Universitat Autònoma de Barcelona

Correlatos neuronales y neuropsicológicos de las alteraciones cognitivas y conductuales en las fases prodrómica e inicial de la enfermedad de Huntington

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TESIS DOCTORAL

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A mi padre, arquitecto del Universo de mi curiosidad.
A mi madre, por darme la vida, por ser la vida, porque siempre supiste que yo podía.
A mi hermana, por todo cuanto quisiste ser, fuiste y allá donde estés, eres y serás.
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Son inquietos primero, y hablan y se agitan, como si se luchara contra la herencia negra con la conciencia onírica. Después será al revés. Adulto ya y cansado de tanto salto inútil, el coreico se duerme sin mover ni el aliento. Un sueño de cansancio lo postra por la noche. Tarde ya, del insomnio que sufre casi todas las noches. Es la sombra del alma y la sombra del cuerpo. Nunca vendrá la aurora de salud y alegría y trabajo y reposo, de los huesos inquietos. Agitarse es su sino. La inquietud que no muere. Salta siempre en la vida; y después de la muerte, salta de un cuerpo a otro sobre puentes de almas. Oh látigo terrible. Mina cuerpo y espíritu; inutiliza al hombre. Quita el juicio y suicida a quien no tiempla el nervio. Deja huérfano al niño estando el padre vivo. Y cuando muere el padre, deja recado al hijo para que siembre horror.

Americo Negrette. "Corea de Huntington". 1963 (Zulia, Maracaibo)

ABREVIATURAS Y ACRÓNIMOS:

^{18}F-FDG: ^{18}F-fluorodesoxiglucosa

ASO: Oligonucleótido antisentido

CAG: Citosina – Adenina - Guanina

CT: Tomografía computarizada

DBS: *Disease Burden Score* (carga patológica de la enfermedad)

DCL: *Diagnostic confidence level* (nivel de confianza diagnóstica)

EH: Enfermedad de Huntington

EHJ: Enfermedad de Huntington de inicio juvenil

HTT: Huntingtina

LCR: Líquido cefalorraquídeo

mHTT: Huntingtina mutante

NFL: Neurofilamento

PET: Tomografía por emisión de positrones

TFC: *Total Functional Capacity* (Capacidad funcional total)

RMN: Resonancia magnética nuclear

UHDRS: *Unified Huntington's Disease Rating Scale*

UHDRS-TMS: *Unified Huntington's Disease Rating Scale – Total Motor Score*

ÍNDICE

RESUMEN:

El carácter minoritario de la enfermedad de Huntington ha supuesto, en comparación a otros procesos neurodegenerativos más frecuentes, un desajustado y lento avance en la comprensión de los mecanismos neuropatológicos responsables de la enfermedad y en la identificación y descripción pormenorizada de los fenotipos clínicos que la caracterizan.

Históricamente, las manifestaciones clínicas de la enfermedad de Huntington, han sido preferentemente atribuidas a la característica atrofia subcortical que presentan todos los pacientes. En correspondencia con esta atrofia de los ganglios basales, desde el punto de vista neuropsicológico, la enfermedad de Huntington ha sido considerada un paradigma de demencia subcortical con un perfil neurocognitivo frontal-disejecutivo caracterizado por enlentecimiento cognitivo, disfunción ejecutiva, apatía y cambios de personalidad.

El desarrollo de estudios observacionales de carácter multicéntrico e internacional, ha permitido a lo largo de los últimos 15 años, ahondar de manera notable en el conocimiento de la enfermedad gracias al seguimiento de grandes cohortes de personas afectadas. Estos estudios han ilustrado que, desde etapas tempranas de la enfermedad e incluso durante la fase asintomática, algunos de los cambios neuropatológicos más evidentes se extienden más allá de los ganglios basales y afectan a extensos territorios corticales, principalmente en áreas parieto-occipitales y temporales.

En paralelo a estos hallazgos, los trabajos que han explorado la correspondencia de las anomalías cerebrales con las manifestaciones clínicas de la enfermedad, han desvelado que las alteraciones cognitivas desbordan ampliamente el perfil disejecutivo y que la alteración de múltiples dominios y procesos ilustran un fenotipo cognitivo bastante más complejo y diverso al inicialmente descrito.

A pesar de ello, quedan muchas incógnitas por resolver. Actualmente sabemos que cambios cognitivos y conductuales sutiles, objetivables a través del rendimiento en determinadas tareas, pueden

ponerse de manifiesto hasta 15 años antes de que las primeras manifestaciones motoras sean evidentes. Ello ha supuesto que la comunidad científica dedicada a la enfermedad haya centrado importantes esfuerzos en explorar las variables cognitivas que caracterizan la enfermedad y que predicen su progresión, así como el modo en que podemos capturar de manera eficiente las primeras manifestaciones preclínicas. También sabemos, que independientemente de la carga genética de la enfermedad, existe una notable variabilidad tanto en la edad de inicio como en la forma y en el curso que adquiere la enfermedad a lo largo de su evolución. Ampliar nuestro campo de visión más allá de los ganglios basales ha contribuido a desvelar un conjunto de elementos todavía difíciles de encajar con precisión en el conjunto de la enfermedad, pero que reafirman la necesidad de profundizar en el estudio de sus mecanismos causales. Seguimos sin comprender claramente: 1) porque la enfermedad se comporta de distinto modo en personas cuya carga genética y edad es la misma; 2) qué papel tienen algunos de los cambios cerebrales más sutiles y tempranos que acontecen en el curso de la enfermedad; 3) cuál es el patrón de neurodegeneración cerebral asociado a determinadas manifestaciones neuropsiquiátricas con la limitación que ello conlleva para los planteamientos terapéuticos; 4) cuál es el perfil neurocognitivo concreto de las formas graves de deterioro cognitivo en la enfermedad, ni cómo podemos medir estos perfiles en sus formas leves y graves ni, 5) cuál sea el patrón neurodegenerativo que presentan los pacientes que desarrollan demencia.

Los objetivos de esta tesis, como ponen de manifiesto los trabajos publicados que la conforman, se han dirigido a la búsqueda de algunas respuestas para estas incógnitas que supongan avances concretos para el conocimiento y el manejo clínico de esta devastadora enfermedad.

En el cuerpo de esta tesis describimos: 1) cómo hemos constatado que una variable ambiental, tal que el uso del bilingüismo a lo largo de la vida, modula la reserva cerebral y cognitiva de los pacientes e impacta en la expresión clínica de la enfermedad; 2) que existe un fenómeno de alteración neurocognitiva nunca antes descrito del cual precisamos sus correlatos neurofisiológicos, que acontece más de 10 años antes del inicio de los síntomas motores; 3) que hemos identificado los sustratos

neuronales relacionados con la gravedad de la irritabilidad y la agresividad en la enfermedad; 4) que se ha validado un instrumento de cribado del estado cognitivo global lo que aporta vez primera una metodología operativamente válida para la detección de formas leves y graves de deterioro cognitivo en la enfermedad, lo que también ha supuesto incrementar el conocimiento sobre los distintos perfiles de afectación neuropsicológica que caracterizan las formas más y menos agresivas de deterioro cognitivo en la enfermedad; y 5) que hemos descrito por primera vez los cambios cerebrales característicos de las formas más y menos graves de deterioro cognitivo, lo que ha permitido identificar el papel de los cambios corticales y subcorticales en la demencia asociada a la enfermedad de Huntington.

Quedan por supuesto muchas cuestiones sin resolver y de estos hallazgos nacen nuevas preguntas. Nuestro compromiso con el futuro de la investigación en la enfermedad de Huntington es que estas nuevas preguntas y el trabajo para resolverlas, sean las más adecuadas para contribuir desde nuestro puesto de lucha, a un rápido y efectivo cambio de en la forma trágica en que hoy conocemos la progresión de la enfermedad de Huntington.

SUMMARY:

The minority nature of Huntington's disease has meant, in comparison to other more frequent neurodegenerative processes, an imbalanced and slow progress in the understanding of the neuropathological mechanisms responsible for the disease and in the identification and detailed description of the clinical phenotypes that characterize it.

Historically, the clinical manifestations of Huntington's disease have been preferentially attributed to the characteristic subcortical atrophy that all patients present. In correspondence with this atrophy of the basal ganglia, from the neuropsychological point of view, Huntington's disease has been considered a paradigm of subcortical dementia with a frontal-dysexecutive neurocognitive profile characterized by cognitive slowing, executive dysfunction, apathy and personality changes.

Over the last 15 years, the development of multicenter and international observational studies has made it possible to significantly deepen our knowledge of the disease thanks to the follow-up of large cohorts of affected people. These studies have illustrated that, from the early stages of the disease and even during the asymptomatic phase, some of the most obvious neuropathological changes extend beyond the basal ganglia and affect extensive cortical territories, mainly in parieto-occipital and temporal areas.

Parallel to these findings, studies that have explored the correspondence of brain abnormalities with the clinical manifestations of the disease have revealed that cognitive disturbances go far beyond the dysexecutive profile and that the alteration of multiple domains and processes illustrate a fairly cognitive phenotype more complex and diverse than initially described.

Despite this, many unknowns remain to be resolved. We now know that subtle cognitive and behavioral changes, observable through performance in certain tasks, can become apparent up to 15 years before the first motor manifestations are evident. This has meant that the scientific community dedicated to the disease has focused important efforts on exploring the cognitive variables that

characterize the disease and that predict its progression, as well as the way in which we can efficiently capture the first preclinical manifestations. We also know that regardless of the genetic load of the disease, there is a notable variability both in the age of onset and in the form and course that the disease acquires throughout its evolution. Expanding our field of vision beyond the basal ganglia has contributed to uncovering a set of elements that are still difficult to fit precisely into the disease as a whole, but which reaffirm the need to deepen the study of its causal mechanisms. We still do not clearly understand: 1) why the disease behaves differently in people whose genetic makeup and age is the same; 2) what role do some of the most subtle and early brain changes that occur in the course of the disease have; 3) what is the pattern of brain neurodegeneration associated with certain neuropsychiatric manifestations with the limitation that this entails for therapeutic approaches; 4) what is the specific neurocognitive profile of severe forms of cognitive impairment in the disease, or how can we measure these profiles in their mild and severe forms, or 5) what is the neurodegenerative pattern that patients who develop dementia present.

The objectives of this thesis, as evidenced by the published works that comprise it, have been aimed at finding some answers to these unknowns that represent concrete advances in the knowledge and clinical management of this devastating disease.

In the body of this thesis we describe: 1) how we have verified that an environmental variable, such that the use of bilingualism throughout life, modulates the brain and cognitive reserve of patients and impacts on the clinical expression of the disease; 2) that there is a phenomenon of neurocognitive alteration never before described, of which we need its neurophysiological correlates, which occurs more than 10 years before the onset of motor symptoms; 3) that we have identified the neuronal substrates related to the severity of irritability and aggressiveness in the disease; 4) that a global cognitive status screening instrument has been validated, which for the first time provides an operationally valid methodology for the detection of mild and severe forms of cognitive impairment in the disease, which has also meant increasing knowledge about the different profiles of

neuropsychological affectation that characterize the more and less aggressive forms of cognitive deterioration in the disease; and 5) that we have described for the first time the characteristic brain changes of the more and less severe forms of cognitive deterioration, which has allowed us to identify the role of cortical and subcortical changes in dementia associated with Huntington's disease.

Of course, many unresolved questions remain, and new questions arise from these findings. Our commitment to the future of Huntington's disease research is that these new questions and the work to solve them, are the most appropriate to contribute from our position of struggle, to a rapid and effective change in the tragic way in which today we know the progression of Huntington's disease.

1. INTRODUCCIÓN

1.1. Enfermedad de Huntington:

La enfermedad de Huntington (EH) es una enfermedad neurodegenerativa, genética, que sigue un patrón de herencia autosómica dominante y que clínicamente se caracteriza por el desarrollo progresivo de una constelación de síntomas motores, cognitivos y psiquiátricos(1-3). En palabras de George Huntington, en su ensayo "Sobre la Corea" publicado en 1872, esta enfermedad se caracteriza por ser minoritaria, hereditaria, de inicio en la edad adulta y por encontrarse en ella, frecuentemente, una tendencia a la demencia y el suicidio(4).

Históricamente, las manifestaciones motoras caracterizadas por movimientos 'coreiformes', se han considerado el síntoma característico de la enfermedad y es por ello, que durante mucho tiempo se la denominó "Corea de Huntington". Ahora sabemos que no todos los pacientes presentarán "corea" como síntoma central y que tanto las alteraciones cognitivas como psiquiátricas podrán ser el síntoma central e incluso preceder en muchos años el inicio de las primeras manifestaciones motoras de la enfermedad. Por todo ello, el término "Enfermedad de Huntington" resulta a todos los niveles más adecuado(1).

Con una prevalencia media estimada de entre 8 y 12 casos por cada 100.000 habitantes(5-7), la EH constituye una enfermedad minoritaria. A pesar de ello, existen determinadas zonas geográficas donde la prevalencia se muestra significativamente incrementada. Se han descrito amplios clústeres de pacientes afectados en determinados territorios latinoamericanos como los barrios San Luis o Barranquita en el estado de Zulia en Maracaibo (Venezuela) o la comunidad de Juan de Acosta en Barranquilla (Colombia)(8).

La edad media de diagnóstico de la EH se encuentra en la edad adulta, entre los 35-45 años. La enfermedad afecta por igual a varones y mujeres(1, 3). Un 6 % de los casos representan formas tempranas de inicio juvenil e infantil de la enfermedad y un 10 % de los casos son formas seniles o de

inicio tardío (agregar aquí edades límites en las que se han presentado casos). Mientras que las formas tardías se relacionan con fenotipos más benignos, las formas de inicio temprano son mucho más agresivas y asocian una esperanza de vida significativamente más corta que la estimada en la población adulta, además de presentar un fenotipo clínico característico. El tiempo medio de supervivencia tras el diagnóstico de la enfermedad es de entre 10 a 20 años. Las causas de fallecimiento más frecuentes son las complicaciones derivadas de sobreinfecciones en el contexto de neumonía tras bronco aspiración, la patología cardiovascular y el suicidio(9).

1.1.1. Genética de la enfermedad de Huntington:

La EH está causada por una única mutación en el gen *HTT* localizado en el brazo corto del cromosoma 4(1). Esta mutación fue identificada en 1993 gracias a los estudios realizados en la región de Maracaibo (Venezuela) en el mayor foco de personas afectadas por la enfermedad(10). El primer exón del gen *HTT* (inicialmente *IT15)* codifica para la proteína Huntingtina (HTT) y contiene un elemento de ADN consistente en tres nucleótidos (A = Adenina, C = Citosina y G = Guanina) que se repiten un determinado número de veces. En las personas que desarrollan la enfermedad, esta región codificante presenta un número igual o superior a 40 repeticiones CAG. En consecuencia, la mutación del gen *HTT* da lugar a una forma anormal o mutante de la proteína HTT (mHTT), promoviendo la ganancia de función tóxica y, posiblemente, cierta pérdida de función normal, que de manera gradual alteran el funcionamiento celular normal y promueven la muerte neuronal. Es característica la gran sensibilidad de las neuronas espinosas medianas y de las neuronas corticales a la toxicidad de la mHTT, por lo que tanto los ganglios basales como determinados territorios corticales se ven prominentemente afectados en los pacientes con EH.

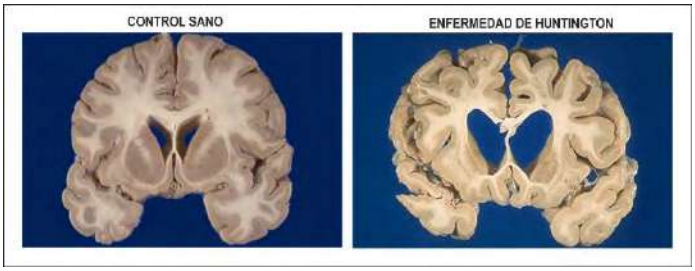

Figura 1: *Corte cerebral coronal donde destaca la prominente atrofia de ganglios basales, dilatación ventricular y atrofia cortical en la enfermedad de Huntington (fuente: imágenes cortesía del Dr. Edward C. Klatt. WebPath®)*

En personas sin antecedentes familiares de la EH, el número de repeticiones CAG en el gen *HTT* oscila en un rango de entre 7 y 24 repeticiones. Con 40 o más repeticiones CAG existe una penetrancia completa de la mutación. Cualquier persona portadora de dicho tamaño de expansión desarrollará inexorablemente la enfermedad en algún momento a de su vida. Las personas con un rango de repeticiones CAG entre las 36 y las 39 repeticiones presentan una penetrancia incompleta de la mutación y por ello es esperable que desarrollen la enfermedad a edad relativamente avanzada respecto a la media de presentación. Estas personas siguen un curso más benigno y conformando los casos que conocemos como corea senil(1, 11, 12). Las personas con un rango de repeticiones CAG entre las 27 y 35 repeticiones se consideran en el "rango intermedio". Estas personas no deberían desarrollar la enfermedad, si bien algunos estudios sugieren que en aquellos casos donde existe un mayor tamaño de expansión en el rango intermedio y una mayor edad, se encuentra incrementada la frecuencia de sintomatología motora y de deterioro cognitivo(13). A pesar de ello, hasta la fecha ningún estudio realizado en personas con alelos intermedios ha podido demostrar la existencia de cambios neuropatológicos compatibles con una EH.

Tanto en los casos de alelos intermedios, como de baja penetrancia y de penetrancia completa, existe una inestabilidad genética que favorece los conocidos como fenómenos de anticipación(14, 15). Ello es, la posibilidad de que los descendientes hereden una copia del gen defectuoso conteniendo un tamaño de la expansión significativamente mayor al de su predecesor. Como consecuencia de la inestabilidad meiótica del gen *HTT* durante la espermatogénesis, estos fenómenos de anticipación, suceden con mucha mayor frecuencia cuando la mutación se transmite por parte de un varón(16, 17). Los fenómenos de anticipación entre progenitores y descendientes explican la aparente existencia de

casos "*de Novo*" o sin antecedentes familiares. En estos casos, las explicaciones biológicas más plausibles son: a) La existencia de un predecesor portador de una mutación en rango intermedio o de baja penetrancia, que transmite a la descendencia una copia que contiene un número de repeticiones CAG significativamente mayor; b) el fallecimiento del predecesor antes del inicio de los síntomas; o c) la paternidad desconocida.

Tabla 1: *Clasificación del número de repeticiones CAG, nivel de afectación y riesgo en la descendencia*

Número repeticiones	**Clasificación**	**Enfermedad**	**Riesgo en la descendencia**
< 27	Normal	No afecto	Ninguno
27 – 35	Rango intermedio	No afecto	Posible; < 50 %
36 – 39	Penetrancia reducida	Puede estar afecto	50 %
> 39	Penetrancia completa	Afecto	50 %

La EH sigue un patrón de herencia autosómica dominante. Por ello, la descendencia de cualquier persona portadora de la mutación tendrá un riesgo del 50 % de haber heredado la copia defectuosa del gen, siendo la presencia de una única copia alterada suficiente para que la enfermedad se desarrolle en algún momento a lo largo de la vida(1).

Existe una relación inversa entre el tamaño de la expansión, la edad de inicio de la enfermedad y su severidad. De este modo, cuanto mayor sea en número de repeticiones CAG, antes debutará la enfermedad y más agresivo será el fenotipo(18, 19). Es por ello, que en las formas de inicio juvenil se encuentra habitualmente un número de repeticiones CAG mayor a 55. A pesar de la incuestionable relación entre el tamaño de la expansión y la edad de inicio de la EH, existe una muy notable variabilidad de hasta 20 años en la edad de inicio de la enfermedad entre personas que presentan un mismo número de repeticiones. Este fenómeno, se observa de manera más evidente en los rangos de repeticiones CAG que oscilan entre las 40 y 49 repeticiones, donde se demuestra que el tamaño de la mutación explica un 60 % de la variabilidad en la edad de inicio de la enfermedad, viéndose el 40 % restante modulado por mecanismos parcialmente conocidos hoy en día(20, 21).

Entre los posibles mecanismos relacionados con la variabilidad observada en la edad de inicio de la EH, destacan de manera significativa otros factores genéticos y factores ambientales. Entre los mecanismos genéticos, son importantes los hallazgos realizados mediante estudios de asociación genética (GWAS) que han confirmado la participación de determinados alelos en los cromosomas 15 y 8 que jugarían un importante papel en la anticipación y el retraso en la edad de inicio de la EH(20, 22). Entre los mecanismos ambientales, distintos estudios han relacionado la variabilidad en la edad de inicio de la enfermedad con los hábitos tóxicos, el nivel educativo y con el estilo de vida(23-25). En ausencia de tratamientos efectivos, el estudio de las variables capaces de modificar la edad de inicio de la enfermedad constituye una importante línea de investigación pensando en posibles intervenciones orientadas a retrasar el inicio, enlentecer o detener la progresión de la enfermedad.

1.1.2. Características clínicas:

Desde el punto de vista clínico, la EH se caracteriza por el desarrollo lentamente progresivo de una compleja constelación de síntomas motores, cognitivos y psiquiátricos(3, 26). Otros síntomas como los trastornos del sueño o la pérdida de peso y de masa muscular son también característicos(1, 3).

La progresiva exacerbación de los síntomas de la EH supone una pérdida gradual de la funcionalidad y del nivel de independencia de las personas afectadas. Esta pérdida de la funcionalidad, define los distintos estadiajes de la enfermedad acorde a la clasificación de Shoulson y Fahn(27). Así, en los estadios iniciales, los primeros síntomas coexisten con una ausencia o mínima pérdida de la funcionalidad y del nivel de independencia con respecto al nivel premórbido, mientras que las fases más evolucionadas se definen por la absoluta dependencia del paciente en todas las áreas de la vida.

Este nivel de funcionalidad, se evalúa y determina mediante un instrumento estandarizado conocido como escala de “capacidad funcional total” o *Total Functional Capacity* (TFC) que forma parte de la Escala Unificada de Evaluación de la Enfermedad de Huntington o *Unified Huntington’s*

Disease Rating Scale (UHDRS)(28). Este instrumento, evalúa la capacidad de desempeño de la actividad laboral, las operaciones financieras, las tareas domésticas y las actividades de la vida diaria, así como la necesidad de cuidados. Su puntuación va de 0 a 13 puntos, donde mayor puntuación es sinónimo de mejor capacidad funcional. De acuerdo con las puntuaciones obtenidas en la TFC, los estadios de Shoulson y Fahn clasifican a los pacientes acorde a cinco posibles estadios: Estadio I o inicial (TFC > 10), estadio II o inicial intermedio (TFC = 7 – 10), estadio III o intermedio (TFC = 3 – 6), estadio IV o intermedio-avanzado (TFC = 1 – 2) y estadio V o avanzado (TFC = 0).

La disponibilidad de un test predictivo permite determinar qué personas a riesgo son portadoras de la mutación que da lugar a la enfermedad y que aún no han desarrollado síntomas inequívocos de EH. Esta fase asintomática engloba el periodo comprendido entre el nacimiento y el diagnóstico clínico en personas portadoras de la mutación. En función de la proximidad al tiempo estimado de inicio de la enfermedad y del desarrollo de algunos signos o síntomas de tipo motor, cognitivo o conductual, la fase asintomática se puede dividir en una fase preclínica o perimanifiesta donde no se detectan ni signos ni síntomas de la enfermedad y una fase prodrómica donde pueden emerger algunos signos sutiles de afectación cognitiva y ciertos cambios conductuales. Esta etapa suele comprender el periodo que abarca los 15 y 10 años anteriores al tiempo estimado de inicio de la enfermedad. En las etapas más tardías de esta fase prodrómica, generalmente durante los 5 años anteriores al tiempo estimado de inicio de la enfermedad, algunos de estos signos cognitivos y conductuales sutiles podrán exacerbarse y podrían ser evidentes a la exploración algunos signos motores sutiles.

La posibilidad de clasificar y estudiar a los pacientes portadores de la mutación acorde al cálculo del tiempo estimado hasta el inicio de la enfermedad, deriva de los estudios realizados acerca de la relación entre el número de repeticiones CAG, la edad y los cambios neuropatológicos(29). A grandes rasgos, el número de repeticiones CAG no explica en sí mismo los cambios neuropatológicos de la enfermedad, sino que es la relación entre el número de repeticiones y la edad lo que determina el daño acumulado. Por ello, una persona con 47 repeticiones CAG y 20 años de edad, tendrá menos

cambios neuropatológicos que una persona con 41 repeticiones CAG y 60 años de edad. Por ello, el cálculo de la carga patológica de la enfermedad o *Disease Burden Score* (DBS) nos permite obtener un valor relativo al tiempo de exposición a la mHTT a lo largo de la vida y este valor, tiene una importante correlación con los cambios neuropatológicos. El DBS, se obtiene a través del cálculo de la relación entre edad y tamaño de la expansión mediante la fórmula [EDAD x (CAG – 33,6)]. El valor resultante puede ser empleado para calcular el tiempo estimado (en años) hasta el inicio de la enfermedad con una probabilidad mayor a 0,6 mediante la fórmula desarrollada por Langbehn(30).

Esta ecuación, nos permite clasificar a la población asintomática como personas "lejos", "cerca" o en la franja "intermedia" del tiempo estimado hasta el inicio de la enfermedad. A nivel general, las personas cuyo tiempo estimado es mayor a los 15 años se consideran que están lejos del inicio, las personas cuyo tiempo estimado es menor a 5 años se consideran que están cerca del inicio y entre ambos valores se sitúan las personas en la franja intermedia. Debe tenerse en cuenta que esta estimación que nos permite clasificar a la población en estudio acorde al tiempo estimado a inicio de la enfermedad adquiere su valor más importante a nivel de investigación pero que dicha estimación nunca debe ser empleada a nivel clínico para establecer el pronóstico de una persona asintomática portadora de la mutación.

1.1.2.1. Síntomas motores:

Los síntomas motores característicos de la EH engloban un complejo espectro de manifestaciones hipercinéticas e hipocinéticas(1, 3, 26). Entre los síntomas hipercinéticos destaca la progresiva instauración de movimientos involuntarios de tipo coreo-atetósico. Estos adquieren el aspecto de movimientos espasmódicos, irregulares, no suprimibles e impredecibles que pueden afectar cara, extremidades y tronco. Las posturas distónicas, tanto en reposo como durante la acción voluntaria y la marcha atáxica son igualmente frecuentes. La pérdida de la destreza y la coordinación, junto a las alteraciones oculomotoras y la impersistencia motora, son también elementos centrales del espectro de

trastornos del movimiento de la EH(31-33). El parkinsonismo suele ser menos evidente en las etapas iniciales y puede verse enmascarado por la corea. A pesar de ello, la rigidez, el enlentecimiento y la torpeza son también elementos característicos de la EH. La evaluación de la gravedad de los síntomas motores en la EH se realiza de manera estandarizada mediante los ítems motores de la UHDRS o UHDRS-TMS(28).

Una mayor puntuación de la UHDRS-TMS siempre indicará una mayor gravedad de los síntomas. Acorde a la exploración realizada, el evaluador deberá determinar el nivel de confianza diagnóstica o hasta qué punto está convencido de que los síntomas motores que ha registrado solo pueden ser explicables por una EH. Los distintos niveles de confianza diagnóstica o DCL podrán encontrarse en un rango de 0 a 5 como:

- 0 = Normal (sin alteraciones)
- 1 = Sin alteraciones motoras específicas (< 50 % de confianza)
- 2 = Alteraciones motoras que podrían ser signos de la EH (50 % – 89 % de confianza)
- 3 = Alteraciones motoras que son signos probables de EH (90 % - 98 % de confianza)
- 4 = Alteraciones motoras que son signos inequívocos de EH (>99 % de confianza)

1.1.2.2. Síntomas neuropsiquiátricos:

A lo largo de la EH, prácticamente todos los pacientes desarrollaran algún tipo de psicopatología de variable gravedad(34, 35). Los primeros cambios conductuales podrán detectarse durante las fases preclínicas y prodrómicas de la EH, en ausencia de síntomas motores, sugiriendo que, en la etiología de estos síntomas, participa el incipiente fracaso o disfunción de sistemas neuronales responsables del mantenimiento de la eutimia con el consiguiente desarrollo de las manifestaciones conductuales(36-38). Es por ello por lo que el estudio y seguimiento de la evolución de los síntomas neuropsiquiátricos en la EH ha constituido una temática central durante los últimos años atendiendo al

posible papel de las manifestaciones neuropsiquiátricas como biomarcador de progresión de la enfermedad.

A pesar de ello, es posible que no sea el proceso neuropatológico de la EH el único agente causal de las primeras manifestaciones conductuales detectables en la fase prodrómica. Así, el impacto por sí mismo de los importantes estresores vitales y personales que acompañan a las personas a riesgo o asintomáticas, parece jugar también un papel significativo en la exacerbación de determinados cambios conductuales durante la fase presintomática(37).

La **sintomatología afectiva** (depresión, ansiedad, ideación suicida), la apatía, el comportamiento perseverativo y la irritabilidad, representan los síntomas neuropsiquiátricos centrales que característicamente definen el fenotipo conductual de los pacientes con EH(35).

A lo largo de la enfermedad, la prevalencia de la sintomatología depresiva se sitúa entre el 9 % y el 65 % de los casos(34, 37, 39). Explorando separadamente la sintomatología depresiva en la población sintomática, aislada de otras manifestaciones como la ideación suicida o la ansiedad, un 30 % de los casos presenta formas leves de sintomatología depresiva y un 13 % formas severas. Combinando estos distintos factores relacionados con la sintomatología depresiva, un 32 % de los individuos asintomáticos lejos del inicio de la enfermedad y un 52 % de los individuos cerca del inicio de la enfermedad ya manifiestan sintomatología depresiva clínicamente relevante(35, 37, 39).

La **apatía** constituye el síntoma neuropsiquiátrico central en la EH(34, 37, 39). Hasta un 90 % de los pacientes desarrollará formas graves de alteración de la motivación a lo largo de la enfermedad(39, 40). A diferencia de otros síntomas, la apatía en la EH muestra un patrón de empeoramiento lineal a lo largo de la evolución de la enfermedad, siendo el síntoma que mejor correlaciona con la progresiva pérdida de la funcionalidad(41-43). En comparación a personas genéticamente negativas, el riesgo a manifestar síntomas de apatía clínicamente relevantes es 15 veces mayor en portadores asintomáticos lejos del tiempo estimado a inicio de la enfermedad y 88 veces mayor en aquellos cerca del tiempo estimado a inicio de la enfermedad(37). Conforme la enfermedad

progresa, la frecuencia, gravedad e impacto de la apatía sobre la funcionalidad y calidad de vida de los pacientes y cuidadores es cada vez mayor(39, 42). El autor de esta tesis, publicó en 2018 como primer firmante el primer trabajo realizado específicamente para estudiar los correlatos estructurales y metabólicos que en la EH se relacionan con la severidad de la apatía(43). En este estudio demostramos que la gravedad de la apatía en la EH correlaciona no solo con una mayor atrofia de estructuras de los ganglios basales - como son el núcleo caudado, el putamen o el estriado ventral-, sino que de forma muy significativa la apatía se relaciona con un mayor nivel de atrofia en el giro temporal, hipocampo, amígdala, córtex cingulado anterior y áreas parieto-occipitales, además de observarse una significativa disminución del metabolismo de glucosa en extensos territorios fronto-mediales, temporales y parietales. Estos hallazgos, refuerzan la idea de que algunas de las manifestaciones clínicas de la EH en fases iniciales no dependen exclusivamente de la desintegración y disfunción de los ganglios basales y sus respectivos circuitos fronto-subcorticales, sino que la afectación cortical, temporo-parieto-occipital y del sistema límbico, también contribuye, de manera muy significativa, a la etiología y exacerbación de determinados síntomas.

El **comportamiento y pensamiento perseverativo** representa un síntoma igualmente característico de la EH. La perseveración se confunde en muchas ocasiones con la sintomatología obsesivo-compulsiva(34, 35, 39). La mayoría de trabajos publicados sobre el tema, adolecen de una falta de distinción entre ambas entidades, de modo que resulta difícil determinar, sobre la base de los datos reportados, la prevalencia real de los fenómenos perseverativos de manera independiente a la sintomatología obsesivo-compulsiva(44). Considerada de manera conjunta, esta sintomatología afecta a cerca del 50 % de los casos si bien la observación clínica sugiere una prevalencia significativamente mayor(35, 39).

La **irritabilidad y la agresividad**, de manera conjunta, son síntomas igualmente incrementados en la EH que muestran una prevalencia que varía en torno al 38 % y el 73 % de los casos(45-48). En la EH, la irritabilidad y los episodios de agresividad se caracterizan por no ser

premeditados y responder a la pérdida de control de inhibición sobre los impulsos, adquiriendo fenomenológicamente distintos aspectos que pueden ir desde la agresividad verbal, a la agresión física o los actos criminales.

La **sintomatología psicótica**, en forma de ideación delirante y en menor frecuencia de alucinaciones visuales y auditivas, no representa un síntoma característico de la EH. Sin embargo, su prevalencia en torno al 3 % - 13 % de los casos sitúa este complejo delirante-alucinatorio por encima de la prevalencia estimada en la población general(37, 39). A pesar de no ser un síntoma patognomónico de la EH, cabe destacar la existencia de fenotipos de la enfermedad tipo "esquizofrenia-like" donde el primer síntoma en manifestarse y en predominar es la psicosis(49). En estas formas de esquizofrenia-like, suele encontrarse un claro componente de agregación familiar existiendo múltiples miembros de una misma familia afectados por el mismo patrón de EH manifiesta en forma de trastorno psicótico.

A pesar de ser un síntoma atribuible o relacionado con la sintomatología depresiva, la **ideación suicida** merece un apartado específico dentro de la descripción de la fenomenología de las manifestaciones conductuales de la EH(50). La ideación suicida es un síntoma frecuente en la EH que estará presente en un 25 % de los pacientes, especialmente en aquellos con sintomatología de ansiedad. La tentativa suicida ocurrirá en uno de cada 10 pacientes(51, 52). Ello sitúa la prevalencia del suicidio en la EH entre 8 y 12 veces por encima de la prevalencia estimada para la población general.

1.1.2.3. Síntomas cognitivos:

La progresiva disfunción y degeneración cerebral que se desarrolla en el curso neuropatológico de la EH, se acompaña de toda una serie de manifestaciones cognitivas que pueden evidenciarse desde etapas tempranas(1, 3). Algunos signos cognitivos serán claramente identificables más de 15 años antes de la presentación de los primeros síntomas motores(36, 53). La progresión del deterioro cognitivo seguirá un curso inexorable, siendo la demencia una consecuencia inevitable en todos

aquellos pacientes cuya supervivencia se extienda a lo largo de los estadios intermedios y avanzados de la enfermedad(3).

