Universitat Autònoma de Barcelona

Correlatos clínicos, cognitivos y de neuroimagen estructural de los síntomas neuropsiquiátricos en pacientes con degeneración frontotemporal

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TESIS DOCTORAL

CORRELATOS CLÍNICOS, COGNITIVOS Y DE NEUROIMAGEN ESTRUCTURAL DE LOS SÍNTOMAS NEUROPSIQUIÁTRICOS EN PACIENTES CON DEGENERACIÓN FRONTOTEMPORAL

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Resumen

Presentación. La degeneración frontotemporal (DFT) ocupa el segundo lugar después de la enfermedad de Alzheimer (EA) en cuanto a la prevalencia de enfermedades neurodegenerativas en menores de 65 años. Se manifiesta en tres modalidades o variantes: frontal o comportamental (DFTvc), semántica (DS) y afasia primaria progresiva (APP). Su inicio es más temprano que el de la EA (entre los 45 y 65 años), con un prolongado curso individual de la enfermedad. La gravedad de las alteraciones clínicas, el deterioro progresivo, la larga duración de la enfermedad y la carencia de intervenciones terapéuticas efectivas generan serios y diversos impactos: mayor pérdida de años de vida productivos (Galvin et al., 2017), necesidad de cuidado con importantes exigencias para los familiares (quienes generalmente se hacen cargo) (Nicolaou et al., 2010), rechazo y aislamiento social (Rasmussen et al., 2019) y demandas repetidas a los servicios de salud por las dificultades diagnósticas que erróneamente la clasifican dentro de las patologías psiquiátricas más conocidas (Wylie et al., 2013). Esta tesis y los cinco estudios que la conforman se desarrollaron siguiendo el curso o historia de la enfermedad, en torno a un aspecto primordial en la DFT: los síntomas neuropsiquiátricos (SNP) o alteraciones conductuales (AC), enfatizando en sus correlatos neurales, clínicos, cognitivos generales y de cognición social y su impacto cognitivo, funcional y clínico en distintas etapas de la enfermedad.

Objetivo general. Estudiar la relación entre los SNP, la presentación clínica, el funcionamiento cognitivo general, de cognición social y los patrones de atrofia cerebral en pacientes con DFT en distintos momentos del curso de enfermedad.

Hipótesis general. Los SNP en la DFT determinan el patrón de atrofia cerebral, neural, cognitivo, de cognición social y clínico en distintas etapas de la DFT.

Metodología. Esta tesis compendia cinco estudios publicados. Los objetivos de cada uno determinaron la metodología particular, con cinco diseños distintos: 1) observacional descriptivo de corte retrospectivo, 2) análisis secundario de un estudio poblacional, 3) observacional de casos y controles, 4) experimental y 5) longitudinal.

Resultados. Reconociendo el papel de los SNP en el diagnóstico y en el seguimiento de la progresión del TN, se resumen los resultados principales:

- En pacientes colombianos, el tipo y frecuencia de las SNP no es similar a la descrita en la literatura, aunque la labilidad emocional es más usual. Su etiología corresponde en primer lugar a la DFTvc (se observó en el 100 % de estos pacientes), seguida por la enfermedad de Alzheimer (77,29 % de los pacientes). Estos hallazgos resaltan la necesidad de una indagación sistemática en la valoración por la presencia de SNP.
- Dos tipos de SNP, incluyendo la depresión y queja subjetiva de memoria vinculados a la hipertensión arterial, constituyen factores de riesgo para el deterioro neurocognoscitivo en personas mayores. Particularmente los síntomas depresivos parecen ser un predictor de desarrollo de deterioro cognoscitivo en presencia de hipertensión arterial.
- Apatía y desinhibición, dos SNP cruciales en el inicio y en la evolución de la DFTvc, determinan patrones neurocognitivos y clínicos diferenciales en esta condición por primera vez en la literatura. De estos hallazgos se observó entonces la presencia de dos variantes neurocognitivas de la enfermedad: la DFTvc variante apática y la DFTvcD variante desinhibida.
- Los pacientes con DFTvc presentan exacerbación de dos tipos de emociones sociales-morales, incluyendo la envidia y el *Schadenfreude*. Esta exacerbación

constituye una impronta distintiva de la DFTvc, determinada por unos correlatos neuronales particulares que a su vez también se relacionan con procesos cognitivos, afectivos y de cognición social en esta condición. Tal incremento es una nueva expresión de la desregulación social y afectiva que podría impactar en el diagnóstico y la progresión de la DFTvc.

