanifest and symptomatic patients with Huntington's disease.
Methods: We prospectively recruited premanifest and symptomatic Huntington's disease mutation carriers as well as healthy controls. Clinical and sociodemographic data were obtained from all participants, and resting-state functional connectivity data, using both time-averaged and dynamic functional connectivity, was acquired from whole-brain and cognitively oriented brain parcellations.
Results: A total of 64 gene mutation carriers and 23 healthy controls were included; 21 patients with Huntington's disease were classified as premanifest and 43 as symptomatic Huntington's disease. Compared with healthy controls, patients with Huntington's disease showed decreased network connectivity within the posterior hubs of the default-mode network and the medial prefrontal cortex, changes that correlated with cognitive ($t = 2.25$, $P = 0.01$) and disease burden scores ($t = -2.42$, $P = 0.009$). The salience network showed decreased functional connectivity between insular and supramarginal cortices and also correlated with cognitive ($t = 2.11$, $P = 0.02$) and disease burden scores ($t = -2.35$, $P = 0.01$). Dynamic analyses showed that network variability was decreased for default-central executive networks, a feature already present in premanifest mutation carriers (dynamic factor 8, $P = 0.02$).
Conclusions: Huntington's disease shows an early and widespread disruption of large-scale cognitive networks. Importantly, these changes are related to cognitive and disease burden scores, and novel dynamic functional analyses uncovered subtler network changes even in the premanifest stages. © 2021 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

Key Words: Huntington's; cognition; functional MRI

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Huntington's disease (HD) is a neurodegenerative disorder caused by an abnormal CAG repeat expansion in the *HTT* gene on chromosome 4.[1] The clinical onset of the disease is marked by the presence of unequivocal extrapyramidal movement disorders—such as chorea, dystonia, or bradykinesia—but cognitive and behavioral features can be detected up to 15 years before the emergence of the first motor symptoms.[2] Subtle cognitive changes are present from the early stages, with the development of dementia as a likely outcome in the majority of the cases.[3] The progression of cognitive decline has been attributed to a pattern of whole-brain

atrophy, with the basal ganglia and its fronto-subcortical connections as the most affected by disease progression.[4] However, recent works have shown that progressive atrophy of a wide range of cortical regions is linked to the clinical profile of the disease from the early stages. This cortical atrophy involves several regions that participate in cognitive functions such as the precuneus,[5] the anterior cingulate cortex,[6] and the supramarginal, fusiform, and lateral occipital gyrii.[7] The majority of these regions are integral to the functioning of large-scale cognitive networks,[8] such the salience network (SN) or default-mode network (DMN). Thus, cognitive manifestations of HD might be related both to structural brain damage and the disruptions in the architecture of large-scale brain cognitive networks.

Structural damage in the basal ganglia and motor and visual regions has been shown to correlate with alterations in both motor and visual functional networks,[9,10] even from the premanifest stage.[11,12] Studies focusing on the DMN using resting-state functional magnetic resonance imaging (fMRI) showed decreases in functional connectivity (FC) within the network in manifest HD but no changes in premanifest patients.[13] In this latter population, task-based fMRI found an increased connectivity within the DMN.[14] In the executive networks, a dissociated pattern was found between posterior cortical decreases in activity[10] and an increase in frontoparietal connectivity,[15] but again, studies in the premanifest population have shown no differences.[16]

Finally, to our knowledge, no study has tackled the study of dynamic FC of cognitive networks in HD. Although static FC has proven to be demonstrable across task and resting-state conditions,[17] and even across species,[18] there is growing evidence that brain networks are not immutable across time, but inherently "multistable."[19] This includes the notion that cognitive hubs such as the posterior cingulate cortex (PCC) can dynamically engage with different networks.[20,21] Previous studies have established the relevance of the frequency of connectivity states in the cognition of neurodegenerative diseases such as Parkinson's disease,[22] showing that patients with an associated dementia have a higher frequency of a segregated connectivity state than healthy controls. On the other hand, high variability of these connectivity circuits is considered to be a feature of normal organization in the brain[23] that decreases with normal aging[24]; it has also been found to be decreased within default-mode and frontoparietal networks in patients with schizophrenia.[25] It is conceivable that the subtler aspects of network disruption could become more apparent when considering the dynamic nature of brain circuits.

The main aim of the present study was to conduct a functional analysis of the different large-scale cognitive networks in premanifest HD (pre-HD) and symptomatic HD (sHD). Although cognitive manifestations may represent the earliest indicators of the disease, there is a lack of studies exploring the integrity of cognitive networks and its clinical impact on HD. Specifically, we performed classical averaged FC and graph theory analyses, and we also conducted a novel dynamic FC analysis through dynamic independent component analysis (dyn-ICA). We also performed a structural analysis of brain atrophy using cortical thickness while adopting both a standard whole-brain approach and a cognitive network-focused parcellation, similar to our previous work.[26]

Patients and Methods

Participants and Clinical Assessment

A total of 65 gene mutation carriers (CAG ≥ 39) who attended the outpatient clinic at the Movement Disorders Unit and 23 healthy controls who were willing to participate were prospectively recruited. Patients with HD were classified as premanifest HD (pre-HD) and sHD. Individuals with a Unified Huntington's Disease Rating Scale (UHDRS) total motor score below 5 and a diagnostic confidence level (DCL) <3 were classified as pre-HD, whereas those with a DCL = 4 were classified as sHD. Cognitive measures were obtained using the UHDRS cognitive score (Cogscore). The disease burden score (DBS)—a measure of livelong exposure to mutant huntingtin—was calculated using the following formula based on age and CAG repeat length: age × (CAG − 35.5).[27] However, healthy controls only had sociodemographic data available. Exclusion criteria based on image quality were (1) pathological magnetic resonance imaging (MRI) findings beyond mild white matter hyperintensities and (2) the presence of head motion or other MRI artifacts. After reviewing images for quality control, one patient was excluded because of excessive head motion.

MRI Acquisition and Preprocessing

All participants had available structural and resting-state fMRI. Details regarding image acquisition and preprocessing are available in Appendix S1 in the supplementary material. Briefly, T1-weighted scans and resting-state (blood-oxygen-level-dependent) BOLD images (12 minutes) were acquired in a 3 T Philips Achieva station (Philips Medical System, Best, the Netherlands). To assess cortical atrophy differences we applied a surface-based cortical thickness pipeline using FreeSurfer 6.0. (free software: Fisch et al, 10.1016/j.neuroimage.2012.01.021) Functional imaging processing was performed using CONN v19b software and its standard processing pipeline,[28] which includes functional preprocessing and brain parcellation and first-level and second-level analyses steps. For preprocessing, scans were functionally realigned

and unwarped, slice-timing corrected, realigned, and spatially normalized to the Montreal Neurological Institute (MNI) space using coregistration with the associated anatomical data. For brain parcellation, we adopted both the Harvard-Oxford Atlas[29] provided within the CONN toolbox and the set of functional brain networks described in the Shirer atlas[30] to provide both whole-brain macroanatomical coverage and functionally oriented parcellations[31]; time courses for all of these regions of interest (ROIs) were derived from MNI-normalized images. Thereafter, ROI time courses were submitted to CONN's standard denoising pipeline, which combines linear regression of potential confounding effects and temporal band-pass filtering. For the first-level signal processing, we adopted both time-averaged static FC measures and a dyn-ICA. Dyn-ICA matrices represent a measure of different modulatory circuits expression and rate of connectivity change between each pair of ROIs. For the second-level analysis, averaged metrics of FC and graph theoretical parameters were computed in ROI-to-ROI analyses as well as dyn-ICA parameters: frequency was defined as the recurrence of the modulatory circuits in each participant and variability as the standard deviation in bivariate, multivariate, or semipartial correlation or regression measures between pairs of ROIs. A detailed description of the preprocessing, denoising, and first-level and second-level analyses as well as an in-depth discussion of dyn-ICA parameters is provided in Appendix S1 in the supplementary material.

Statistical Analyses

Clinical and sociodemographic data were compared across groups using two-sample t test analyses for continuous variables and χ^2 for categorical variables. Differences were considered significant using a probability (P) value < 0.05. On the structural analyses, only surface clusters surviving $P < 0.05$ family-wise error corrected by permutation were considered.

On the structural analysis, we compared vertex-wise cortical thickness data between HD (pre-HD/sHD) and healthy controls using age, sex, and education as nuisance covariates. For this purpose, vertex-wise cortical thickness maps were normalized to a standard fsaverage space and smoothed using a Gaussian kernel of 10 mm full width at half maximum. Only surface clusters surviving $P < 0.05$ and family-wise error correction by permutation testing (10,000 permutations) were considered significant.

Functional and graph theoretical metrics were introduced into a generalized linear model within CONN to compare controls, pre-HD groups, and sHD groups using age, sex, and education as covariates of no interest. Furthermore, total gray matter volume was explored as a covariate of no interest to analyze the interaction between functional and structural changes. Results were considered significant using a threshold of P value < 0.05 corrected for multiple comparisons at the cluster level using the false discovery rate for all the functional and graph theoretical analyses. Temporal data regarding dyn-ICA analysis of frequency and variability of dynamic components were also introduced into a generalized linear model using age, sex, and education as covariates of no interest and considered significant using a P value < 0.05. Finally, regression analyses were performed using DBS, UHDRS, and Cogscore data in the relevant connections (which had previously been found as statistically significant between groups in a $P < 0.05$ corrected analysis) and dynamic components and considered significant using a P value of <0.05. Statistical analyses concerning clinical and sociodemographic comparisons as well as clinical

TABLE 1 *Demographics, genetics, and clinical data of the study population, according to disease stage*

Variables	HD	Pre-HD	Symptomatic HD	Healthy controls	HD vs. controls, *P* value	Pre-HD vs. symptomatic HD, *P* value
N	64	21	43	23		
Age, y	45.77 ± 12	38.33 ± 7.5	49.4 ± 12.1	39.34 ± 9.3	0.01	<0.001
Sex	41/64 women	15/21 women	26/43 women	8/23	0.92	0.76
Education, y	13 ± 4.1	14.05 ± 3.3	12.08 ± 4.36	12 ± 1.6	0.05	0.03
CAG repeats	43.18 ± 2.6	42.7 ± 2.2	43.4 ± 2.85	N/A	N/A	0.88
UHDRS	17.55 ± 20	0.3 ± 0.7	25.95 ± 19.6	N/A	N/A	<0.001
Cogscore	240.39 ± 97	328.33 ± 46.7	195.34 ± 85	N/A	N/A	<0.001
Disease burden score	334.49 ± 108	266.53 ± 77.5	367.64 ± 105.3	N/A	N/A	<0.001
Years to disease onset	N/A	14.5 ± 6.07	N/A	N/A	N/A	

Data are provided as n or mean ± standard deviation.
Abbreviations: HD, Huntington's disease; N/A, Not available; UHDRS, Unified Huntington's Disease Rating Scale.

imaging associations were conducted using the SPSS version 15 (IBM Corp. Armonk, NY) software package.