Dada la importante afectación de los ganglios basales y la consecuente disfunción de los distintos circuitos fronto-subcorticales, los signos de alteración neuropsicológica característicos de la EH son de prominente naturaleza frontal-disejecutiva(54). Es por ello por lo que el perfil neurocognitivo prototípico del paciente con EH contempla la destacada afectación de la velocidad de procesamiento y las funciones ejecutivas(55-57). En este sentido, se verá una progresiva afectación de la planificación, la flexibilidad cognitiva, la memoria de trabajo, el mantenimiento atencional, el acceso al léxico, la recuperación de información aprendida y la codificación en memoria episódica. Otros dominios cognitivos que se encuentran alterados en la EH se relacionan con la también importante afectación cortical, la cual puede ya detectarse durante la fase prodrómica y que implica extensos territorios corticales-posteriores a nivel de corteza parieto-temporal y occipital(53, 58-63). Estas alteraciones, incluyen defectos en las funciones visuoperceptivas y visuoespaciales, en la rotación mental de objetos, en el reconocimiento de las expresiones faciales de emociones, en la afectación del lenguaje a nivel de pragmática y gramática, en la memoria espacial y en la memoria autobiográfica(64-74). No menos importantes son las disfunciones relativas a la cognición social, la que puede llegar a alterar de manera muy significativa la capacidad de los pacientes para entender la conducta de los demás y adecuar su propia conducta a las circunstancias sociales(75).

Durante la fase prodrómica es frecuente que se reporten quejas subjetivas de cambios cognitivos sin que ello asocie un claro impacto sobre la funcionalidad(76). En esta fase, no se puede detectar un patrón evidente y homogéneo de alteración con respecto a la población de referencia, si bien es cierto, que el empeoramiento progresivo en determinadas tareas o el rendimiento diferente con respecto a controles sanos, se hace evidente. Estas diferencias y cambios son frecuentemente visibles en tareas dirigidas a la evaluación de la velocidad de procesamiento, como el test de sustitución de dígitos y símbolos o *Symbol Digit Modalities Test* (SDMT), la velocidad de lectura de palabras o

denominación de colores en el test de Stroop, la tasa de acierto en el reconocimiento de expresiones faciales de emociones o el rendimiento en tareas de integración visuomotora(53, 57, 64, 77). La frecuente coexistencia en la fase prodrómica de sintomatología conductual de tipo ansioso-depresiva o motivacional, juega un incuestionable papel sobre algunas de las manifestaciones cognitivas. Es por ello necesario contemplar que algunas de las disfunciones cognitivas de tipo atencional-ejecutivo que pueden observarse en población asintomática son en muchas ocasiones parte constituyente del síndrome o del complejo sindrómico psiquiátrico que las acompaña.

En el momento del diagnóstico clínico de la EH, la presencia de cierto grado de alteración en tareas específicas típicamente relacionadas con la velocidad de procesamiento o la función ejecutiva es un hallazgo habitual en la práctica totalidad de los pacientes. Conforme la enfermedad progresa, el síndrome disejecutivo se hace cada mes más evidente y a su vez emergen alteraciones en otros dominios cognitivos. Estas nuevas alteraciones en otros dominios pueden atribuirse en parte al fracaso progresivo de las propias funciones ejecutivas pero también a la superposición de alteraciones corticales(78). En los estadios intermedios y más evolucionados de la EH el impacto causado por el deterioro cognitivo sobre el nivel de autonomía de los pacientes llega a ser muy alto hasta el punto de cumplir, en la mayoría de los casos, criterios diagnósticos generales para demencia asociada a una EH(2, 3).

Como hemos mencionado antes, las manifestaciones típicamente corticales en forma de afasia progresiva, apraxia o agnosia no se consideran un hallazgo frecuente en la EH ni elementos definitorios del perfil neurocognitivo característico de esta enfermedad. Es por ello, que el síndrome demencial y el perfil de deterioro cognitivo en la EH ha sido históricamente considerado prototípicamente subcortical. A pesar de ello, tanto los estudios de neuroimagen como de rendimiento neuropsicológico, sugieren que los signos de afectación cortical han sido históricamente poco explorados en la EH y posiblemente infravalorados.

1.1.2.4. Enfermedad de Huntington de inicio juvenil:

Las formas de inicio juvenil o en edad infantil constituyen formas muy minoritarias de EH que se observan en un 5.4 % de los casos y que se relacionan con la presencia de un número de repeticiones CAG generalmente por encima de 55(79). Por definición consensuada, se consideran casos de EH de inicio juvenil (EHJ) aquellos donde el diagnóstico se realiza antes de los 21 años edad, a pesar de que recientemente el grupo de trabajo en EHJ de la Red Europea de Enfermedad de Huntington ha sugerido que la edad máxima de diagnóstico debería establecerse en los 18 años.

Desde el punto de vista clínico, la EHJ manifiesta un fenotipo distinto al que habitualmente caracteriza la EH en el adulto(26). En la EHJ predomina de manera temprana un marcado deterioro cognitivo y conductual rápidamente progresivo, que emerge en forma de una pérdida sobre las habilidades previamente adquiridas o un retraso en el desarrollo normal. A nivel motor, predomina de manera característica un muy importante síndrome rígido-acinético en ausencia de corea, un trastorno de la marcha y alteraciones orofaciales. Las mioclonías y las crisis convulsivas son frecuentes y la esperanza de vida es significativamente más corta que en la EH del adulto(80, 81).

1.2. Neuropatología de la enfermedad de Huntington:

1.2.1. Mecanismos neuropatológicos primarios:

La proteína HTT se expresa de forma ubicua en todas las células del organismo siendo sus concentraciones más elevadas en los testículos y en las neuronas del estriado, hipocampo y corteza cerebral(82, 83). La HTT es una proteína grande con una masa de 347 kilo-Daltons hecha de 3144 aminoácidos. En la región próxima al inicio de la cadena de aminoácidos, la proteína contiene una región donde se repiten entre 11 y 34 residuos de glutamina que son codificados por una región de repeticiones CAG del ADN(84). Las expansiones en el número de glutaminas en esta región de la proteína, denominada la región de poliglutaminas, son la causa de la EH. A pesar de que el hallazgo

de esta región expandida ha sido crucial para el estudio de la EH, actualmente sigue siendo poco comprendida la función de la proteína.

Los estudios que han comparado la secuencia de HTT humana con la de otros organismos han revelado que la HTT es una proteína antigua desde el punto de vista evolutivo. El gen que codifica para la HTT está ampliamente conservado entre los vertebrados, de modo que una secuencia muy similar se encuentra en distintos animales incluyendo ratones, cerdos o peces(85). Paralelamente, algunas similitudes pueden encontrarse también entre especies filogenéticamente distantes como la mosca de la fruta, a pesar de que en estas especies existen importantes diferencias con respecto al humano en cuanto a la secuencia y función de la proteína. Por ejemplo, en la mosca de la fruta, el gen que codifica para HTT no contiene la secuencia de repeticiones CAG. Ello sugiere que cuando los humanos y moscas de la fruta tomaron rutas distintas a lo largo de la evolución, la función de su proteína HTT también evolucionó de distinta manera. Antecediendo aún más en el curso evolutivo, la ameba *Dictyostelium discoideum* tiene un gen similar al que codifica para HTT, sugiriendo que el gen HTT viene evolucionando desde tiempo inmemorial(85, 86).

El papel que desempeña la HTT en su estado normal o salvaje resulta, hoy por hoy, muy poco conocido(86, 87). A pesar de ello, sabemos que desempeña un papel fundamental en una serie de procesos que incluyen el transporte intracelular a través de las vesículas, la regulación transcripcional que permite iniciar o parar las señales que promueven la expresión de determinados genes, la inhibición de la apoptosis y el neurodesarrollo embrionario. El importante papel de la HTT en el neurodesarrollo queda patente en los estudios de modelos de ratón knock-out, cuya viabilidad no supera los 7 días posteriores a la fertilización y los modelos con silenciamiento parcial de la HTT total que demuestran que los animales con niveles iguales o inferiores al 50 % de HTT total sobreviven más de 8 días postfertilización pero con muy importantes defectos en el neurodesarrollo y que llegan a sobrevivir a la edad adulta con importantes manifestaciones conductuales. Paralelamente, resulta interesante que introducir una copia sana del gen en animales knock-out que previamente expresaron el gen defectuoso

con hasta 128 repeticiones CAG, consigue hacer sobrevivir a los animales. Ello sugiere, que la HTT tiene un papel distinto durante la fase embrionaria que durante la vida adulta, algo que también apoya la certeza de que las personas homocigotos para el gen defectuoso no tienen alteraciones evidentes en el momento del nacimiento(84, 87).

Desde el punto de vista de los mecanismos de la mHTT que desencadenan la EH se sugiere la ganancia de función tóxica como mecanismo principal, sin dejar de contemplar la posibilidad de que exista un componente de pérdida de alguna función normal de la HTT en el neurodesarrollo. Incuestionablemente, la presencia de mHTT en el cuerpo humano desencadena una cascada de procesos que a nivel cerebral promueven la muerte masiva del 95 % de las neuronas GABAérgicas espinosas medianas además de precipitar un patrón de atrofia focal cortical, de sustancia blanca subcortical, tálamo, de determinadas regiones del hipotálamo y de otras regiones cerebrales(88, 89). En los casos más evolucionados y especialmente en la EH juvenil, existe un patrón global de atrofia cerebral(81, 89). Presumiblemente, el defecto de conformación que adquiere la mHTT desencadena una amplia cascada patogénica (ver figura 2) que aboca a la muerte neuronal(86).

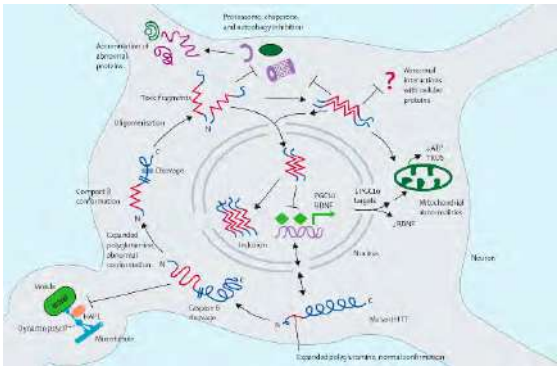

Figura 2: *HTT mutante (en azul) con una expansión anormal de poliglutaminas (en rojo) sufre un cambio conformacional e interfiere con el tráfico celular, especialmente de BDNF. La mHTT se adhiere a múltiples localizaciones generando fragmentos tóxicos con una conformación β compacta anormal. Las formas patogénicas pueden ser monoméricas o mayoritariamente pequeños oligómeros. Los efectos tóxicos en el citoplasma incluyen inhibición de chaperonas, proteasomas y autofagia, que causan una acumulación de proteínas anormalmente plegadas y de otros constituyentes celulares. Podría haber interacciones directas entre mHTT y la mitocondria. Otras formas de interacción entre mHTT y proteínas celulares en el citoplasma son poco conocidas. Las inclusiones patognomónicas se encuentran en el núcleo (inclusiones pequeñas también se encuentran en regiones citoplasmáticas). Las inclusiones no son la especie patogénica primaria. Uno de los principales mecanismos de mHTT es la interferencia con la transcripción genética, en parte vía PGC1α, desencadenando una disminución en la transcripción de BDNF y de proteínas mitocondriales codificadas en el núcleo. Fuente: Figura adaptada de Ross CA et al. Lancet Neurol. 2011 Jan;10(1):83-98.*

El marcador neuropatológico principal de la EH es la presencia de inclusiones intranucleares de mHTT con neurodegeneración estriatal en los ganglios basales(89). La atrofia de los ganglios basales es identificable más de 15 años antes del diagnóstico clínico de la enfermedad y su disfunción se asocia de manera primaria como mecanismo etiopatogénico del complejo sintomático exhibido por

los pacientes con EH(89, 90). La progresiva atrofia de los ganglios basales sigue una determinada trayectoria topográfica de pérdida neuronal y gliosis reactiva(91). En lo estudios anatomo-patológicos, la porción posterior del caudado muestra un mayor compromiso que el cuerpo del caudado, que a su vez está más comprometido que la cabeza de este núcleo. De manera similar, la región caudal del putamen aparece más degenerada que la región rostral. A lo largo el eje dorsoventral del estriado, las regiones dorsales y rostrales del estriado se muestran más comprometidas que la región ventral. Finalmente, a lo largo del eje laterolateral, la mitad paraventricular del núcleo caudado se muestra más comprometida que la mitad paracapsular. A lo largo de la secuencia temporal, la degeneración estriatal muestra un patrón de degeneración simultáneo en las direcciones rostrocaudal, dorsoventral y mediolateral. A nivel general, el grado de degeneración estriatal, correlaciona con el nivel de atrofia en otras regiones cerebrales incluyendo el globo pálido, el tálamo, el núcleo subtalámico, la sustancia nigra y la corteza cerebral(92, 93).

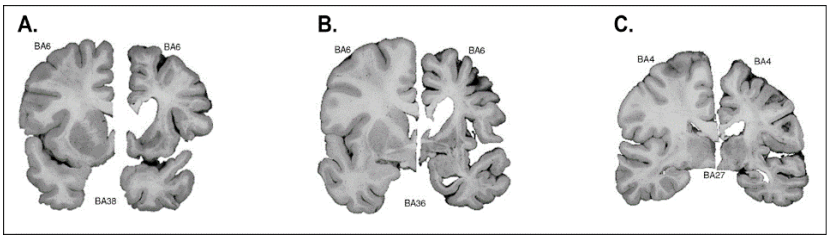

Figura 3: *Sección coronal a través de: A) núcleo accumbens mostrando severa atrofia de la porción anterior del estriado; B) comisura anterior mostrando severa atrofia del estriado; C) cuerpo geniculado lateral mostrando completa desintegración de la cola y cuerpo del caudado pero relativa preservación del tálamo. Fuente: Figura adaptada de Vonsattel JP. Handb Clin Neurol. 2008;89:599-618.*

A nivel microscópico, la presencia de inclusiones nucleares de mHTT en neuronas y células gliales, se pueden detectar décadas antes del inicio de los síntomas motores en los cerebros de personas totalmente asintomáticas. En los cerebros de las personas afectadas estas inclusiones pueden detectarse en un 7 % de las neuronas corticales y un 4 % de las neuronas estriatales(93).

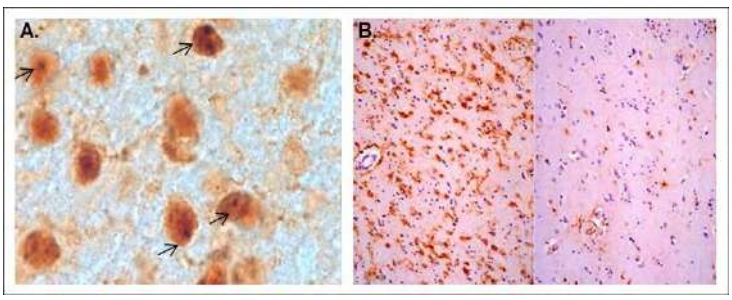

Figura 5: *4) Inclusiones de mHTT en cerebro de ratón. B) Gliosis en caudado (izquierdo en EH, derecho en control sano).*

Atendiendo al patrón general que sigue el curso del proceso neuropatológico que define la EH, muchos de los atributos clínicos que la caracterizan resultan totalmente compatibles con un modelo de progresiva disfunción generalizada de los ganglios basales y de los correspondientes circuitos cortico-ganglios basales-tálamo-corticales. Es por ello, que a todos los niveles (motor, cognitivo y conductual) la EH ha sido considerada como paradigma de una enfermedad motora y de una demencia subcortical.

El grado de atrofia cortical en las etapas intermedias e intermedias avanzadas de la EH es relativamente heterogéneo. En los estudios anatomopatológicos, incluso cuando el nivel de atrofia es prominente, resulta particularmente difícil apreciar y cuantificar la perdida neuronal cortical en los estudios menos exhaustivos de los cortes cerebrales(89). Los estudios realizados al respecto, muestran hallazgos variables y en algunos casos contradictorios. A nivel general, a simple vista destaca la prominente atrofia del ribete cortical siendo la zona más severamente afectada la región occipital(94). En las etapas intermedias y avanzadas se detecta una progresiva pérdida neuronal en las capas III, IV y V sin aparente astrogliosis destacable, pero con un incremento de la densidad oligodendrocítica(95). En las áreas de Brodmann, destaca una disminución cortical progresiva que oscila entre el 28 % y el 80 % en las áreas BA9, BA46, BA17 y BA10(96, 97). La pérdida neuronal también se considera destacable en la corteza entorrinal y el subículo.

El tálamo se encuentra generalmente preservado al examen visual, detectándose cierto componente de astrogliosis y pérdida neuronal en los estadios más evolucionados(93). La pérdida neuronal en la sustancia nigra pars reticulata es muy evidente, mientras que la pars compacta se encuentra aparentemente preservada(98). En las etapas intermedias de la enfermedad se observa una marcada pérdida neuronal en el núcleo subtalámico(89).

1.2.2. Mecanismos neuropatológicos secundarios: Proteína TAU en la enfermedad de Huntington:

La proteína TAU es una proteína microtubular codificada por el gen *MAPT* que se encuentra en los cuerpos neuronales del sistema nervioso donde se asume que ejerce funciones relativas a la regulación de la dinámica de los microtúbulos, al desarrollo de las neuritas, el transporte axonal y la plasticidad sináptica(99). Las funciones de unión a microtúbulos y de estabilización que ejerce la proteína TAU se regulan mediante fosforilación, que a su vez esta mediada por distintas quinasas y fosfotasas. El ayuste de TAU parece jugar también un papel en la regulación de la función de la proteína. Distintas formas de ayuste del exón 10 de la región pre-ARN de *MAPT* dan lugar a dos isoformas distintas de la proteína que expresan respectivamente tres o cuatro puntos de unión (TAU-3R y TAU-4R). La forma TAU-4R presenta una mayor afinidad a los microtúbulos y es por ello más eficiente promoviendo el enlace entre microtúbulos(99).

Las taupatías forman parte de un grupo heterogéneo de enfermedades caracterizadas por la presencia de agregados de formas anormales de proteína TAU como marcador neuropatológico principal. La proteína TAU se considera anormal cuando sufre modificaciones post-traslacionales como hiperfosforilación, truncamiento u oligomerización(99, 100). Las taupatías se dividen en primarias, donde la proteína TAU tiene un papel central en la enfermedad (ej.: Paralisis Supranuclear Progresiva, degeneración lobar fronto-temporal, síndromes cortico-basales, etc.) y secundarias, donde la proteína TAU acompaña agregados de otras proteínas (ej.: enfermedad de Parkinson, enfermedad de Alzheimer, encefalopatía traumática crónica, etc.)(101, 102).

La razón a través de la cual determinadas formas anormales de TAU resultan tóxicas y por qué estas formas aparecen en una gran cantidad de enfermedades con componente neurodegenerativo no es algo completamente comprendido(100). No obstante, se considera que no puede ser un mero epifenómeno de la neurodegeneración ya que la presencia de la proteína correlaciona tanto con la severidad de la demencia en la enfermedad de Alzheimer, como con la pérdida de memoria en el envejecimiento normal y en el deterioro cognitivo leve(103-108). Además, los haplotipos de TAU

añaden susceptibilidad a determinadas enfermedades como la enfermedad de Alzheimer, la enfermedad de Parkinson, la Parálisis Supranuclear Progresiva o el síndrome de Down(109, 110).

Si bien la EH no ha sido referida como una taupatía, ya en 1978 se describió en un paciente sintomático de 54 años de edad, la presencia de numerosos ovillos neurofibrilares, los cuales no son otra cosa que formas hiperfosforiladas de proteína TAU unidas en forma de filamentos helicoidales(111). Posteriormente, en varias series de casos, se confirmó la presencia de patología TAU en estadios de Braak I-III en el 60 % de los pacientes con EH(112). Mas recientemente, un estudio retrospectivo sugirió que en el 80 % de los pacientes con EH de mayor edad y con demencia existía una importante presencia de ovillos neurofibrilares compatible con estadios de Braak V-VI(113). Estudios aún más recientes, demostraron niveles elevados de proteína TAU en el LCR de los pacientes con EH, siendo estos niveles similares a los reportados en la enfermedad de Alzheimer(114). Finalmente, los trabajos más recientes han demostrado la presencia de taupatía no solo en los pacientes con EH, sino también en los modelos animales de la enfermedad(115, 116). Estos trabajos han puesto de manifiesto que las alteraciones patológicas relacionadas con la EH pueden acompañarse de anomalías en la expresión de TAU y de modificaciones post-traslacionales(117).

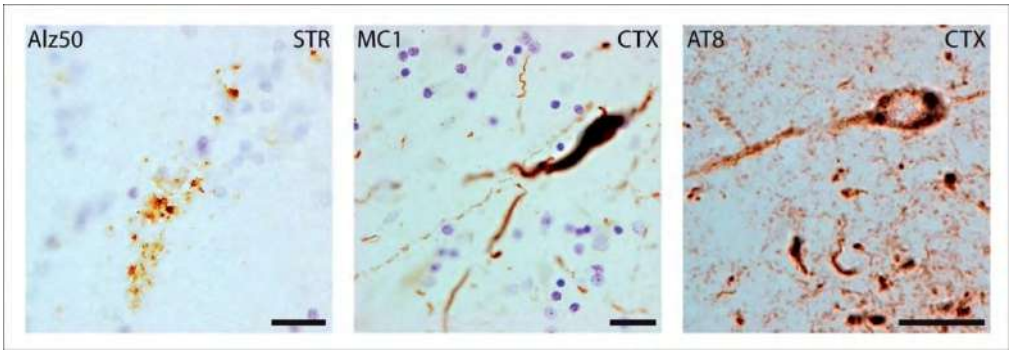

Figura 5: *Distintas formas de TAU fosforilada en la corteza y estriado de dos pacientes con EH. Fuente: Gratuze M et al. Brain. 2016 Apr;139(Pt 4):1014-25.*

Se han descrito diversos mecanismos que parecen contribuir al ayuste y fosforilación de TAU en la EH, destacando la participación de mecanismos alterados de manera inherente a la EH, así como de mecanismos directamente mediados por la función de mHTT. La proteína mHTT interactúa con TAU y con los microtúbulos, secuestra los factores de ayuste de TAU y promueve la hiperfosforilación de TAU a través de la desregulación de la calcineurina(116-118).

Desde el punto de vista clínico, cobra especial relevancia el papel que parece tener TAU en la variabilidad fenotípica de la enfermedad y especialmente en la gravedad del deterioro cognitivo. De manera similar a lo observado en otras enfermedades, la patología TAU parece desempeñar un papel crítico en la forma en que progresa la disfunción cognitiva en la EH, existiendo además una relación entre la velocidad de progresión del deterioro cognitivo y el haplotipo H2 de *MAPT*. Mas allá de esta relación observada entre TAU y cognición en la EH, los modelos animales también apoyan la contribución de TAU a la sintomatología motora(118).

Con todo ello, resulta biológica y conceptualmente plausible incorporar la EH dentro del grupo de las taupatías secundarias. Estas evidencias hacen necesario tanto explorar el tipo de influencias que la patología TAU puede ejercer en la variabilidad clínica de la EH, como contemplar el diseño de terapias no dirigidas únicamente a mHTT(119).

1.2.3. Ganglios basales, movimiento, cognición y conducta en la enfermedad de Huntington:

Los ganglios basales están formados por un conjunto de núcleos situados en la base del cerebro copiosamente interconectados con la corteza cerebral, el tálamo y el tronco del encéfalo. Este conjunto de núcleos participa en numerosas funciones incluyendo el control voluntario del movimiento, el aprendizaje procedimental, la formación de hábitos, la cognición, la emoción y la motivación(120).

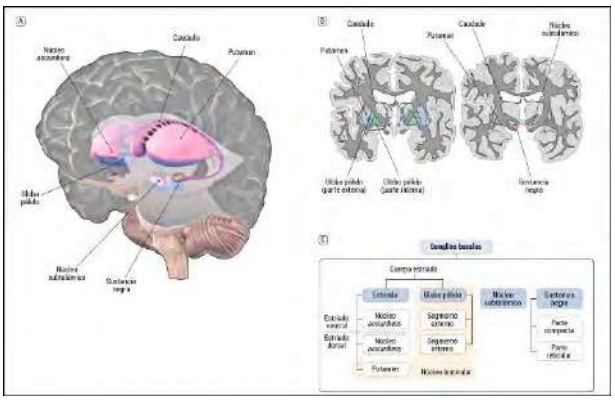

Figura 6: *A) Ganglios basales; B) Visión de los ganglios basales en sección coronal; C) Subdivisiones de los núcleos que componen los ganglios basales. Fuente: Figura adaptada de Redolar D. 2018. ISBN: 9788498354683.*

Bajo el término ‘ganglios basales’ se entiende por tanto un conjunto de estructuras que muestran una compleja organización interna a nivel anatómico y químico y que se dividen en el

estriado (núcle caudado y putamen), pálido (interno y externo), sustancia negra (pars reticulata y pars compacta), y el núcleo subtalámico

Si bien tanto el estriado como el núcleo subtalámico constituyen las principales vías de entrada a los ganglios basales, el estriado recibe inputs de múltiples áreas corticales y subcorticales incluyendo la sustancia nigra pars compacta mientras que el núcleo subtalámico solo recibe aferencias corticales.

Por su lado, el globo pálido interno y la sustancia nigra pars reticulata representan las principales estaciones de salida. Cada uno de los núcleos de salida tiene territorios motores, asociativos y límbicos topológicamente organizados. Esto significa, que a través de un sistema de circuitos o *loops* cortico-ganglios basales-tálamo-corticales, distintos territorios de los ganglios basales, reciben y proyectan a distintos territorios corticales. Estas conexiones conforman a globalmente al menos tres circuitos bien diferenciados, motor, asociativo y límbico, funcionalmente coordinados a través de un sistema inhibitorio y excitatorio constituido por las vías directa e indirecta.

Los distintos *loops* cortico-ganglios basales-tálamo-corticales han sido segregados acorde a su organización estructural y a sus funciones relativas a las dianas corticales con las que están relacionados(121). Como se ha mencionado, el modelo de circuitos segregados contempla tres grandes circuitos (motor, asociativo y límbico), pudiendo estos ser subdivididos en cinco circuitos:

- **El circuito o *loop* motor** está formado por proyecciones de las áreas corticales motora suplementaria, premotora, motora y somatosensorial hacia el putamen; Este a su vez proyecta al segmento ventrolateral del globo pálido interno y a la zona caudolateral de la sustancia nigra pars reticulata, cerrándose el circuito de reentrada en las dianas corticales correspondientes con el retorno de proyecciones desde el núcleo ventral lateral y ventral anterior del tálamo(122).
- **El circuito oculomotor** se origina en el campo ocular frontal que proyecta a la cabeza del caudado y retornando a través del complejo caudal dorsomedial del globo pálido

interno/sustancia nigra pars reticulata, proyectando de nuevo a la corteza a través de la región ventral anterior y dorsal medial del tálamo.

- **El circuito asociativo dorso-lateral prefrontal** se origina en la corteza prefrontal dorso-lateral y parietal posterior, proyectando a la región dorsolateral de la cabeza del caudado que a su vez proyecta a la región dorsomedial lateral del globo pálido interno/rostrolateral de la sustancia nigra pars reticulata y vuelve a la corteza a través de la región ventral anterior y dorsal medial del tálamo(123).
- **El circuito lateral orbito-frontal** que proyecta a la región ventromedial de la cabeza del caudado, la cual a su vez proyecta a la región dorsal medial del globo pálido interno/rostromedial de la sustancia nigra pars reticulata retornando a la corteza a través de la porción ventromedial del tálamo.
- **El circuito cingulado anterior** que se origina en la corteza cingulada anterior proyectando al estriado ventral a través de la región rostrolateral del globo pálido interno/rostrodorsal y de la sustancia nigra pars reticulata y retornando a la diana cortical a través de la región ventromedial y dorsomedial del tálamo(124).

Los circuitos motor, asociativo y límbico del complejo cortico-ganglio basal-tálamo-cortical, conforman los circuitos fronto-subcorticales, cuyo funcionamiento normal es indispensable para el adecuado despliegue de toda una serie de procesos, cognitivos, de regulación emocional y motivacional, que forman parte indisociable del funcionamiento adaptativo del ser humano(125). Las áreas corticales que componen cada uno de estos circuitos, han sido extensamente estudiadas desde el punto de vista de su relación con la cognición y la conducta. El funcionamiento normal de estas áreas y en consecuencia de los procesos que dependen de ellas, depende a su vez críticamente del funcionamiento conjunto de todo el complejo fronto-subcortical. Por ello, la disfunción o lesión de cualquiera de las estructuras subcorticales que conforman la circuitería fronto-subcortical, resulta semejante a la disfunción o lesión aislada de la corteza correspondiente, y puede, sin lesionar

directamente a la corteza desencadenar o asociar dificultades o alteraciones compatibles con la disfunción de las propias dianas corticales con las que establecen sus conexiones. En este sentido, las lesiones circunscritas a nivel de estructuras subcorticales que conforman la vía asociativa, como la región dorsal del caudado, dan lugar a síndromes cognitivos llamativamente análogos a los que se encuentran en pacientes con afectación directa de la corteza prefrontal dorso-lateral. Esto es, producirán dificultades en las funciones ejecutivas tales como la flexibilidad, la planificación, el razonamiento abstracto, el control atencional o la memoria de trabajo y alteraciones conductuales, tales como el comportamiento perseverativo o disejecutivo. De igual modo, las lesiones a nivel de región ventromedial del caudado con la consecuente disrupción del circuito lateral-orbital, desencadena sintomatología cognitiva típicamente referida a la corteza orbitofrontal en forma de dificultades la toma de decisiones, así como manifestaciones conductuales tales como desregulación emocional, irritabilidad, impulsividad o desinhibición. Finalmente, las lesiones en el estriado ventral, asocian dificultades cognitivas en el aprendizaje basado en reforzadores, en el aprendizaje reverso y en la monitorización de la acción, y manifestaciones conductuales como la apatía e inercia cognitiva, el aplanamiento emocional o el déficit de autoactivación(120, 125).

Atendiendo a este modelo de organización funcional de los distintos sistemas que conforman la arquitectura de los ganglios basales, resulta previsible asumir que en una enfermedad donde desde etapas tempranas existe una marcada y progresiva degeneración de los ganglios basales, se producirán un conjunto de síntomas motores, cognitivos y conductuales atribuibles a la inexorable desintegración de estos sistemas.

1.2.4. Neuroimagen estructural y funcional en la enfermedad de Huntington:

En la mayoría de los casos asintomáticos que se encuentran relativamente cerca del tiempo estimado a inicio de la enfermedad, la inspección visual de imágenes de resonancia magnética en

secuencias T1 evidencia una disminución del volumen del núcleo caudado y una expansión de los espacios ocupados por líquido cefalorraquídeo, que se hace aún más evidente en los pacientes iniciales(53).

Figura 7: *Corte sagital de RMN en un control de 50 años de edad, un individuo asintomático de 55 años de edad y un paciente sintomático inicial de 49 años de edad. Fuente: Tabrizi et al. Lancet Neurol. 2009 Sep;8(9):791-801.*

En los casos asintomáticos cerca del tiempo estimado de inicio de la enfermedad, los estudios de metabolismo mediante tomografía de emisión de positrones (PET) de ^{18}F- Fluorodesoxiglucosa (^{18}F-FDG) pueden poner de manifiesto cierta disminución de captación del trazador en los núcleos caudado y lenticular, que resulta muy manifiesta en los casos sintomáticos, en los que destaca en ocasiones un patrón de hipometabolismo frontal e hipermetabolismo occipital(58, 126).

Durante los últimos años varios estudios transversales y longitudinales con extensas cohortes de pacientes, han ayudado a delinear la topografía y la dinámica de los cambios estructurales y moleculares que acontecen a lo largo del curso natural de la EH. Además, el estudio de correlaciones entre estructura y metabolismo cerebral y determinadas variables clínicas, ha contribuido notablemente a comprender las bases neurales de las manifestaciones clínicas de la enfermedad. Los estudios de grosor cortical han puesto de manifiesto que, desde las etapas asintomáticas y a lo largo de los primeros estadios sintomáticos de la enfermedad, existe una notable y progresiva disminución del grosor cortical, que afecta preferentemente y de manera temprana a extensos territorios corticales-posteriores(53, 59-61). Esto incluye un patrón de atrofia cortical, detectable años antes del inicio de los síntomas, en regiones de la corteza occipital, parietal, temporal superior y frontal superior. Esta

pérdida de grosor cortical muestra un patrón progresivo a lo largo de la enfermedad, extendiéndose ampliamente por otras zonas de la corteza, pero preservando relativamente las áreas frontales anteriores y temporales laterales. Centrándonos en la población asintomática, no existen cambios corticales detectables que se remonten a más de 15 años anteriores al inicio de los síntomas(53, 61). Entre los 15 y 9 años antes del tiempo estimado de inicio de la enfermedad y hasta el momento del diagnóstico, destaca un patrón progresivo de atrofia cortical que se inicia en la corteza lateral y medial occipital y parietal, el giro temporal superior y la pars triangularis. La atrofia se extiende a lo largo de toda la corteza, siendo las zonas más significativamente afectadas la corteza occipital y el giro temporal superior, y las menos afectadas las áreas ventrales y mediales frontales y la corteza temporal(53, 61).

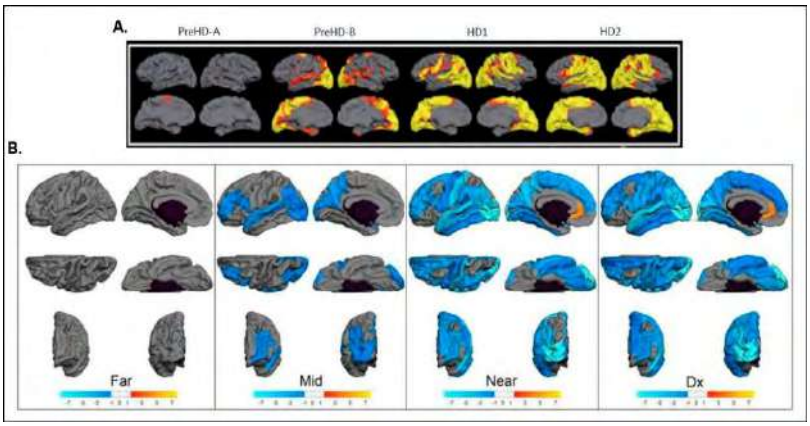

Figura 8: *Regiones corticales con pérdida de volumen en las fases asintomáticas e iniciales de la enfermedad de las cohortes del estudio Track-HD (a) y Predict-HD (b). Fuentes: Tabrizi et al. Lancet Neurol. 2009 Sep;8(9):791-801 y Nopoulos PC et al. Neurobiol Dis. 2010 Dec;40(3):544-54.*

Como se hace evidente por lo que llevamos expuesto, con la identificación de extensos cambios corticales-posteriores ya durante las etapas más tempranas de la enfermedad se hace necesario reconsiderar algunos de los modelos explicativos disponibles y, sobre todo, cuestionar el modelo conceptual general que históricamente ha considerado la EH como una enfermedad prototípicamente subcortical mediada por la degeneración preferente de los ganglios basales.