- La presencia de distintos tipos de SNP (conductuales, afectivos y psicóticos, entre otros) durante las etapas tempranas de la enfermedad en pacientes con DFT y EA predice, en un estudio longitudinal, la progresión cognitiva y funcional diferenciada y particular en cada tipo de enfermedad neurocognitiva. Para la DFT, los mayores valores predictivos corresponden a alteraciones conductuales, delirios y cambios en la alimentación. Para la EA, la presencia de síntomas depresivos y las alteraciones del sueño.

Conclusiones: Se logró avanzar en el conocimiento de las enfermedades neurodegenerativas, específicamente en la DFT, y en la EA (patrón de referencia de estos trastornos), resaltando la función decisiva de los SNP durante toda la historia de la enfermedad, sustentada en sus correlatos clínicos, cognitivos y de neuroimagen estructural.

Es necesario identificar desde etapas tempranas cada uno de los SNP, pues dicha identificación puede ayudar a predecir y tipificar el curso de la enfermedad. Igualmente, los SNP conductuales, afectivos y psicóticos, durante las primeras etapas de la DFT y la EA, pronostican el deterioro cognitivo de esos pacientes. De aquí la utilidad de una subdivisión clínica de la DFT basada en los SNP y la importancia de su identificación y seguimiento longitudinal.

Nuevas opciones de investigación pueden encontrarse al evaluar de manera más sistemática los SNP en otras condiciones neurodegenerativas y al emprender estudios que busquen establecer vínculos entre estos síntomas y otros procesos (cognitivos generales, motores, interoceptivos de cognición social-moral) y las interacciones de estos diálogos con condiciones orgánicas.

Tabla de contenidos

Agradecimientos 3
Resumen 5
1. Presentación 11
2. Objetivos 17
2.1 Objetivo general 17
2.2 Objetivos específicos 17
3. Marco teórico 19
3.1 Envejecimiento, vejez y trastornos neurocognoscitivos (TN) 19
3.2 Trastorno neurocognoscitivo mayor (TNM): clasificación y características clínicas 23
3.2.1 Degeneración frontotemporal (DFT) 25
3.2.2 Enfermedad de Alzheimer (EA) 28
3.3 Trastornos neurocognoscitivos (TN) y los síntomas neuropsiquiatricos (SNP) 30
3.3.1 Los síntomas neuropsiquiátricos (SNP) y su correlación neuroanatómica en la degeneración frontotemporal (DFT) 35
3.3.2 Los síntomas neuropsiquiátricos (SNP) como primera manifestación clínica en trastornos neurocognoscitivos (TN) 38
3.3.3 Los síntomas neuropsiquiátricos (SNP) como expresión psicopatológica de la cognición social 39
4. Hipótesis general 45
5. Metodología 47
5.1 Diseños 47
5.2 Variables e instrumentos 48
6. Consideraciones éticas 49

7. Resultados y discusión 51
7.1 Estudio 1: Alteraciones del comportamiento de pacientes con diagnóstico de trastorno neurocognoscitivo en Bogotá (Colombia) 51
7.2 Estudio 2: Association of Depressive Symptoms and Subjective Memory Complaints with the Incidence of Cognitive Impairment in Older Adults with High Blood Pressure 63
7.3 Estudio 3: First Symptoms and Neurocognitive Correlates of Behavioral Variant Frontotemporal Dementia 71
7.4 Estudio 4: A Lesion Model of Envy and Schadenfreude: Legal, Deservingness and Moral Dimensions as Revealed by Neurodegeneration . 105
7.5 Estudio 5: Neuropsychiatric Symptoms as Predictors of Clinical Course in Neurodegeneration. A Longitudinal Study 126
8. Discusión 141
9. Conclusiones 151
Bibliografía 153