All patients provided written informed consent according to the Declaration of Helsinki. The study was approved by the Ethics Comitee for Clinical Research at the Hospital de la Santa Creu i Sant Pau.

Results

Clinical and Sociodemographic Data

A total of 64 gene mutation carriers (mean age, 45.77 ± 12 years; mean CAG, 43.18 ± 2.6; mean DBS, 334.49 ± 108) and 23 healthy controls (mean age, 39.34 ± 9.3 years) were included; 21 patients with HD were classified as pre-HD (mean age, 38.3 ± 7.5 years; mean CAG, 42.7 ± 2.2; mean DBS, 266.53 ± 57.5) and 43 were classified as sHD (mean age, 49.4 ± 12 years; mean CAG, 43.4 ± 2.85; mean DBS, 367.64 ± 105.3). For full demographic data, see Table 1.

Patients with pre-HD were comparable in age and sex to controls but had a slightly higher education level (14 vs. 12 years for controls). Patients with sHD were older than controls (49 vs. 39 years in controls). All of these differences were accounted for in imaging analyses by using these variables as covariates of no interest.

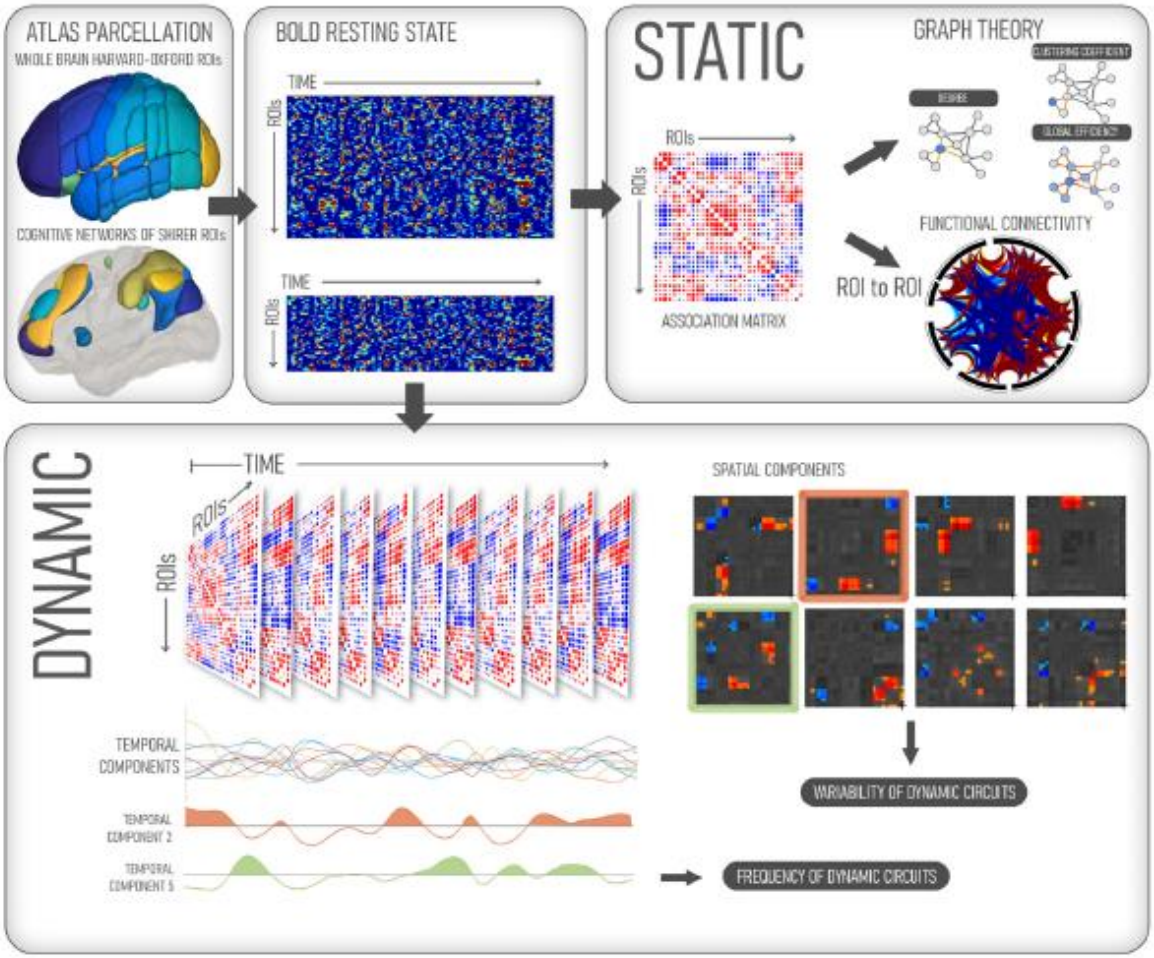

FIG. 1. Summary of the imaging analysis methodology. On the upper left corner, the two parcellations (whole-brain Harvard-Oxford and the cognitive networks of the Shirer atlas) are used to obtain the time series of their respective brain regions. These time series are averaged to produce static association matrices that result in region-of-interest (ROI) functional connectivity data and network architectural analysis via graph theory. On the lower half of the picture, time series are analyzed using a dynamic independent component analysis (dyn-ICA), which identifies changes in temporal fluctuations of the dynamic components (frequency) and in spatial relations between the components (variability). [Color figure can be viewed at wileyonlinelibrary.com]

Structural Analysis: Cortical Thickness

On the structural analysis, patients with HD showed reduced widespread cortical thinning in frontal, parietal, and temporo-occipital regions. These changes were more pronounced when comparing patients with sHD with healthy controls, whereas patients with pre-HD showed no differences in cortical thickness relative to controls. Figure 1 and Appendix S1 in the supplementary material display the cortical thickness differences between these groups.

Time-Averaged FC

Whole-Brain FC

On a whole-brain approach, patients with HD showed decreased FC on a wide range of cortical regions, chiefly the motor cortex (Fig. 2, left). Precentral, postcentral, and supplementary motor areas showed decreased FC with visual associative cortices ($P = 0.002$ corrected) and fronto-opercular regions, including the bilateral insular and anterior cingulate cortices ($P = 0.01$ corrected). Importantly, these decreases were clinically associated with both the UHDRS scores and with the DBS. The regression analysis showed that reduced FC between the postcentral gyrus and the occipital fusiform gyrus was associated with higher DBS ($t = -2.57$, $P = 0.006$) and UHDRS ($t = -5.27$, $P < 0.001$), and similarly, decreased FC between the right insular and supplementary motor cortex was correlated with higher DBS ($t = -2.83$, $P = 0.003$) and UHDRS ($t = -4.73$, $P < 0.001$). The basal ganglia also showed reduced connections with the superior and mid frontal gyrii ($P = 0.01$ corrected). Specifically, reduced caudate–mid frontal gyrus connections were associated with higher DBS ($t = -2.98$, $P = 0.002$) and UHDRS ($t = -2.60$, $P = 0.004$) for the caudate–mid frontal gyrus connections. The main increase in FC among patients with HD compared with controls was found between visual regions—fusiform cortex, occipital pole—and the PCC and precuneus, both cortical hubs of the DMN ($P = 0.003$ corrected). The regression analysis showed that higher FC between the precuneus and the right fusiform cortex was associated with higher DBS ($t = 1.99$, $P = 0.02$).