A nivel subcortical, en los grupos clasificados como lejos del tiempo estimado a inicio de la enfermedad ya se pueden detectar diferencias estructurales en el volumen, especialmente del putamen y mínimamente del núcleo caudado. Este patrón se hace significativamente evidente en los grupos de personas asintomáticas cerca del tiempo estimado a inicio de la enfermedad, exhibiendo un patrón de

progresión de la atrofia durante las fases iniciales de la enfermedad que se extiende más allá de los ganglios basales e implica la corteza prefrontal, occipital, temporal, parietal y cíngulo(53).

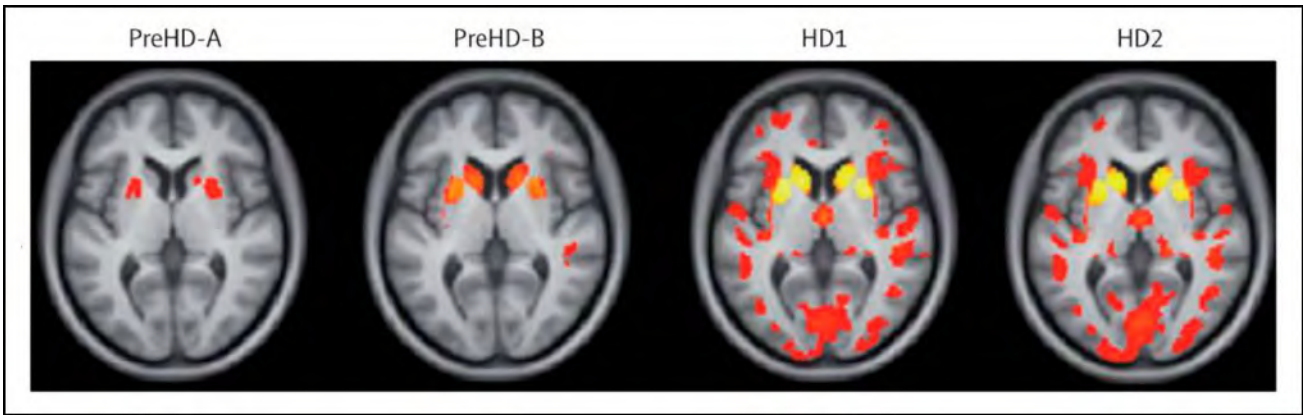

Figura 9: *Regiones subcorticales con progresiva atrofia a lo largo de las fases asintomáticas e iniciales. Fuente: Tabrizi et al. Lancet Neurol. 2009 Sep;8(9):791-801.*

La aparente poca implicación de la atrofia frontal en una enfermedad históricamente caracterizada desde el punto de vista cognitivo y conductual como una demencia fronto-subcortical puede resultar llamativa. En un estudio realizado por nuestro grupo, demostramos que en la EH existe un patrón disociado en cuanto a la atrofia y pérdida de metabolismo que de manera prominente afecta distintas regiones cerebrales(127). Así, existe una asincronía entre la pérdida neuronal (cuantificada mediante indicadores de atrofia cortical) y la pérdida de metabolismo cortical (cuantificada mediante PET de ^{18}F-FDG). Esta asincronía se manifiesta de modo que, mientras que la atrofia cortical, pero no la pérdida de metabolismo es detectable en extensos territorios parieto-occipitales, el hipometabolismo, pero no la atrofia cortical, es detectable en extensos territorios fronto-temporales. Ello sugeriría, que parte de las manifestaciones de la enfermedad son consecuencia de alteraciones funcionales mediadas por la desintegración de los sistemas fronto-subcorticales, otras son consecuencia exclusivamente de la atrofia cerebral y otras, en gran medida, son consecuencia de una relación sinérgica entre ambos mecanismos.

1.3. Diagnóstico de la enfermedad de Huntington:

1.3.1. Diagnóstico clínico:

El diagnóstico de la EH es un diagnóstico clínico que se realiza por parte del neurólogo sobre la base de la constatación de la existencia de alteraciones motoras incuestionablemente atribuibles a una EH en personas genéticamente positivas para la enfermedad (CAG > 36) o con antecedentes familiares directos conocidos. El momento de transición o fenoconversión de persona asintomática a sintomática (desde el punto de vista motor) no resulta evidente dado que los signos y síntomas motores progresan de manera insidiosa. De manera consensuada, las alteraciones motoras deberán ser, desde el punto de vista del evaluador, síntomas probables (DCL = 3) o inequívocos (DCL = 4) de enfermedad de Huntington(1, 3).

Si bien es ampliamente reconocido que los síntomas cognitivos y conductuales constituyen características clínicas inherentes a la EH, el uso de criterios clínicos basados en la sintomatología motora es la aproximación aceptada para el diagnóstico. Esta aproximación elude la importante variabilidad observada en el momento de aparición, severidad y forma de progresión de la sintomatología no motora. A pesar de este consenso, recientemente se ha propuesto la posible utilidad de criterios diagnósticos basados en el curso natural de la enfermedad(128). Estos criterios (tabla 2), tendrían en cuanta la historia familiar en ausencia de confirmación genética, así como también cobrarían protagonismo las manifestaciones cognitivas y conductuales.

Tabla 2: *Criterios diagnósticos de la EH basados en el curso natural*

EH genéticamente confirmada (G10.1)	**Características**	**EH no confirmada genéticamente (G10.2)**
EH presintomática (G10.1.1)	-Ausencia de signos y síntomas motores (DCL = 0 o 1) -Ausencia de signos o síntomas cognitivos -Pueden existir o no cambios en biomarcadores incluyendo imagen, LCR y cuantificación motora -Tratamiento sintomático no indicado	EH a riesgo (G10.2.1)
EH prodrómica (G10.1.2)	-Signos motores sutiles (DCL = 2) y/o signos cognitivos sutiles -Pueden existir (pero no se requieren) mínimos cambios en la funcionalidad con respecto a nivel premórbido no cuantificables mediante TFC -Pueden existir síntomas de apatía, depresión u otros cambios conductuales -Habitualmente se observarán cambios en las evaluaciones de imagen y cuantificación motora -Se puede requerir tratamiento sintomático (ej.: depresión)	EH clínicamente prodrómica (G10.2.2)
EH manifiesta (G10.1.3)	-Presencia de síntomas motores y/o cognitivos que tienen un impacto en la vida. -Cambios funcionales cuantificables en TFC. -DCL motor = 3 o 4 (DCL = 2 si los síntomas cognitivos son significativos y existe evidencia de progresión) -Se requiere tratamiento sintomático	EH clínicamente manifiesta (G10.10.2.3)

**G10 es la clasificación para EH en el actual sistema internacional de clasificación de las enfermedades [ICD-10-GM-2014] publicado por la Organización Mundial de la Salud*

1.3.2. Diagnóstico genético y test predictivo:

La disponibilidad de un test genético que permite determinar que personas a riesgo son portadoras de la mutación, define la posibilidad de realizar un diagnóstico predictivo en la población a riesgo de desarrollar la enfermedad(129). Atendiendo a los criterios diagnósticos formales de la EH, el test genético predictivo no supone un diagnóstico como tal, puesto que para ello es necesaria la existencia de síntomas motores compatibles con la EH. Evidentemente, el test genético puede tener un carácter de apoyo diagnóstico cuando se realiza en personas cuyas manifestaciones clínicas sugieren una posible EH, aun en ausencia de antecedentes familiares conocidos.

La realización del test genético predictivo para EH debe desarrollarse acorde a las recomendaciones elaboradas por la *Huntington's Disease Society of America* en relación con el proceso de consejo genético. Estas recomendaciones se realizaron y se desarrollan atendiendo a la enorme complejidad que acompaña el proceso de reflexión, decisión, recepción y convivencia con los resultados genéticos. Las guías elaboradas acerca del proceso de consejo genético y de realización del test predictivo en la EH incluyen una serie de recomendaciones centrales que los centros podrán adaptar a sus posibilidades, considerando siempre como elemento central el ofrecer un servicio de cuidado y acompañamiento acorde a la magnitud del escenario.

Tanto el diagnóstico clínico como la aproximación predictiva mediante el test, suponen eventos vitales personales muy importantes con una clara repercusión sobre el individuo afectado y su entorno próximo. Por ello, tanto el proceso de diagnóstico clínico como el test predictivo, contarán siempre con recursos de apoyo psicológico e incluirán en algún momento, siempre que sea posible, a los distintos miembros que directa e indirectamente puedan verse afectados por la EH.

Otras aproximaciones diagnósticas a la EH contemplan aquellas realizadas con el fin de garantizar descendencia libre de la enfermedad. En este ámbito de actuación se contempla el diagnóstico genético preimplantacional, que permite el estudio del material genético en embriones humanos fecundados in vitro. Esto permite seleccionar aquellos embriones libres de determinadas mutaciones y rechazar los que se encuentren afectados. La segunda aproximación es el diagnóstico prenatal a través de la biopsia corial, cuyos resultados permiten valorar la posible interrupción del embarazo en caso de confirmarse la presencia de la mutación, cuando la legislación vigente en el país donde se realiza la técnica así lo permite.

2. HIPÓTESIS:

1. La presencia y la gravedad de determinados síntomas cognitivos y conductuales en pacientes asintomáticos y en pacientes en estadios iniciales con la EH se relaciona con determinadas anomalías cerebrales estructurales y funcionales que no se circunscriben exclusivamente a los ganglios basales, sino que implican territorios corticales-posteriores y funciones dependientes de estas regiones.

2. Determinadas variables ambientales, como la reserva cognitiva, modulan la integridad estructural y cerebral en pacientes sintomáticos y actúan como modificadores de la expresión clínica de la enfermedad.

3. Existe un cierto solapamiento entre los correlatos neuronales de determinados síntomas conductuales y los correlatos neuronales de determinadas manifestaciones cognitivas.

4. En la EH pueden evidenciarse distintos fenotipos cognitivos que se caracterizan por expresar formas más o menos agresivas de progresión del deterioro cognitivo, que no dependen exclusivamente del número de repeticiones CAG y que se asocian con diferencias neuroanatómicas.

5. La alteración de los ganglios basales y de los circuitos fronto-subcorticales desempeña un papel importante en las manifestaciones cognitivas y conductuales en la EH, pero este es menos relevante que el inicialmente postulado por lo que su atención preferencial puede oscurecer la importancia de otras alteraciones corticales como factores de seguimiento y pronóstico de la EH.

3. OBJETIVOS

3.1. Objetivo principal:

Estudiar mediante técnicas de neuroimagen, registro neurofisiológico y evaluación cognitiva-conductual los correlatos cerebrales y los procesos implicados en la etiopatogenia y modulación de las manifestaciones de la enfermedad de Huntington.

3.2. Objetivos secundarios:

1. Estudiar en pacientes sintomáticos el impacto del despliegue de recursos de bilingüismo a lo largo de toda la vida sobre la integridad estructural y funcional cerebral y su relación con el estado clínico global, así como los correlatos neuronales estructurales específicos que caracterizan la demencia en esta enfermedad.

2. Estudiar en pacientes asintomáticos patrones de actividad neurofisiológica y patrones conductuales relativos a alteraciones tempranas de procesos visuoperceptivos que permitan sumar conocimiento al papel de las alteraciones corticales-posteriores en las manifestaciones de la EH.

3. Estudiar los correlatos estructurales subyacentes a la irritabilidad y a la agresividad en la enfermedad de Huntington buscando aportar un modelo explicativo, biológicamente plausible, acerca de la fisiopatología de estos síntomas en la EH.

4. Estudiar la utilidad y las principales características psicométricas de un instrumento de evaluación del estado cognitivo global para el cribado (screening) de los cambios cognitivos leves y de la demencia en la EH.

4. COMPENDIO DE PUBLICACIONES

4.1. Artículo 1:

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The impact of bilingualism on brain structure and function in Huntington's disease

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ABSTRACT

Introduction: Bilingualism exerts neuroprotective effects against neurodegeneration. In Huntington's disease (HD), the systems involved in bilingual control show early compromise, but the effect of bilingualism on the course of HD is unknown.

Methods: We addressed the impact of livelong use of bilingualism on the clinical features, brain structure and function in 30 early-mild stage HD patients. Using voxel-wise regression analysis, we explored the effect of levels of use of bilingualism on grey-matter volume (GMV) and 18F-FDG metabolism.

Results: Higher use of bilingualism was associated with better performance in inhibitory control and set-shifting independently of age and education and with higher GMV in the inferior frontal gyrus. 18F-FDG data revealed a significant effect on multiple fronto-temporal regions, specifically, in the dorsal anterior cingulate cortex, the anterior insula, the ventromedial orbital prefrontal cortex and the inferior frontal gyrus. These changes contributed to better inhibitory control and set-shifting and to more preserved motor and functional capacity.

Conclusion: In HD, lifelong use of bilingualism is associated with structural and metabolic brain changes that have an impact on cognition, movement and functionality. These findings highlight the importance of stimulating cognitive and brain reserve in HD and in other neurodegenerative conditions.

1. Introduction

The learning and use of two or more languages during lifespan has been associated with neuroprotective effects against age-related cognitive decline, outcome after stroke, and delayed onset of dementia [1,2]. To select and speak one language without interference from the other, bilinguals display lifelong use of action monitoring and executive control mechanisms [3]. A well-known consequence of this continual use of two languages is that bilinguals exhibit better performance in linguistic and non-linguistic tasks requiring conflict monitoring, set shifting and inhibitory control [4].This effect is explained by the multimodality (non-language specificity) of the structures recruited to monitor and control two or more languages. Consequently, bilingualism tunes brain structures and networks that are critical for executive control, such as the dorsal-lateral prefrontal cortex (DLPFC), the anterior cingulate cortex (ACC), the caudate nucleus, the temporal lobe, and the inferior parietal lobe [3]. Bilingualism is also associated with higher preservation of multiple white matter tracts and is known to influence resting-state functional brain activity as seen in the form of more efficient connectivity of the frontal-executive and the default-mode network [5,6]. Overall, lifelong use of bilingualism appears to enrich brain and cognitive reserve, leading to neuroprotective effects [2,6].

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Brain and cognitive reserve capacities moderate between brain pathology and clinical outcome. Brain reserve refers to the passive capacity of the brain (i.e.: more neurons or synapse) to deal with pathology whereas cognitive reserve refers to how the brain actively copes with brain pathology by using cognitive processes or by enlisting compensatory mechanism [24]. Although cognitive reserve has shown to positively impact cognitive performance and disease onset in Huntington's disease (HD) [12], almost nothing is known about the influence of bilingualism in this disease.

HD is a fatal neurodegenerative disorder that is fully explained by a single mutation of the *HTT* gene in the short arm of chromosome 4 [7]. HD usually manifests around mid-adulthood in all individuals carrying a CAG expansion of more than 38 repeats. Clinically, HD is characterized by progressive motor, cognitive and neuropsychiatric alterations that lead to complete loss of functional independence [7]. The primary neuropathological hallmark of HD is the massive loss of the medium spiny neurons of the basal ganglia, leading to marked atrophy of the caudate nucleus and putamen [8]. Functional alterations and degeneration of the prefrontal cortex (PFC), the ACC, the temporal lobes, and posterior-cortical territories also define HD [9]. Accordingly, deficits in set-shifting, inhibitory control, planning, verbal fluency, psychomotor speed and retrieval strongly define the cognitive phenotype exhibited by HD patients [10,11]. Most of these brain structures and cognitive functions that are affected in early HD have a critical role in the optimal control of bilingualism. However, the impact of bilingualism on HD has not been previously addressed.

Here we explore the effect of bilingualism in HD in a sample of early-stage bilingual HD patients. We addressed the degree of use and competence of bilingualism across the lifespan. We then assessed the impact of bilingualism on clinical parameters and on brain structure and metabolism by combining measures of grey-matter volume (GMV) and 18F-fluorodeoxyglucose (18F-FDG) metabolic uptake (SUVr).

2. Materials and methods

2.1. Participants

Thirty Catalan-Spanish bilinguals confirmed as gene mutation carriers (CAG ≥ 39) were prospectively recruited from the outpatient clinic of the Movement Disorders Unit at Hospital de la Santa Creu i Sant Pau. Informed consent was obtained from all individual participants included in the study. Participants were classified as early or mild-stage HD (Shoulson and Fahn stages 1 and 2) based on a total motor score on the Unified Huntington's Disease Rating Scale (UHDRS-TMS) greater than four and a total functional capacity (TFC) greater than seven [15,16]. We calculated the disease burden score (DBS), a measure of total exposure to mutant huntingtin across the lifespan, using the formula based on age and CAG length [age x (CAG-35.5)] [17]. All participants were free of any neurological disorder other than HD. We excluded individuals with a history of traumatic brain injury, epilepsy, drug abuse, or non-compensated systemic disease (i.e.: diabetes).

Socio-demographic and clinical data included age, sex, education, age at diagnosis, cognitive status, presence and severity of neuropsychiatric symptoms, and use of medication. The use, exposure and competence of bilingualism across the lifespan were addressed using a modified version of the Anderson et al. bilingualism questionnaire [18]. A bilingualism index (BI) was defined and values were measured for BI relative to use (BIuse) and relative to competence (BIcomp). These values were computed according to the formula [$BI = 1 - (\%L1\text{-}\%L2)$], where % was based on the answers provided for the number items. BIuse provided a measure of how a person used both languages throughout life. BIuse = 1 indicates that a person used both languages equally (i.e.: speaking half the time in Spanish and half the time in Catalan), whereas a BIuse = 0.25 indicates that a person used one language 75% of time). Accordingly, the higher the BIuse, the higher the number of between-language switching throughout life. In contrast, BIcomp measured proficiency writing, speaking and understanding the two languages. A BIcomp = 1 indicates that a person is highly proficient in both languages.

The study protocol defining all the procedures performed in the present study was reviewed and approved by the local research ethics committees at Hospital de la Santa Creu i Sant Pau in Barcelona. All procedures were performed in accordance with the Helsinki Declaration (1964) and its later amendments.

2.2. Behavioral and cognitive assessment

Behavioral assessment was addressed using the Problem Behaviors Assessment Scale for HD (PBA-s) [19]. This 11-item semi-structured instrument specifically focuses multiple neuropsychiatric symptoms related to HD, rating them according to frequency and severity.

Cognition was assessed through the cognitive subtests of the UHDRS (cogscore) and additional measures [16]. Assessment included the FAS test for phonetic verbal fluency, the semantic verbal fluency test, the symbol digit modality test (SDMT), the Stroop test, and the Trail Making Test parts A and B. In the FAS test and in the semantic verbal fluency test, we recorded the total number of words per letter and the total number of names of animals produced in one minute. In the SDMT, the total score was the total number of correct substitutions given in 90 s. In the Stroop test, the total score was the total number of correct responses in 45 s. In the TMT, the total score was expressed as the total time required to complete the task, with the maximum time being defined as 240 s. This assessment provided measures of frontal-executive performance, processing speed and attention.

2.3. Neuroimaging acquisition

T1-weighted MRI scans were acquired in a 3T Philips Achieva. MRI was performed 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). 18F-FDG PET/CT data were acquired on a Philips Gemini TF PET/CT 60 min after the intravenous injection of 277 MBq/ml of 18F-FDG. During the uptake phase, all participants were resting with eyes closed and ears plugged to reduce background stimulations. The reconstruction method was iterative (LOR RAMLA, three iterations and 33 subsets) with a 128 × 128 matrix size included in a FOV of 256 mm, resulting in 2 mm pixel size and 2 mm pixel slice thickness. Time of acquisition was 10 min 18F-FDG PET/CT scans were performed according to the EANM procedure guidelines for PET brain imaging [20].

2.4. Data analysis

2.4.1. Socio-demographic and clinical data

The participants' socio-demographic and clinical variables are expressed as means ± standard deviations (SD) for continuous variables and as percentages for categorical variables. Multivariate logistic regression analysis was used to explore associations between the obtained imaging measures and clinical data.

2.4.2. T1-MRI image analysis

Grey-matter volume (GMV) analysis from T1-weighted images was performed by a voxel-based morphometry (VBM) analysis using the Statistical Parametrical Mapping (SPM12) software package [http://www.fil.ion.ucl.ac.uk/spm/]. Segmented GMV maps for each subject were normalized to the Montreal Neurological Institute (MNI) space by applying DARTEL transformations. The resulting GMV maps were smoothed using an isotropic spatial filter of 8 mm full-width at half maximum (FWHM) to reduce inter-individual variability.

These normalized and smoothed GMV images were entered into a voxelwise regression analysis to study the effect of the different IB scores. Age, sex, education, total intracranial volume (TIV), CAG length,

and UHDRS-TMS were used as covariates within the model.

Finally, GMV values for each patient were computed at the identified clusters using build-in SPM functions to perform further regression analyses with other clinical variables of interest.

2.4.3. 18F-FDG PET image analysis

Brain glucose metabolism analysis, as measured by 18-FDG PET relative standardized uptake value (SUVr), was performed using SPM and the biological parametric mapping (BPM) toolbox [21]. First, 18F-FDG PET scans were intensity scaled by the mean tracer uptake within the pons-cerebellar vermis reference region [22] to obtain SUVr images. These images were then spatially normalized to the MNI space, and smoothed using a Gaussian kernel of 12 mm FWHM.

Next, the resulting images were entered into a voxelwise regression analysis to study the effect of IB scores into brain metabolism. The following covariates were used: Age, sex, education, CAG length, and UHDRS-TMS. Additionally, partial volume correction to control for the effect of a possible underlying atrophy within the voxelwise model was performed by entering each subject's GMV map in MNI space as a voxelwise covariate within the model.

SUVr values at the identified clusters were computed for each patient using build-in SPM functions to perform further regression analyses with other clinical variables of interest.

In both imaging modalities, clusters surviving $p < 0.05$ corrected for family-wise error (FWE) were considered significant. For exploratory and depicting purposes, we also report results showing $p < 0.001$ (uncorrected) and a minimum extent of $k = 100$ voxels.

3. Results

3.1. Clinic and sociodemographic data

Thirty participants (CAG = 44 ± 3; age = 52 ± 10) completed all the study procedures. Participants' characteristics are summarized in Table 1. As seen, the mean UHDRS-TMS score was 32 ± 17 and the TFC was 10.3 ± 2, confirming all participants were stage 1 or 2 and thus classified as early and mild HD.

Table 1
Clinical and sociodemographic characteristics.

	Participants
Age (years)	52.5 ± 11
Gender (f/m)	20/10
Education (years)	11.7 ± 5
CAG length	43.7 ± 3
DBS	407 ± 90
UHDRS-TMS[a]	33 ± 17
TFC[b]	10 ± 2.5
PBA-s total score[c]	8.6 ± 5
COGSCORE[d]	152 ± 76
FAS[e]	17.6 ± 12
SDMT[f]	22 ± 13
Stroop	
Color	37.1 ± 19
Word	54.3 ± 26
Word-color	19.2 ± 13
Interference score	−2.6 ± 6.8
TMT-A (seconds)	96.5 ± 60
TMA-B (seconds)	201.4 ± 69
TMT-B – TMT-A[g]	1.6 ± 1.2
Semantic verbal fluency (animals)	11.3 ± 4.2

[a] Unified Huntington's Disease Rating Scale – Total Motor Score.
[b] Total Functional Capacity.
[c] PBA apathy score.
[d] UHDRS cognitive score.
[e] Phonetic verbal fluency using letters F, A and S.
[f] Symbol Digit Modality Test.
[g] Subtraction TMT-B minus TMT-A.

The mean BIuse relative to use and exposure of two languages across the lifespan was 0.4 ± 0.2 and followed a homoscedastic distribution between 0.08 and 1. The BIcomp was 0.6 ± 0.3. Whereas competence appeared significantly associated with educational level ($r = 0.653$; $p < 0.001$), no significant correlations were found between BIuse, age and education.

Focusing on BIuse, higher scores appeared significantly associated with better performance on the Stroop word-color interference ($r = 0.389$; $p < 0.05$) and completion time on the TMT-B ($r = -0.403$; $p < 0.05$), independently of the educational level and age. Thus, when controlling for the effect of age and education, IBcomp was not associated with any measure.

3.2. MRI results

In the MRI analysis no clusters survived correction for multiple comparisons ($p < 0.05$ FWE). A single uncorrected cluster was found in form of higher GMV in the right inferior frontal gyrus associated with higher BIuse (Fig. 1; Table 2). GMV measured for each participant in the identified cluster showed a positive association between GMV in right inferior gyrus and better performance on the Stroop word-color interference ($r = 0.492$; $p < 0.01$) and TMT-B time of completion ($r = -0.419$; $p < 0.05$).

3.3. 18F-FDG PET/CT results

In the 18F-FDG analysis (Fig. 2; Table 2), higher BIuse was strongly associated with increased SUVr in a set of fronto-temporal regions, independently of GMV atrophy. Specifically, higher BIuse was associated with a bilateral higher glucose metabolism in the dorsal ACC (dACC), the ventromedial orbital PFC (vm-OPFC), the insula, the superior OPFC, the left orbital BA 47, the left inferior frontal gyrus and the right inferior temporal gurus (Fig. 2; Table 2).

After calculating the SUVr uptake in all the identified clusters, we found a set of significant associations between the modulation exerted by the BIuse and clinical measures. Increased SUVr in the dACC was strongly associated with better performance on the Stroop word-color interference ($r = 0.514$; $p < 0.01$). Increased SUVr in the left BA47 was associated with a lower UHDRS-TMS score ($r = -0.496$; $p < 0.01$) and better functional capacity as assessed through the TFC ($r = 0.546$; $p < 0.01$). Increased SUVr in the left insula was associated with better Stroop interference performance ($r = 0.497$; $p < 0.01$). Significant associations were also found between higher irritability scores and lower SUVr in the inferior frontal gyrus ($r = -0.389$; $p < 0.05$), lower SUVr in the superior OPFC ($r = -0.369$; $p < 0.05$), and lower SUVr in the insula ($r = -0.413$; $p < 0.05$).

4. Discussion

Our results show that more frequent lifelong use of bilingualism is associated with significant changes on 18F-FDG metabolic uptake in a set of brain regions and a slight tendency of increased GMV in a single frontal region. This effect exerts a strong impact on cognitive measures related to inhibitory control and cognitive flexibility. These results suggest that, even in this devastating disease, higher use of bilingualism moderates the degree of neural integrity and clinical expression of neurodegenerative disorders.

Our findings concerning better executive control in bilinguals are congruous with previous reports both in healthy and clinical populations. In healthy controls, use of bilingualism tunes the functional and structural brain architecture in an experience-dependent manner and these changes have a significant impact on task performance [5]. Specifically, the dACC is critically sensitive to use of bilingualism [4,23]. Given the role exerted by the dACC on conflict monitoring, bilinguals exhibit better performance to solve cognitive conflict in domain-general cognitive tasks [4,5]. Similarly, the effects of bilingualism have been

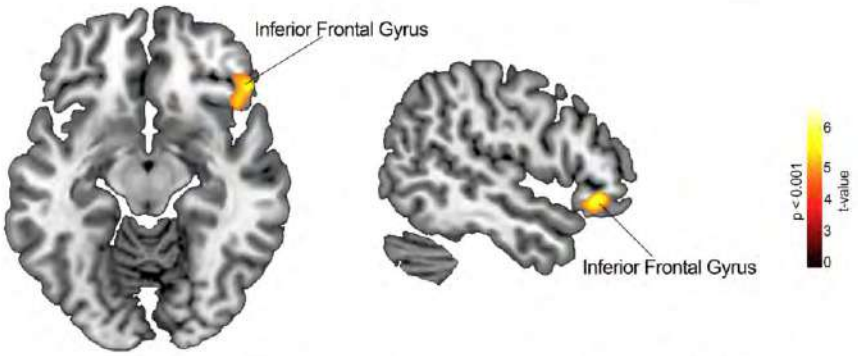

Fig. 1. Results of the voxel-based morphometry analysis of the structural T1-weighted images. The slices show regions of a significant GMV increase in association with lifelong bilingualism use. For depiction purposes results are showed with a $p < 0.001$ (uncorrected) and $k = 100$.

Table 2
Results of the voxel-based morphometry analysis of GMV and 18F-FDG.

Anatomical region	Cluster size	*T* value	MNI coordinates (*x*, *y*, *z*)
Voxel-based morphometry analysis of GMV			
Right inferior frontal gyrus	355	5.80	51, 32, −9
Results of the 18F-FDG PET analysis			
vmOPFC/Insula/sup OPFC/ dACC[a]	2863	5.59	12, 38, −24
Right inferior temporal gyrus[a]	1301	5.53	52, −42, −26
Left mid inferior frontal gyrus/ left BA47[a]	1366	4.49	−38, 48, −8
Right sup frontal gyrus	334	4.98	20, 26, 58
Left ACC	264	4.11	−6, 38, 24
Right supramarginal gyrus	193	4.27	64, −46, 32
Left inferior temporal gyrus	176	4.49	−56, −32, −20
Right precentral gyrus	138	4.09	64, 4, 29
Left DLPFC	129	4.90	−38, 14, 34

[a] Clusters surviving $p < 0.05$ FWE.

noted on structures mediating set-shifting and cognitive flexibility such as the DLPFC [5,23].

Regarding neurodegenerative diseases, multiple mechanisms participate in age-of-onset and in the clinical course of the disease [24]. Brain and cognitive reserve are currently recognized as modeling factors of aging and neurodegeneration [25]. Use of bilingualism has shown to be an important aspect of cognitive and brain reserve enrichment [26]. Thus, in mild cognitive impairment and Alzheimer's disease, it appears to delay the onset of dementia for up to 4.5 years. Use of bilingualism also appears to mitigate the functional disintegration of networks such as the default mode network and the central executive network, which is associated with a better global cognitive performance [1]. Preservation of white matter integrity has also been associated with use of bilingualism and a more benign course of cognitive deterioration in the context of aging [5,6].

Here we demonstrate that in HD, in absence of an association with age, education, and DBS, higher use of bilingualism contributes to better performance in tasks requiring inhibition, attention, anticipation, monitoring, and task-switching [27] and that these effects were independent of the level of competence in each language. Consistent with previous reports, higher use of bilingualism in our sample was also associated with higher GMV in the inferior frontal gyrus, possibly reflecting greater structural integrity.

Whereas these GMV changes appeared to be circumscribed to small territories, they exerted a significant impact on cognitive performance. Specifically, they notably modulated inhibitory control as observed in the better performance in the Stroop interference condition.

In the 18F-FDG analysis, higher use of bilingualism was associated with a widespread pattern of increased metabolism in multiple fronto-temporal regions. Specifically, the most robust effects were seen on the dACC, the ventro-medial orbital PFC, the anterior insula, the inferior temporal gyrus, and the DLPFC. Importantly, quantifications of SUVr in all these regions showed that higher 18F-FDG metabolism led to better performance in inhibitory control and set-shifting and better motor and functional status. This shows that the effects that use of bilingualism exerted on brain function had a positive impact on motor and functional outcomes.

Progressive loss of GMV and 18F-FDG uptake is evident in the course of HD [14,28]. These changes can be tracked as early as 15 years before the first clinical manifestations of the disease and are strongly associated with the motor, cognitive and behavioral signs and symptoms defining the clinical picture of HD. All these structural and functional changes occur during HD progression and contribute to the complex presentation of this disease [29]. Among these changes, disruption of the neural circuitry underlying inhibitory control and action monitoring is evident in both premanifest and early HD in the form of progressive damage to many brain regions such as the SMA, the ACC, the insula, and the medial frontal cortex [9,14]. Changes in these regions are strongly associated with deficits in response inhibition and action monitoring [30] and could contribute to characteristic behavioral disturbances such as poor temper control, irritability and dysexecutive behavior. From a neuropsychological testing perspective, damage of this circuitry can be inferred based on difficulties in tasks such as in Go/NoGo paradigms or in the Stroop interference condition. Accordingly, our data show an expected association between structural and functional changes in nodes of the action monitoring system and in performance on the Stroop interference. However, we show that the degree of damage along this circuitry and its impact on cognitive performance is positively modulated as a function of greater lifelong use of bilingualism.

Our data, however, do not provide evidence supporting an effect of bilingualism on key pathological hallmarks of HD such as the caudate nucleus and the putamen. This may be because basal ganglia atrophy is already prominent in symptomatic participants with early and mild stages of the disease.

The absence of a matched sample of monolingual HD participants may be a limitation. By including such a group in a cross-sectional study of this type we could have compared the clinical status of two groups of the same age at disease onset and with similar CAG length. A second limitation is the absence of follow-up data as this would have allowed us to study possible differences in disease progression as a function of use of bilingualism. This could be of particular interest to explore whether the observed changes are already present in premanifest individuals and whether they have an impact on age of onset and disease progression.