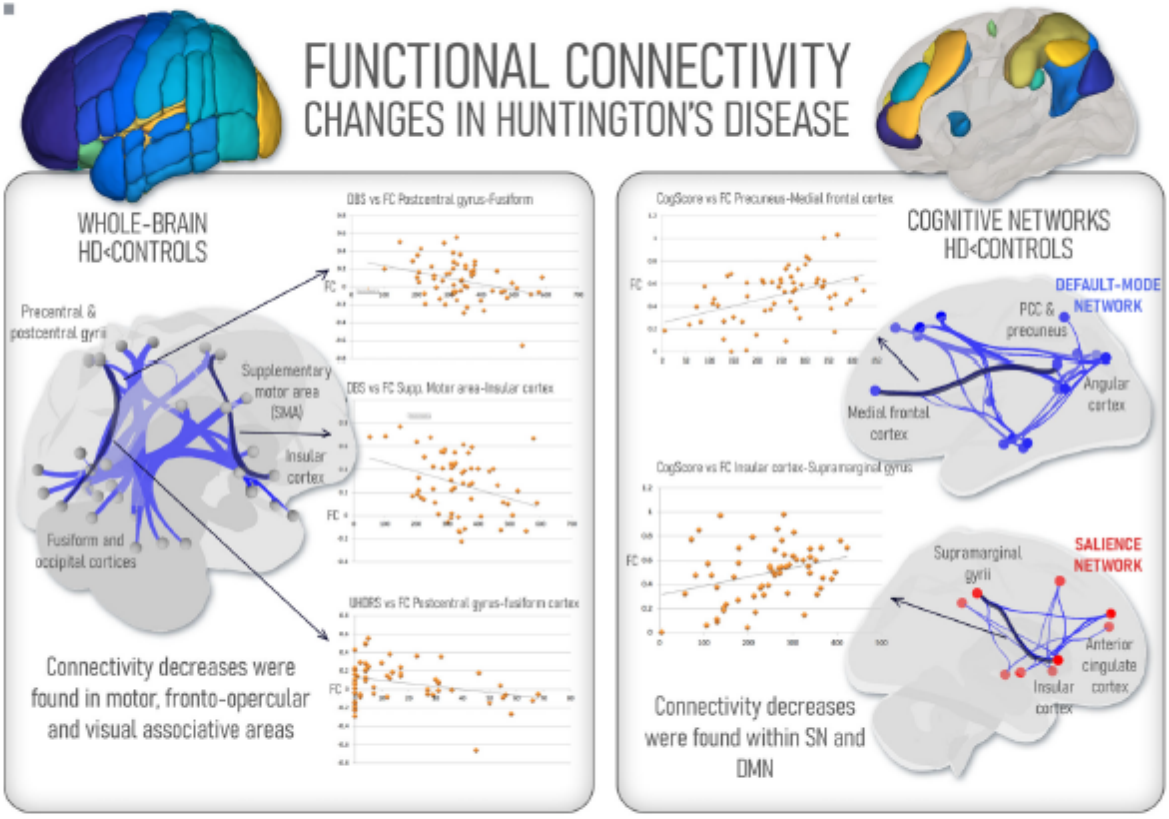

FIG. 2. Changes in region-of-interest (ROI)-to-ROI functional connectivity between patients with Huntington's disease (HD) and healthy controls both using a global brain parcellation (left) and a cognitive networks parcellation (right). DMN, default-mode network; PCC, posterior cingulate cortex; SN, salience network. [Color figure can be viewed at wileyonlinelibrary.com]

FC in Cognitive Networks

Considering cognitive networks, patients with HD showed decreased connectivity within posterior hubs of the DMN such as the precuneus and PCC, and of these hubs with anterior regions of the same network such as the medial prefrontal cortex ($P < 0.001$ corrected; Fig. 2, right). A key aspect is that the posterior cingulate cortex (PCC)-Med frontal connection showed a positive correlation with cognitive scores as measured by the Cogscore ($t = 2.25$, $P = 0.01$) and an inverse correlation with DBS ($t = -2.42$, $P = 0.009$). The salience network of patients with HD showed decreased FC between insular, supramarginal, and anterior cingulate cortices ($P = 0.009$), and the connection between the right insular and supramarginal regions also showed a positive correlation with the Cogscore ($t = 2.11$, $P = 0.02$) and an inverse correlation to DBS ($t = -2.35$, $P = 0.01$).

FC in Pre-HD

Patients with pre-HD showed similar results both on a whole-brain and cognitive networks approach, albeit in a reduced fashion. Differences with healthy controls were centered on motor and visual associative regions on a whole-brain approach ($P = 0.02$ corrected), and connectivity increases between the PCC/precuneus and visual associative regions were also observed ($P = 0.04$ corrected). Meanwhile, in cognitive networks, changes were mainly observed as decreases of connectivity between anterior and posterior nodes of the DMN ($P = 0.02$).

Importantly, after controlling for gray matter volume (GMV), all results remained significant with the following exceptions: in patients with pre-HD, increased precuneus/PCC connectivity with visual associative regions in a whole-brain approach (not present after correcting for GMV) and decreases in connectivity between anterior and posterior nodes of the DMN ($P = 0.06$ after correcting for GMV).

Graph Theoretical Metrics

Whole-Brain Graph Metrics

On a whole-brain analysis, patients with HD showed decreased node degrees compared with controls in

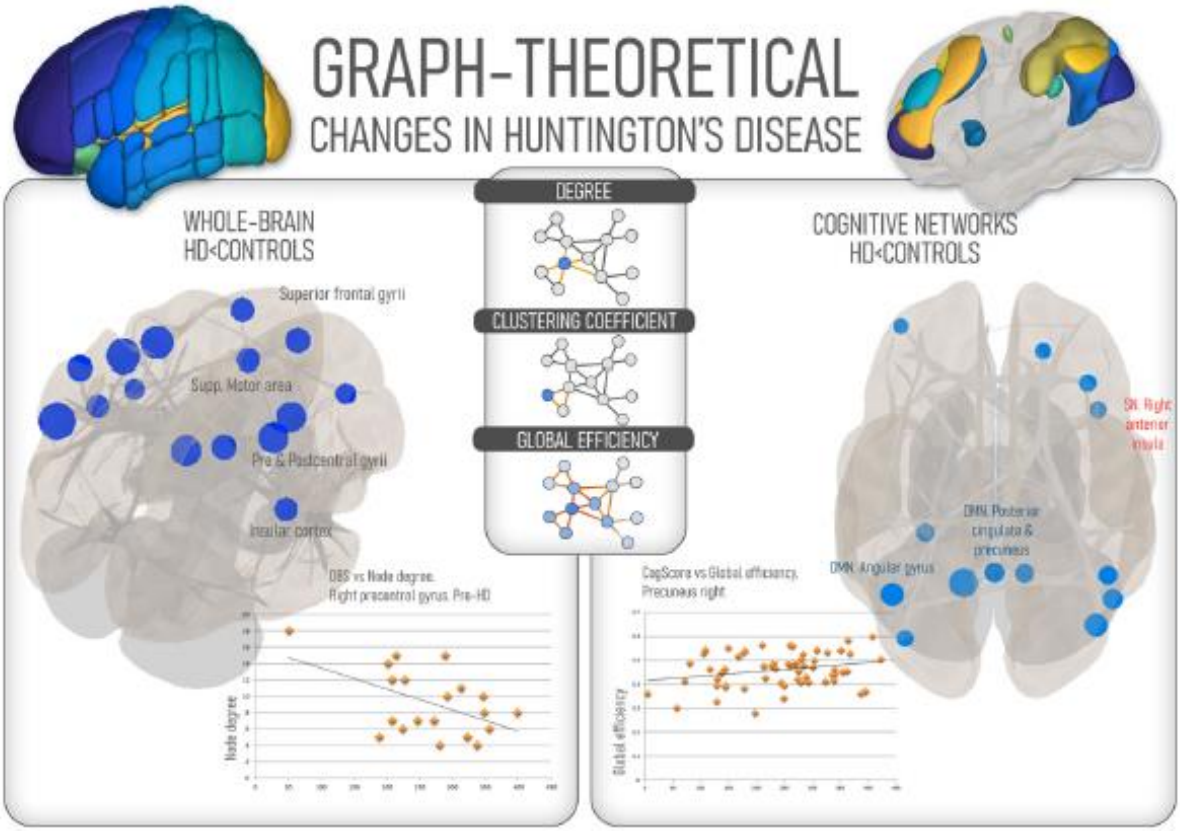

FIG. 3. Graph theoretical changes in Huntington's disease (HD) compared with healthy controls, according to both global and cognitive-oriented parcellations. Regressions with clinical parameters (disease burden score and Cogscore) are shown in the lower part of the image. DBS, disease burden score; DMN, default-mode network; PCC, posterior cingulate cortex; SN, salience network [Color figure can be viewed at wileyonlinelibrary.com]

bilateral postcentral and precentral gyrii ($P = 0.007$ corrected) and the supplementary motor area ($P = 0.04$ corrected) and decreases in other nonmotor regions such as the bilateral supramarginal gyrus ($P = 0.04$ corrected) and the PCC ($P = 0.006$ corrected; Fig. 3, left). All of these regions also showed a reduction in global efficiency, and in the left postcentral gyrus, decreases in node degree and global efficiency were correlated with higher UHDRS scores in patients with manifest HD ($t = -2.31$, $P = 0.01$), whereas a lower node degree was correlated with higher DBS in pre-HD ($t = -1.98$, $P = 0.03$).

Graph Metrics in Cognitive Networks

Using a cognitive networks approach, decreases in node degree were found on the bilateral precuneus ($P = 0.02$ corrected), bilateral angular ($P = 0.02$ corrected), occipital ($P = 0.03$ corrected), and parahipoccampal gyrii ($P = 0.03$ corrected)—all DMN nodes—and the right anterior insula from the SN ($P = 0.04$ corrected; Fig. 3, right). Clustering coefficient was also reduced in the PCC ($P = 0.001$ corrected) and left anterior insula ($P = 0.02$ corrected). Finally, global efficiency was decreased in the right precuneus ($P = 0.03$ corrected). This decrease correlated directly with the Cogscore ($t = 2.23$, $P = 0.01$).