In conclusion, the present study shows that lifelong use of bilingualism has a positive effect on structural and functional brain integrity in

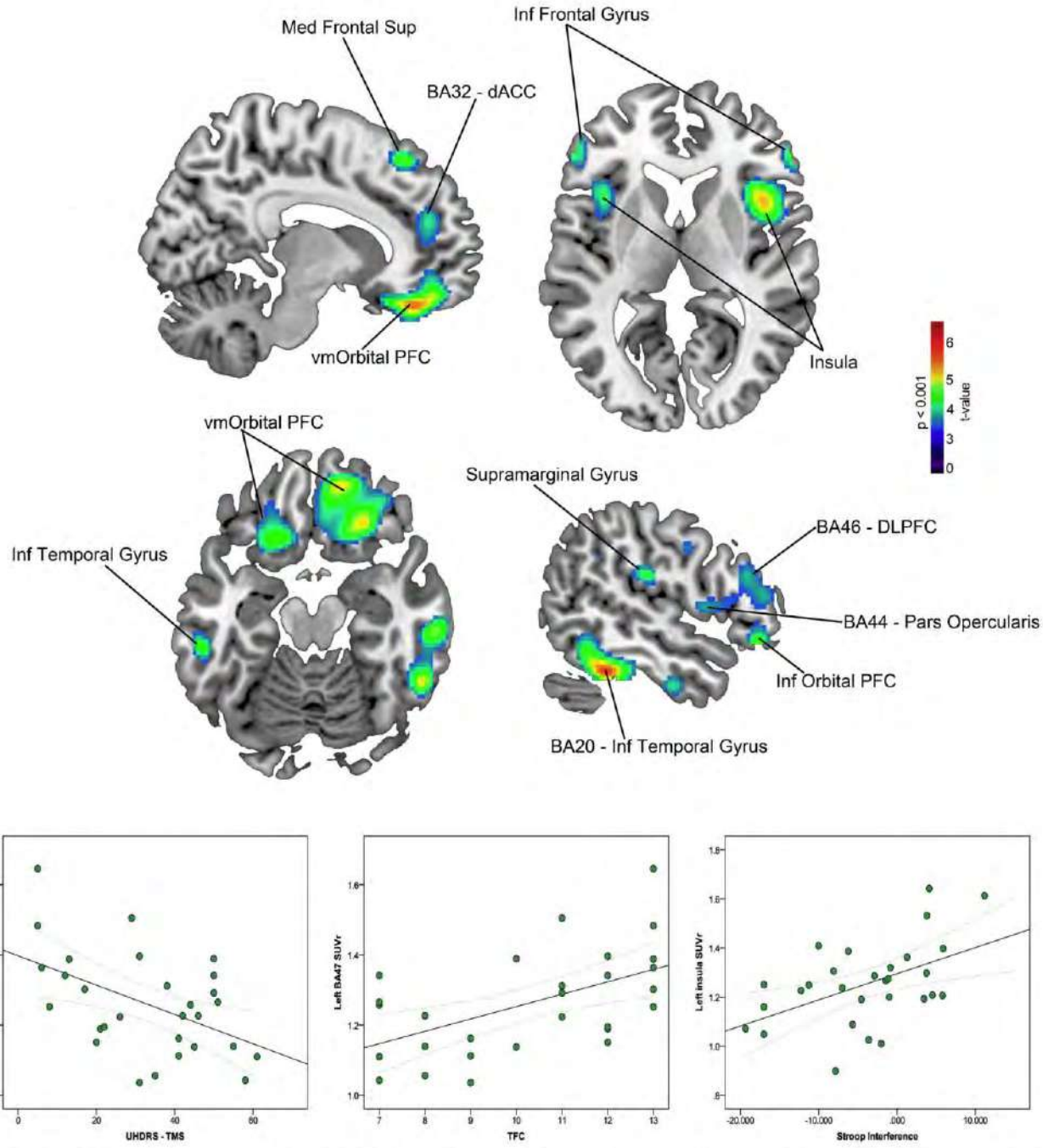

Fig. 2. Top: Results of the voxelwise analysis of the 18F-FDG PET scans. The slices show regions of significant SUVr increase in association with lifelong bilingualism use. For depiction purposes results are showed with a $p < 0.001$ (uncorrected) and $k = 50$. Bottom: Correlations between SUVr and other clinical measures.

early and mild HD. Essentially, this effect benefits on cognitive, functional and motor status that is not explained by years of education or level of linguistic competence. These data highlight the positive effect of cognitive and brain reserve enrichment as modulators of the neuropathological process associated with neurodegenerative conditions.

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4.2. Artículo 2:

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Research Report

Impaired face-like object recognition in premanifest Huntington's disease

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ABSTRACT

Progressive striatal atrophy has long been considered the pathological hallmark of Huntington's disease (HD), but is it now recognized that malfunction and degeneration of posterior-cortical territories are also prominent characteristics of the disease. The limited knowledge about the functional impact of these posterior-cortical changes could be partially attributed to the lack of sensitive measures to capture them. We hypothesized that early malfunction of specific territories of the ventral visual pathway in premanifest HD would lead to difficulties in the recognition of complex stimuli and to differences in their neurophysiological correlates. To test this idea, we used an object, face and face-like object recognition task to be conducted during an electroencephalographic recording. Compared to healthy-matched controls, premanifest participants showed a significantly increased number of recognition errors in the face-like object condition. Moreover, premanifest participants showed a dramatic decrease in the N170 component elicited for the face-like objects. This N170 decrease was significantly associated with the number of recognition errors and with severity of apathy and global cognitive performance. The lack of differences in other clinical and cognitive measures supports a selective deficit in recognition of face-like objects and their neurophysiological correlates in premanifest HD. These deficits occurred in participants up to 15 years before the estimated time to disease onset and correlated strongly with cognitive and behavioral measures known to be sensitive to HD progression. This finding highlights the existence of selective visuoperceptive deficits years before motor-based onset of HD and emphasizes the need to develop sensitive measures to capture early visual system changes in this population. Assessing the integrity of the visual cortex and its related functions in HD could help to identify early markers of disease progression.

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1. Introduction

Huntington's disease (HD) is a neurodegenerative condition inherited in an autosomal dominant manner and caused by cytosine-adenine-guanine (CAG) polyglutamine expansion in the Huntingtin gene (HTT) (Walker, 2007). Although clinical diagnosis of HD is based on the presence of unequivocal motor symptoms, progressive compromise of cognitive and psychiatric functioning are also recognized as cardinal clinical features of the disease (Tabrizi et al., 2009, 2012).

Early striatal degeneration has been described as the main neuropathological hallmark of HD (Dogan et al., 2013; Tabrizi et al., 2009; Vonsattel et al., 1985). Accordingly, progressive functional disruption and atrophy of the basal ganglia and related frontal-subcortical circuitry appear to strongly contribute to the complex clinical phenotype of HD (Tang et al., 2018). However, cross-sectional and longitudinal studies have consistently shown that a prominent pattern of posterior-cortical changes also occurs early in the course of HD (Nopoulos et al., 2010; Rosas et al., 2005; Tabrizi et al., 2009). Among these changes, increasing evidence highlights early degeneration of the visual cortex, spreading from associative areas (lingual, fusiform and lateral occipital) to the primary visual cortex (Coppen, Grond, Hafkemeijer, Barkey Wolf, & Roos, 2018). Assessing the integrity of the visual cortex and its related functions in HD could thus be used as an early marker of disease progression and is necessary to a better understand of the neuropathological changes occurring in this disease (Coppen, Jacobs, van der Zwaan, Middelkoop, & Roos, 2019).

Some degree of impaired performance in visual-dependent tasks has been described in HD (Coppen, Jacobs, van der Zwaan, Middelkoop, & Roos, 2019; Gomez-Anson et al., 2009; Johnson et al., 2015; Labuschagne et al., 2016; Say et al., 2011; Wolf et al., 2014), but major visual deficits are not commonly reported as typical clinical features in this population. Although changes in the visual cortex are already found in premanifest individuals, clinical alterations in the visual perceptive domains are not evident. The design and validation of sensitive methods is therefore needed to assess visual perceptive function in HD.

The fusiform gyrus is located in the inferior portion of the temporo-occipital gyrus and has systematically been found to be affected by neurodegeneration in the early stage of HD (Coppen et al., 2018; Wilson et al., 2016). It is a key node of the ventral visual pathway and has a well-known role in object and facial recognition (Kanwisher, McDermott, & Chun, 1997). In HD, previous research has shown that changes in visual areas, including the fusiform gyrus, participate in visuospatial reasoning and visual scanning but not in object recognition deficits (Labuschagne et al., 2016; Wolf et al., 2014). Given the specificity of the fusiform gyrus in face processing and recognition, we hypothesized that early compromise of this structure in HD could translate to subtle visual recognition deficits in the face-recognition domain. Accordingly, we aimed to investigate the possible existence of deficits in the recognition of face and face-like objects in premanifest HD.

To address this aim, we used an object recognition task based on the presentation of objects, faces, and face-like objects. The task elicits the perceptual phenomenon of facial pareidolia. Pareidolia is the tendency to perceive a specific, often meaningful image in a random or ambiguous visual pattern. Face pareidolia or the perception of faces in objects or ambiguous stimuli (i.e.,: clouds) is the most frequently reported pareidolic illusion.

This phenomenon is assumed to be sub-served by the early activation of specialized face-processing areas of the ventral visual pathway (i.e.,: face fusiform area) in front of a set of visual stimuli arranged in a form resembling a face (Liu et al., 2014). To explore this process in more depth, using electroencephalography (EEG), we obtained a neurophysiological signature related to face processing known as the N170 component (Bentin, Allison, Puce, Perez, & McCarthy, 1996; Eimer, 2000). The N170 is an event-related brain potential (ERP) that raises maximum amplitude in the temporo-occipital locations around 130–200 ms after the presentation of objects, and gains a maximum amplitude when faces are presented. When faces are shown, the N170 component shows a right-hemisphere lateralization (Bentin et al., 1996). Compelling evidence demonstrates that the fusiform gyrus and the inferior occipital gyrus are the major neural contributors to the N170 (Gao, Conte, Richards, Xie, & Hanayik, 2019; Jacques et al., 2019). In symptomatic HD, a significant reduction of the N170 component was found, suggesting the occurrence of early visual processing deficits in this population (Croft, McKernan, Gray, Churchyard, & Georgiou-Karistianis, 2014). As previously reported, facial pareidolia also elicits the N170 component but has a longer latency than face-related N170 which suggests the recruitment of extended processual resources elicited this stimuli (Caharel et al., 2013; Hadjikhani, Kveraga, Naik, & Ahlfors, 2009).

We hypothesized that in premanifest HD, early disruption of the ventral visual pathway may be insufficient to promote a clear compromise on common visual processing tasks but not on more demanding or visual specific tasks. Specifically, we hypothesized that the early disruption of the fusiform gyrus will contribute to some degree of abnormality in face and/or in face-like object processing.

Accordingly, we studied task-performance and related neurophysiological correlates of object, face and face-like object recognition in a sample of premanifest gene-mutation carriers and a group of healthy controls.

2. Methods

2.1. Participants

Thirty-two participants were prospectively recruited from the outpatient clinic of the Movement Disorders Unit at Hospital de la Santa Creu i Sant Pau after providing signed informant consent. Sixteen participants were premanifest gene mutation-carriers (preHD) and sixteen were gene-negative relatives matched for age, gender and education.

The minimum sample size for the experiment was assumed in accordance with previous literature on ERPs (Hadjikhani et al., 2009). Inclusion/exclusion criteria were established prior to data analysis. All data exclusions, all manipulations, and all measures in the study are reported.

Inclusion criteria for preHD were a CAG length ≥39, a total motor score <5 points as assessed by the Unified Huntington's Disease Rating Scale (UHDRS) (Group, 1996), a diagnostic confidence level ≤ 2 and a total functional capacity (TFC) equal to 13 (Shoulson & Fahn, 1979). The disease burden score (DBS) was calculated using the formula based on *age* x [*CAG*-35.5], which allowed us to estimate the probability of disease onset in years (Penney, Vonsattel, MacDonald, Gusella, & Myers, 1997).

All participants had normal or corrected-to-normal vision. Both preHD and controls were free of any neurological and/or psychiatric disorder at the time of assessment. We excluded individuals with a history of traumatic brain injury or neurosurgery. No part of the study procedures/analysis was preregistered prior to the research being conducted. All procedures performed in the present study were in accordance with the standards of the local Ethic Review Board of the Sant Pau hospital in Barcelona, and with the 1964 Helsinki declaration and its later amendments.

The conditions of our ethics approval do not permit public archiving of anonymized study data. Readers seeking access to the data should contact the corresponding author. Access will be granted to named individuals in accordance with ethical procedures governing the reuse of sensitive data requestors must complete a formal data sharing agreement. The experiment including the set of stimuli has been stored in public resources (https://osf.io/2rzf5/). However, formal permission from the developers applies to the set of neutral face stimuli corresponding to the NimStim Face Stimulus Set (Tottenham et al., 2009) used in the experiment. Accordingly, readers seeking permission to use the whole set of stimuli are advised to contact the developers (https://danlab7.wixsite.com/nimstim) to obtain formal permission to use the NimStim Face Stimulus Set.

2.2. Cognitive and behavioral assessment

Cognition was assessed using the subtests composing the UHDRS cognitive score (cogscore) and other measures (Group, 1996). Cognitive assessment was comprised of the FAS test for phonetic verbal fluency, the semantic verbal fluency test, the symbol digit modality test (SDMT), the Stroop test, and the trail making test parts A and B. Cognitive assessments also focused on specific measures of visuo-perceptive performance. Specifically, we assessed facial recognition using Benton's Facial Recognition Test (BFRT) (Benton, Hamsher, Varney, & Spreen, 1994).

Behavior was assessed using the Problem Behaviors Assessment Scale for HD (PBA-s) (Callaghan et al., 2015). This 11-item semi-structured interview rates the frequency and severity of behavioral symptoms related to HD. Given that apathy is the most characteristic neuropsychiatric feature of HD and can be found in premanifest individuals, we also administered the Starkstein Apathy Scale (AS) to more specifically cover this symptom (Starkstein et al., 2009).

2.3. Face and face-like object recognition task

We developed a face and face-like object recognition task adapted from those used in previous studies (Hadjikhani et al., 2009). Stimuli consisted of 105 different pictures divided into three categories: neutral faces (n = 35 different pictures), face-like objects (n = 35 different pictures), and objects (n = 35 different pictures). The neutral faces were obtained from the NimStim Face Stimulus Set (Tottenham et al., 2009). For the face-like objects, as there is no standardized test to explore the neural correlates of this category, we used a selection of stimuli from the book "Faces" as in previous studies about face pareidolia (Hadjikhani et al., 2009). For the objects part of the task, we used 35 stimuli objects chosen to have a similar global shape as the face-like objects. To control for any differences that could result from tone and size, all pictures were converted to black and white, equated to luminance and contrast and resized to 7 × 9 cm.

Participants were seated at a distance of approximately 60 cm from a computer screen and instructed to classify each stimulus as "looks like a face" or "does not look like a face" as fast and as accurately as possible. They were instructed to respond to each picture by pressing one of two buttons. To control for any deficits in the use of either hand, we counterbalanced the administration of the task so that the right button indicated "yes" in 50% of the sample and "no" in the other 50%.

When the task started, a small fixation cross appeared in the center of the screen for 700 ms. On continuation, the first stimulus was displayed for 700 ms. This order of fixation cross followed by stimulus display was repeated until the task was completed, but the interval between each display was randomized and varied: 600, 700 or 800 ms. The stimuli were presented in the center of the screen on a white background in a random order (Fig. 1 summarizes the schema of the stimulus presentation).

Each 35 stimuli comprising each condition were presented four times, giving a total number of presentations of 420 stimuli. To minimize ocular artefacts during the acquisition of the electroencephalogram (EEG), the task was divided into blocks of 10 stimuli. Participants were given a short period between each block to rest and blink.

From the performance of this task we obtained a set of behavioral measures: Rate of correct and error responses for each stimulus condition (object, faces and face-like objects) and mean reaction time (RT) for each stimulus condition (i.e.,: RT for correct response in face condition; RT for error response in face condition). The experiment was prepared and performed using Presentation® software (Version 0.70, www.neurobs.com).

2.4. Electrophysiological recording

The EEG was recorded with BrainVision Recorder v.1.22 (Brain Products GmbH) from 19 standard sites according to the international 10/20 system placed at Fp1/2, F3/4, C3/4, T3/4, T5/6, P3/4, O1/2, F7/8, Fz, Cz, and Pz. As in previous N170 studies, electrodes were referenced to the tip of the nose. Electro-oculographic (EOG) signals were also recorded for further ocular artifact rejection. Vertical eye movements were monitored using a bipolar montage with two electrodes linked together and placed below each eye referenced to a third electrode placed centrally above the eyes. Horizontal eye movements were monitored using two electrodes placed on

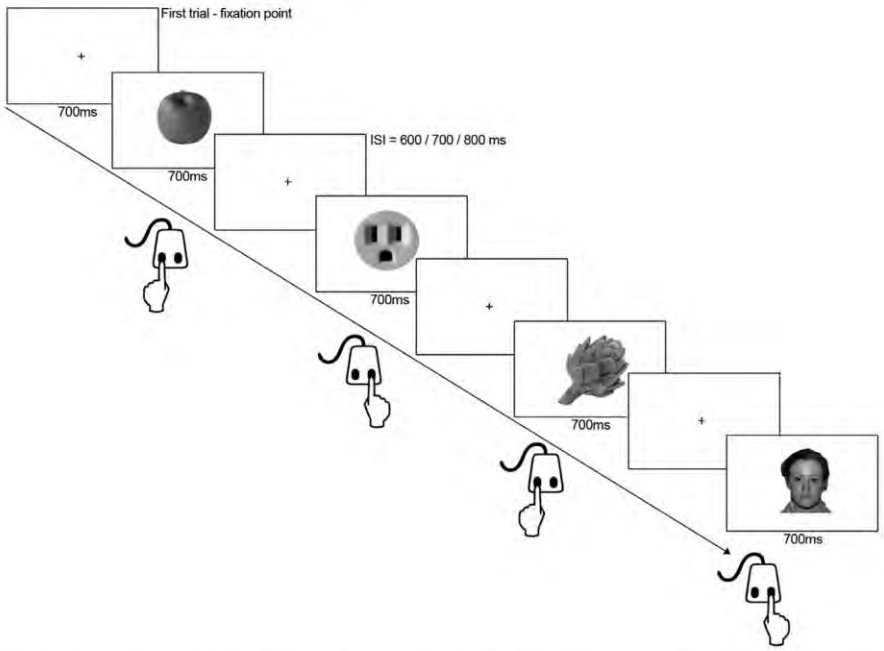

Fig. 1 – Schematic representation of the task. Each trial started with a fixation cross (pseudorandomized duration = 600/700/800 ms) followed by the presentation of a target stimulus (face/object/face-like object). Participants were instructed to respond fast and as accurately as possible, indicating whether or not the stimulus was a face or an object resembling a face. For further details, see Materials and Methods.

the external canthi of each eye. Electrode impedances were kept below 5 kOhm. The electrophysiological signals were filtered with a bandpass of .1–35 Hz and digitized at a rate of 250 Hz. The ERPs were obtained averaging from −100 ms before until 1000 ms after stimulus presentation. Epochs containing amplitudes at any channel exceeding ±30 μV were removed from further analysis. This method was used to reject ocular, muscular and other artifacts. The mean amplitude value in the interval between −100 and 0 ms was used as baseline. Averages were calculated for each condition.

2.5. *Statistical analysis*

Data are expressed as means ± standard deviations (SD) for continuous variables and as percentages for the categorical variables. To assess clinical and sociodemographic differences across groups, we used the unpaired T-test, Mann–Whitney test for ordinal data and the $\chi 2$ for categorical variables. Relative to the EEG task, behavioral data included reaction times and total correct and error responses for each participant. All the behavioral measures were subjected to repeated measures ANOVAs with between-subjects factor "group" and within-subject factors "condition" (face, face-like object and objects). *p* values for the ANOVAs were calculated after Greenhouse-Geisser correction. In case of significant group x condition interaction, consecutive T-tests were performed.

2.5.1. *Neurophysiological data analysis*

ERP effects were quantified with BrainVision Analyzer v.1.0 (Brain Products GmbH) measuring the mean amplitude of the ERP between 100 and 200 ms following stimulus presentation. This measure was obtained for the temporo-occipital sites (T3/4, T5/6) and subjected to repeated measures ANOVAs with within-subject factors such as "electrode" (T3/4, T5/6) and "condition" (face, face-like object, object), and a between-subjects factor "group" (preHD/healthy controls). *p* values for the ANOVAs were calculated after Greenhouse-Geisser correction. Pairwise comparisons were performed using Student's *t*-test and regression analysis was done between neurophysiological measures, task-performance and clinical variables. Results were considered significant for *p* values $< .05$.

2.5.2. *Source localization analysis*

Standardized low-resolution electromagnetic tomography (sLORETA) was used to estimate the localization of the electrical sources of the N170. sLORETA computes a unique three-dimensional source distribution by assuming the most plausible possible inverse solutions of the non-unique EEG inverse solution, which is based on the assumption that neighboring neurons are simultaneously and synchronously active (Lantz et al., 1997; Pascual-Marqui, 2002; Pascual-Marqui, Michel, & Lehmann, 1994). sLORETA software divides the brain into 6239 cubic voxels with 5 mm resolution and estimates the source current density (i.e., the sum of electric neuronal activity on each defined voxel) (Pascual-Marqui, 2002). The source current density is calculated from the scalp-recorded ERP using a realistic head model from the Montreal Neurological Institute (MNI) (Mazziotta et al., 2001). In this model the solution space was restricted to the cortical gray matter only. Source location was determined at the time window corresponding to the latency of the N170 (100–200 ms) using voxel-wise randomization tests with 5000 permutations based on statistical non-

parametric mapping. Voxels with significant differences (corrected p-value < .0001) were located in the MNI brain and Brodmann areas provided by the software.

3. Results

3.1. Sociodemographic and clinical data

Sixteen preHD participants (mean age = 35.2 ± 7.6; mean CAG length = 43.3 ± 2.7, mean estimated time to diagnosis = 16.5 ± 8.4 years) and sixteen healthy controls (mean age = 33.2 ± 3) completed the study. As shown in Table 1, groups were accurately matched for all sociodemographic variables. Despite ranging below the proposed clinical cutoff of AS > 13, preHD scored significantly higher in apathy as seen in the AS [t(32) = 2.68, p = .01] and in the PBA-s apathy severity score [t(32) = 2.04, p = .04]. No differences were found in global cognitive performance or in the BFRT. Looking at each separated test, preHD scored significantly lower in the Stroop color naming [t(38) = -3.12, p = .004] and in the Stroop interference [t(38) = -2.09, p = .04] test.

Table 1 – Sociodemographic and clinic data.

	PreHD	Controls	p
	Mean (SD)	Mean (SD)	
Age	35.2 ± 7.6	33.3 ± 5.6	.425
Education (years)	13.6 ± 2.8	13.2 ± 4	.755
CAG length	43.3 ± 2.7	–	
DBS[a]	266.8 ± 96.6	–	
Years-to-onset	16.5 ± 8.4	–	
UHDRS-TMS[b]	.7 ± 0.9	–	
TFC[c]	13	–	
UHDRS-Cogscore	319 ± 43.8	352.6 ± 56	.076
FAS Total	43.8 ± 16.7	43.1 ± 16.6	.905
SDMT	52.6 ± 5.7	55.1 ± 9.2	.385
Stroop color	71.1 ± 10.3	83.8 ± 11.9	.004
Stroop word	106.9 ± 20.9	120.3 ± 20.7	.092
Stroop interference	44.4 ± 7.2	50.3 ± 8.2	.045
BFRT[d]	47.6 ± 3.6	47.1 ± 3.8	.724
HADS-A[e]	4.8 ± 3.1	4.7 ± 4.5	.945
HADS-D[f]	3.3 ± 4.1	1.3 ± 2	.109
AS[g]	5.2 ± 7	.1 ± 0.3	.012
PBA-S[h]			
Depression	2.3 ± 3.7	1.6 ± 3.2	.572
Suicidality	0	0	–
Anxiety	1.7 ± 2.4	.8 ± 1.5	.250
Irritability	2 ± 2.7	.6 ± 1.3	.092
Aggression	1.5 ± 2.4	.2 ± 0.8	.060
Apathy	1.8 ± 3.3	0	.045
Perseverative behavior	1.2 ± 2.6	.3 ± 0.7	.203
OCB	.5 ± 1.5	.4 ± 1.1	.071
Delusion/Paranoid thinking	0	0	–
Hallucinations	0	0	–
Disorientation	.1 ± 0	0	–

[a] Disease burden score.
[b] Unified Huntington's Disease Rating Scale – Total Motor Score.
[c] Total functional capacity.
[d] Benton Facial Recognition Test.
[e] Hospital Anxiety and Depression Scale – Anxiety score.
[f] Hospital Anxiety and Depression Scale – Depression score.
[g] Apathy scale.
[h] Problems Behavior Assessment scale.

3.2. Task performance

In the overall sample, the RT exhibited for correct responses was significantly slower for the object [t(36) = 3.8; p < .01] and the face-like object condition [t(36) = 8.1; p < .001] than for the face condition. No significant differences were seen between the object and face-like object condition.

In the control group, RT to perform correct responses in the face-like object condition was significantly slower than in the face condition [t(16) = 5.1; p < .001]. Conversely, the preHD group showed slower responses both in the object [t(16) = 7.3; p < .001] and in the face-like object condition [t(16) = 6.9; p < .001] compared to the face condition (Table 2).

The comparison of RTs performed by the two participant groups showed an absence of significant differences in the obtained measures.

Relative to accuracy on task performance, a significant group x condition interaction was found [F(1,31) = 6.6, p < .05]. Consecutive T-tests showed no between-group differences in the number and rate of correct responses in the object and face conditions. However, performance on the face-like object condition was significantly worse in the preHD group where there was a dramatic increase in the number and rate of error responses [t(36) = 3.52, p = .001] (see Table 3 and Fig. 2). Since no differences were seen on the RT elicited in error responses [t(36) = -1.46, p = .568], this finding cannot be attributed to more impulsive or faster responses during performance.

Correlation analysis showed a strong positive association between total errors in the face-like object condition and severity of apathy as measured with the AS scale (r = .686; p < .001). A weaker association was also found between total errors in the face condition and AS score (r = .441; p < .05). However, severity of apathy was below the clinical range (AS < 14) in all cases, indicating that participants were not affected by clinically relevant apathetic symptoms. No other associations were found between the obtained behavioral measures and other clinical and sociodemographic variables such as age, CAG length or DBS.

3.3. N170 analysis

The number of EEG epochs included in the averages did not differ between groups in any of the conditions. Fig. 3 shows the grand average waveforms for the overall sample respect to objects, faces and faces-like objects.

Following the presentation of a face, we observed a temporo-occipital negative deflection peaking around 170 ms with maximum amplitude in the right-sided posterior electrodes, specifically in the T6 location. Repeated-measures ANOVA analysis using mean amplitude for each stimulus type and electrode site showed a main effect of stimulus type [F(1,31) = 29.5, p < .001] and an interaction with the electrode site [F(1,31) = 75.2, p < .001]. Post-hoc paired comparisons showed an enhanced N170 effect between the object condition and the face condition [t(32) = 12.1, p < .001] and between the object condition and the face-like object condition [t(32) = 4.8, p < .001].

Table 2 – Within-group description and comparison of the reaction time for each condition.

	Mean RT ± SD					
	Object condition[a]	Face condition[b]	Face-like object condition[c]	$^{a\text{-}b}p$	$^{a\text{-}c}p$	$^{b\text{-}c}p$
PreHD	494 ± 137	415 ± 110	480 ± 135	<.001	.216	<.001
Controls	468 ± 151	430 ± 540	475 ± 425	.420	.961	<.001

a-b: T-test comparison between object condition and face condition.
a-c: T-test comparison between object condition and face-like object condition.
b-c: T-test comparison between face condition and face-like object condition.

Table 3 – Behavioral performance on the recognition task.

	PreHD	Controls	p
	Mean ± SD	Mean ± SD	
Object condition			
Correct response (RT)	494 ± 137	468 ± 151	.652
Error response (RT)	408 ± 119	468 ± 104	.212
Number errors	11.8 ± 5.3	13.9 ± 13	.588
Face condition			
Correct response (RT)	415 ± 110	430 ± 540	.682
Error response (RT)	415 ± 871	447 ± 616	.652
Number errors	8.4 ± 9.3	4.9 ± 5.3	.269
Face-like object condition			
Correct response (RT)	480 ± 135	475 ± 425	.813
Error response (RT)	480 ± 148	511 ± 124	.568
Number errors	36.6 ± 34.2	6.3 ± 3.9	.008

The brain maps generated using the sLORETA solution showed that the main neural source of the N170 was in the right inferior occipito-temporal area (BA37), which largely corresponds to the face fusiform area (FFA). The right visual associative area (BA18) and the right angular gyrus (BA39) also appeared to contribute to the N170.

The analysis of the latency of each component showed a significant effect mediated by the stimulus type [$F(1,31) = 60.7$, $p < .001$]. Post-hoc comparisons showed a longer latency of the N170 elicited in the face-like object condition and in the object condition than in the face condition [$t(32) = 8.2$, $p < .001$].

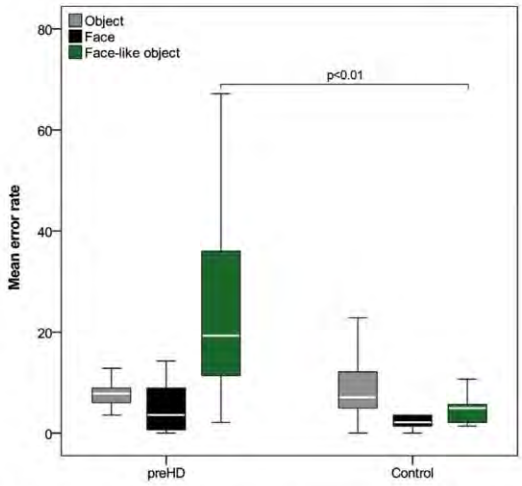

Fig. 2 – Behavioral results: Mean error rate in % for each stimulus category and group. Each bar represents the mean % ± SD of error responses in the three possible stimulus categories and the participant group. A significant difference was found for the number of error responses in the face-like object condition in the preHD group [$t(36) = 3.52$, $p = .001$].

Adding the participant group as between-group factor, we found a significant triple interaction between stimulus type, electrode site and group [$F(2,30) = 5.79$, $p < .001$]. As seen in Fig. 4, this effect appeared robustly mediated by a significant reduction in the N170 mean amplitude associated with face-like object condition at T6 electrode in the preHD group [$F(1,31) = 19.6$, $p < .001$]. Consecutive comparisons also showed the existence of less pronounced but significant between-group differences for the face condition [$F(1,31) = 6.89$, $p < .01$] and a trend to significance for the object condition [$F(1,31) = 3.63$, $p = .06$]. Latency of each component showed no significant between-group differences.

Given these group differences in the mean voltage of the ERPs seen as an overall voltage reduction in the preHD, we calculated the difference waveform in each condition to more precisely address the existence of differences in the ERPs. This measure was obtained by subtracting the object condition mean amplitude from the face condition mean amplitude, and the object condition mean amplitude from the face-like object condition mean amplitude (Fig. 5). Through this method, we suppressed any difference that could be task-unspecific but inherent to a particular group, such as global mean ERP voltage reduction in preHD.

One-way ANOVA using the mean amplitude of the difference waveform revealed a significant reduction in the preHD group of the N170 component elicited by the face-like object condition [$F(1,31) = 27.6$, $p < .001$]. However, difference in the N170 for faces vs. objects did not differ between groups [$F(1,31) = .77$, $p = .386$].

Regression analyses were conducted to explore potential relations between the obtained neurophysiological measures, task performance and clinical variables. The mean amplitude of the difference waveform elicited by face-like object condition showed a negative correlation with the number of errors in this condition ($r = .548$, $p < .01$). Moreover, this measure also correlated with the cogscore ($r = -.530$, $p < .01$), the AS score ($r = .450$, $p < .05$), the SDMT performance ($r = -.404$, $p < .05$), the Stroop word reading ($r = -.465$, $p = .01$), the Stroop color naming ($r = -.463$, $p < .05$) and the Stroop interference ($r = -.486$, $p < .01$). Time latency of the N170 component elicited by face-like objects was negatively associated with the SDMT performance [$r = -.474$; $p < .01$].

4. Discussion

In the present study we aimed to further characterize early visual recognition deficits in premanifest HD. We

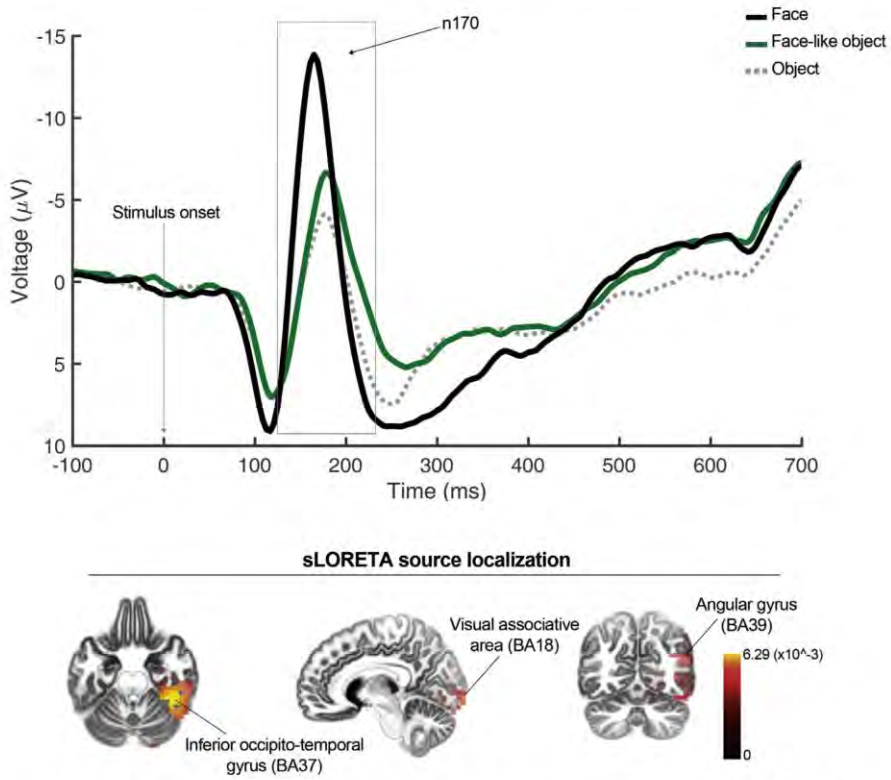

Fig. 3 – ERPs at T6 position and source localization associated with the presentation of object, face, and face-like object. The figure shows a negative peak of maximum amplitude around 170 ms following the presentation of faces (N170). The component is less pronounced in the face-like object condition but significantly different from that elicited in the object condition. Source localization involves BA37, BA18 and BA39 as neural origin of the N170.

hypothesized that in premanifest HD, early disruption of the ventral visual pathway will contribute to some degree of abnormality in face and/or in face-like object processing.

To explore our hypothesis, we used an object, face, and face-like object recognition task that was administered to the participants within an EEG setting. We found that premanifest participants exhibited a dramatic increase in the number of errors in the face-like object condition that was not explained by more impulsive responses. Moreover, premanifest participants showed a significant reduction of the N170 component evoked by face-like objects that correlated with the increased number of errors seen in the behavioral task.

Our findings illustrate a specific form of selective recognition deficit for face-like objects, which we have called "prosopagnosia to facial pareidolia", occurring in premanifest individuals up to 15 years before estimated time to diagnosis. This impairment was closely associated with alterations in a neurophysiological signature of face processing, the N170, supporting a functional disruption of the ventral visual pathway, and specifically the face fusiform area, in premanifest HD participants. Importantly, this disruption did not seem to be sufficiently severe to compromise more simple perceptual processes, highlighting the need to develop sensitive instruments to capture early changes in the preclinical stages of neurodegenerative disorders.

In the total sample, the RT elicited to perform correct responses was longer in the face-like object condition than in the other conditions. This finding is congruent with previous data supporting that face-like object recognition is more demanding than simple object and face processing (Caharel et al., 2013).

Whereas no differences were found in accuracy between groups regarding object and face condition, premanifest participants exhibited a dramatic increase in the number of error responses in the face-like object condition. These errors consisted of classifying 30% of the face-like objects as simple objects. As no between groups differences were found in the RT elicited during error responses in this condition, the increased rate of error responses seen in premanifest participants cannot be attributed to more impulsive and faster responses.