Graph Metrics in Pre-HD

On a whole-brain approach, the pre-HD group showed similar decreases in node degree compared with controls, centered around bilateral precentral and postcentral gyrii and the PCC (all $P = 0.03$ corrected). We also found that some of these nodes—the bilateral precentral and postcentral gyri—also showed decreased global efficiency compared to controls. Furthermore, path length was increased in motor and nonmotor regions of the cortex, including the bilateral insular cortex, bilateral fusiform gyri, and the bilateral amygdalae (all $P = 0.04$ corrected). Considering cognitive networks, pre-HD already showed a loss of clustering

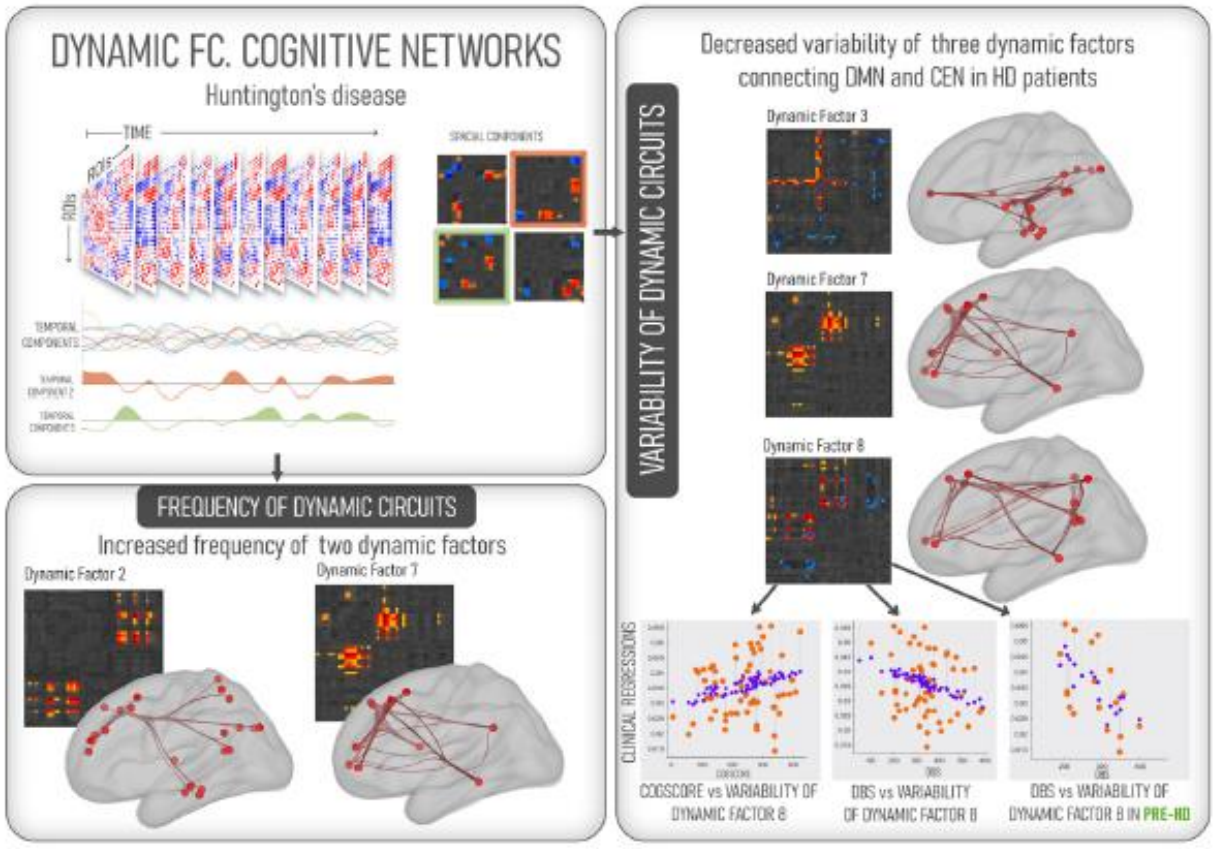

FIG. 4. Analysis of dynamic factors in patients with Huntington's disease (HD) compared with healthy controls. On the lower left, dynamic factors that showed increased frequency in patients with HD are shown. On the right, decreases in variability of three dynamic factors compared with healthy controls; on the lower part, clinical regressions are shown related to the loss of variability in dynamic factor 8. DMN, default-mode network; ROI, region of interest; CEN, Central executive network. [Color figure can be viewed at wileyonlinelibrary.com]

coefficient in the PCC ($P = 0.01$ corrected) and the left anterior insula ($P = 0.03$ corrected).

After controlling for GMV, all results remained significant with the following exceptions: node degree decreases in the supplementary motor area ($P = 0.06$ corrected after controlling for GMV); clustering coefficient decreases in the left anterior insula ($P = 0.09$ corrected after controlling for GMV); global efficiency decreases in the left precuneus ($P = 0.06$ corrected after controlling for GMV); and in pre-HD, path length increases in bilateral insular cortex and bilateral amygdalae (not present after controlling for GMV) and clustering coefficient decreases in the PCC and left anterior insula (not present after correcting for GMV).

Dynamic Independent Component Analysis

A total of 12 dynamic factors corresponding to within-network and between-network connectivity patterns were identified in the whole sample: 4 components captured SN-DMN interactions, 4 identified CEN-DMN interactions, 1 corresponded to CEN-SN interactions, and 3 corresponded to within network connections. The outlook of the 12 dynamic factors is displayed in Appendix S1 in the supplementary material and Figure 2.

Comparing the HD group with healthy controls, patients had higher frequencies of DMN-CEN coupling, with the strongest connections between parahippocampal and precuneus DMN and orbitofrontal Central executive network (CEN) (factor 7, $P = 0.04$), whereas the controls showed an increased frequency of dynamic SN-DMN connections, highlighted by the links between the anterior cingulate and frontal cortex with the bilateral precuneus of the DMN (factor 2, $P = 0.03$; Fig. 4, bottom left). On the variability analysis, all of the dynamic factors showed increases in controls, related to DMN-CEN couplings, in which the right caudate of the CEN shows increased dynamic connectivity with DMN structures such as the bilateral precuneus, bilateral angular, and bilateral occipital cortices (factor 7, $P = 0.04$; factor 3, $P = 0.03$; factor 8, $P = 0.002$; Fig. 4, right). After performing a post hoc correction for the number of dynamic factors, only the variability of factor 8 remained statistically significant ($P < 0.05$ corrected). Importantly, the variability of factor 8, which connects frontal nodes of the CEN and posterior hubs of the DMN such as the PCC and precuneus, was directly correlated to the Cogscore ($t = 1.98$, $P = 0.02$) and inversely with the DBS ($t = -2.32$, $P = 0.02$).

Comparing pre-HD with controls, the controls preserve the higher frequency in the previously mentioned SN-DMN component (factor 2, $P = 0.04$), and variability remained higher for the DMN-CEN coupling in the control group, with higher connectivity between the frontal CEN hubs and the bilateral precuneus (factor 8, $P = 0.02$). The variability of factor 8 also correlated inversely with DBS in patients with pre-HD ($t = -2.60$, $P = 0.02$). Comparing pre-HD with sHD, the latter group presented a higher frequency of within-SN connections, highlighted by insular–precuneus connections (factor 4, $P = 0.04$), whereas patients with pre-HD showed an increased variability in SN connectivity, mainly insular cortex, with frontal regions of both the DMN and CEN (factor 9, $P = 0.04$).

Discussion

In the present study, we analyzed the landscape of FC changes associated with pre-HD and manifest HD and how they compare to healthy controls. Adopting both a whole-brain and a cognitive networks approach, we found commonalities with previous descriptions of brain networks in HD, but also a number of salient points that are derived from newer approaches such as dynamic FC analysis. We also examined the brain atrophy of the patients with HD compared with healthy controls to frame this functional analysis.

In patients with HD, widespread cortical thinning was observed compared with healthy controls. This pattern of extensive atrophy has been previously reported by our group[7,32] and others[2,4] and shows that the loss of cortical thickness occurs in frontal, temporo-parietal, and occipital cortices in patients with HD. Patients with pre-HD showed no differences compared with healthy controls using stringent statistical thresholds, a fact that has been shown in previous studies in patients with early HD,[33] although others have shown cortical thinning in the early stages.[5] However, this could be explained by the long time to onset in the patients with pre-HD in our sample (14.05 ± 6 years; see Table 1) because previous studies have shown almost no cortical thinning in patients with an estimated onset to disease higher than 5 years.[2] Furthermore, we observed that the structural changes did not have a pronounced effect in the functional analyses when gray matter volume was used as a covariate of no interest.

Using a whole-brain parcellation scheme, the changes in FC observed in our sample were mainly related to visual associative and motor regions. These changes involved the fusiform gyrus, occipital pole, and precentral/postcentral cortices and were also found when comparing patients with pre-HD with healthy controls. In previous studies, reduced FC in the somatomotor cortex has been related to the severity of motor symptoms.[9,10] Similarly, the visual networks have shown reduced FC in HD,[12] and this decrease was related to impairment in visual scanning and motor speed. Therefore, the reduced FC between motor and visual associative regions in our sample could underlie these clinical changes that are present, albeit in a reduced fashion, even in the premotor stage.[34] Importantly, these changes in our sample were linked to

increasing disease burdens and worse motor scores. Graph theoretical findings also support these results, showing decreased degree and efficiency in precentral and postcentral hubs even in the premotor stage, and a widespread increase in path lengths across the network, signaling a decrease in the efficient transfer on information across its nodes. Of note, some cognitive regions were highlighted in this global analysis, mainly via an increase of FC between the PCC and the visual associative cortex, which correlates with higher DBSs. However, these changes are much less prominent compared with the visuomotor impairment.

The cognitive networks approach showed that patients with HD lose connectivity in the major large-scale networks in the resting state. These decreases were particularly consistent regarding the DMN, which had already been reported in sHD.[10,13,35] In our sample, decreases of FC affected key nodes of the DMN, and this reduced connectivity translated into lower Cogscores as well as higher DBSs, especially for connections between the anterior and posterior components of the DMN. Furthermore, these decreases were accompanied by lower node degree, clustering coefficients, and global efficiency properties in these nodes, the latter showing a correlation with cognitive scores. Changes outside of FC had previously been documented only in relation with depression[36] or using regional metrics such as amplitude of low-frequency fluctuations.[37] More significant for us were the decreases found within the SN, which had not been found in previous studies of cognitive networks in HD.[38] We found a loss of FC within SN hubs such as the insula, the supramarginal gyrus, and the anterior cingulate and a further decrease in node degree and efficiency in the anterior insula. These changes were again correlated with clinical outcomes both in cognitive and DBSs. These findings are important given that the SN plays a critical role in the attribution and signaling of relevant inner and external information and thus in the engagement of goal-directed behavior and emotional processing.[39] Therefore, our findings may provide new insights on the functional mechanisms leading to the reduction on goal-directed behavior and emotional processing observed in HD.[34] We also found disruptions in these networks in the premanifest group, with lower FC within the DMN and decreased clustering coefficients both in the SN and DMN.