Regarding the neurophysiological measures and in comparison with the object condition, both the face and the face-like object conditions elicited higher negative deflections around 170 ms, with topography compatible with the N170. Source localization showed that the main neural contributor to the N170 was the right visual associative cortex, and specifically, the right fusiform gyrus.

The latency of the N170 elicited in the face condition was significantly shorter than that in the objects and face-like objects conditions (Caharel, d'Arripe, Ramon, Jacques, & Rossion, 2009). These data are comparable with previous studies of the N170 in face and face-like objects, suggesting that extended resources are engaged in front of an ambiguous stimulus that could be perceived as a face, such as inverted faces or face-like objects (Caharel et al., 2009;

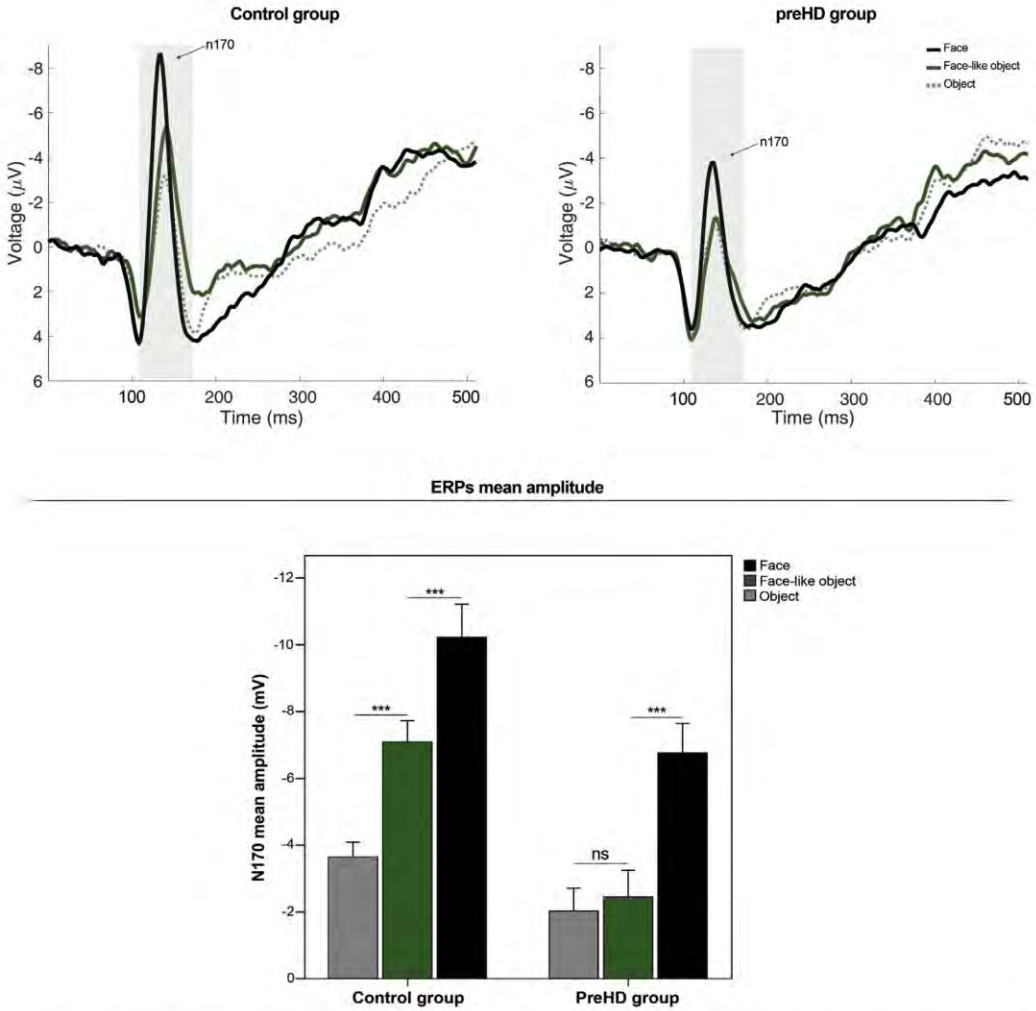

Fig. 4 – ERPs at T6 and mean amplitude of the N170 after object, face, and face-like objects in the two participant groups. The top right panel shows the abolition of the N170 component elicited after presentation of the face-like object in the preHD group. The bars illustrate the reduction of the mean amplitude in all the components obtained in the preHD group.

Caharel et al., 2013). The significant reduction in the N170 component elicited in the face and face-like object condition and the tendency to reduction in the object condition in the preHD group indicate some level of reduction in all the neurophysiological measures. This suggests that mechanisms related to aberrant neural synchronization in HD may induce an overall reduction of all ERPs or at least, those involved in visual processing. Aberrant neural synchronization and reduced amplitude elicited by visual stimulus has been seen in both premanifest and early manifest HD patients and would support this suggestion (Antal et al., 2003; Ellenberger, Petro, & Ziegler, 1978; Oepen, Doerr, & Thoden, 1982, 1981). However, the study of neural synchronization was not the focus of the present work. Moreover, retinal thinning, thalamic abnormalities, and pathological changes in the primary visual area are known to contribute to reduced visual evoked potential amplitude in HD (Dhalla, Pallikadavath, & Hutchinson, 2019).

To overcome effects that could be explained by a generalized reduction of the ERPs in premanifest HD, we computed the difference waveform between each condition. This allowed us to obtain comparable measures suppressing any difference that could be task-unspecific but inherent to a particular group. Following this approach, we saw that the N170 difference wave-form obtained for the face-like object condition was only significantly reduced in the premanifest group. Moreover, the mean amplitude of this component was strongly associated with task performance accuracy. Accordingly, the disruption of the N170 component has a direct impact on the difficulties observed in the ability to perceive faces in face-like objects.

As previously reported (Martinez-Horta et al., 2016), premanifest participants scored higher in measures of apathy and performed worse in measures of visual scanning, speed processing, and control of interference (Martinez-Horta et al., 2016; Tabrizi et al., 2009). All these measures - known to be sensitive to the earliest changes in HD - showed a significant association with the decreased mean amplitude of the N170 component elicited by the premanifest participants in the face-like object condition. Additionally, a longer latency of this component was also associated with performance on visual scanning and processing speed.

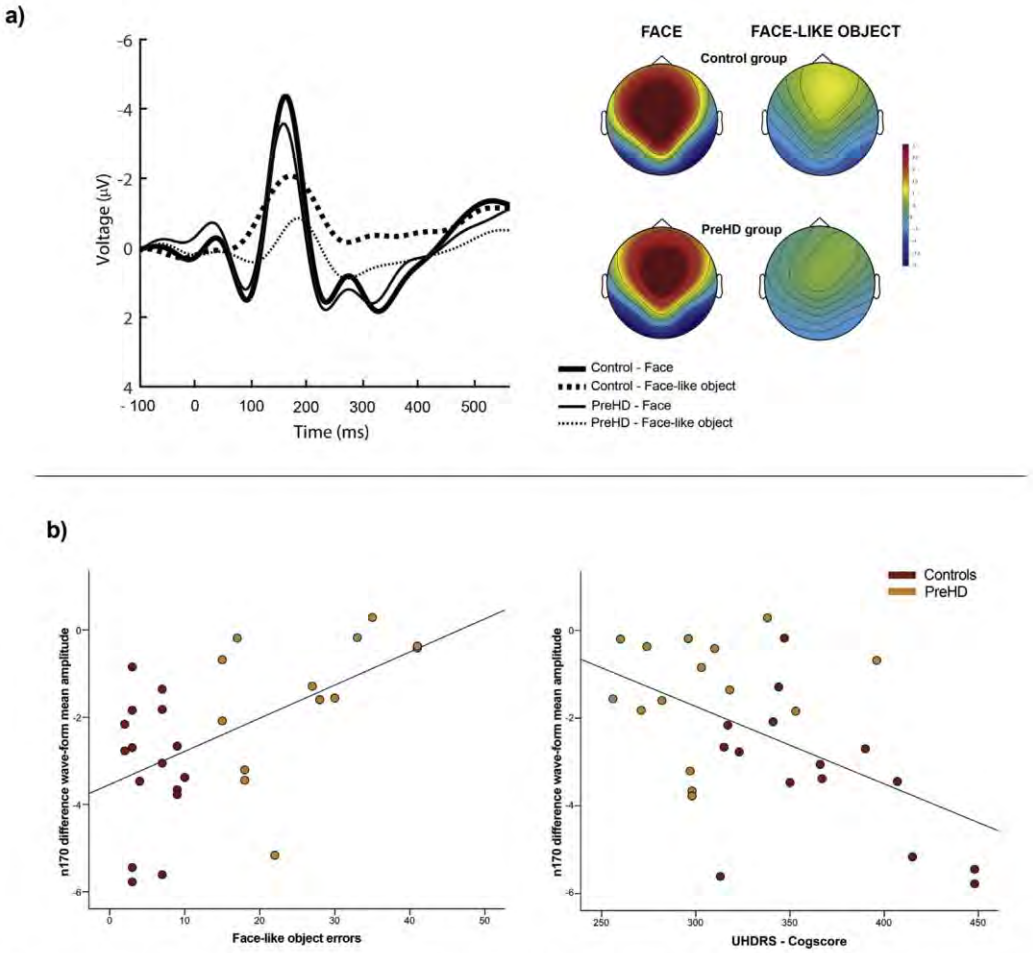

Fig. 5 – A) Difference wave-form at T6 of the face and face-like object condition in each participant group and topographical maps. A reduction in the N170 component associated with face-like objects is evident. B) Scatter plot depicting the significant correlation between mean amplitude of the difference wave-form elicited by the face-like object condition in T6 and rate of errors in face-like object recognition (top) and mean cognitive performance (bottom).

Interestingly, studies in other neurodegenerative diseases involving posterior-cortical degeneration and striatal atrophy (i.e.,: Lewy body dementia and PD), found opposite behavioral results. The authors reported that patients tended to perceive facial pareidolia more easily than healthy controls (Mamiya et al., 2016; Uchiyama et al., 2012, 2015; Yokoi et al., 2014). However, among other symptoms, Lewy body dementia and PD are characterized by the occurrence of complex visual hallucinations, an infrequent symptom in HD. Why posterior-cortical deficits promote visual hallucinations in PD and Lewy body dementia but not in HD patients is poorly understood.

The main limitations of the current study are the relatively small sample size which is in part justified due to the low-prevalence of HD and the rejection to participate in studies that often characterize the premanifest population. Another important limitation is the lack of structural brain imaging. Further studies are required to explore the association between the present findings and the structural integrity of the visual cortex in a larger sample of HD patients. Moreover, the inclusion of symptomatic HD participants could help determine whether a pattern of worsening in face-like object recognition occurs along the course of HD. Further studies involving a large sample are also required to confirm the replicability of the behavioral findings illustrated in the present work.

In conclusion, premanifest HD participants have a specific visuoperceptual deficit that selectively disrupts the perception of face-like objects as early as 15 years before estimated time to diagnosis. This deficit can be measured as an increased number of errors in the recognition of face-like object stimulus and as an abolition of the N170 component elicited by face-like objects. The occurrence of selective impairment in face-like object processing in the clinical group emphasizes the need to develop specific instruments to capture early changes in premanifest HD.

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Declaration of Competing Interest

The authors declare no competing financial and/or non-financial interests in relation to the work described in the present manuscript.

CRediT authorship contribution statement

Saul Martínez-Horta: Conceptualization, Data curation, Project administration, Formal analysis, Writing - original draft. **Andrea Horta-Barba:** Data curation, Project administration, Writing - review & editing. **Jesús Perez-Perez:** Data curation, Formal analysis, Project administration, Writing - review & editing. **Mizar Antoran:** Data curation, Project administration, Formal analysis, Writing - original draft. **Javier Pagonabarraga:** Conceptualization, Formal analysis, Writing - original draft. **Frederic Sampedro:** Formal analysis, Writing - original draft. **Jaime Kulisevsky:** Conceptualization, Data curation, Writing - original draft.

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4.3. Artículo 3:

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ORIGINAL RESEARCH

Structural brain correlates of irritability and aggression in early manifest Huntington's disease

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Abstract

In Huntington's disease (HD), irritability and aggressive behavior represent highly prevalent and disabling neuropsychiatric symptoms. However, their structural brain correlates have not been extensively explored. Here, we rated the severity of irritability and aggression (IAs) using the Problem Behaviors Assessment for HD (PBA-s) in 31 early HD participants. The IAs score was computed as the mean severity score for the irritability plus the mean severity aggression PBA-s items. Seventeen patients were classified as IAs (IAs score > 2) and 14 as non-IAs. All participants had available T1-MRI data. A grey matter volume voxel-based morphometry group comparison was performed, using age, motor status, severity of other PBA-s items and disease burden as covariates. Aside from irritability, aggression and obsessive-compulsive behavior, both groups were comparable in terms of other clinical and sociodemographic variables. In the IAs group, a significant reduction of grey-matter volume (GMV) was found in the bilateral caudate, putamen and globus pallidus, left pulvinar nucleus, right superior temporal pole (BA 38), left mid temporal gyrus (BA 21), right inferior temporal gyrus (BA 20) and left medial OPFC (BA 11). Lower GMV in the left pulvinar nucleus was significantly associated with higher anxiety and lower GMV in the left medial OPFC was significantly associated with higher suicidality. In sum, IAs in HD is associated with structural brain damage in a set of key nodes involved in the expression and down-regulation of negative emotions.

Keywords Huntington's disease; irritability · VBM · MRI

Introduction

Huntington's disease (HD) is a monogenetic, autosomal dominant neurodegenerative disorder caused by a CAG polyglutamine expansion in the *HTT* gene (Walker 2007). Even though the clinical diagnosis of HD is based on the presence of unequivocal motor abnormalities, the progressive presentation of multiple neuropsychiatric symptoms and cognitive decline also define the clinical signature of HD, and can be identified many years before the onset of motor symptoms (Paulsen et al. 2017; Tabrizi et al. 2009).

Among the different neuropsychiatric symptoms of variable severity occurring in HD, depressive mood, apathy, perseverative behavior and irritability are frequently reported (Craufurd et al. 2001; Martinez-Horta et al. 2016; van Duijn et al. 2007). Together with depression and anxiety, irritability, aggressive behavior and angry mood represent core features of the disease's psychiatric profile even in premanifest HD individuals. In association with aggressive outbursts, irritability maintains a relatively high prevalence between 38% and 73% of patients at different disease stages (Bouwens et al. 2015; Maltby et al. 2017; Reedeker et al. 2012; van Duijn et al. 2014).

Irritability is conceptualized as an internal state or mood characterized by a feeling of frustration and anger. This state

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usually involves short and bad temper and makes individuals experiencing this emotion especially prone to easily react to environmental stressors (Craig et al. 2008; Snaith and Taylor 1985). At the same time, aggression is the planned or reactive expression of hostility, injury and destructive behavior directed to others or to ourselves (Siever 2008). Although irritability not always result in aggressive behaviors, there is a continuum between irritable mood and violent assaultive behavior (Snaith and Taylor 1985).

In HD, irritability and aggressive behavior are characterized by a poor or lack of control over anger and impulse, and ranges from bad temper to violent outbursts including verbal, physical aggression, and criminal behavior (Craufurd et al. 2001; Fisher et al. 2014). In contrast to premeditated forms of aggression, the nature of anger and aggressive behavior in HD is eminently impulsive and precipitated. Thus, violent outbursts in HD are characterized by high levels of autonomic arousal and precipitation by provocation associated with negative emotions in the context of a more or less persistent irritable mood. Although irritability refers to a mood state and aggression reflects harmful behavior, in the HD literature both symptoms are frequently grouped together in an "anger" cluster (Craufurd et al. 2001). Although these symptoms are unquestionably associated with negative consequences for both patients and caregivers, they have been scarcely studied in HD. Moreover, very little is known about its structural brain substrates.

Previous clinical studies in HD showed an association between anger and both obsessive-compulsive behavior (OCB) and higher rates of suicidal ideation (Anderson et al. 2010; Hubers et al. 2013; Thompson et al. 2012). Conversely, there is little evidence suggesting an association between anger and cognitive deterioration, depression or psychosis (Reedeker et al. 2012). Only a few neuroimaging studies targeted irritability and aggressive behavior in HD, which focused on premanifest individuals and addressed their functional correlates within a task-related fMRI setting. In one study, a decreased top-down control by the orbital prefrontal cortex (OPFC) over excessive bottom-up drives signaled by the limbic system is reported as a risk factor for aggressive behavior in HD (Kloppel et al. 2010). These results were coherent with the model suggesting that impulsive and precipitated irritability and aggressive behavior results from the failure of the frontal-executive control mechanisms (top-down) to downregulate the expression of impulsive emotional responses (bottom-up). However, in this study no differences in the measures of irritability were found between the controls and HD participants, and thus, specific functional brain differences associated with the objective presence of irritability were not reported.

In another study, a novel task was administered to induce different emotional states through the recollection of autobiographical events. In premanifest individuals, during this task, anger was associated with increased activity across a distributed network that included the pulvinar nuclei, the anterior cingulate cortex and the somatosensory associative cortex. Decreased activity in the amygdala and atrophy in the basal ganglia were also found (Van den Stock et al. 2015). Taken together, previous functional studies in premanifest subjects support that irritability and aggression in HD is associated with a malfunction across a frontal-subcortical network strongly implicated in emotional regulation and action control.

In this work we aimed to address the grey-matter volume (GMV) correlates of irritability/aggression (IAs) in early manifest HD. We hypothesized that a structural compromise in brain regions involved in top-down emotion control and bottom-up emotional salience. For that, we rated the severity of IAs along with other clinical measures. We used the short version of the Problem Behaviors Assessment Scale for HD (PBA-s) (Callaghan et al. 2015; Kingma et al. 2008), and compared a sample of early manifest HD patients free of symptoms of irritability and aggression with a matched sample of patients presenting clinically relevant irritability and/or aggression. To specifically address the GMV differences associated with these symptoms in our sample, we controlled for the effect mediated by other clinical (motor, cognitive, psychiatric and genetic) variables associated with HD.

Methods

Participants

We recruited 31 symptomatic gene-mutation carriers (CAG ≥ 39) from the outpatient clinic of the Movement Disorders Unit at Hospital de la Santa Creu i Sant Pau in Barcelona. Informed consent was obtained from all individual participants included in the study. Severity of motor symptoms was rated by an experienced neurologist in movement disorders (JPP) using the Unified Huntington's Disease Rating Scale (UHDRS-TMS) and all study participants were rated with a diagnostic confidence level equal to 4 (motor abnormalities that are unequivocal signs of HD with ≥99% confidence) (Group 1996). All participants were classified as early or mild HD (Shoulson and Fahn stages 1 and 2) based on the UHDRS-TMS and a total functional capacity (TFC) greater than seven (Shoulson and Fahn 1979). The disease burden score (DBS) assumed as an index of the livelong exposure to mutant huntingtin was calculated using the formula based on age and CAG repeat length: [age x (CAG-35.5)] (Penney Jr. et al. 1997). Sociodemographic and clinical data including age, sex, education, medication (use of selective serotonin reuptake inhibitors; SSRI and neuroleptics; NLP), and global cognitive functioning were recorded.

The cognitive subtests of the UHDRS (Cogscore) were administered in addition to other cognitive measures (Group 1996). Accordingly, the cognitive assessment was composed of the phonetic verbal fluency test (FAS), the Stroop color

naming, word reading and interference test, the symbol digit modalities test (SDMT), the semantic verbal fluency (animals) and the parts A and B of the Trail Making Test.

All participants were free of any neurological disorder other than HD and had no history of brain surgery, traumatic brain injury, or drug abuse. All procedures performed in the present study were in accordance with the standards of the local Ethic Review Board of the Sant Pau hospital in Barcelona, and with the 1964 Helsinki declaration and its later amendments.

Behavioral assessment

The short version of the Problem Behaviors Assessment for HD (PBA-s) was used to rate the frequency and severity of multiple common neuropsychiatric symptoms of HD (Callaghan et al. 2015; Kingma et al. 2008). The IAs score was computed as the mean severity score for the irritability plus the mean severity aggression PBA-s items. According to previous literature on the administration and scoring of this scale, PBA-s items are considered clinically relevant when severity score is equal or over 2 points (Callaghan et al. 2015). Thus, an IAs score ≥ 2 was considered indicative of significant symptoms of irritability and/or aggression. Based on the IAs we grouped participants as "presenting significant IAs" (IAs group) and "without IAs" (Non-IAs group). The PBA-s scale also allowed us to measure the severity of other neuropsychiatric symptoms including depressive mood, suicidal ideation, anxiety, apathy, perseverative behavior, OCB, delusions, hallucinations and disoriented behavior.

Neuroimaging acquisition and preprocessing

Magnetic resonance imaging (MRI) scans were obtained 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).

Gray matter volume (GMV) data was obtained from T1-weighted images using a standard voxel-based morphometry (VBM) approach in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/). The processing pipeline methods are described in detail in our previous works (Martinez-Horta et al. 2017). Briefly, the original T1-MRI images were segmented to obtain their corresponding gray matter tissue probability maps. These maps were then spatially normalized into Montreal Neurological Institute (MNI) space of voxelsize 2x2x2mm using DARTEL and smoothed using a Gaussian kernel of 8 mm Full-Width-at-Half-Maximum (FWHM).

Statistical analysis

Clinical and socio-demographic variables were subjected to independent *t*-test comparisons between the two groups of interest for continuous variables and $\chi 2$ for categorical variables. A correlation analysis was used to explore the contribution of IAs severity over other clinical variables. For these analyses, a $p < 0.05$ was considered significant.

Regarding GMV differences across groups, a voxelwise t-test analysis between IAs and non-IAs groups was performed. Age, sex, education, DBS, UHDRS-TMS, total PBA score (excluding the IAs score) and total intracranial volume (TIV) were entered as covariates of no interest.

Voxelwise imaging results showing $p < 0.005$ (uncorrected) and a minimum cluster extent size of k = 100 voxels was considered significant (Lieberman and Cunningham 2009; Martinez-Horta et al. 2017; Vaquero et al. 2017). Clusters surviving family-wise error (FWE) correction are reported in the corresponding cluster description table.

Finally, GMV values in the identified clusters were computed using build-in SPM functions to perform further regression analyses with other clinical variables of interest, for which a $p < 0.05$ was considered significant.

Results

Clinic and sociodemographic data

The sample consisted on 31 early-mild HD symptomatic confirmed gene-mutations carriers (mean age = 53.7 ± 13; mean CAG repeat length = 43 ± 2; mean UHDRS-TMS = 32 ± 18; mean TFC = 10 ± 3). According to the IAs score, $n = 14$ participants were included in the Non-IAs group (mean IAs score = 0.43 ± 0.6) and $n = 17$ in the IAs group (mean IAs score = 3.47 ± 1.6). This indicates a IAs prevalence of 54.8% in this sample. As seen in Table 1, both groups were otherwise similar in terms of clinical and sociodemographic variables.

Both groups showed equivalent cognitive performance. Regarding behavioral measures, the IAs group showed higher severity scores on irritability ($p < 0.001$), aggression ($p < 0.001$), and OCB ($p < 0.05$) (Table 2).

In the overall sample, correlation analysis showed a significant association between higher IAs score and OCB severity (r = 0.565; $p < 0.001$). Exploring the components conforming the IAs score, the analysis revealed that this association was exclusively mediated by a strong correlation between OCB and PBA-s aggression severity (r = 0.615; $p < 0.001$).

Voxel-based morphometry results

The voxelwise group comparison revealed a significant reduction of GMV in the IAs group within a set of frontal, subcortical and temporal regions (see Fig. 1). Specifically, the IAs group exhibited lower GMV in bilateral caudate, putamen and globus pallidus, left pulvinar nucleus of the thalamus, the right superior temporal pole (BA 38), the left mid temporal gyrus

Table 1 Sample's clinical and sociodemographic characteristics

	IAs group	Non-IAs group	*P*
Age	53.7 ± 14	53.7 ± 10	0.999
Gender (f/m)	10/4	10/7	$\chi^2 = 0.364$
Education (years)	12 ± 5.8	11 ± 4	0.644
CAG	43.1 ± 3	43 ± 2.6	0.853
DBS[a]	375.2 ± 67.3	380.9 ± 1	0.834
UHDRS-TMS[b]	27.4 ± 17	37.7 ± 18	0.116
TFC[c]	10.4 ± 3	9.7 ± 3.5	0.535
SSRI[d]	8 (47%)	6 (42%)	$\chi^2 = 0.551$
NLP[e]	3 (17%)	1 (7%)	$\chi^2 = 0.378$
IAs score	3.5 ± 1.5	0.4 ± 0.6	<0.001
Cogscore	153.4 ± 90	131.8 ± 80	0.492
FAS[f]	18 ± 11	18 ± 12	0.987
SDMT[g]	22.6 ± 17	18.7 ± 11	0.476
Stroop color naming	36.5 ± 22	32.5 ± 22	0.617
Stroop word naming	55.7 ± 32.3	46.8 ± 29.5	0.433
Stroop interference	20.5 ± 15.4	15.8 ± 11.6	0.358
Semantic verbal fluency	12.8 ± 5.3	11 ± 5	0.318
TMT-A[h]	88.7 ± 67.7	115.9 ± 70.6	0.283
TMT-B[i]	184.7 ± 70	220 ± 36.6	0.084

[a] Disease burden score; [b] Unified Huntington's Disease Rating Scale – Total motor score; [c] Total functional capacity; [d] Selective serotonin reuptake inhibitors; [e] Neurolepties; [f] Phonetic verbal fluency; [g] Symbol Digit Modalities Test; [h] Trail Making Test part A; [i] Trail Making Test part B

(BA 21), the right inferior temporal gyrus (BA 20) and the left medial OPFC (BA 11) (Table 3).

Apart from its contribution to IAs, GMV values at some of the identified clusters showed significant correlations with other clinical variables. The overall cogscore showed a mild correlation with GMV in the left medial OPFC ($r = 0.415$; $P < 0.05$). Semantic verbal fluency showed a mild correlation with GMV in the bilateral basal ganglia ($r = 0.405$; $P < 0.05$) and with the right mid temporal gyrus ($r = 0.474$; $P < 0.01$) and a strong correlation with GMV in the left medial OPFC ($r = 0.634$; $P < 0.001$). The GMV in the left medial OPFC also showed a mild positive correlation with the SDMT ($r = 0.457$; $P < 0.05$), Stroop color naming ($r = 0.382$; $P < 0.05$), Stroop word-reading ($r = 0.373$; $P < 0.05$) and Stroop interference ($r = 0.432$; $P < 0.01$). Higher PBA-s scores on anxiety correlated with lower GMV in the left pulvinar nucleus ($r = -0.435$; $P < 0.01$) and higher PBA-s scores on suicidality correlated with lower GMV in the left medial OPFC ($r = -0.417$; $P < 0.05$).

Table 2 PBA-s assessment

	IAs group	Non-IAs group	*P*
Depressive mood	1.3 ± 1.3	1 ± 1.1	0.511
Suicidality	0.5 ± 0.8	0.4 ± 1	0.777
Anxiety	1.3 ± 1.3	0.5 ± 1.1	0.070
Irritability	2.6 ± 0.7	0.5 ± 1.1	<0.001
Aggression	1.7 ± 0.3	0.1 ± 0.5	<0.001
Apathy	1.7 ± 1.4	1.6 ± 1.6	0.910
Perseverative behavior	2 ± 1.2	1.3 ± 1.1	0.109
OCB	1 ± 1.4	0.1 ± 0.5	0.035
Delusion	0.2 ± 0.6	–	0.197
Hallucinations	–	–	–
Disorientation	0.5 ± 0.7	0.4 ± 0.8	0.713

Discussion

In the present study, we assessed whether significant symptomatology of irritability and or aggression (IAs) in early HD was associated with structural brain alterations. To focus on the relationship between GMV and IAs, we controlled the influence of other potential confounders like CAG repeat length, severity of motor symptoms and severity of other coexisting neuropsychiatric features.

A pattern of GMV atrophy was revealed, which included a set of fronto-temporal and basal ganglia regions with a well-known involvement in cognitive control, emotional regulation, appearance of hostility and spontaneous aggression in human and in other mammals (Anderson et al. 2006; Bouwens et al. 2015; Damasio et al. 2000; Tonkonogy and Geller 1992; Vytal and Hamann 2010). Most of the identified areas are anatomically interconnected through segregated basal ganglia–thalamo–cortical circuits with other regions that participate in the expression of emotions and in cognitive control, such as the amygdala or the anterior cingulate cortex (Damasio et al. 2000; Denson et al. 2009).

Of particular importance is the role of GMV atrophy at the pulvinar thalamic nucleus in association with IAs in HD, a significant association that needs to be replicated in a larger sample. This structure has been previously associated with the expression of anger and with the emotional recognition of fear (Damasio et al. 2000; Vaquero et al. 2017; Ward et al. 2007). Critically, the pulvinar nucleus maintains reciprocal connections with multiple limbic, PFC and temporal regions such as the dorsomedial pulvinar connection with the amygdala, the medial pulvinar with the orbital PFC and the ACC, and the lateral pulvinar with the parietal and temporal lobes (Benarroch 2015; Pessoa and Adolphs 2010; Romanski et al. 1997). Altogether, the pulvinar nucleus is proposed to participate on the amplification of evoked responses in behaviorally-relevant stimuli via these PFC-limbic circuits (Pessoa and Adolphs 2010). Hence, pulvinar alterations may promote changes on the limbic system valuation of incoming stimulus, having a profound impact on subsequent behavior. In a previous work, increased pulvinar activation during anger experience was observed in premanifest HD (Van den Stock

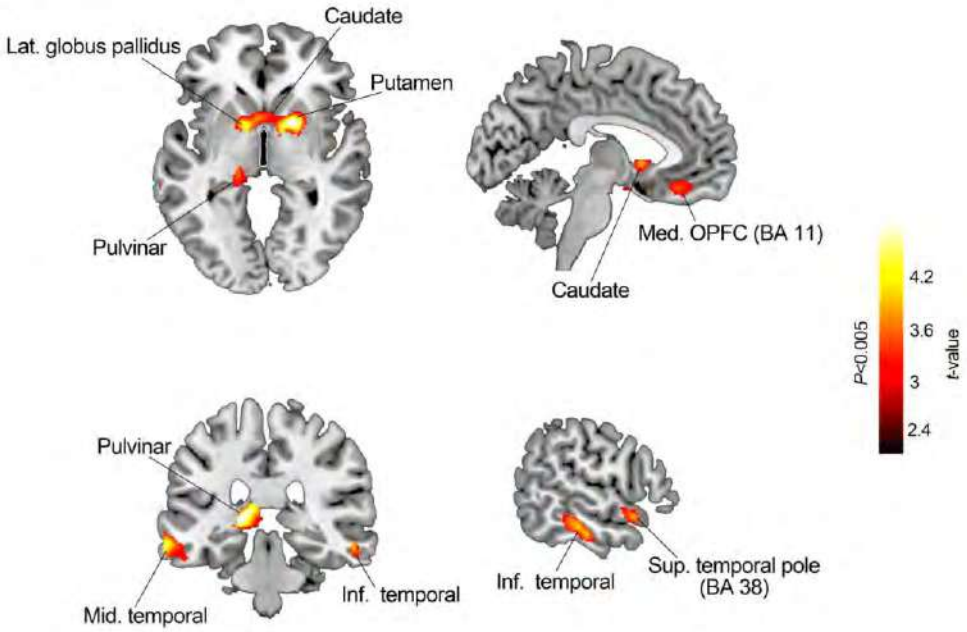

Fig. 1 Regions showing lower GMV in the "IAs group" compared to the "Non-IAs group". There were no regions showing a significant increase in grey matter volume. For depicting purposes the image is shown at $p < 0.005$

et al. 2015). Critically, this pattern of pulvinar over-activation was associated with concomitant putaminal atrophy, highlighting the important relationship between the structural integrity of the basal ganglia and the functionality of other brain regions related to emotion an anger control.

Our data also reveals interesting negative associations between the observed GMV compromise and clinical outcomes. First, GMV in the pulvinar nucleus was negatively associated with the severity of anxiety. This association goes in the proposed direction regarding the "amplification" role of the pulvinar nucleus and how the dysregulation of this nucleus might influence the overexpression of negative emotions (Pessoa and Adolphs 2010). Secondly, GMV in the medial OPFC was negatively associated with suicidal ideation. This association goes in line with previous studies supporting the involvement of structural and functional changes in the left OPFC and suicidal ideation and lethality (Monkul et al. 2007; Oquendo et al. 2003). The mechanisms involved in how OPFC damage participates in suicidal behavior are partially understood. However, the OPFC interacts with the limbic system, particularly with the amygdala. This circuit plays a major role in the adaptation of behavior, decision making, encoding of emotional stimuli and predicting expected outcomes. OPFC damage has been associated with impulsivity and with difficulties adjusting behavior. Thus, as proposed in previous studies focusing on depression or borderline personality disorders, poor cognitive control over the expression of negative emotions and decision making deficits might lead to suicidality (Monkul et al. 2007).

Interestingly, the overall cognitive performance did not differed between both groups. This supports the idea that significant IAs occur in HD independently of the degree of cognitive deterioration. However, we found an interesting association between IAs and OCB severities, which has been previously reported (Anderson et al. 2010). As OCB partially reflects inefficient cognitive control over extremely salient emotional signatures, the association between IAs and OCB would be expected in a model proposing the existence of a pattern of over-salience coexisting with disrupted cognitive control.

Of note, anterior temporal pole and OPFC abnormalities have also been associated with poor cognitive control and aggressive behavior in multiple psychiatric and neurological disorders, including temporal lobe epilepsy (Ito et al. 2007), Alzheimer's disease (Eastley and Wilcock 1997), frontotemporal dementia (Miller et al. 1997), antisocial personality disorder and traumatic brain injury (Anderson et al. 2006; Critchley et al. 2000; Denson et al. 2009).