All of these concepts, however, are based on the premise that FC is "static" across resting-state acquisition, a concept that seems at odds with the dynamic nature of brain functioning. Reconciling classical resting-state network knowledge with a dynamic approach is challenging, but canonical large-scale networks could be considered as approximate static representations of the underlying dynamic brain.[40] Using dyn-ICA, we tried to retain the spatial identification of classical cognitive networks while adding temporal data such as frequency and variability, and we obtained two main conclusions. First, our results show that the dynamic connection between SN and DMN is less frequent in HD. These two networks were the most affected by the loss of intrinsic connectivity and topographical features in time-averaged analyses, and our results show that their interplay is also disrupted in a dynamic framework. An altered relationship between the SN and DMN can be found in previous static analyses of neurodegenerative diseases as a loss of anticorrelations,[26,41,42] but so far, to our knowledge, not in a dynamic framework. Our results lead us to believe that a time-dependent connection between these supposedly anticorrelated networks might be a trait of healthy participants and become lost in HD. This effect might probably be related to the SN's role as a "network fulcrum"—pivoting between executive and default-mode predominant settings—a concept proposed since the independent description of this network[43] that has been further confirmed using dynamic causal modeling.[44] Second—and perhaps more important given its clinical repercussion—although patients with HD show a higher frequency of DMN-CEN connections, their variability seems to be decreased across different dynamic factors. Above all, this loss in the dynamic interplay of the CEN and the DMN correlates with worse cognitive scores and higher DBS and can be found even in the premanifest group. Variability in brain networks is related to cognitive performance[45] and decreases with age,[24] and it could be conceived of as the repertoire of possible configurations of a brain network.[23] Thus, patients with HD seem to have a decreased range of network configurations that link DMN hubs, such as the precuneus, with CEN hubs such as the caudate nucleus. This altered dynamic resulted in worse clinical outcomes and is related to a more severe disease in our sample. We speculate that this lack of variability might be compensated by a higher frequency of this state, suggesting that CEN-DMN connections may assume maladaptive configurations that trade reduced efficiency for higher coupling.

We acknowledge some limitations to this study. First, cognition was explored mainly via the Cogscore, a widely employed and validated tool for cognitive assessment in HD. However, detailed neuropsychological evaluation might reveal more subtle disruptions of cognitive function, especially in patients with pre-HD, in which we found fewer cognitive correlations with networks disruption. Further studies will need to evaluate the link between more precise clinical evaluation and network dysfunction. Second, our resting-state acquisition time might not sufficiently represent all the dynamic variability of the HD brain; however, given the intrinsic difficulties of imaging acquisition in patients (especially given the disease-specific symptoms such as chorea) we believe this is a realistic rendering of

the dynamic brain states in these patients. Third, healthy controls only had sociodemographic data available in this study. Finally, the choice of cortical parcellation could influence the results, and it is still up for debate as recent publications show.[46] However, we think this work strikes a balance between whole-brain, microanatomical, and functionally oriented parcellations as has been suggested in recent reviews.[31]

Conclusions

To sum up, our results show that cognitive networks in HD are particularly affected, even in the premotor stages of the disease. These disruptions follow well-known patterns in neurodegenerative disease, with decreases in the intrinsic connectivity of the networks and the loss of graph-theoretical properties. Furthermore, a dynamic approach uncovers network interactions unapparent in static analyses of FC that extend into the premanifest stage. Further studies will be needed to replicate these findings and link them to the diverse phenotypical and neuropsychological aspects of HD. ■

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

5. RESUMEN GLOBAL DE RESULTADOS

El estudio de las redes cognitivas en las enfermedades que cursan con trastornos del movimiento ha estado en muchas ocasiones supeditado al predominio motor en la clínica, lo que ha desviado gran parte de los esfuerzos hacia el estudio de la disrupción de los circuitos motores. Además, enfermedades como la EP presentan la complejidad añadida de contar con tratamientos sintomáticos que pueden modificar la expresión de estas redes, y una gran cantidad de herramientas neuropsicológicas que aumentan el reto de definir y clasificar el deterioro cognitivo en sus estadios iniciales. Finalmente, enfermedades minoritarias como la EH presentan un reto aún mayor en el que estos retos mencionados para la EP se multiplican por la menor prevalencia de la enfermedad y la escasez comparativa de estudios dirigidos a ella. No obstante, ambas enfermedades presentan la ventaja, respecto a otros síndromes neurodegenerativos, de contar con fases iniciales relativamente asintomáticas en lo cognitivo, como en la EP, o periodos en el que el diagnóstico es certero- al tratarse de una enfermedad determinada genéticamente- antes de que se manifiesten los primeros síntomas, como en la EH. Ello nos permite estudiar las fases en las que el diagnóstico precoz y los tratamientos son potencialmente más eficaces para ralentizar y potencialmente revertir el daño que sufren las redes cognitivas a gran escala.

Nuestro primer objetivo fue estudiar los fenómenos de conectividad funcional en un grupo de pacientes sin demencia reclutados de forma prospectiva en nuestro centro. Para ello se reclutaron 53 pacientes diagnosticados de EP clasificándolos en EP-CN y EP-DCL utilizando los criterios de nivel 1 de la MDS. Adquirimos secuencias de RM estructural y funcional y planteamos un análisis de sustancia gris usando morfometría basada en vóxel (VBM) y un análisis de conectividad funcional que incluía parámetros de teoría de grafos. Buscamos, además, la correlación de estas medidas con parámetros clínicos y neuropsicológicos. Nuestros resultados mostraron que los pacientes con EP-DCL presentaban una disminución de volumen en el precuneus, nodo fundamental de la DMN, que no iba acompañado de una alteración

correspondiente de parámetros de conectividad funcional o teoría de grafos. En cambio, los pacientes presentaron una menor conectividad de SN acompañada de un deterioro de sus propiedades topológicas, como el número de conexiones de estos nodos. Los cambios funcionales en SN se correlacionaron con medidas de función cognitiva global, funciones ejecutivas y visuoespaciales.

De estos resultados, una de las primeras preguntas que surgieron fue investigar qué relación guardaban los instrumentos validados para el diagnóstico del EP-DCL con la obtención de correlatos en redes cognitivas, y si estos instrumentos describían alteraciones de conectividad cerebral consistentes entre ellos. Para ello reclutamos 53 pacientes con EP y los clasificamos en EP-CN y EP-DCL de acuerdo a dos escalas aceptadas como nivel 1 (PD-CRS y MoCA) y mediante una exploración exhaustiva de nivel 2 incluyendo dos pruebas por dominio cognitivo. Adquirimos imágenes de RM estructural y funcional y realizamos un análisis VBM, grosor cortical (Cortical Thickness, Cth) y conectividad funcional/teoría de grafos para obtener los correlatos propios del EP-DCL según cada clasificación. Desde el punto de vista clínico, los criterios exhaustivos de nivel 2 clasificaron como EP-DCL al 32% de la muestra, en línea con publicaciones previas. PD-CRS mostró una proporción similar del 33%, mientras que MoCA, en su punto de corte más aceptado, sobreestimó la prevalencia de EP-DCL situándola en un 60%. Desde el punto de vista de los correlatos estructurales, tanto la clasificación de nivel 2 como la PD-CRS mostraron la pérdida de volumen en el precuneus como característica del EP-DCL. PD-CRS fue la escala que mostró los cambios estructurales más extensos, especialmente una pérdida de grosor cortical posterior que ha sido descrito en otras series como propio del EP-DCL. En cuanto a los correlatos funcionales, las tres clasificaciones mostraron una pérdida de propiedades topológicas en teoría de grafos asociada a SN, mientras que PD-CRS fue la escala que mostró más cambios de conectividad funcional en forma de pérdida de anticorrelaciones entre SN y DMN.

Otra de las preguntas surgidas de nuestros primeros fue desentrañar el papel del tratamiento sustitutivo dopaminérgico: estudios previos sugerían que su administración normalizaba la conectividad aberrante en los circuitos motores, pero el efecto sobre las

redes cognitivas no era conocido. Este efecto de normalización podría tener implicaciones sobre mecanismos de compensación en los estadíos iniciales, suprimiendo o incrementándolos de forma artificial. Para este trabajo se reclutaron 35 pacientes con diagnóstico de EP, sin demencia, además de 16 controles apareados por edad, y se realizaron evaluaciones clínicas y neuropsicológicas basales además de un seguimiento de conversión a demencia a 10 años. Se adquirieron imágenes de RM estructural, y la RM funcional se adquirió bajo tratamiento habitual y también con una retirada de medicación previa de 12 horas (estados de ON y OFF práctico, respectivamente). Los resultados mostraron que los pacientes con EP presentan una mayor conectividad frontoparietal que sujetos sanos de su misma edad, pero esta mayor conectividad cambiaba con la administración de medicación, pasando de un predominio de nodos frontales de DMN en OFF práctico a un predominio de SN cuando los pacientes se encontraban en ON. Comparando a los mismos pacientes en las condiciones de ON/OFF práctico, los pacientes bajo los efectos de la medicación mostraban más conectividad de SN y menor conectividad de DMN. En el seguimiento a 10 años, que completaron 25 de los 35 pacientes, un 52% convirtieron a demencia. De forma relevante, las resonancias basales de los pacientes que convirtieron a demencia no mostraban diferencias estructurales, pero sí una mayor conectividad funcional en nodos de SN cuando se encontraban en ON.

Respecto a la EH, nuestro objetivo era comprobar si las alteraciones de estructura y dinámica observadas en la EP se podían describir también en la EH. Para ello reclutamos de forma prospectiva un grupo de 64 pacientes portadores de la mutación y 23 controles sanos; se realizó una exploración clínica y neuropsicológica completa. En todos los sujetos obtuvimos imágenes de RM estructural y funcional. Además de las métricas estructurales de grosor cortical, analizamos la conectividad funcional y teoría de grafos utilizando el paradigma estático clásico, y añadimos un análisis de conectividad funcional dinámica. En comparación con controles sanos, los pacientes con EH mostraron, al igual que en series previas, una alteración de la conectividad funcional en redes visuomotoras cuando analizamos una parcelación que incluía todo el córtex, con algunos cambios escasos en DMN. Al centrarnos en los nodos de las tres redes cognitivas, los pacientes con EH mostraron cambios similares a los encontrados

en otras enfermedades neurodegenerativas, con pérdida de la conectividad intrínseca en nodos de DMN y SN que se correlacionaron con métricas de carga de enfermedad (Disease Burden Score, DBS) y puntuación cognitiva (CogScore); algunos de estos cambios ya estaban presentes en pacientes presintomáticos. De forma significativa, el análisis de conectividad funcional dinámica mostró alteraciones en la frecuencia y variabilidad de los estados de conectividad de las redes cognitivas, pero especialmente en los acoplamientos entre DMN-CEN, un rasgo ya presente en la población presintomática.

6. RESUMEN GLOBAL DE LA DISCUSIÓN

Los resultados de los cuatro trabajos que comprende esta tesis apuntan a una disrupción precoz y específica de las redes cognitivas a gran escala en enfermedades que cursan con trastornos del movimiento. Partiendo de un modelo ampliamente estudiado- la EP-, hemos podido demostrar cambios específicos en estas redes en los estadíos iniciales del deterioro cognitivo, y comprobar cómo los tratamientos de reposición dopaminérgica modifican la expresión de estos cambios. Finalmente, haciendo uso de los conocimientos adquiridos en la EP, hemos demostrado cómo el estudio dirigido a las redes cognitivas pueden encontrar cambios en una enfermedad menos estudiada- la EH-, y hemos aplicado técnicas novedosas de conectividad funcional dinámica para desentrañar relaciones aberrantes entre redes a gran escala que no son aparentes en un paradigma clásico de conectividad estática.

En lo relativo a los correlatos funcionales y en teoría de grafos de los estadíos de EP-DCL, nuestro hallazgo principal fue una trayectoria divergente en la disfunción de dos de las redes cognitivas a gran escala. Mientras que DMN mostraba una pérdida de volumen en precuneus sin alteración funcional, en SN observamos alteraciones funcionales en ausencia de atrofia significativa cuando comparamos pacientes con cognición normal respecto a EP-DCL. Además, la presencia de déficits ejecutivos y visuoespaciales se correlacionó con el deterioro de conectividad en SN, pero no en DMN. Esto es explicable dado que el precuneus es un nodo jerárquicamente superior, responsable de las funciones cognitivas más relevantes [55], y que pueden encontrarse intactas en la EP-DCL pero deteriorarse en fases más avanzadas de la enfermedad. En cambio, la progresiva denervación dopaminérgica que afecta a los circuitos motores implica también desde fases más tempranas de la enfermedad a las regiones frontoparietales de SN, como la ínsula o el córtex cingulado anterior [56]. Si bien la denervación de la vía dorsal tiene una traducción en los circuitos motores desde el inicio clínico de la enfermedad, la aparición del DCL parece relacionarse con la afectación progresiva de SN [45], más dependiente de la vía mesocorticolímbica. La diferente tasa de degeneración de ambas vías en la EP explica esta discrepancia temporal[48]; en nuestro trabajo, el estadío de EP-DCL viene marcado por la pérdida de

propiedades topológicas de los nodos de SN, especialmente de la ínsula anterior, así como por una pérdida de anticorrelación entre SN y DMN. La definición de redes particularmente vulnerables en los estadíos iniciales del deterioro cognitivo puede ser útil para definir subgrupos de pacientes particularmente en riesgo, y coincide con el concepto de que las enfermedades neurodegenerativas inciden particularmente sobre redes cognitivas diferentes [34]. No obstante, este artículo nos dejó unas cuantas líneas de investigación futuras. La primera es que, dada la ausencia de controles en este estudio, no fue posible comprobar la existencia de un fenómeno de hiperconectividad en pacientes con EP-CN, sólamente constatar la caída de conectividad iniciada en el estadío de EP-DCL. Por otro lado, los datos de este estudio se adquirieron con medicación (estado “ON”) y ello plantea la pregunta de si estos cambios pueden verse modificados por la administración de dopamina exógena. Finalmente, la definición de EP-DCL admite, como se ha mencionado, dos niveles de confianza en el diagnóstico: el correspondiente a pruebas de cribado, o nivel 1, y el que se realiza con una valoración exhaustiva o por dominios, de nivel 2. Al haber clasificado a los pacientes con una herramienta de nivel 1, pese a coincidir los correlatos obtenidos con lo descrito en la literatura, cabía la duda de si una valoración más pormenorizada cambiaría la arquitectura de redes que define el estado de EP-DCL en este estudio.

De forma similar, la comparación entre distintos métodos recomendados por la MDS para evaluar el DCL nos mostró que la valoración neuropsicológica del deterioro cognitivo influye en los correlatos obtenidos tanto en imagen estructural como en funcional. Esto es especialmente cierto en el caso del nivel 2 o exhaustivo, que es el idealmente recomendado por la MDS para la evaluación del EP-DCL. Este tipo de evaluación permite escoger las pruebas que evalúan cada uno de los dominios cognitivos, además de encontrarse en la literatura diferentes criterios para el diagnóstico de alteración por dominio, siendo 1.5 desviaciones estándar respecto a los datos poblacionales normativos el criterio más aceptado[20], pero no el único. Por otro lado, las pruebas de nivel I presentan puntos de corte bien establecidos en la literatura, pero tienen el inconveniente de haber sido diseñadas como instrumentos de cribado, y no para el diagnóstico de certeza. No obstante, nuestro trabajo demostró la existencia de correlatos comunes para las distintas formas de valoración del EP-DCL, destacando

entre ellos la pérdida de eficiencia y número de conexiones de SN, así como la atrofia de regiones corticales posteriores correspondientes a la DMN. No obstante, las diferencias existentes entre las escalas son notorias: esto es especialmente cierto en el caso de PD-CRS, la única escala que muestra signos de extensa pérdida de grosor cortical en territorios posteriores, además de disminución de anticorrelaciones entre SN y DMN, y pérdida de parámetros topológicos en teoría de grafos, todos ellos cambios descritos previamente en la literatura. La clasificación exhaustiva de nivel 2 es la que más se acerca a replicar estos datos en nuestra muestra, pero no muestra el mismo grado de consistencia en sus resultados. Nuestra hipótesis es que esta falta de resultados en el nivel 2 es atribuible a la señalada falta de estandarización de puntos de corte y selección de pruebas por dominio, lo que dificulta la obtención de resultados reproducibles. Esto es especialmente importante dado que el nivel 2, al ser el preferible para las evaluaciones en centros que dispongan de medios para llevarlo a cabo, suele ser la herramienta habitual en los estudios de neuroimagen asociada al EP-DCL.

Por otro lado, para tratar de dar respuesta a algunas de las preguntas surgidas tras la definición de los correlatos en redes del EP-DCL nos planteamos dos líneas de investigación. En primer lugar, hasta qué punto la medicación dopaminérgica atenúa o realza las diferencias de conectividad; en segundo lugar, cómo se comparan estas diferencias con sujetos sanos de la misma edad; y finalmente, si estas diferencias de conectividad tienen implicaciones en la conversión a demencia. Sobre estas tres cuestiones está el telón de fondo de los posibles mecanismos de hiperconectividad frontoparietal descritos previamente en la literatura [47] (Gorges), lo que implicaría un período inicial en el que los pacientes con EP sin demencia presentan una mayor conectividad frontoparietal, sugiriendo un mecanismo de compensación. Nuestros hallazgos mostraron que la hiperconectividad frontoparietal es un rasgo característico de la EP sin demencia, con o sin medicación, si bien el tratamiento parece promover la hiperconectividad de las regiones frontoparietales de SN. En cambio, en ausencia de medicación dopaminérgica los nodos más activos en estos pacientes corresponden a DMN. Esto podría deberse a que los circuitos correspondientes a SN frontoparietal tienen una inervación dopaminérgica importante, y de este modo, presentan una mayor respuesta a la administración exógena de dopamina. Estudios recientes han

demostrado que existe un vínculo entre la síntesis de dopamina en la vía mesocórtico-límbica y la coherencia funcional de SN [57], por lo que es plausible que la administración de tratamiento dopaminérgico promueva cambios de esta índole. Esto se ve respaldado por la comparación directa entre pacientes con y sin medicación, donde el estado ON mostraba una mayor activación de nodos de SN comparado con la resonancia funcional de los pacientes en OFF. Por otro lado, estos hallazgos suponen una ruptura con el paradigma aceptado en otras redes a gran escala, especialmente motoras -pero no sólo- donde el consenso es que la dopamina normaliza una actividad aberrante propia del estado OFF. En lugar de esto, el tratamiento dopaminérgico parece promover configuraciones de red concretas, dentro de un marco de hiperconectividad frontoparietal, que favorecen una mayor coherencia de SN, la pérdida de anticorrelaciones con DMN y una menor coherencia de esta última. Finalmente, el grado en que todos estos cambios contribuyen a una posible compensación al deterioro cognitivo fue objeto de la segunda parte de nuestro estudio, en el que hicimos un seguimiento de la conversión a demencia de estos pacientes. El hallazgo fundamental fue que, en contra de nuestras expectativas, los pacientes que convirtieron a demencia presentaban una mayor activación de SN al recibir medicación. Por tanto, lejos de constituir un mecanismo de compensación, la hiperconectividad frontoparietal podría ser un rasgo de vulnerabilidad. Es sabido que aunque la hiperconectividad puede ser un rasgo de compensación (Hillary 2015), también puede suponer un coste añadido en términos de gasto metabólico (Tomasi, Wang). En el caso de nuestra muestra, estos resultados sugieren que los pacientes que presentan activaciones mayores de SN con medicación exógena pueden corresponder a aquellos que tienen una vía mesocórtico límbica más denervada y, por tanto, corresponder a pacientes con un mayor grado de neurodegeneración. Estudios futuros que combinen el análisis de redes con la administración de trazadores específicos para evaluar la integridad de la vía dopaminérgica podrían contribuir a cimentar esta hipótesis.