Table 3 Results of the GMV voxel-based morphometry analysis

Voxel-based morphometry analysis of GMV			
Anatomical region	Cluster size	*T* value	MNI coordinates (*x*, *y*, *z*)
Basal ganglia (Lat. Globus pallidum / caudate / putamen)*	1758	4.53	20, 5, −5 −12, 6, −3
Left pulvinar nucleus*	804	5.39	−15, −30, 6
Left mid temporal gyrus	780	4.38	−61, −52, −17
Right inferior temporal gyrus	330	3.65	58, −21, −23
Right temporal pole	287	3.65	51, 11, −11
Left medial OPFC	258	2.87	−6, 35, −13

*Clusters surviving $p < 0.05$ FWE

In accordance with current models on the neural substrates of aggressive behavior (Siever 2008), in HD, structural damage in subcortical and temporal lobe regions that represent key nodes involved in the processing and expression of emotions, coexist with structural damage in OPFC regions that are critical both in the integration of emotional/affective signals and in the top-down regulation of emotional expression. Phenomenologically, anger in HD clearly reflects a form of impulsive –and not premeditated– aggressiveness. Despite there are no clear precipitants for aggressive behavior in HD, a pattern of exaggerated emotional response in association with a deficient regulation over it appears to be a reasonable explanation for the production of this symptom. Our results support a neurobiological origin of irritability and aggression in HD mediated by the disruption of multiple systems associated with emotional expression and regulation. Thus, subcortical and temporal damage may facilitate a pattern of excessive bottom-up drive of negative emotions and anger. Conversely, OPFC degeneration may participate on the failure to suppress these behaviors due to the disruption of the top-down modulation of these emotions and patterns of actions. The co-existence of increased negative emotions and poor cognitive control would then contribute to the behavioral expression of anger in HD.

A main limitation of this study is the relatively low sample size. Additionally, the inclusion of individuals at different disease stages would allow abetter characterization of the the interaction between GMV changes and IAs as a function of disease progression. Finally, a more accurate assessment and differentiation of irritability and aggressive behavior will also contribute to identify more specific associations between these symptoms and the observed volumetric brain differences.

Taking together, IAs in HD are subserved by structural brain changes disrupting subcortical regions that are critical in the appearance of irritability and aggressive behavior, along with a PFC compromise disrupting proper inhibitory or top-down control. Further research is needed to delineate the possible associations between irritability, aggression, anger, and measures of inhibitory control and disinhibition in HD. Overall, our findings revealed structural brain alterations in HD patients with irritability and/or aggression that contribute to a better understanding of the pathological basis of this highly prevalent and disrupting neuropsychiatric symptom in this population, and may help in the design of future preventive or therapeutic strategies in this clinical setting.

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Compliance with ethical standards

Conflict of interest Saul Martinez-Horta, Frederic Sampedro, Andrea Horta-Barba, Jesus Perez-Perez and Beatriz Gomez-Anson declare that they have no conflict of interest.

Javier Pagonabarraga: Has received honoraria for lecturing or consultation from Boehringer Ingelheim, UCB, Allergan, Ipsen, and Lundbeck.

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Informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, and the applicable revisions at the time of the investigation. Informed consent was obtained from all patients for being included in the study.

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4.4. Artículo 4:

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ORIGINAL COMMUNICATION

Utility of the Parkinson's disease-Cognitive Rating Scale for the screening of global cognitive status in Huntington's disease

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Abstract

Background Cognitive impairment is an essential feature of Huntington's disease (HD) and dementia is a predictable outcome in all patients. However, validated instruments to assess global cognitive performance in the field of HD are lacking.

Objectives We aimed to explore the utility of the Parkinson's disease-Cognitive Rating Scale (PD-CRS) for the screening of global cognition in HD.

Methods A multicenter cohort of 132 HD patients at different disease stages and 33 matched healthy controls were classified as having preserved cognition, mild cognitive impairment (HD-MCI) or dementia (HD-Dem) according to the Clinical Dementia Rating and Functional Independence Score. The PD-CRS and the Mini-Mental State Examination were administered. Receiver operating characteristic curve analysis was used to determine optimal cutoffs to differentiate patients according to their cognitive status.

Results A PD-CRS cutoff score ≤ 81/82 was optimal to detect HD-MCI (sensitivity = 93%; specificity = 80%; area under the curve (AUC) = 0.940), and ≤ 63/64 was optimal to detect HD-Dem (sensitivity = 90%; specificity = 87%; AUC = 0.933). MMSE scores failed to show robust psychometric properties in this context.

Discussion The PD-CRS is a valid and reliable instrument to assess global cognition in HD in routine clinical care and clinical trials.

Keywords Huntington's disease · Neuropsychology · Cognition · Cognitive assessment · Psychometrics

Introduction

Huntington's disease (HD) is a monogenetic, autosomal dominant neurodegenerative disorder caused by a CAG polyglutamine expansion in the *HTT* gene [1]. Clinical diagnosis is based on the presence of unequivocal motor abnormalities such as chorea, dystonia, parkinsonism and gait abnormalities. However, almost all patients with HD will also exhibit behavioral disturbances and cognitive decline [2]. Cognitive deterioration is progressive and can be tracked as early as 15 years before the emergence of the first motor symptoms [3, 4]. Although a clear pattern of transition from normal cognition to mild cognitive impairment has not been strictly defined in HD, dementia appears to be a predictable outcome [2, 5].

Cognitive impairment and dementia in HD have mostly been ascribed to progressive basal ganglia atrophy [4, 6]. Accordingly, it has been proposed that disruption of the frontal–subcortical circuitry is the main contributor to the prototypical frontal–executive neuropsychological profile of cognitive impairment and dementia in HD [5, 6]. More

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recently, widespread brain changes involving white matter alterations and posterior–cortical thinning have also been shown to contribute to the clinical picture of this disorder [4, 7–10].

Cross-sectional and longitudinal observational studies of HD have illustrated that performance in many cognitive tasks, especially in those addressing executive functions and processing speed, worsens linearly as disease progresses [11, 12]. These studies have identified important cognitive biomarkers to monitor the progression of HD. From a clinical and practical perspective, these measures allow clinicians to track disease progression or capture differences with healthy individuals, but they do not classify patients according to their global cognitive status in terms of cognitive normality, mild cognitive impairment, or dementia.

Formally, mild cognitive impairment (MCI) can be suspected when performance in standardized neuropsychological measures is below age- and education-adjusted means but no significant impact on activities of daily living (ADL) is evident. Dementia is assumed when objective cognitive impairment is sufficiently severe to significantly interfere with ADL. In neurodegenerative diseases, both MCI and dementia are formally diagnosed on the basis of Level II assessment, a comprehensive neuropsychological examination covering several cognitive domains. However, Level I assessments, that is, screening approaches using brief instruments that have been tested in specific diseases is also accepted. Testing general screening instruments in different diseases is of major importance, because cutoff scores for MCI and dementia may differ significantly between diseases. Such differences indicate that the same diagnostic criteria and assessment approaches do not apply equally for all neurodegenerative diseases. Although cognitive deterioration is a predictable outcome in HD, specific diagnostic criteria for MCI or dementia and validated instruments in HD are lacking [13]. Furthermore, few studies have addressed the prevalence and profile of MCI and dementia in HD [5, 14, 15].

The validation of instruments to evaluate global cognition in HD is of major importance [13]. Besides the value of characterizing global cognitive status for the work-up of HD patients in clinical practice, global cognitive assessments may be a requirement for the inclusion of patients in clinical trials. Currently, however, validated HD-specific scales for measuring global cognition are lacking and the global cognitive instruments usually used in clinical practice, such as the Mini-Mental State Examination (MMSE) or the Montreal Cognitive Assessment Battery (MoCA), or the HD Cognitive Assessment Battery (HD-CAB) or the Unified Huntington's Disease Rating Scale (UHDRS) cognitive score, offer no specific cutoff scores for the screening of cognitive status in the HD population [13, 16, 17].

The Parkinson's Disease-Cognitive Rating Scale (PD-CRS) is a screening instrument that addresses global cognition. It is freely accessible for non-profit scientific research (www.movementscales.com). It was specifically developed to capture the whole spectrum of cognitive changes in Parkinson's disease (PD) [18, 19]. In PD, frontal–executive deficits characterize the profile of early cognitive changes and MCI, but the addition of posterior–cortical alterations define the transition from MCI to dementia [18, 20]. Accordingly, the PD-CRS tests performance in frontal–executive and posterior–cortical-dependent tasks, and could be a powerful approach to characterize both frontal–striatal and posterior–cortical alterations in HD. It has demonstrated excellent psychometric attributes to differentiate patients with normal cognition from those with MCI and dementia in PD [18, 19], and it has been recommended by the NINDS and MDS task force on PD-MCI. It has an alternative form for use in re-testing as it has been translated into 19 languages. Besides, it has shown reliability and discriminative capacity equivalent to a comprehensive neuropsychological assessment using two tests for each cognitive domain [21]. In the present work, using a large multicenter HD sample, we validated and tested the psychometric properties of the PD-CRS as a screening instrument to assess global cognition in this population.

Methods

Participants

One hundred and seventy-two participants were recruited in a multicentric study from ten hospitals in five European countries (78 participants from Spain, 59 from Italy, 11 from Portugal, 21 from Germany, and 3 from Poland). One hundred and thirty-nine participants were symptomatic gene mutation carriers (CAG > 38) and 33 were gene-negative healthy controls. Participants were classified as symptomatic based on a UHDRS-TMS > 4 and a diagnostic confidence level = 4, indicating that motor abnormalities were unequivocal signs of HD with ≥ 99% of confidence. All participants were free of any neurological disorder other than HD. We excluded individuals with a history of traumatic brain injury, epilepsy, drug abuse, or non-compensated systemic disease (i.e., diabetes).

Assessments

Clinical and sociodemographic variables recorded were age, gender, education, and CAG repeat length. The severity of motor symptoms was rated by trained neurologists using the UHDRS-TMS [22]. The UHDRS Functional Independence Scale (FIS) and total functional capacity (TFC) test were administered to obtain measures of independence in instrumental and basic activities of daily living (ADL) [22,

23]. The FIS scale is based on 25 questions (with yes/no responses) that qualify abilities to independently perform ADLs. A score of "independence" is computed from the answers provided, ranging from 100% (no special care needed) to 10% (tube fed, total bed care). Patients at a more advanced disease stage were excluded due to their incapacity to perform the assessments.

The TFC rates occupation, finances, domestic chores, ADLs and care, giving a total score from 0 to 13. Disease stage was determined according to the Shoulson and Fahn criteria for HD staging (TFC > 10 for stage I, TFC 6–10 for stage II and TFC < 6 for stage III). The disease burden score (DBS)—a measure of livelong exposure to mutant Huntington—was calculated using the formula based on age and CAG repeat length: [age × (CAG − 35.5)] [24].

In the absence of a comprehensive neuropsychological assessment and a validated gold standard to classify patients according to their cognitive status in HD, we followed the approach previously used during the development of the PD-CRS [18] and the study of its psychometric properties for MCI in PD [19]. Accordingly, we used the information provided by the Clinical Dementia Rating Scale (CDR) [25]. The CDR assesses cognitive and functional performance in six areas: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. A CDR of 0 indicates no cognitive deficits, 0.5 indicates very mild cognitive impairment, and 1–3 indicate mild to severe cognitive impairment. The CDR was used as the gold standard in the first validation study of the PD-CRS. This scale has been used as the main cognitive outcome in many studies [18]. Moreover, to follow the same approach as that used in previous studies addressing the usefulness of a screening instrument to assess cognition in HD, we added the FIS [5]. As in these previous works, we used a FIS score > 80%, which indicates a decline from pre-disease level of employment, impaired performance in household chores, and difficulties managing finances. Accordingly, patients with a CDR score of 0 and an FIS score > 80% were classified as cognitively preserved (HD-NC), patients with a CDR = 0.5 and a FIS > 80% were classified as MCI (HD-MCI), and patients with a CDR > 0.5 and a FIS < 80% were classified as demented (HD-Dem).

The PD-CRS was administered to all study participants. It is composed of 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 and two independent frontal–subcortical and posterior–cortical subscores. The frontal–subcortical score is obtained by adding the immediate verbal memory, sustained attention, working memory, unprompted drawing of a clock, delayed free recall, alternating verbal fluency, and action verbal fluency. The posterior–cortical score is obtained by adding naming and the copy of a clock. Administration and scoring procedures for the different tasks composing the PD-CRS are stated in the source document of the scale which is available at www.movementscales.com. Time of administration varies as a function of the patient's cognitive status but is around 15–25 min in patients with PD. We also administered the commonly used MMSE screening test for comparative analyses. The idea behind adding this test was to explore the comparative accuracy in terms of discriminative properties of the MMSE vs the PD-CRS. Presence and severity of behavioral symptoms were addressed using the short form of the Problem Behavior Assessment Scale for HD (PBA-s) [26].

All procedures performed in the present study were approved by the ethics committee at Hospital de la Santa Creu i Sant Pau in Barcelona and conducted in accordance with the 1964 Helsinki Declaration and its later amendments.

Statistical analysis

Data are expressed as means ± standard deviations (SDs) for continuous variables and as percentages for the categorical variables. Group comparisons were performed using independent *t* tests and analyses of variance (ANOVAs) for continuous variables, Mann–Whitney for ordinal data, and the χ^2 test for categorical variables. To calculate the effect size of the differences observed between cognitive groups we used Cohen's *d* coefficient (*d* value: 0–0.3, small effect size; 0.3–0.6, moderate effect size; > 0.6, large effect size). Binary logistic regression analysis was performed to test the classification capacity of the obtained cognitive measures and the influence of other collected variables. Receiver operator characteristic (ROC) curves were generated to explore the discriminative capacity of both the PD-CRS and the MMSE. Total scores in the PD-CRS and MMSE were used as predictor variables and cognitive groups as state variables. We calculated sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the obtained cutoffs. Scores reflecting the maximum accuracy cutoff (maximum combined sensitivity and specificity) were chosen. To explore the PD-CRS performance in each group, we conducted comparisons between each subtest of the PD-CRS. All the statistical procedures were performed using the SPSS v16.0 statistical software package.

Results

Clinical and sociodemographic data

The sample consisted of 139 symptomatic gene mutation carriers (mean age = 51.6 ± 10; mean CAG repeat

length = 43 ± 2; mean education = 12.2 ± 4.5) and 33 healthy controls (mean age = 52.1 ± 8.7; mean education = 12.7 ± 4) matched for age, gender and education. As expected, significant differences were found in all the clinical (motor, cognitive, functional and behavioral) variables when comparing healthy controls and the whole HD group.

According to the CDR and the FIS, all healthy controls were classified as cognitively preserved. In the HD sample, 36 cases were classified as HD-NC, $n = 63$ were classified as HD-MCI, and $n = 41$ were classified as HD-Dem. Regarding disease stage, 75% of the HD sample were stage I, 43% were stage II, and 21% were stage III. Regarding cognitive groups, in the HD-NC group 35 patients were stage I, 1 was stage II and no patients were stage III. In the HD-MCI group, 31 patients were stage I, 29 were stage II, and 2 were III. In the HD-Dem group, 9 patients were stage I, 13 were stage II and 19 were stage III (see Table 1).

Correlation analysis

Partial bivariate correlation analysis was performed between the PD-CRS, the MMSE, age, education, CAG repeat length, PBA scores, and TFC. In this analysis, the influence of motor symptoms in terms of UHDRS-TMS was controlled. The PD-CRS and the MMSE showed moderate correlation coefficients with educational level (PD-CRS: $r = 0.522$; $P < 0.001$; MMSE: $r = 0.403$; $P < 0.001$) and with TFC (PD-CRS: $r = 0.294$; $P < 0.005$; MMSE: $r = 0.346$; $P < 0.001$). Moreover, the MMSE showed a moderate correlation with the severity of psychotic symptoms ($r = -0.322$; $P < 0.001$) and apathy ($r = -0.201$; $P < 0.05$). A mild association was found between total PD-CRS score and severity of depressive symptoms ($r = -0.195$; $P < 0.05$).

Discriminative validity between cognitive groups

One-way ANOVA showed significant differences between the HD cognitive groups in education ($P < 0.001$), CAG repeat length ($P < 0.002$), PD-CRS total score ($P < 0.001$), MMSE ($P < 0.001$), UHDRS-TMS ($P < 0.001$), TFC ($P < 0.001$), FIS ($P < 0.001$), PBA apathy score ($P < 0.005$), and PBA executive dysfunction score ($P < 0.005$).

We used stepwise logistic regression analysis (forward; conditional) to determine the variables that independently differentiated HD-MCI and HD-Dem from HD-NC. The variables found to be significantly different between cognitive groups in the one-way ANOVA were included in the analysis to assess their contribution to group discrimination. The PD-CRS total score ($P < 0.001$; odds ratio, 0.90; 95% confidence interval, 0.81–0.91), the PBA executive dysfunction score ($P < 0.01$; odds ratio, 0.84; 95% confidence interval, 0.78–0.91) and the TFC ($P < 0.01$; odds ratio, 0.47; 95%

Table 1 Clinic and sociodemographic characteristics of the sample

	Controls	HD	HD-NC	HD-MCI	HD-Dem	P^*	$P^\dagger$
Age	52.1 ± 8.7	51.6 ± 10	50.6 ± 7.3	52.5 ± 10.4	51.1 ± 11	0.788	0.618
Gender (f/m)	17/16	75/64	24/12	29/33	22/19	$\chi^2 = 0.525$	$\chi^2 = 0.163$
Education	12.7 ± 4	12.2 ± 4.5	15 ± 3.4	11.9 ± 4.5	10.4 ± 4.3	0.604	< 0.001
CAG	–	43.3 ± 2.5	42.3 ± 1.8	43.2 ± 2.3	43.3 ± 2.8	–	< 0.005
DBS	–	493 ± 100	445 ± 91	495 ± 100	498 ± 92	–	< 0.001
UHDRS-TMS	0	31 ± 20	14.4 ± 10.4	30.5 ± 15.8	47.6 ± 19.8	< 0.001	< 0.001
TFC	13	10 ± 2.7	12.2 ± 0.9	10.5 ± 1.7	7.7 ± 3.2	< 0.001	< 0.0001
Disease stage							
Stage I	–	75 (54%)	35 (97.2%)	31 (50%)	9 (22%)	–	< 0.001
Stage II	–	43 (30.9%)	1 (2.8%)	29 (45.8%)	13 (31.7%)	–	< 0.001
Stage III	–	21 (15.1%)	–	2 (3.2%)	19 (46.3%)	–	< 0.001
FIS	100	85.1 ± 14.3	97.5 ± 4.8	86.7 ± 8.1	71.9 ± 16.3	< 0.001	< 0.001
MMSE	29.1 ± 1.2	25.8 ± 3.8	28.6 ± 1.8	26.6 ± 2.4	22.2 ± 4.1	< 0.001	< 0.001
PD-CRS	102.7 ± 11	73.2 ± 22.8	97.4 ± 12.4	74.3 ± 15	50.2 ± 15	< 0.001	< 0.001
PBA-s							
Depression	0.3 ± 0.9	4.8 ± 5.9	3.1 ± 3.8	5.6 ± 6.5	5 ± 6.4	< 0.001	0.128
Irritability	0.2 ± 1	3.3 ± 4.8	1.9 ± 3.2	3.7 ± 5.2	4 ± 5	< 0.005	0.131
Apathy	0	3 ± 3.7	1.8 ± 2.7	2.8 ± 3.6	4.6 ± 4.1	< 0.001	< 0.005
Psychosis	0	0.3 ± 1.3	0.4 ± 1.5	0.2 ± 0.8	0.4 ± 1.6	0.190	0.842
Executive dysfunction	0	3.8 ± 4.6	1.5 ± 2.5	4.5 ± 5.1	4.8 ± 4.7	< 0.001	< 0.005

*P values were determined with t test for independent samples between healthy controls and HD

†P values were determined with ANOVA between HD-NC, HD-MCI and HD-Dem

confidence interval, 0.78–0.92) were identified as the best variables differentiating HD-NC from HD-MCI. The PD-CRS total score ($P<0.001$; odds ratio, 0.90; 95% confidence interval, 0.87–0.94) was the best variable to differentiate HD-Dem from non-demented HD patients.

The PD-CRS total score was excluded from the stepwise logistic regression analysis to focus on the capacity of the MMSE to differentiate between cognitive groups. The performance of the MMSE at independently differentiating HD-NC from HD-MCI was poor ($P>0.05$; odds ratio, 0.74; 95% confidence interval, 0.714–0.970) but it discriminated HD-Dem from non-demented HD ($P<0.001$; odds ratio, 0.60; 95% confidence interval, 0.498–0.721). Moreover, education and UHDRS-TMS contributed significantly to differentiating HD-MCI ($P<0.005$; odds ratio, 0.80; 95% confidence interval, 0.693–0.913) and UHDRS-TMS contributed significantly to differentiating HD-Dem ($P<0.001$; odds ratio, 0.64; 95% confidence interval, 0.529–0.786).

ROC curve analysis conducted within the HD sample indicated that a PD-CRS total score ≤ 81/82 of 134 was the maximum accuracy cutoff to detect MCI (sensitivity, 93%; specificity, 80%; PPV, 65%. NPV, 89%; area under the ROC curve, 0.940; 95% confidence interval, 0.908–0.971) and a PD-CRS total score ≤ 63/64 of 134 was the maximum accuracy cutoff to classify patients as HD-Dem (sensitivity, 90%; specificity, 87%; PPV, 80%. NPV, 88%; area under the ROC curve, 0.933; 95% confidence interval, 0.896–0.970). Table 2 summarizes the different accuracy using different PD-CRS cutoff scores.

For the MMSE, the maximum accuracy cutoff to detect MCI was a total score ≤ 26/27 of 30 (sensitivity, 80%; specificity, 39%; PPV, 58%; NPV, 80%; area under the ROC curve, 0.773; 95% confidence interval, 0.674–0.871) and at a total score ≤ 24/25 of 30 to detect dementia (sensitivity, 85%; specificity, 65%; PPV, 53%; NPV, 91%; area under the ROC curve, 0.884; 95% confidence interval, 0.825–0.942). Table 2 shows the cutoff values and their sensitivity, specificity, PPV, and NPV (see Fig. 1).

PD-CRS performance between cognitive groups

We compared the PD-CRS total score and all the scores obtained in each subtest of the PD-CRS between each cognitive group (see Fig. 2 in supplementary data). As seen in Table 3, the only subtest that differed between healthy controls and HD-NC was the unprompted drawing of a clock ($P<0.01$). Significant differences were also found in all the subtests between healthy controls and HD-MCI and HD-Dem. Focusing on the HD sample, the only subtests that did not differ significantly between HD-NC and HD-MCI groups were the unprompted drawing of a clock ($P=0.846$) and the copy of a clock ($P<0.210$). As reflected by Cohen's *d*, large effect sizes were found for all the significantly different comparisons.

Table 2 Accuracy measures for the screening of MCI and dementia using different PD-CRS cutoff scores

	Sensitivity	Specificity
PD-CRS cutoff for MCI		
79/80	0.93	0.74
80/81	0.93	0.76
81/82[a]	*0.93*	*0.80*
82/83	0.89	0.81
83/84	0.86	0.82
PD-CRS cutoff for dementia		
61/62	0.91	0.75
62/63	0.90	0.82
63/64[a]	*0.90*	*0.87*
64/65	0.89	0.87
65/66	0.88	0.87

[a]Area under the receiver operating characteristic curve analysis indicates that this was the optimum cutoff score to distinguish between cognitive groups

Italicized value indicates the cutoff score showing the best discriminative capacity

Discussion

The present study demonstrates the utility of the PD-CRS as a practical and valid method to capture global cognitive deficits in HD. To our knowledge, this is one of the first studies to address the psychometric properties of a screening instrument for global cognition in HD [5, 24, 27–29]. Importantly, specific cutoff scores were determined to detect not only patients with dementia but also patients with mild cognitive deficits that were not sufficiently severe to significantly interfere with their functional independence.

In absence of a formally validated cognitive gold standard for use as a comparator, we used the combination of the CDR and the FIS [5, 18]. Using this classification, we found no significant differences between HD patients classified as cognitively preserved and age and education-matched healthy controls, thus supporting the reliability of our gold standard.

The PD-CRS total score showed excellent discriminative capacity to differentiate between cognitive groups. Notably, although the prevalence of HD-Dem was higher in Stage III, a non-depreciable prevalence of cases with HD-Dem was already observed in stages I and II. A PD-CRS total score ≤ 81/82 was found to be the optimum cutoff score to detect mild cognitive changes that associate mild to no interference with functional independence in HD. Conversely, a PD-CRS total score ≤ 63/64 was found to indicate that

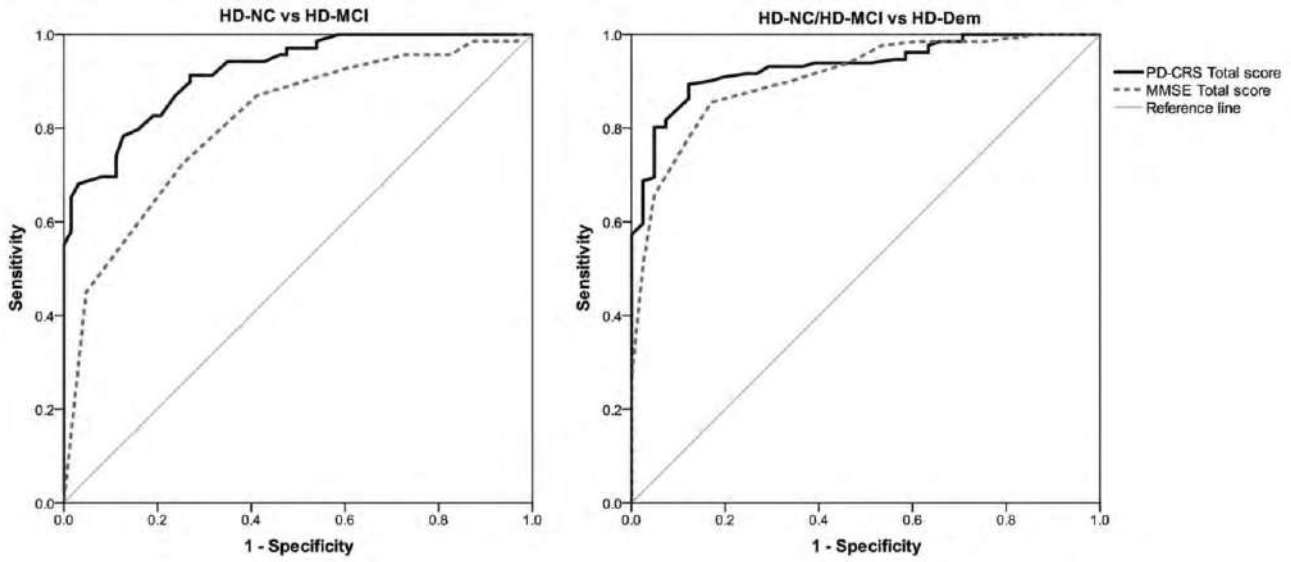

Fig. 1 Receiver operating characteristic (ROC) curves illustrating the discriminative properties of the PD-CRS and the MMSE

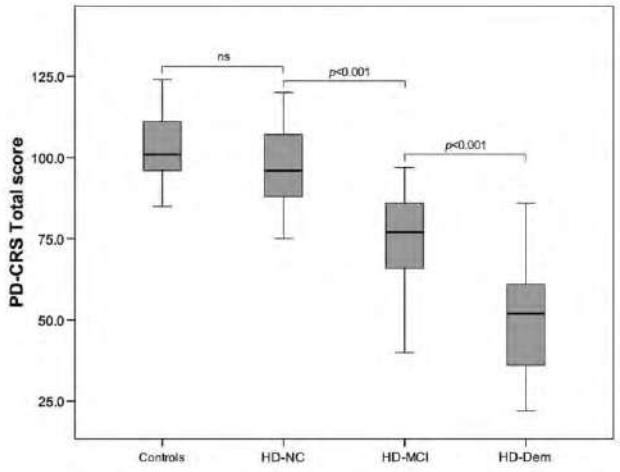

Fig. 2 Comparison of the PD-CRS total score between cognitive groups and controls

cognitive impairment is severe and compatible with the general definition of dementia based on the degree of interference on ADL. Interestingly, the observed PD-CRS cutoff scores for MCI and dementia in this large HD sample are equivalent to those previously found in the PD population [18, 19]. Equivalent properties were not found for a commonly used instrument like the MMSE. The MMSE cutoff score ≤ 26/27 showed very low specificity (36%) at detecting MCI and the cutoff score ≤ 24/25 showed poor specificity (65%) to detect dementia.

In HD, progressive cognitive deterioration is inseparable from the progression of other coexisting motor and behavioral symptoms [5, 11, 12]. When addressing the possible influence of these additional symptoms on the discrimination among cognitive groups, the PD-CRS total score was the best variable independently differentiating each cognitive group. In contrast, the MMSE on its own failed to serve this purpose, and when the PD-CRS was excluded from the model, both the UHDRS-TMS and education level were better predictors of cognitive status than the MMSE.

In all groups, both the PD-CRS and the MMSE showed strong correlations with education and mild correlations with TFC. However, in the logistic regression analysis, neither education nor TFC appeared to influence the capacity of the PD-CRS to predict the cognitive status. Conversely, performance on the MMSE was associated with the severity of apathy and psychotic symptoms. Accordingly, as seen with other cognitive measures, educational level seemed to influence the PD-CRS performance but did not alter its discriminative capacity.

The PD-CRS was significantly lower in the main HD sample than in healthy controls. According to the PD-CRS subtests, it was lower in the HD sample than in healthy controls. Looking at each group separately, PD-CRS was lower in HD-NC but not significantly different from that in healthy controls. The only task that was significantly different between these two groups was the unprompted clock drawing. Beyond constructional abilities, this task assesses planning, sequencing and conceptualization, a set of processes that are intimately associated with frontal–striatal functioning and known to be disrupted early in the course of HD. The comparison between HD-NC and HD-MCI revealed that performance was significantly lower in the HD-MCI group for all the frontal–subcortical tasks but comparable for the posterior–cortical tasks (confrontation naming and

Table 3 PD-CRS performance between cognitive groups

	Mean ± SD						
	Controls	HD-NC	HD-MCI	HD-Dem	ANOVA	Tukey's test[a]	Cohen's *d*
Total score	102.7 ± 11	97.4 ± 12.4	74.2 ± 15.1	50.2 ± 15.3	< 0.001	< 0.001[b]/< 0.001[c]/> 0.05[d]/< 0.001[e]	1.686[b]/1.584[c]
Frontal–subcortical score	74.6 ± 9.8	69.4 ± 11.7	48.6 ± 13.3	29.1 ± 11.3	< 0.001	< 0.001[b]/< 0.001[c]/> 0.05[d]/< 0.001[e]	1.660[b]/1.580[c]
Immediate verbal memory	9.3 ± 1.6	8.9 ± 1.5	7.6 ± 2	5.6 ± 1.7	< 0.001	< 0.01[b]/< 0.001[c]/> 0.05[d]/< 0.001[e]	0.735[b]/1.077[c]
Sustained attention	9.6 ± 0.6	8.2 ± 1.8	5.9 ± 3	3.4 ± 2.7	< 0.001	< 0.001[b]/< 0.001[c]/> 0.05[d]/< 0.001[e]	0.929[b]/0.875[c]
Working memory	6.3 ± 2.1	6.3 ± 1.6	4.4 ± 2	2.2 ± 1.8	< 0.001	< 0.001[b]/< 0.001[c]/> 0.05[d]/< 0.001[e]	1.049[b]/1.156[c]
Clock draw	9.6 ± 0.5	8.1 ± 2	7.9 ± 1.6	5 ± 2.5	< 0.001	> 0.05[b]/< 0.001[c]/< 0.01[d]/< 0.001[e]	1.381[c]/1.028[d]
Delayed verbal memory	7.5 ± 1.8	7.5 ± 2	4.9 ± 2.6	3.4 ± 2.3	< 0.001	< 0.001[b]/< 0.01[c]/> 0.05[d]/< 0.001[e]	1.120[b]/0.611[c]
Alternating verbal fluency	13.3 ± 4.1	12.9 ± 4.9	7.5 ± 3.7	3.8 ± 2.7	< 0.001	< 0.001[b]/< 0.001[c]/> 0.05[d]/< 0.001[e]	1.243[b]/1.142[c]
Action verbal fluency	18.5 ± 5.6	17.2 ± 6.1	10.2 ± 4.4	5.6 ± 3.5	< 0.001	< 0.001[b]/< 0.001[c]/> 0.05[d]/< 0.001[e]	1.316[b]/1.157[c]
Posterior–cortical score	28.1 ± 1.9	28 ± 1.9	25.6 ± 3.6	21.1 ± 5.5	< 0.001	< 0.05[b]/< 0.001[c]/> 0.05[d]/< 0.05[e]	0.833[b]/0.968[c]
Confrontation naming	18.3 ± 1.8	18.3 ± 1.7	16.4 ± 3	13.7 ± 4.3	< 0.001	< 0.05[b]/< 0.001[c]/> 0.05[d]/< 0.05[e]	0.779[b]/0.728[c]
Copy of a clock	9.7 ± 0.5	9.6 ± 0.6	9.1 ± 1.1	7.3 ± 2.3	< 0.001	> 0.05[b]/< 0.001[c]/> 0.05[d]/> 0.05[e]	0.998[c]

[a]Controls vs HD-Dem = $P < 0.001$ in all the variables

[b]HD-NC vs HD-MCI

[c]HD-MCI vs HD-Dem

[d]Controls vs HD-NC

[e]Controls vs HD-MCI

copy of a clock). Conversely, compared to the HD-NC and HD-MCI groups, performance of the HD-Dem group was significantly lower in all the tasks, including those associated with posterior–cortical areas. These findings suggest that although early cognitive changes in HD are prominently circumscribed to frontal–subcortical dysfunction, the transition to more severe cognitive impairment is accompanied by additional cognitive alterations in more cortical-dependent tasks (i.e., confrontation naming and visuoconstructional/visuospatial abilities) [30–32]. Interestingly, these results are comparable with those reported in previous studies addressing other neurodegenerative diseases, such as PD [18, 20].

Although progressive cognitive impairment leading to dementia will affect mostly all individuals with HD, standardized methods to address cognitive assessment and specific diagnostic criteria for MCI and dementia in HD are lacking [13]. Several cognitive measures were found to be extremely sensitive for tracking the progression of the disease from the prodromal stage or to distinguish patients from healthy controls. All these measures, including the SDMT, the Stroop word-reading and color-naming tests, the indirect circle drawing test, the facial emotion recognition test and the UHDRS cognitive composite score, provide valuable indirect information regarding cognitive and disease progression. However, they do not allow patients to be classified according to global cognitive status in terms of cognitive normality, MCI or dementia. To achieve this, specific standards must be followed. However, although specific diagnostic criteria for MCI and dementia and assessment recommendations are available for almost all neurodegenerative processes involving cognitive deterioration (i.e., Alzheimer's disease, Parkinson's disease, ALS, fronto-temporal lobar degeneration, multiple sclerosis), such criteria are lacking for HD [13]. Studies from other disorders have highlighted that diagnostic criteria for one disease do not necessarily capture the specificity of cognitive changes characterizing other diseases. Accordingly, when general and unspecific approaches are used the rate of false negatives/positives increases significantly. To solve this issue, cutoff scores in specific diseases have been established by addressing the discriminative properties of screening instruments against a gold standard. This approach illustrates that some screening instruments have good discriminative properties in one disease but poor properties in others, or that a specific cutoff score in a given test is valid in one disease but not in another. Although such testing has been performed systematically in some fields, little has been done in HD. As a result, currently used cutoff scores for the MMSE or the MoCA in HD are those originally developed to assess diseases with cognitive characteristics that differ from those in HD. In this sense, although the absence of a validated gold standard and a formal definition of MCI and dementia in HD implies a limitation, our results provide evidence on the utility of the PD-CRS as a screening procedure in HD. Instruments currently being used in care settings, clinical trials and observational studies in HD (i.e., MoCA or the MMSE) also have this limitation, highlighting the need to develop a formal definition of MCI and dementia in HD [13]. At the same time, further research is needed to determine the psychometric properties of the PD-CRS in HD.

In conclusion, our results support the usefulness of the PD-CRS as a screening instrument to assess global cognition in HD in clinical routine and in clinical trials. As our results show that the trajectory of global cognitive deterioration in HD is heterogeneous between patients, the characterization of different cognitive phenotypes in HD should be further addressed.

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Compliance with ethical standards

Conflicts of interest The authors declare no conflict of interest.

Ethical approval All procedures were performed in accordance with the standards of each regional local Ethic Review Board after protocol approval.

Informed consent Informed consent was obtained from all individual participants included in the study.

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4.5. Artículo 5:

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Structural brain correlates of dementia in Huntington's disease

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ABSTRACT

Background: Huntington's disease (HD) is a fatal genetic neurodegenerative disorder with no effective treatment currently available. Progressive basal ganglia and whole-brain atrophy and concurrent cognitive deterioration are prototypical aspects of HD. However, the specific patterns of brain atrophy underlying cognitive impairment of different severity in HD are poorly understood. The aim of this study was to investigate the specific structural brain correlates of major cognitive deficits in HD and to explore its association with neuropsychological indicators.

Participants: Thirty-five symptomatic early-to-mild HD patients and 15 healthy controls (HC) with available T1-MRI imaging were included in this study.

Methods: In this cross-sectional study, HD patients were classified as patients with (HD-Dem) and without (HD-ND) major cognitive impairment in the range of dementia. This classification was based on previously validated PD-CRS cutoff scores for HD. Differences in brain atrophy across groups were studied by means of grey-matter volume voxel-based morphometry (GMV-VBM) and cortical thickness (Cth). Voxelwise and vertexwise general linear models were used to assess the group comparisons, controlling for the effects of age, sex, education, CAG repeat length and severity of motor symptoms. Clusters surviving $p < 0.05$ and family-wise error (FWE) correction were considered statistically significant. In order to characterize the impact on cognitive performance of the observed brain differences across groups, GMV and Cth values in the set of significant regions were computed and correlated with specific neuropsychological tests.

Results: All groups had similar sociodemographic profiles, and the HD groups did not significantly differ in terms of CAG repeat length. Compared to HC, both HD groups exhibited significant atrophy in multiple subcortical and parietal brain regions. However, compared to HC and HD-ND groups, HD-Dem patients showed a more prominent pattern of reduced GMV and cortical thinning. Importantly, this thinning was restricted to regions of the parietal-temporal and occipital cortices. Furthermore, these brain alterations were further associated with poorer cognitive performance in tasks assessing frontal-executive and attention domains as well as memory, language and constructional abilities.

Conclusions: Major cognitive impairment in the range of dementia in HD is associated with brain and cognitive alterations exceeding the prototypical frontal-executive deficits commonly recognized in HD. The observed posterior-cortical damage identified by MRI and its association with memory, language, and visuoconstructive dysfunction suggest a strong involvement of extra-striatal atrophy in the onset of severe cognitive dysfunction in HD patients. Critically, major cognitive impairment in this sample was not associated with CAG repeat length, age or education. This finding could support a possible involvement of additional neuropathological mechanisms aggravating cognitive deterioration in HD.

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1. Introduction

Huntington's disease (HD) is a monogenic, autosomal dominant, neurodegenerative disease caused by the an abnormal CAG expansion on the *HTT* gene (Walker, 2007). Its inevitably progressive course is characterized by progressive motor abnormalities and neuropsychiatric symptoms, early cognitive deterioration, and the development of dementia (Ross et al., 2014; Peavy et al., 2010).

The key neuropathological hallmark of HD is progressive atrophy of the basal ganglia, which may be detected up to 15 years before motor symptoms appear and the diagnosis is made. Compelling evidence, however, shows that HD affects not only basal ganglia but the whole-brain(Rosas et al., 2008). Cross-sectional and longitudinal studies have illustrated that even in the premanifest stage of the disease, grey matter volume (GMV) reductions, cortical thinning (Cth), and reduced brain metabolism affect multiple extra-striatal regions. These regions comprise extensive territories of the parietal, temporal and occipital lobes that also contribute to the clinical expression of the disease(Rosas et al., 2008, 2005; Nopoulos et al., 2010; Tabrizi et al., 2009; Coppen et al., 2018; Rub et al., 2015; Kuwert et al., 1990).

From a neurocognitive perspective, HD has been described as a prototypical frontal-subcortical dementia due to striatal, but also thalamic degeneration(Kassubek et al., 2005), with frontal-executive disturbances, attention deficits, and processing speed reduction as the most consistently affected cognitive domains(Snowden, 2017). Involvement of the caudate nucleus and putamen in cognitive aspects of HD is characteristic(Tabrizi et al., 2009; Dogan et al., 2013). However, many studies in HD have shown that as the neuropathological changes extend to multiple extra-striatal regions, cognitive domains other than frontal-executive functions become affected. These include alterations in visuomotor integration(Gomez-Anson et al., 2009; Say et al., 2011), episodic and autobiographical memory(Carmichael et al., 2019; Harris et al., 2019), visual perception(Martinez-Horta et al., 2019; Coppen et al., 2019), mental rotation(Wolf et al., 2014; Labuschagne et al., 2016) and language production and organization(Hinzen et al., 2018; Chan et al., 2019; Chenery et al., 2002; Podoll et al., 1988), suggesting that the cognitive phenotype of HD cannot be attributed solely to frontal-striatal dysfunction.

Longitudinal studies have demonstrated that CAG repeat length plays a key role in the linear decline of cognitive capacity throughout disease progression(Tabrizi et al., 2012; Paulsen et al., 2014; Consortium, 2015; Langbehn et al., 2019). However, age-at-onset (AAO) and the rate of progression of cognitive deterioration varies greatly among individuals even when age, education level and CAG repeat length are equivalent(Consortium, 2015; Braisch et al., 2019). This heterogeneity suggests that, besides CAG repeat length, other mechanisms such as environmental and genetic variables also contribute to the neuropathological and clinical progression of cognitive deterioration in HD. It has recently been shown, for example, that genetic variability in chromosome 15, contributes to age at onset of motor and cognitive symptoms (Consortium, 2015). Other mechanisms, such as *MAPT* haplotypes and their role in the expression of TAU, have also been associated with cognitive progression in HD (Vuono et al., 2015).

Studies addressing the mechanisms involved in the differential expression of cognitive deterioration in HD are scarce, probably due to the lack of specific diagnostic criteria to differentiate HD patients with mild cognitive impairment from those with severe or major cognitive impairment in the range of dementia, and even from those with normal cognition (Mestre et al., 2018). The specific patterns of brain alterations underlying major cognitive impairment in HD thus remain elusive, partly because of the difficulty in appropriately grouping patients according to cognitive status. To overcome this limitation, we recently validated the Parkinson's Disease – Cognitive Rating Scale (PD-CRS) as a screening tool for global cognition in HD(Martinez-Horta et al., 2020). We showed that the HD-specific PD-CRS cutoff scores have a good capacity to discriminate between categories of cognitive status in patients with HD. Although this approach may have limitations, it distinguishes patients with normal or mild global cognitive defects from those with severe cognitive impairment in the range of dementia.

In the present study, our main aim was to explore specific structural brain differences underlying major cognitive impairment in the range of dementia in HD and to explore their association with poorer cognitive performance.

2. Methods

2.1. Participants

We included thirty-five symptomatic gene-mutation carriers with CAG repeat length $>$ 38 regularly attending the outpatient HD-Clinic of the Movement Disorders Unit at Hospital de la Santa Creu i Sant Pau in Barcelona, and fifteen age- and education-matched healthy controls (HC). HC were non-consanguineous relatives of the HD participants. None of the HCs had a history of neurologic, psychiatric or uncompensated systemic diseases. Similarly, all HD participants were free of any neurological disorder other than HD and had no history of brain surgery, traumatic brain injury, epilepsy, drug abuse, or uncompensated systemic disease.

Written informed consent was obtained from all participants and all procedures were performed in accordance with the standards of the Ethics Committee at Hospital de la Santa Creu i Sant Pau in Barcelona and in accordance with the 1964 Declaration of Helsinki and its later amendments.

2.2. Assessments

HD patients were classified as with severe or without severe cognitive impairment using the HD-specific PD-CRS cutoff scores(Martinez-Horta et al., 2020). These cutoff scores were determined in HD population in a previous study using as gold standard the presence of major cognitive and functional impairment. Thus, in accordance with this previous study we used the PD-CRS total score $\leq$ 64 to classify patients as with major cognitive impairment in the range of dementia(Martinez-Horta et al., 2020). This instrument assesses nine subtests: immediate and delayed verbal memory, confrontation naming, attention, working memory, unprompted draw of a clock, copy of a clock, alternating verbal fluency, and action verbal fluency. The total score is computed by summing all the raw scores obtained in each subtest, but specific scores can be grouped to compute a "frontal-subcortical" score and a "posterior-cortical" score(Pagonabarraga et al., 2008). In the present study, the PD-CRS total score was used to group patients according to their cognitive status. Accordingly, patients who obtained a PD-CRS total score $>$ 64 were included in the "non-demented" group (HD-ND) whereas patients who obtained a PD-CRS total score $\leq$ 64 were considered as with major cognitive impairment in the range of dementia (HD-Dem). The non-demented group included a slight proportion of participants with mild cognitive deficits whereas in the demented group all participants exhibited severe cognitive deficits. Accordingly, this approach allowed us to compare participants with severe cognitive impairment vs those with minor or absent cognitive impairment according to the PD-CRS. Additionally, we administered the Mini-Mental State Examination (MMSE) screening test for comparative analyses with the classification done with the PD-CRS.

We also administered the composite cognitive score of the Unified Huntington's Disease Rating Scale (UHDRS cogscore) and other measures commonly used in cognitive assessment protocols in HD (Landwehrmeyer et al., 2017). Accordingly, assessments included the Symbol Digit Modalities Test (SDMT), the phonetic fluency test with letters F, A and S, the Stroop color-naming, word-reading and interference tests, the semantic fluency test (animals) and parts A and B of the Trail Making Test (TMT). Raw scores for all these measures were adjusted for age and education level and then converted to z-scores. A

Table 1
Clinical and Sociodemographic characteristics of the sample.

	Controls	HD	HD-ND	HD-Dem	*P*
Age	45.9 ± 8	51.8 ± 12	50.85 ± 11	53.2 ± 14	[a]0.096; [b]0.156; [c]0.102; [d]0.590
Gender (f/m)	4/11	23/12	12/8	11/4	[a]0.012; [b]0.052; [c]0.013; [d]0.324
Education	12.3 ± 2	11.5 ± 4	11.2 ± 5	12 ± 4	[a]0.376; [b]0.346; [c]0.778; [d]0.615
CAG	–	43.7 ± 3	43.3 ± 3	44 ± 3	[d]0.424
DBS[1]	–	492 ± 84	469 ± 80	523 ± 83	[d]0.061
UHDRS-TMS[2]	–	28.5 ± 17	22.5 ± 18	37.2 ± 11	[d] < 0.01
TFC[3]	–	11.2 ± 2	12.1 ± 1	10 ± 2	[d] < 0.01
PD-CRS total score	106.7 ± 10.7	70.17 ± 21	84.3 ± 15	51.2 ± 10	[a] < 0.001; [b] < 0.001; [c] < 0.001; [d] < 0.001
UHDRS cogscore	–	170.2 ± 78	212 ± 72	114 ± 47	[d] < 0.001
MMSE	29.3 ± 0.8	25.2 ± 3.8	27.8 ± 1.8	21.6 ± 2.6	[a] < 0.001; [b] < 0.005; [c] < 0.001; [d] < 0.001

[1] Disease burden score; [2]Unified Huntington's disease rating scale – Total motor score; [3]Total functional capacity.
[a] HC vs HD
[b] HC vs HD-ND
[c] HC vs HD-Dem
[d] HD-ND vs HD-Dem

global composite z-score was also calculated combining all these measures.

Screening for global cognitive status was also performed in all HC using the PD-CRS and the MMSE. In this group, all participants obtained a PD-CRS > 81 (mean = 106.7 ± 10.7) and a MMSE > 27 (mean = 29.3 ± 0.8), indicating absence of cognitive impairment.

For the HD participants, a neurologist specialized in HD (JPP) rated the severity of motor symptoms using the Unified Huntington's Disease Rating Scale – Total motor score (UHDRS-TMS)(Hs, 1996). All HD participants obtained a diagnostic confidence level = 4, indicating that motor abnormalities were unequivocal signs of HD with a confidence level of 99%. All HD patients were classified as having early stage or mild disease according to a total functional capacity score (TFC) > 6(Shoulson and Fahn, 1979). The disease burden score (DBS), an index assumed to reflect lifelong exposure to mutant huntingtin, was calculated using the following formula based on age and CAG repeat length: DBS = age × (CAG-35.5)(Penney et al., 1997). We also recorded socio-demographic and clinical data, including age, sex, education and global cognitive functioning.

2.3. Neuroimaging acquisition and preprocessing

Volumetric MRI was available for all participants. 3D-T1 images were acquired on a 3 T Philips Achieva using an MP-RAGE sequence (TR/TE = 6.74/3.14 ms, flip-angle = 8°, field of view = 23 cm, matrix = 256x256 and slice thickness = 1 mm).

We applied voxel-based morphometry (VBM) and cortical thickness (Cth) neuroimaging preprocessing procedures. A standard VBM pipeline using the Statistical Parametrical Mapping software package (SPM12, http://www.fil.ion.ucl.ac.uk/spm) was performed(Martinez-Horta et al., 2019). Briefly, GMV tissue probability maps were computed from T1-MRI scans. These maps were then normalized to the Montreal Neurological Institute (MNI) space by applying the DARTEL algorithm. The resulting normalized GMV maps were then smoothed using an isotropic spatial filter of 8x8x8mm full-width at half-maximum (FWHM) to reduce inter-individual variability.

Cth 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 fully described elsewhere(Fischl and Dale, 2000). In short, 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. The resulting cortical surfaces are normalized to average space and smoothed using a Gaussian kernel of 15 mm FWHM.

2.4. Statistical analysis

Socio-demographic and clinical variables were subjected to ANOVA between the three groups. Post-hoc independent *t*-test comparisons were performed between the three groups for continuous variables and $\chi 2$ for categorical variables. To calculate the effect size of the differences observed between cognitive groups we used Cohen's *d* coefficient (*d* values: 0–0.2, small effect size; 0.6, moderate effect size; ≥ 0.8, large effect size).

Voxelwise and vertexwise measures derived from VBM and Cth analyses were introduced into a generalized lineal model (GLM) to compare these measures across groups, using age, sex, education, CAG repeat length and UHDRS-TMS as covariates. The following pairwise group comparisons were performed: HC > HD-ND, HC > HD-Dem, and HD-ND > HD-Dem. The set of clusters surviving $p < 0.05$ and family-wise error (FWE) correction for multiple-comparison (cluster-level Bonferroni correction for VBM and Monte-Carlo simulation with 10,000 repeats for Cth) were considered statistically significant.

To investigate the clinical translation of the imaging findings, we computed quantitative volumetric and mean Cth information at the identified clusters where we observed significant differences across groups. Using linear regression analysis, we then studied the association of these imaging measures with the different cognitive variables within an exploratory analysis, controlling again for the effect of potential confounders such as age, education, CAG repeat length and UHDRS-TMS, for which a p-value < 0.05 was considered significant.

3. Results

3.1. Clinical and sociodemographic data

The sample consisted of 35 HD patients (mean age = 51.8 ± 12; mean CAG = 43.7 ± 2.8; mean years of education = 11.5 ± 4.5; mean TFC = 11.2 ± 2) and 15 HC (mean age = 45.8 ± 8; mean years of education = 12.3 ± 1.6). According to the PD-CRS score, n = 20 were included in the HD-ND group (mean PD-CRS total score = 84.3 ± 15; mean age = 50.8 ± 11; mean CAG = 43.3 ± 3) and n = 15 in the HD-Dem group (mean PD-CRS total score = 51.2 ± 10; mean age = 53.2 ± 14; mean CAG = 44 ± 3). As summarized in table 1, no significant differences were found between HC, HD-ND and HD-Dem groups regarding age and education. In the HD groups, no significant differences were found between HD-ND and HD-Dem regarding age, gender, education, CAG repeat length or DBS, but the HD-Dem group showed a significantly higher UHDRS-TMS, lower TFC, lower UHDRS cogscore, lower PD-CRS total score, and lower MMSE score. In the HD-ND group, the mean MMSE score was 27.85 ± 1.8 (no impairment) while in the HD-Dem group it was 21.6 ± 2.6 (below the

Table 2
Performance in neuropsychological measures.

		HD-ND	HD-Dem	*P*	*d*
PD-CRS Total	84.3 ± 16	51.2 ± 10	< 0.001	1.543	
	PD-CRS frontal-subcortical	57.2 ± 14	28.9 ± 7	< 0.001	1.560
	PD-CRS posterior-cortical	27.1 ± 3	22.2 ± 6	< 0.005	0.993
	Immediate verbal memory	8.1 ± 1	5.5 ± 2	< 0.001	1.168
	Naming	17.6 ± 2	14.5 ± 4	< 0.005	0.946
	Sustained attention	6.7 ± 2	2.2 ± 2	< 0.001	1.418
	Working memory	5.1 ± 1	3 ± 2	< 0.005	1.084
	Clock drawing	8.3 ± 2	6.2 ± 3	< 0.01	0.866
	Clock copying	9.4 ± 1	7.6 ± 2	< 0.005	0.957
	Delayed verbal memory	6.2 ± 2	3.3 ± 2	< 0.001	1.203
	Alternating verbal fluency	9.6 ± 5	3.7 ± 2	< 0.001	1.202
	Action verbal fluency	12.9 ± 6	5.5 ± 1	< 0.001	1.251
SDMT	31.8 ± 15	15.9 ± 6	< 0.001	1.391	
	Z-score	−1.1 ± 1.3	−2.2 ± 1	< 0.05	1.039
	% cases Z-score < -1.5 SD	35%	66.7%	χ^2 = 0.65	
Stroop color-naming	51.2 ± 16	28.2 ± 12	< 0.001	1.626	
	Z-score	−1.3 ± 1.1	−2.6 ± 0.5	< 0.001	1.272
	% cases Z-score < -1.5 SD	55%	93.3%	χ^2 < 0.05	
Stroop word-reading	76.6 ± 25	41.3 ± 20	< 0.001	1.559	
	Z-score	−1.3 ± 1.3	−2.4 ± 0.8	< 0.01	1.143
	% cases Z-score < -1.5 SD	50%	80%	χ^2 = 0.07	
Stroop interference	28 ± 11	14.5 ± 8	< 0.001	1.493	
	Z-score	−1.3 ± 1	−2.2 ± 0.7	< 0.005	0.948
	% cases Z-score < -1.5 SD	50%	80%	χ^2 = 0.07	
FAS	24.2 ± 13	14.5 ± 11	< 0.05	0.805	
	Z-score	−1.6 ± 0.9	−2.1 ± 1	0.116	0.561
	% cases Z-score < -1.5 SD	60%	80%	χ^2 = 0.18	
Semantic fluency	14.8 ± 4	9 ± 3	< 0.001	1.640	
	Z-score	−1.3 ± 0.8	−2.3 ± 0.5	< 0.005	0.994
	% cases Z-score < -1.5 SD	30%	80%	χ^2 < 0.005	
TMT-A	57.2 ± 32	118.8 ± 62	< 0.005	1.248	
	Z-score	−0.7 ± 1.4	−2.1 ± 1	< 0.005	1.416
	% cases Z-score < -1.5 SD	0%	100%	χ^2 < 0.001	
TMT-B	149.6 ± 80	221.8 ± 34	< 0.01	1.174	
	Z-score	−1 ± 1.5	−2.3 ± 0.8	< 0.01	1.250
	% cases Z-score < -1.5 SD	40%	80%	χ^2 = 0.05	
Composite Z-score	−1.2 ± 0.9	−2.3 ± 0.7	< 0.005	1.078	
	% cases Z-score < -1.5 SD	35%	73.3%	χ^2 = 0.05	

general < 24 cutoff for dementia).

3.2. Neuropsychological performance in HD groups

The HD-ND group obtained a mean PD-CRS total score of 84.3 ± 15 which, according to PD-CRS criteria, situates this group in the range between cognitive normality and mild cognitive deficits. Looking at the prevalence of cases scoring above the proposed cutoff score for mild cognitive impairment in the HD-ND group (PD-CRS ≤ 81), we saw that 45% of the patients scored for mild cognitive impairment while 55% scored for cognitive normality. None of the defects, however, were severe enough to fulfill the criteria for dementia per specific PD-CRS criteria in HD.

As reported in table 2, after adjustment for age and education, all the measures obtained through the UHDRS cogscore and through the other Enroll-HD assessments were significantly different between groups in all the cases with the exception of the phonetic verbal fluency. In the HD-ND group, all the obtained z-scores were in the lower range of normality, but above the critical cutoff of −1.5 SD with the exception of the phonetic verbal fluency (-1.6 ± 0.9). In this group the mean composite z-score was −1.2 ± 0.9 with 35% of cases scoring below −1.5 SD. Conversely, in the HD-Dem group all measures scored below −2 SD and the mean composite z-score was −2.3 ± 0.7 with 73.3% of cases scoring below −1.5 SD. In congruence with the range of PD-CRS scores obtained by the HD-ND group, performance below −1.5 SD was found in more than half of the non-demented cases for the Stroop color-naming, Stroop word-reading, Stroop interference, and for the phonetic verbal fluency (FAS). In the HD-Dem group, performance below −1.5 SD was found in > 80% of cases in most of the tasks Table 3.

Group comparisons between HD-ND and HD-Dem groups showed that HD-Dem scores were significantly lower on all the cognitive tests. We found a large effect size in all groups according to *d* Cohen's coefficient > 0.8.

3.3. GMV differences between groups

The voxelwise group comparison revealed significant GMV differences when comparing the HD-ND and HD-Dem groups with the HC group, and also when comparing the HD-ND group with the HD-Dem group. Specifically, compared to the HC group, HD-ND showed significantly lower GMV in large cortico-subcortical clusters. The set of significant clusters included the bilateral caudate nucleus and putamen, the bilateral insula, the bilateral inferior orbital prefrontal cortex (oPFC), and also the right rolandic operculum, the right mid-occipital gyrus, the right superior parietal gyrus, and the right mid-frontal and mid- and superior oPFC. Comparing HC and HD-Dem, we found marked GMV differences bilaterally in the whole basal ganglia and in the insular cortex, in the left superior and medial frontal cortex, and in several posterior-cortical clusters, including the right superior and inferior occipital gyrus and the right lingual gyrus.

When we compared the HD-ND and HD-Dem group, the latter showed significantly reduced GMV in parietal-temporal regions, specifically in the bilateral anterior and posterior insular cortex, the superior temporal gyrus, and the left supramarginal gyrus (Fig. 1).

Table 3
Cluster description table of the VBM-GMV analyses.

HD-ND > HD-Dem	MNI coordinates (x, y, z)	Cluster size	*T* value
Right insula	48–8 5	2298	5.22
Right posterior insula	36–27 17		3.79
Right superior temporal gyrus	45–24 3		3.54
Left superior temporal gyrus	−56–6 −2	2568	4.31
Left supramarginal gyrus	−45–26 24		4.10
Left posterior insula	−36–23 23		4.82
HC > HD-ND			
Left insula	−31 9 10	6473	7
Left inferior oPFC	−41 38–9		6.33
Left caudate/putamen	−12 3 20		6.13
Right insula	31 14 8	6871	6.17
Right caudate/putamen	9 14–1		6.15
Right rolandic operculum	36–15 20		5.75
Right inferior oPFC	30 30–8		5.69
Right mid-occipital	36–68 26	1115	5.15
Right parietal superior	26–69 51		4.23
Right mid-frontal	33 59 15	1330	4.84
Right superior oPFC	29 51–3		4.54
Right mid- oPFC	53 42–6		4.24
HC > HD-Dem			
Bilateral caudate/putamen/ insula	−20 14 6	37,308	8.18
Right superior occipital	21–90 17	3970	6.21
Right lingual gyrus	17–86 −11		6
Right inferior occipital gyrus	30–87 −6		5.81
Right precentral gyrus	45 0 35	857	5.18
Left frontal superior medial	−6 24 42	2957	4.89
SMA	−9 21 51		4.02
Left superior frontal	−17 44 38		4.77

FWE corrected ($p < 0.05$)

3.4. Cth differences between groups

The vertexwise comparison between HC and HD-ND groups showed a pattern of cortical thinning bilaterally in multiple fronto-temporal and parieto-occipital regions in the HD-ND group. These regions were the rostral mid-frontal and superior frontal gyrus, the orbital PFC, the superior temporal gyrus, the supramarginal, inferior and superior parietal gyrus, the lateral occipital gyrus, the precuneus, the precentral gyrus, and the pars triangularis. Compared to the HC group, the HD-Dem group showed a similar but more significant thinning pattern than that in the HD-ND group. Differences were also found in the post-central gyrus, the inferior and the mid-temporal gyrus, and the fusiform gyrus.

Comparing the HD-ND and HD-Dem groups we found that the HD-Dem group was characterized by a pattern of cortical thinning predominantly affecting fronto-temporal and parietal regions of the left hemisphere and temporo-occipital regions of the right hemisphere. In the left hemisphere, significant differences involved the inferior temporal and the fusiform gyrus, the supramarginal and inferior parietal gyrus, the precentral and postcentral gyrus, the caudal and rostral mid-frontal gyrus, the insula, the pars triangularis, and the rostral middle frontal gyrus. Conversely, in the right hemisphere, differences were eminently circumscribed to the temporal pole, the superior and inferior temporal gyrus, the fusiform gyrus and the lateral occipital gyrus (Fig. 2).

3.5. Cognitive-imaging regression analysis:

Linear regression analysis showed that after adjusting for age, education, CAG repeat length and UHDRS-TMS, GMV at multiple clusters obtained in the VBM analysis contributed strongly to global cognitive performance. PD-CRS total score performance was strongly associated with GMV in the basal ganglia ($\beta = 0.456$; $P = 0.017$), the frontal lobes ($\beta = 0.586$; $P = 0.005$), the temporal lobes ($\beta = 0.587$; $P = 0.004$), the insular cortex ($\beta = 0.621$; $P = 0.002$), the mid cingulate ($\beta = 0.431$; $P = 0.036$), and the occipital lobe ($\beta = 0.441$; $P = 0.043$). PD-CRS performance was also associated with GMV in the parietal lobe ($\beta = 0.373$; $P = 0.043$). However, this association was also influenced by the UHDRS-TMS ($\beta = -0.390$; $P = 0.038$) (Fig. 3).

Following the same linear regression analysis approach, we looked at specific clusters of GMV and their association with PD-CRS total score and performance in each subtest as well as with performance in all the other cognitive measures administered. Given the high number of correlation analyses performed between each cluster and each PD-CRS subtest, these results are reported in supplementary data. The PD-CRS total score was associated with GMV in the left ($\beta = 0.491$; $P = 0.013$) and right putamen ($\beta = 0.556$; $P = 0.006$), with the left ($\beta = 0.523$; $P = 0.011$) and right inferior oPFC ($\beta = 0.531$; $P = 0.009$), with the left ($\beta = 0.602$; $P = 0.003$) and right insular cortex ($\beta = 0.632$; $P = 0.002$), with the left ($\beta = 0.666$; $P = 0.001$) and right superior temporal gyrus ($\beta = 0.495$; $P = 0.011$), with the left ($\beta = 0.563$; $P = 0.009$) and right inferior temporal gyrus ($\beta = 0.548$; $P = 0.010$), with the right cuneus ($\beta = 0.508$; $P = 0.019$), with the left mid oPFC ($\beta = 0.515$; $P = 0.020$), with the right mid-temporal pole ($\beta = 0.473$; $P = 0.014$), with the left ($\beta = 0.648$; $P = 0.002$) and right mid-frontal gyrus ($\beta = 0.579$; $P = 0.007$), with the left ($\beta = 0.591$; $P = 0.003$) and right-mid temporal gyrus ($\beta = 0.567$; $P = 0.006$), with the right inferior parietal lobe ($\beta = 0.482$; $P = 0.007$), with the right rectus gyrus ($\beta = 0.573$; $P = 0.006$), with the right superior oPFC ($\beta = 0.501$; $P = 0.019$), and with the left ($\beta = 0.520$; $P = 0.013$ and right medial superior PFC ($\beta = 0.545$; $P = 0.011$).

Focusing in the other cognitive measures, we observed that SDMT

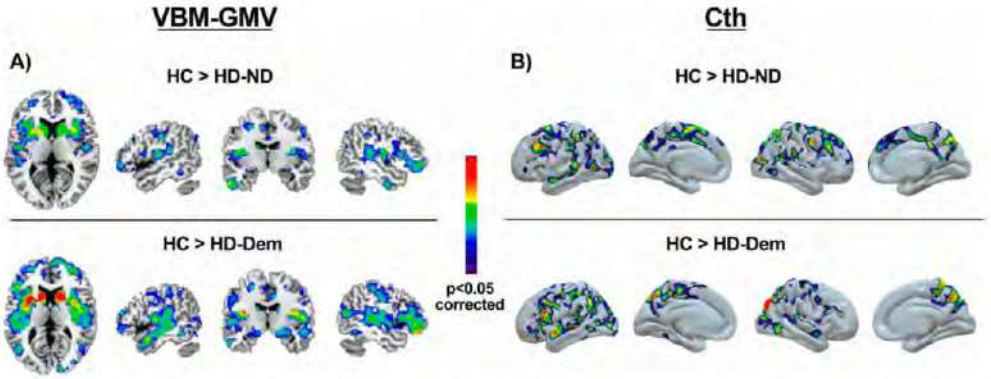

Fig. 1. Regions showing lower GMV (A) and lower Cth (B) in the HD-ND and in the HD-Dem groups compared to the HC group. No regions showed a significant increase in grey matter volume. For depicting purposes, the image is shown at $p < 0.001$.

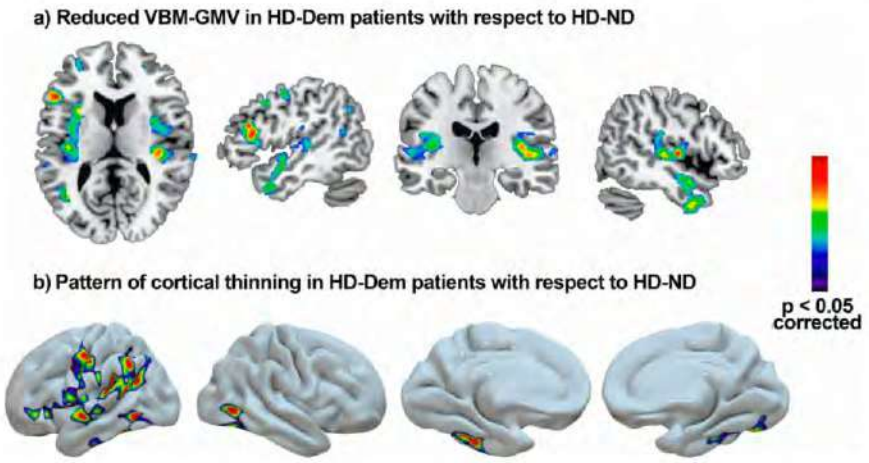

Fig. 2. Regions showing lower GMV (A) and lower Cth (B) in the HD-Dem group than in the HD-ND group. No regions showed a significant increase in grey matter volume. For depicting purposes, the image is shown at p < 0.005.

performance correlated with GMV in the left mid-temporal gyrus (β = 0.515; P < 0.005), the left superior temporal gyrus (β = 0.409; P < 0.05) and the inferior frontal gyrus (β = 0.450; P < 0.05). Semantic fluency correlated strongly with GMV in the right insular cortex (β = 0.493; P < 0.01), the left superior temporal gyrus (β = 0.500; P < 0.01), the right inferior temporal gyrus (β = 0.489; P < 0.01), the bilateral mid-temporal pole (β = 0.522; P < 0.005), and the right mid-frontal gyrus (β = 0.463; P < 0.05).

In the Cth analyses, multiple regions overlapping the VBM-GMV findings were strongly associated with cognitive performance by means of the PD-CRS total score. The most significant clusters were found at the level of posterior-cortical regions, specifically at the fusiform gyrus in the temporo-occipital region (β = 0.491; P = 0.008). The PD-CRS posterior-cortical score was associated with cortical thickness in the right lateral occipital (β = 0.392; P < 0.05) and in the right fusiform gyrus (β = 0.512; P < 0.01). Focusing on PD-CRS subtests, immediate verbal memory was associated with the left inferior temporal cortex (β = 0.435; P < 0.05). Confrontation naming (β = 0.465; P < 0.05), sustained attention, and (β = 0.396; P < 0.05), and action verbal fluency (β = 0.446; P < 0.05) where associated with the right fusiform gyrus. Working memory was also associated with the left supramarginal gyrus (β = 0.535; P < 0.005), and the left fusiform gyrus (β = 0.541; P < 0.005). Focusing on the cogscore and related measures, total cogscore was not associated with Cth. The Stroop color-naming was associated with the superior temporal gyrus (β = 0.395; P < 0.05), and with the right lateral occipital gyrus (β = 0.449; P < 0.05), and the semantic verbal fluency was associated with the right fusiform gyrus (β = 0.407; P < 0.05).