Finalmente, nuestro intención fue extender este análisis de las redes cognitivas a otra enfermedad que cursa con trastornos de movimiento, la EH, y ampliar los límites de lo conocido empleando un análisis novedoso de conectividad funcional dinámica. También intentamos abordar este análisis desde dos perspectivas: la del análisis del

cerebro completo, utilizando una parcelación clásica, y de forma complementaria, la parcelación de redes cognitivas utilizada en los artículos anteriores. Uno de los debates más interesantes de la neurociencia actual es el relativo a las maneras de “cartografiar” y denominar el cerebro [58], y en este asunto la comunidad científica aún está lejos de alcanzar un consenso [32]. Nuestros resultados muestran que cuando se considera una parcelación global, los cambios en de conectividad y topología de redes en EH comparados con controles son muy similares a los descritos en la literatura: predominan las alteraciones de la conectividad entre las cortezas visuales y motoras, con cambios muy pequeños en redes cognitivas. Nuestra muestra, por tanto, se asemeja a la de estudios previos[49,50,59]. El empleo de estas aproximaciones, aunque lógico, tiene el inconveniente de ocultar potencialmente alteraciones significativas en otras redes, como las cognitivas, que pueden ser más sutiles. Nuestro análisis centrado en las redes cognitivas a gran escala muestra, en cambio, que en la enfermedad de Huntington se aprecian cambios similares a los de otras enfermedades neurodegenerativas: incremento de conectividad entre redes antagónicas, como SN y DMN, y pérdida de propiedades y arquitectura en nodos clave de estas redes. Probablemente el análisis de parcelaciones globales, a diferencia de nuestro planteamiento dirigido a redes cognitivas, es lo que explique que en revisiones sistemáticas sobre conectividad funcional el papel de DMN, CEN y especialmente SN haya sido más bien discreto[51]. En nuestra muestra, estos cambios no son solamente evidentes y consistentes con el patrón de enfermedades neurodegenerativas, sino que se correlacionan con parámetros clínicos como la carga de enfermedad o la puntuación cognitiva de los pacientes. Además, algunos de estos cambios se observan en población presintomática, un hecho que se había descrito de forma aislada en estudios con RMf asociada a tareas [53], pero no en reposo [52]. Finalmente, el estudio de conectividad funcional dinámica añade una dimensión adicional al contemplar en su diseño el hecho de que el las redes cerebrales no son inmutables en el tiempo, sino que tienen un carácter “multiestable”[60]. Con este estudio hemos analizado las configuraciones más habituales de las redes cognitivas en Huntington, lo que nos permite estudiar la frecuencia de estos acoplamientos y compararlos con población sana. En primer lugar, los pacientes con EH presentaron una conexión dinámica de

menor intensidad entre SN y DMN; en un contexto estático, la anticorrelación de estas redes se ha asociado en otras enfermedades como un rasgo de población sana y de menor gravedad de las patologías [61–63]. En cambio, parece que una interacción tiempo-dependiente entre ambas redes puede considerarse un rasgo de normalidad, probablemente en relación con el rol de SN como “fulcro”, es decir, un mediador en la activación de otras redes a gran escala como DMN o CEN. Por otro lado, los pacientes presentaron una mayor frecuencia de acoplamiento entre DMN y CEN, y la mayor frecuencia de este circuito dinámico se correlacionó con una mayor gravedad de la enfermedad. Este último hecho ha de ponerse en relación con el otro parámetro investigado en este trabajo: la variabilidad intrínseca de los circuitos dinámicos, que puede interpretarse como las diferentes configuraciones que puede adoptar una red a lo largo del tiempo [64]. Los pacientes con EH mostraban en nuestro estudio una mayor frecuencia del acoplamiento CEN-DMN, pero éste mostraba una menor variabilidad que en controles sanos. Una posibilidad es que esta reducción en la variabilidad de configuraciones de esta red pueda verse compensada con una mayor frecuencia de aparición de estas condiciones. Este mecanismo, vista su asociación con una mayor carga de la enfermedad, podría considerarse como una configuración “desadaptativa” o de compensación fallida. Por tanto, y como resumen, los pacientes con EH muestran alteraciones similares a otras enfermedades neurodegenerativas en sus redes cognitivas a gran escala, que se relacionan con la gravedad de la enfermedad y que, además, incluyen disrupciones sutiles en su dinámica desde las fases tempranas.

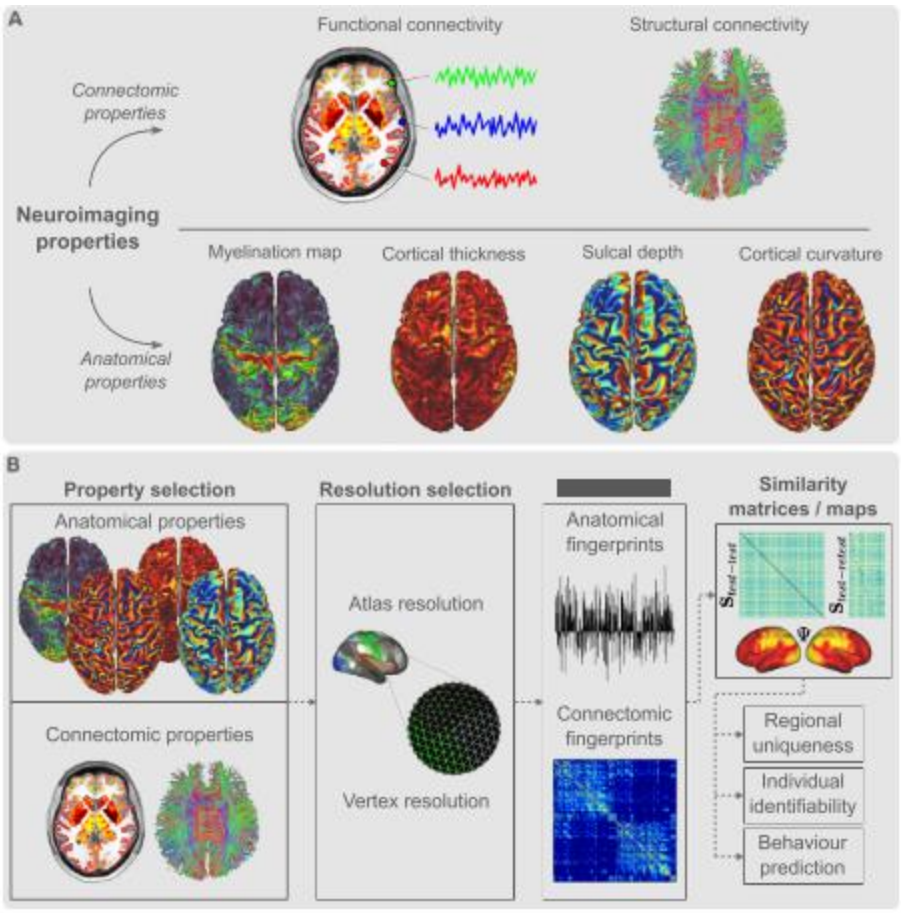
7. CONCLUSIONES

- Las enfermedades que cursan con trastornos del movimiento presentan alteraciones definidas y precoces en sus redes cognitivas a gran escala. Estas alteraciones guardan relación con parámetros clínicos y permiten establecer unos correlatos de red con la aparición del deterioro cognitivo incluso en sus estadíos más iniciales.
- En la EP los pacientes con cognición normal presentan un fenómeno de hiperconectividad frontoparietal que depende fundamentalmente de los nodos de SN. Esta mayor conectividad comparada con la de sujetos sanos se ve modificada por la medicación dopaminérgica, pero no es causada exclusivamente por ella. Es probable que una respuesta de hiperconectividad en SN más intensa tras la administración de medicación dopaminérgica suponga un rasgo de vulnerabilidad para la conversión a demencia en la EP.
- La EH muestra alteraciones de redes cognitivas a gran escala que ya están presentes en población pre-sintomática. Su expresión se correlaciona con la gravedad de la enfermedad y con el deterioro de puntuaciones cognitivas. El análisis dinámico revela que las alteraciones en la frecuencia y variabilidad de las conexiones entre DMN y CEN ya están presentes incluso en fases pre-sintomáticas de la enfermedad.

8. LÍNEAS DE INVESTIGACIÓN FUTURAS

El análisis del estado de las redes cognitivas en las enfermedades que cursan con Trastornos del Movimiento pone de manifiesto una afectación precoz y en algunos casos independiente del daño estructural en forma de atrofia. Tras identificar los rasgos comunes de estas alteraciones, uno de los grandes retos de futuro es la aplicación de este conocimiento al paciente individual.