4. Discussion:

In the present study, major cognitive impairment in the range of

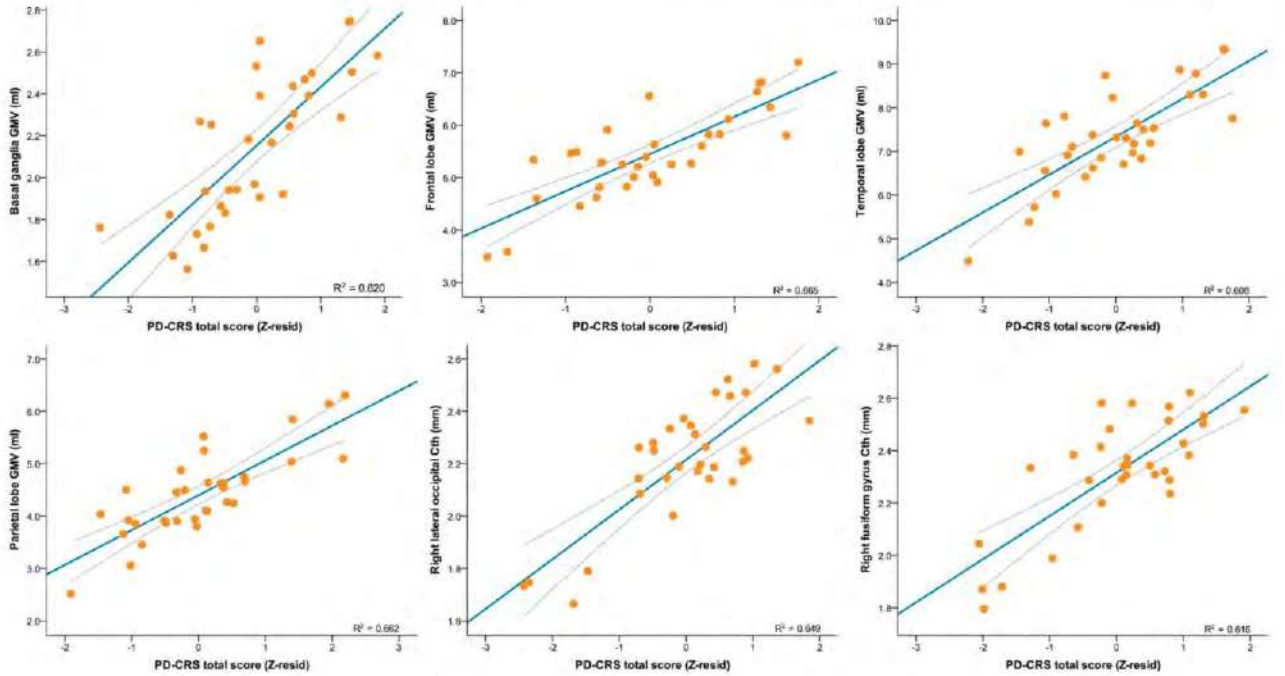

Fig. 3. Linear regression analysis depicting correlations between GMV/Cth clusters and PD-CRS total score.

dementia -as determined using the specific PD-CRS cutoff scores for HD- is associated with brain and cognitive differences that exceed the prototypical pattern of frontal-executive, attention and processing speed deficits attributed to frontal-striatal atrophy, and critically involve more severe atrophy of posterior-cortical brain regions.

Our results highlight that severe cognitive impairment in the range of dementia may occur in the early stages of HD and with relative independence of the CAG repeat length, DBS, age and education. Notably, this more severe form of cognitive impairment is associated with a widespread pattern of cortical thinning and whole-brain atrophy that involves multiple cortical and subcortical clusters. The imaging data, highlights that, as previously reported, GMV atrophy is mostly ascribed to the basal ganglia, frontal and occipital lobe, and Cth involves the temporal and parieto-occipital regions(Rosas et al., 2008, 2005; Tabrizi et al., 2009). Importantly, group comparisons showed that a more prominent decrease of GMV and Cth is present in those participants exhibiting severe cognitive deterioration even when controlling for the effect of age, CAG, education of UHDRS-TMS. Accordingly, more advanced disease stage or higher DBS cannot explain these differences.

Our findings are in accordance with previous works showing that the development of cognitive deterioration in HD cannot be solely attributed to basal ganglia atrophy(Rosas et al., 2008; Nopoulos et al., 2010; Tabrizi et al., 2009; Coppen et al., 2018; Podoll et al., 1988; Say et al., 2011; Carmichael et al., 2019; Harris et al., 2019; Martinez-Horta et al., 2019; Wolf et al., 2014; Labuschagne et al., 2016; Hinzen et al., 2018; Chan et al., 2019). Structures of the basal ganglia, such as the caudate nucleus and putamen, but also the insular cortex, the PFC and the occipital and parietal cortex, strongly differentiated non-demented HD patients from healthy controls. However, the most representative brain changes differentiating patients with major cognitive impairment from non-demented HD patients were found at the level of parieto-temporal regions, including, bilaterally, the anterior and posterior insular cortex, the superior temporal gyrus, and the left supramarginal gyrus. In terms of cortical thinning, our results pointed in the same direction, supporting the critical participation of decreased cortical thinning in fronto-temporal and parietal regions of the left hemisphere and in temporo-occipital regions of the right hemisphere in the more severe forms of cognitive deterioration in HD.

The involvement of cortical atrophy in HD, especially in parietal and occipital regions, is a well-known finding supported by several imaging studies(Rosas et al., 2008, 2005; Kuwert et al., 1990; Tabrizi et al., 2009; Coppen et al., 2018). However, the functional translation of these cortical changes is partially understood. In this sense, our data supports for the first time that more aggressive cortical atrophy is, at least, critically associated with the presentation of a significantly more sever profile of multi-domain cognitive and functional affectation in HD.

As expected, both the measures of GMV and cortical thinning correlated with multiple cognitive variables. However, among the various measures obtained for cognitive performance, those focusing on executive functions, memory, processing speed, language and constructional abilities were those better characterizing patients with dementia. These data suggest that the neurocognitive profile differs between HD patients with and those without major cognitive impairment in the range of dementia according to the PD-CRS classification. Whereas HD patients with normal-to-mild cognitive deficits exhibit a prototypical frontal-executive dysfunction profile, HD patients with major cognitive impairment exhibit a cortical-subcortical profile with deficits extending beyond executive functions and involving amnestic difficulties, constructional apraxia, confrontation naming deficits and reduced semantic abilities. However, these findings emerged performing comparisons with the subtests comprising the PD-CRS, it is, the instrument used to classify patients. Thus, further studies should explore the specific neuropsychological correlates of major cognitive impairment and related brain differences in HD using additional comprehensive neuropsychological assessment.

Previous studies have highlighted the participation of extra-striatal GMV atrophy and cortical thinning in the clinical expression of HD (Rosas et al., 2008, 2005; Nopoulos et al., 2010; Tabrizi et al., 2009). When addressing cognitive aspects, these previous studies focused on specific measures of verbal fluency and psychomotor processing speed but not on multiple measures of global cognitive performance. Although they performed correlational analysis between brain structure and cognitive performance, they did not compared patients according to the severity of cognitive deterioration. Nevertheless, cortical thickness of the pre-central gyrus, the superior temporal gyrus, the superior frontal gyrus, the lingual gyrus, the precuneus and the cuneus were found to be associated with verbal fluency performance. Cortical thickness of the pre-central gyrus, the bilateral paracentral lobule and the occipital cortex were also associated with psychomotor processing speed(Rosas et al., 2008; Nopoulos et al., 2010). Regarding the impact of cortical changes over functional capacity, the most significant associations were found between TFC and the motor cortex, the superior parietal, and the cuneus(Rosas et al., 2008). Similarly, other studies highlighted the involvement of multiple areas related to executive functions and sensorimotor and visuospatial processing in cognitive performance in HD(Garcia-Gorro et al., 2019). Interestingly, more recent data also point to hippocampal-dependent memory deficits in HD that cannot be solely explained as a function of degeneration in the basal ganglia(Carmichael et al., 2019; Harris et al., 2019).

Keeping in mind that the two HD groups were matched for age, gender, education, CAG and disease burden and that healthy controls were also matched in terms of age, and education, our findings suggest that mechanisms other than only those promoted as a function of CAG repeat length, DBS, age or education level contribute to a differential course and expression of cognitive deterioration in HD. Although mutant huntingtin aggregation is the primary mechanism leading to HD (Langbehn et al., 2019; Penney et al., 1997; Wild et al., 2015), multiple mechanisms are also known to participate in the neuropathology of HD (Rub et al., 2016). However, how these additional mechanisms contribute to variability in the phenotypic expression of HD is not fully elucidated. Of these mechanisms, inflammatory, autoimmune activity and TAU pathology have been suggested to play a cardinal role in neurodegeneration and clinical expression of HD(Rocha et al., 2016). The question regarding the possible participation of these mechanisms in the acceleration of cognitive deterioration and related neurodegeneration in HD is only partially understood. TAU pathology and the related *MAPT* H2 haplotype have been associated with the rate of cognitive decline in HD(Vuono et al., 2015; Fernandez-Nogales et al., 2014). Whether these mechanisms contribute to the extent of brain differences observed in our sample is as yet unknown. In this sense, further studies must clarify the role of TAU pathology and other mechanisms on neurodegeneration and related cognitive deficits in HD. Moreover, how and when these mechanisms start promoting clinical and brain changes and why they affect people with equivalent CAG and DBS in a different manner merits further in-depth research. In any case, the present study adds novel evidence on the heterogeneity of HD, and supports the need identifying mechanisms participating in this clinical heterogeneity. This is of major importance taking into account that ongoing and imminent clinical trials on HD are focused on huntingtin-lowering strategies but did not take into account other potential factors contributing to disease severity(Tabrizi et al., 2019).

In any case, pinpointing the pattern of brain changes and the cognitive profile of major cognitive impairment in the range of dementia in HD has valuable implications that merit further research in bigger samples and in a longitudinal design.

The main limitation of the present study is the lack of a gold-standard to classify patients according to cognitive status, but the method we used to classify patients has recently been shown to be reliable in this population(Martinez-Horta et al., 2020). Despite this limitation, it is reasonable to assume that the measure we used for classification differentiates patients with normal cognitive function or mild cognitive

defects from those with severe cognitive alterations. However, the concept of dementia used in the present work must be taken cautiously because of the absence of HD-specific clinical diagnostic criteria for dementia. Moreover, the use of a functional assessment other than the TFC, specifically addressing cognitive-related functional deficits, must be considered in further studies. Other obvious limitations to take in consideration are the small sample size and the cross-sectional design of the study. Accordingly, will be required to confirm our findings in further studies addressing this question in a bigger sample and in a longitudinal setting.

5. Conclusions

Overall, significant patterns of cortical thinning and reduced GMV in parieto-temporal and occipital regions are associated with more severe cognitive deterioration in HD. The addition of cortical-instrumental, semantic and amnestic-like deficits to the prototypical frontal-executive neurocognitive profile of HD is a differentiating characteristic of major cognitive impairment in the range of dementia in HD. Early detection of brain changes and cognitive parameters associated with severe forms of cognitive deterioration in HD may contribute to the early identification of individuals at greater risk of a more rapid and aggressive course of cognitive impairment. Identifying the mechanisms that contribute to this more aggressive cognitive deterioration should be of major relevance in the planning of future clinical trials.

CRediT authorship contribution statement

Saul Martinez-Horta: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing - original draft, Writing - review & editing. **Frederic Sampedro:** Data curation, Formal analysis, Methodology, Writing - original draft, Writing - review & editing. **Andrea Horta-Barba:** Data curation, Formal analysis, Project administration, Writing - review & editing. **Jesús Perez-Perez:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration. **Javier Pagonabarraga:** Conceptualization, Resources, Writing - original draft, Writing - review & editing. **Beatriz Gomez-Anson:** Methodology, Writing - original draft, Writing - review & editing. **Jaime Kulisevsky:** Conceptualization, Funding acquisition, Investigation, Methodology, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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5. RESUMEN GLOBAL DE LOS RESULTADOS

El bilingüismo, específicamente la alternancia entre lenguas y no tanto el nivel de competencia de las mismas, ha demostrado tener efectos sobre la estructura y la función cerebral. Estos efectos, son consecuencia de la constante utilización de recursos de monitorización y flexibilidad cognitiva que la población bilingüe despliega, a lo largo de la vida, para controlar la producción de lenguaje en un idioma sin interferencia del otro. Estos procesos de control ejecutivo reclutan y estimulan estructuras fronto-temporales y subcorticales como la región dorsal de la corteza cingulada anterior, la corteza frontal dorso-lateral y la corteza temporal. La constante utilización de estos sistemas tiene efectos de transferencia frente tareas distintas a las estrictamente lingüísticas. Esta transferencia favorece que los bilingües rindan mejor en tareas no lingüísticas que requieren control cognitivo o flexibilidad. Todo ello tiene a su vez un notable efecto en cuanto al enriquecimiento de la reserva cerebral y cognitiva.

En población bilingüe, esta ganancia se hace evidente en forma de ralentización de la progresión de deterioro cognitivo leve a demencia tipo Alzheimer o en el nivel de recuperación de las funciones dañadas tras un accidente vascular cerebral. Paradójicamente, a pesar de que muchas de las estructuras que sustentan el bilingüismo se ven notablemente afectadas en la EH, no se había dedicado un estudio particular al efecto del bilingüismo sobre la estructura y la función cerebral en esta población.

El estudio que presentamos demostró que la mayor alternancia entre lenguas a lo largo de la vida en distintos escenarios, pero no el nivel de competencia lingüística, se relaciona con una mejor preservación estructural de la región frontal inferior y con un efecto muy significativo sobre el mantenimiento del metabolismo cerebral en múltiples regiones fronto-temporales, especialmente en la región dorsal de la corteza cingulada anterior, la ínsula anterior, el giro frontal inferior y la corteza orbitofrontal ventro-medial. Además, los efectos del bilingüismo sobre la estructura y el metabolismo cerebral mostraron una clara asociación con el rendimiento en tareas de control de inhibición y flexibilidad cognitiva y también con un mejor estado motor y funcional global.

Paralelamente, si bien a lo largo de los últimos años muchos estudios han puesto de manifiesto que las alteraciones cerebrales asociadas a la EH se extienden más allá de los ganglios basales, y que desde etapas tempranas múltiples regiones de la corteza cerebral posterior se ven afectadas, son escasos los trabajos que hayan podido establecer una relación clara entre estos cambios corticales-posteriores y el funcionamiento de los pacientes. Igualmente, no existen indicadores cognitivos relacionados con la afectación cortical-posterior que permitan detectar cambios en población asintomática. De manera particular, aunque en la población asintomática se pueden detectar anomalías en las áreas visuales asociativas, el rendimiento en las tareas donde se requiere procesamiento visual es normal o predominantemente normal. Como explicación plausible a la dificultad para detectar anomalías visuoperceptivas en la población asintomática puede plantearse la baja o nula sensibilidad de los test y las tareas neuropsicológicas disponibles para detectar alteraciones relativamente sutiles. Siguiendo este razonamiento de la posible baja sensibilidad de las exploraciones estándar y tomando como punto de partida el papel de algunas de las áreas visuoperceptivas que aparecen afectadas en la población asintomática, tales como el giro fusiforme, hipotetizamos que se podría corregir la falta de sensibilidad para detectar anomalías en la ejecución de los test estudiando la funcionalidad de los procesos implicados registrando la actividad cerebral evocada durante la ejecución de una tarea relacionada con la actividad del giro fusiforme. Así, se diseñó una tarea específicamente relacionada con la función del giro fusiforme derecho que sería realizada durante un registro neurofisiológico. Concretamente, sé hipotetizó que las alteraciones incipientes en el giro fusiforme derecho podrían asociarse con anomalías en el procesamiento de estímulos con características faciales. A su vez, sé hipotetizó, que estas anomalías podrían no ser evidentes frente estímulos simples como las caras, pero que podrían emerger frente a estímulos más demandantes desde un punto de vista procesual tales como las pareidolias faciales). Así, mientras se estudiaba el comportamiento durante la ejecución de una tarea de discriminación entre objetos, caras y pareidolias faciales, se obtuvo un registro de

electroencefalograma para estudiar la morfología de la onda N170, un componente de los potenciales evocados cognitivos estrictamente relacionado con el procesamiento facial.

Los resultados demostraron que las personas asintomáticas lejos del tiempo estimado de inicio de la enfermedad tienen grandes dificultades en la discriminación de pareidolias faciales frente caras u objetos y que esta dificultad visuoperceptiva (definida por primera vez como prosopagnosia específica a las pareidolias) responde a la abolición de la N170.

En cuanto a los síntomas neuropsiquiátricos, la irritabilidad y la agresividad son síntomas frecuentes en la EH que asocian consecuencias negativas muy importantes para los pacientes y cuidadores. En la EH, las explosiones de ira y de agresividad pueden ir desde enfados o insultos, a agresiones físicas y actos criminales de extrema violencia. Fenomenológicamente, los síntomas de ira y agresividad en la EH no son planeados, sino que parecen obedecer a fenómenos de pérdida de control sobre la tolerancia a la frustración u otras formas de expresión emocional. A pesar de ser síntomas frecuentemente reportados, muy pocos estudios han explorado las bases neurales de la gravedad de estos síntomas en la EH. Los resultados del estudio, demostraron anomalías estructurales que sugieren la disfunción de dos sistemas como elementos facilitadores de la irritabilidad y la agresividad en la EH. De manera global, la gravedad de estos síntomas se relacionó con un mayor grado de atrofia a nivel de caudado, putamen, globo pálido lateral, núcleo pulvinar del tálamo, giros temporal superior, medio e inferior y corteza orbitofrontal medial. Todas las estructuras identificadas forman parte de una red ampliamente descrita en la literatura por su papel en el control cognitivo, la regulación emocional, la aparición de hostilidad y la agresión espontanea en mamíferos y en el ser humano. Los resultados mostraron también la participación crítica del núcleo pulvinar del tálamo, una región que mantiene múltiples conexiones recíprocas con distintas áreas límbicas, prefrontales, temporales y parietales conocida por participar en la amplificación de señales emocionales o relevantes. Por ello, se propone que la amplificación de las señales emocionales por parte de un núcleo pulvinar disfuncional, repercute en la forma en que el sistema límbico evalúa las señales que le llegan y les otorga relevancia, teniendo

ello un impacto significativo sobre el comportamiento. Paralelamente, la atrofia en regiones orbitofrontales críticas en el control cognitivo, y la atrofia en regiones fronto-temporales críticas en los procesos de integración afectiva, propician el fracaso de los mecanismos de control cognitivo sobre las señales emocionales suprasalientes mediadas por la disfunción del núcleo pulvinar.

En la EH, el deterioro cognitivo progresivo y el desarrollo de demencia son consecuencias inevitables. A pesar de ello, a diferencia de lo que encontramos en otras enfermedades neurodegenerativas que también asocian deterioro cognitivo, actualmente no existen instrumentos específicos ni procedimientos recomendados ni criterios diagnósticos específicos para la evaluación del estado cognitivo de los pacientes afectados por la EH tanto para detectar formas leves de deterioro cognitivo como para el diagnóstico formal de demencia. Esta carencia supone una limitación importante para el diseño de las intervenciones terapéuticas en la EH. Si bien se conocen múltiples medidas cognitivas sensibles a la progresión de la enfermedad, se desconoce cuál sea la translación del rendimiento observado en estas medidas en términos de clasificación de los pacientes acorde a su estado cognitivo global. Esto mismo sucede para los test de cribado del estado cognitivo global. La inexistencia de criterios diagnósticos y la ausencia de estudios al respecto hace que actualmente como modo de cribado del estado cognitivo global en los pacientes con EH, se asuman las mismas notas de corte empleadas para la población general o para otras enfermedades. La inespecificidad de esta aproximación ha demostrado asociar importantes limitaciones en otras enfermedades donde, durante los últimos años, se ha trabajado tanto en la definición de criterios diagnósticos específicos como en el estudio de las puntuaciones de corte que aplican los instrumentos de cribado del estado cognitivo global.

Nuestro grupo desarrolló y validó con anterioridad una escala de evaluación del estado cognitivo global para la enfermedad de Parkinson que mostró excelentes propiedades psicométricas en la discriminación del deterioro cognitivo leve y de la demencia asociada al Parkinson. En el presente estudio nos propusimos evaluar la utilidad de esta escala conocida como *Parkinson's Disease* –

Cognitive Rating Scale (PD-CRS) en el cribado del estado cognitivo global de los pacientes con EH. En ausencia de criterios diagnósticos específicos a emplear como 'gold-standard', para la validación de esta escala en población con EH se utilizaron criterios previamente utilizados y aceptados basados el nivel de funcionalidad y en el nivel cognitivo acorde a la escala *Clinical Dementia Rating*. El estudio se realizó de manera coordinada en distintos centros europeos permitiendo recopilar datos de una amplia muestra de pacientes y controles. Los resultados demuestran que con una sensibilidad de 93 %, especificidad del 80 % y área bajo la curva (AUC) de 0.940, una puntuación total de la PD-CRS < 82 resulta adecuada para la detección de deterioro cognitivo leve en la EH y que con una sensibilidad del 90 %, especificidad del 87 % y AUC de 0.933, una puntuación total de la PD-CRS < 64 resulta adecuada para la detección de demencia en la EH. Paralelamente, el estudio del rendimiento de los pacientes en los distintos subtest de la PD-CRS evidenció que mientras que el deterioro cognitivo leve se caracteriza principalmente por dificultades atencionales/disejecutivas, la demencia en la EH asocia de manera importante alteraciones en tareas más dependientes de la función cortical posterior como la denominación por confrontación o la función visuoconstructiva. Además, se estudiaron los atributos psicométricos del MMSE para comparar este instrumento con la PD-CRS. Los resultados pusieron de manifiesto que las puntuaciones < 27 para el deterioro cognitivo leve y < 25 para demencia tienen una muy baja sensibilidad y por tanto este instrumento resulta inadecuado para el cribado del estado cognitivo global en la EH.

A pesar de que se han realizado muchos estudios explorando el impacto de determinados cambios cerebrales sobre el rendimiento cognitivo, la ausencia de criterios diagnósticos específicos para demencia en la EH y la ausencia de procedimientos validados para clasificar a los pacientes acorde a su estado cognitivo global, ha supuesto que lo correlatos neuronales de la demencia en la EH sean desconocidos. Paralelamente, mientras que son muchos los cambios cerebrales que se pueden encontrar a lo largo de la EH, se desconoce el impacto de muchos de estos cambios sobre las manifestaciones cognitivas de la enfermedad. Atendiendo a que previamente validamos un método de

clasificación de los pacientes acorde a su estado cognitivo global (artículo 4), el objetivo del presente trabajo fue explorar los correlatos estructurales de la demencia en la EH. Para ello, se estudió un grupo de controles sanos y se dividió una muestra de pacientes sintomáticos acorde a su estado cognitivo global, según pacientes con demencia y pacientes sin demencia. Resulta importante destacar, que la edad, número de repeticiones CAG y otras variables sociodemográficas eran comparables entre el grupo de pacientes con y sin demencia. En comparación a los controles sanos, el conjunto de los pacientes, con y sin demencia, mostró una clara pérdida de volumen y grosor cortical a nivel de ganglios basales y en distintas áreas parietales. Por su parte, los pacientes con demencia mostraron un prominente patrón de afectación, más amplia, implicando pérdida de volumen de sustancia gris y grosor cortical en extensos territorios parieto-temporales y occipitales. Estas diferencias resultaron independientes de la edad, del sexo, del nivel educativo y del número de repeticiones CAG. Paralelamente, el patrón de afectación cognitiva y su relación con los cambios cerebrales observados demostró que, mientras que en todos los pacientes existen alteraciones frontales-ejecutivas, principalmente mediadas por la desintegración de los ganglios basales, en la demencia asociada a la EH se sobreañade un claro patrón de afectación cortical-posterior. Este patrón se expresa en toda una serie de alteraciones cognitivas que sobrepasan los dominios atencional-ejecutivo atribuibles a la disfunción fronto-subcortical, e incluyen dificultades de tipo amnésico, apraxia constructiva, anomia y alteraciones semánticas. Resulta igualmente interesante destacar respecto a la gravedad de los déficits observados que no fue posible atribuirla al número de repeticiones CAG ni al nivel educativo. Esta circunstancia plantea por tanto la necesidad de explorar en el futuro otros mecanismos neuropatológicos secundarios que, de forma sinérgica al efecto de la mHTT, podrían ejercer una acción moduladora de la variabilidad en la expresión de la enfermedad. Específicamente, planteamos el posible papel de TAU en la exacerbación de la clínica cognitiva.

6. RESUMEN GLOBAL DE LA DISCUSSIÓN:

Del trabajo realizado en relación al efecto del bilingüismo podemos destacar la constatación del papel de las variables ambientales como factor modificador del curso y expresión de la EH, así como el efecto beneficioso del bilingüismo y el consiguiente enriquecimiento de la reserva cerebral como factor modulador del proceso neuropatológico que acompaña las enfermedades neurodegenerativas.

En relación al estudio neurofisiológico de los procesos que de manera temprana participan en el procesamiento facial, los datos reportados nos permiten concluir que las personas asintomáticas tienen defectos perceptivos selectivos, posiblemente atribuibles a alteraciones de la vía visual ventral, y que se reflejan a nivel conductual en forma de una alteración del reconocimiento de pareidolias faciales y a nivel neurofisiológico en forma de la abolición de la N170. Por tanto, el desarrollo de nuevas tareas visuoperceptivas podría servir como posible biomarcador cognitivo temprano.

A nivel neuropsiquiátrico, las estructuras implicadas en la severidad de la irritabilidad y la agresividad en la EH indican que posiblemente existe un exceso de amplificación de las emociones negativas junto al fracaso de los mecanismos de control cognitivo dando lugar a los fenómenos de explosión de ira característicos en la enfermedad. Además, el fracaso de estos sistemas define una circuitería que da plausibilidad biológica y mecanicista a la relación existente entre el nivel de afectación de las estructuras reportadas y la gravedad de otros síntomas conductuales caracterizados también por las dificultades en la gestión emocional y el control cognitivo, como son la ideación suicida, la ansiedad y las rumiaciones obsesivo-compulsivas.

Paralelamente, el estudio del rendimiento de los pacientes mediante la PD-CRS evidencia que que el deterioro cognitivo leve en la EH se caracteriza por dificultades atencionales/disejecutivas, pero que la demencia en la EH asocia alteraciones en tareas dependientes de la función cortical posterior como la denominación por confrontación o la función visuoconstructiva. No menos importante, a nivel psicométrico, los resultados demuestran que la PD-CRS es un instrumento adecuado, con propiedades

muy superiores al MMSE y que las puntuaciones para la diferenciación de deterioro cognitivo leve y demencia tienen una gran sensibilidad y especificidad en esta población.

Finalmente, demostramos que el patrón de afectación cognitiva y cerebral en pacientes con cambios cognitivos leves que eminentemente restringido a la afectación fronto-estriatal mientras que la demencia en la EH asocia un claro patrón de afectación cortical-posterior y que a nivel neuropsicológico, las alteraciones características sobrepasan los dominios atencional-ejecutivo atribuibles a la disfunción fronto-subcortical, e incluyen dificultades de tipo amnésico, apraxia constructiva, anomia y alteraciones semánticas. Paralelamente, resulta destacable que la gravedad de los déficits y cambios cerebrales observados en relación al peor estado cognitivo que no es atribuible al número de repeticiones CAG ni al nivel educativo. Circunstancia que plantea la necesidad de explorar ¡otros mecanismos neuropatológicos secundarios que, de forma sinérgica al efecto de la mHTT, podrían ejercer una acción moduladora de la variabilidad en la expresión de la enfermedad.

7. CONCLUSIONES

- En la EH, el uso del bilingüismo a lo largo de la vida tiene un efecto enriquecedor sobre la reserva cerebral y cognitiva. Este efecto promueve el mantenimiento de la integridad estructural y funcional de múltiples áreas fronto-temporales lo que se traduce en un beneficio en forma de mejor rendimiento cognitivo, menor gravedad de la sintomatología motora y mejor estado funcional global.

- En la EH existen cambios corticales-posteriores muy tempranos, apreciados en los estudios de neuroimagen que no se traducen en alteraciones cognitivas cuantificables mediante el uso de instrumentos neuropsicológicos habituales o tareas estándar. Entre otras regiones, estos cambios tempranos involucran de manera consistente regiones del giro fusiforme derecho muy especializadas en el procesamiento facial. Mientras que la prosopagnosia no es un elemento temprano de la clínica de la EH, lo que hace suponer que estos cambios no son suficientes para alterar el procesamiento y reconocimiento normal de las caras, otros procesos cognitivos más demandantes pueden verse afectados. Ello manifiesta en el notable fracaso en el reconocimiento de pareidolias faciales por alteraciones funcionales atribuibles a la región facial del giro fusiforme. Estas dificultades clínicas dando se fundamentan en anomalías en la morfología de los índices neurofisiológicos relacionados con el procesamiento y reconocimiento temprano de las caras y las pareidolias faciales. Ponemos de manifiesto que en el periodo asintomático ya existen alteraciones subclínicas provocadas por la disfunción de la vía visual ventral que se asocia a alteraciones discretas, solo evidenciables mediante el uso de tareas apropiadas. Por lo tanto, en la EH, el diseño y validación de tareas orientadas a evaluar el funcionamiento de los procesos dependientes de la vía visual ventral podía contribuir a la identificación de biomarcadores cognitivos muy tempranos.

- En la EH, la irritabilidad y la agresividad son síntomas frecuentes que impactan muy negativamente en la calidad de vida de los pacientes y cuidadores, pero cuyos sustratos neuronales han sido poco estudiados. La gravedad de estos síntomas se asocia con una disminución significativa de volumen en diferentes áreas fronto-temporales y subcorticales. La degeneración del núcleo pulvinar del tálamo con la consiguiente disminución de su función integradora, podría ser causa de una excesiva amplificación de las señales procesadas dando lugar a una respuesta incrementada a nivel límbico. Paralelamente, la degeneración de áreas fronto-temporales relacionadas con la integración emocional y el control cognitivo podría asociar alteraciones en el autocontrol emocional. La alteración sinérgica de estos dos sistemas plantea que la gravedad de la irritabilidad y de la agresividad en la EH sea consecuencia del fracaso de los sistemas de autorregulación cognitiva sobre la saliencia excesiva de las señales emocionales. La evidencia de que estas alteraciones ya existen desde las fases iniciales de la enfermedad pone en relieve la importancia del uso de intervenciones cognitivas y conductuales, orientadas a maximizar la capacidad de control cognitiva e inhibir la excesiva amplificación de la respuesta emocional, como modelo de intervención sobre las manifestaciones de irritabilidad y agresividad en la EH.

- En la EH, como sí sucede en otras enfermedades en las que se han abierto vías terapéuticas para tratar específicamente el deterioro cognitivo, no se dispone de criterios diagnósticos ni de una categorización clara para medir los constructos de ‘deterioro cognitivo leve’ o de ‘demencia’. La falta de validación de instrumentos cognitivos redunda también en la falta de un consenso sobre cuáles sean los procedimientos y los instrumentos recomendados para el cribado del estado cognitivo global de los pacientes.

- La PD-CRS, un instrumento inicialmente desarrollado para la evaluación del estado cognitivo global en pacientes con enfermedad de Parkinson, muestra propiedades psicométricas muy buenas para la detección tanto de formas leves como severas de deterioro cognitivo asociado a la EH. Además, el análisis del rendimiento de los pacientes en las tareas que conforman los subapartados de la PD-CRS, diferencia y destaca los dos fenotipos cognitivos de la EH: el deterioro cognitivo leve, donde las dificultades atencionales/ejecutivas caracterizan a toda la población cognitivamente afectada, y el de la demencia, en el que las dificultades en el lenguaje y las capacidades visuoperceptivas y constructivas se superponen a las alteraciones atencionales/ejecutivas. Paralelamente, la ausencia de diferencias en variables tan destacadas como el número de repeticiones CAG, la edad o el nivel educativo refuerza la idea de que la demencia en la EH puede aparecer en estadios tempranos, con independencia de estas variables, lo que sugiere que existen mecanismos secundarios que contribuyen a la progresión más o menos rápida de la sintomatología cognitiva.

- En la EH, a pesar de que múltiples estudios han demostrado la presencia de una gran variedad de cambios cortico-subcorticales relacionados con la progresión de la enfermedad, ningún estudio hasta la fecha ha explorado específicamente cuáles sean los correlatos cerebrales de la demencia. Si bien todos los pacientes con EH muestran cambios muy significativos en los ganglios basales, es de destacar que la degeneración de estas estructuras no parece contribuir significativamente al desarrollo de demencia. Esta en cambio se asocia, de manera muy significativa, con la pérdida de volumen en extensos territorios parieto-temporales y occipitales. Es de destacar nuevamente, que estos cambios cerebrales relacionados con la demencia ocurren con independencia de la edad y del número de repeticiones CAG, reforzando la idea de que en la EH, más allá de la genética, concurren otros mecanismos secundarios,

posiblemente relacionados con TAU, como factores potencialmente mediadores de la variabilidad en la expresión clínica del deterioro cognitivo.

8. CONSIDERACIONES FUTURAS

Con la instauración de las actuales terapias de silenciamiento genético en estudio y la inminente llegada de terapias genéticas, indudablemente existe un nuevo marco desde donde con la oportuna cautela, contemplamos también con optimismo los años venideros y el futuro de las personas afectadas por la enfermedad de Huntington.

La posibilidad de iniciar tratamientos en individuos asintomáticos portadores de la mutación requerirá la validación de múltiples marcadores subrogados de la enfermedad que nos permitan cuantificar la eventual eficacia de los tratamientos. Paralelamente, no cesará la búsqueda de nuevas dianas terapéuticas que permitan mitigar la severidad y el impacto de los síntomas instaurados en los pacientes.

Los resultados presentados en estas tesis, aportan datos de meritorio interés relativos a la identificación de marcadores subrogados detectables muchos años antes del inicio de la enfermedad. Paralelamente, la descripción de los efectos mediados por la exposición al enriquecimiento de la reserva cognitiva refuerza una vez más la necesidad de desplegar programas de estimulación preventiva dirigidos a mitigar el impacto y los efectos de las enfermedades neurodegenerativas. Igualmente, la identificación de la circuitería implicada en la severidad de la irritabilidad y agresividad asienta los primeros pilares conceptuales desde donde plantear posibles nuevas opciones terapéuticas dirigidas a mitigar estos síntomas y sus terribles consecuencias.

La validación por primera vez de un instrumento de cribado del estado cognitivo para la enfermedad de Huntington supone un avance de enorme interés pensando en el diseño de ensayos clínicos. En este sentido, la identificación de los extensos cambios cerebrales relacionados con el desarrollo de formas mucho más severas de deterioro cognitivo con independencia de la carga patológica de la enfermedad, en individuos con una misma carga genética, edad y nivel educativo que otros que mantienen sus funciones cognitivas relativamente estables, abre una apasionante línea de investigación.

Específicamente, más que nunca toca explorar los mecanismos secundarios que de manera heterogénea modulan los distintos fenotipos que adquiere la enfermedad. Si bien la mHTT desempeña un papel incuestionable en la expresión de la enfermedad, los datos aportados sugieren que otros mecanismos contribuyen enormemente en la enfermedad. En este sentido, pensando en las actuales terapias en estudio y en desarrollo exclusivamente centradas en actuar sobre la expresión de la mHTT, resulta imprescindible explorar estos otros posibles mecanismos implicados que nos permitan comprender la eventual heterogeneidad en la respuesta y eficacia de estos tratamientos, así como la necesidad de diseñar terapias dirigidas a múltiples mecanismos.

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