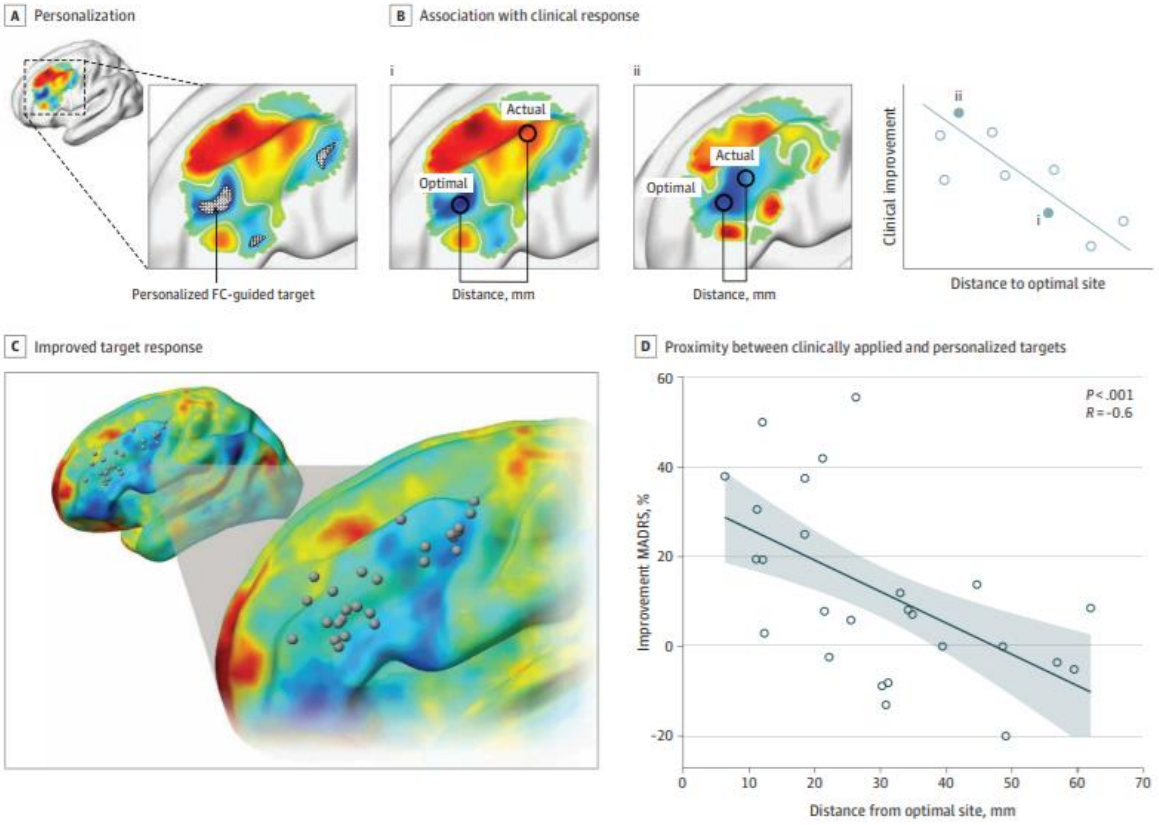
La RMf tiene que superar algunas barreras técnicas antes de poder convertirse en un método aplicable a pacientes individuales y tener capacidad diagnóstica y predictiva. Entre ellas, se encuentran la necesidad de protocolos robustos para tratar el ruido inherente a la técnica, análisis dirigidos al sujeto individual y no a grupos de pacientes, o la fiabilidad y reproducibilidad de los mapas de conectividad funcional generados con la técnica [65]. No obstante, algunos de estos problemas están empezando a ser superados y desde el año 2020 han comenzado a publicarse trabajos que tienen como objetivo analizar marcadores individualizados de conectividad. En el caso del trabajo de Mansour y colaboradores [4] el uso combinado de técnicas de RM funcional y estructural permite identificar a sujetos individuales en una muestra de cientos, exclusivamente a partir de datos de neuroimagen. Además, es posible identificar algunos elementos relativos a la conducta y cognición de los participantes, lo que abriría la puerta en el futuro a la búsqueda de rasgos sutiles de enfermedad en población en riesgo. En nuestro caso, la aplicación de esta metodología a las cohortes de las que disponemos tanto en EP como EH nos permitiría identificar e individualizar marcadores de vulnerabilidad en redes cognitivas para aquellos pacientes que aún no muestran síntomas ni signos clínicos.



Uso de técnicas de imagen estructural y funcional para identificar la "huella dactilar" anatómica y estructural de sujetos individuales a partir de sus datos de RM. Adaptado de: High-resolution connectomic fingerprints: Mapping neural identity and behavior. Mansour et al. Neuroimage. 2021

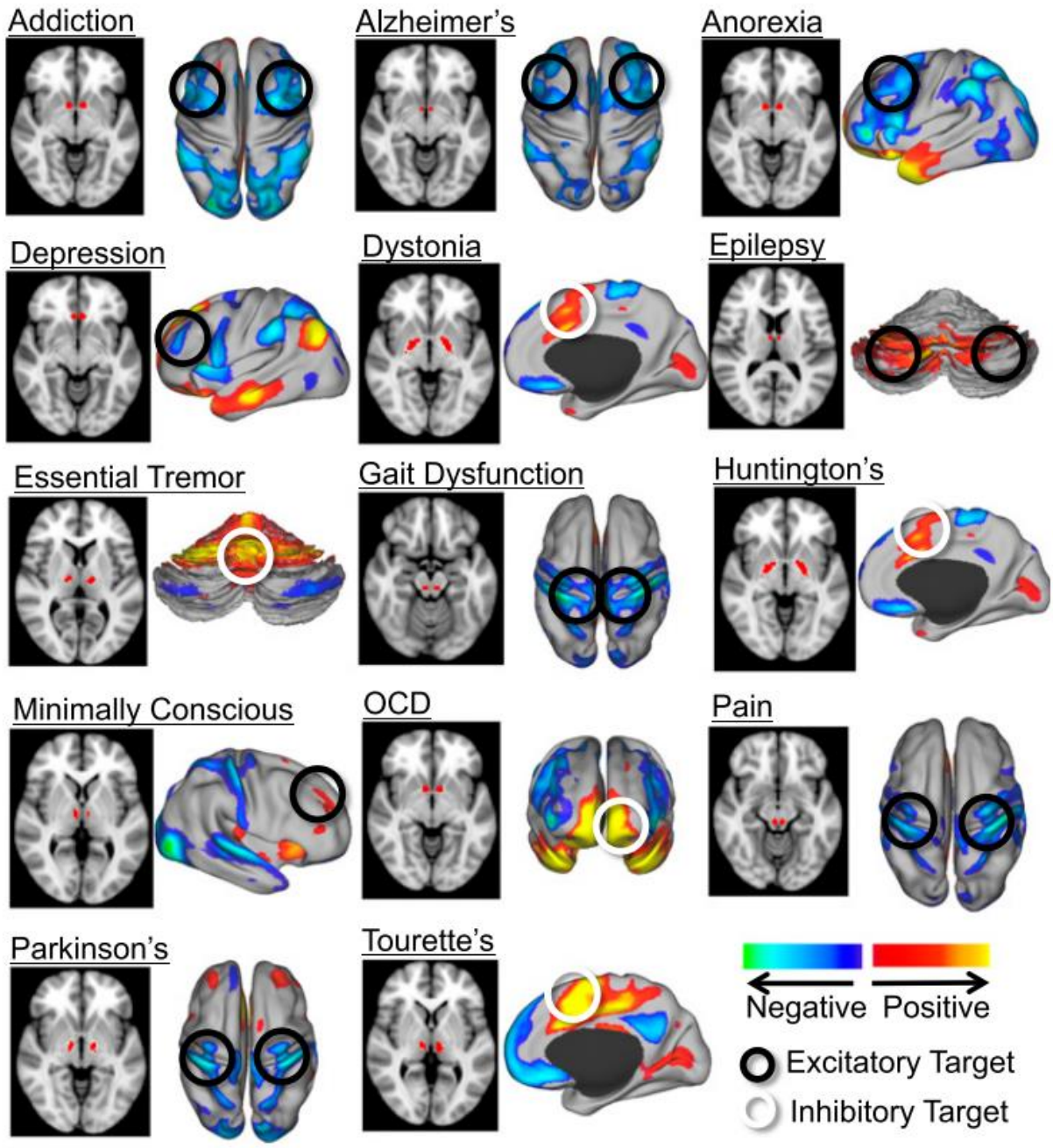
Por otro lado, la identificación de redes a gran escala ya se está empezando a emplear para identificar patrones de conectividad anómalos que puedan ser susceptibles de ser tratados. Una revisión reciente mostró la utilidad de identificar redes alteradas en pacientes con depresión para utilizarlas como diana de estimulación magnética transcraneal [66], en lugar de emplear la aproximación anatómica clásica.

Figure. Closer Proximity to Personalized Stimulation Targets Associated With Improved Response to Repetitive Transcranial Magnetic Stimulation Treatment for Depression



La estimulación magnética transcraneal basada en mapas de conectividad individualizados ha demostrado ser más eficaz para tratar la depresión que el uso de dianas genéricas basadas en localización anatómica clásica. Adaptado de: Functional Magnetic Resonance Imaging–Guided Personalization of Transcranial Magnetic Stimulation Treatment for Depression. Cash et al 2021. JAMA Psychiatry.

El tratamiento de las enfermedades neurodegenerativas como “circuitopatías” es un campo emergente, que requiere de un conocimiento profundo de las redes, su arquitectura e interacciones [67]. Por tanto, una de las líneas naturales de evolución de este trabajo es la aplicación de este conocimiento a las terapias avanzadas en las enfermedades que cursan con trastornos del movimiento. Este campo, que cuenta con una experiencia dilatada en neuromodulación en los últimos 30 años, tiene la posibilidad de enriquecerse con nuevas indicaciones y la posibilidad de aplicar medicina de precisión sobre los aspectos más complejos, como la cognición y la conducta.



Distribución de la alteración de redes afectadas en función de la patología neuropsiquiátrica considerada. Adaptado de: Resting-state networks link invasive and noninvasive brain stimulation across diverse psychiatric and neurological diseases. MD Fox et al. PNAS 2014.

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