1. Presentación

La historia sobre las primeras aproximaciones al estudio de la degeneración frontotemporal se puede rastrear desde finales del siglo XIX y los inicios del XX, momento en el que Bayl atribuyó la demencia a la presencia de lesiones en el sistema nervioso central. En el año 1892, Arnold Pick estableció nexos entre procesos degenerativos en áreas cerebrales y alteraciones del comportamiento, del afecto y del lenguaje. Posteriormente, hacia el año 1911, Alois Alzheimer puntualizó los hallazgos de Pick y encontró cuerpos histológicos similares en la enfermedad que luego llevaría su nombre: la enfermedad de Alzheimer. Hacia finales del siglo pasado, resurge el interés por la degeneración frontotemporal denominada *degeneración lobar* por Lund, Brun y Gustafso en 1986 y *demencia de tipo frontal* por Neary en 1988 (Custodio et al., 2018). A la fecha, existen innumerables investigaciones que evalúan aspectos clínicos, diagnósticos, neurobiológicos, genéticos y de tratamiento de los distintos síndromes clínicos asociados con la degeneración frontotemporal (Convery et al., 2019; Staffaroni et al., 2020; Wauters y Van Broeckhoven, 2020).

Los primeros criterios diagnósticos (clínicos y neuropatológicos) de la degeneración frontotemporal fueron establecidos por Lund y Manchester (Englund et al., 1994), quienes consideraron como relevantes para el diagnóstico los trastornos de la conducta, los síntomas afectivos y las alteraciones del habla, y señalaron que permanecían indemnes la orientación espacial y las praxias. Posteriormente, el grupo de Neary et al. (1998) publica un consenso acerca de los criterios diagnósticos clínicos particulares para las tres variantes de la DFT. Tres años después, el grupo de McKhann et al. (2001) expone el diagnóstico clínico y patológico en el informe del Grupo de Trabajo de Demencia Frontotemporal y

Enfermedad de Pick. En 2007, el grupo de Cairns et al. (2007) presenta los criterios diagnósticos neuropatológicos y la nosología frontotemporal en el consenso que dio sustento al Consorcio para la Degeneración Lobar Frontotemporal, incluyendo los avances en genética molecular, bioquímica y neuropatología en relación con el trastorno (Toribio y Morera, s. f.; Lillo y Leyton, 2016).

En ese mismo año, Rascovsky et al. (2007) revisan los criterios diagnósticos, particularmente los planteados por Neary, y convocan a los investigadores con trayectoria en el área de las demencias para conformar, con el apoyo del Instituto Nacional de Salud de EE. UU. (NIH), un consorcio internacional de criterios, específicamente para la variable conductual de la DFT (DFTvc). En 2011, el consorcio genera el Consenso Internacional de Criterios de la DFT variante conductual (Rascovsky et al., 2011).

La degeneración frontotemporal (DFT) ocupa el segundo lugar después de la enfermedad de Alzheimer (EA) (con la que a veces se la confunde) en cuanto a la prevalencia entre las enfermedades neurodegenerativas. La DFT se manifiesta en tres modalidades o variantes clínicas: variante frontal o comportamental (DFTvc), semántica (DS) y afasia primaria progresiva (APP) (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). En general, el inicio de la DFT (entre los 45 y 65 años) se da de manera más temprana que el de la EA (usualmente entre los 60 y 80 años), dando lugar a un curso individual de la enfermedad de hasta veinte años. La gravedad de las alteraciones comportamentales en la DFT, su deterioro progresivo, la larga duración de la enfermedad y la carencia de intervenciones terapéuticas efectivas generan serios y diversos impactos: mayor pérdida de años de vida productivos (Galvin et al., 2017), necesidad de cuidado con importantes exigencias para los familiares (quienes generalmente se hacen cargo) (Nicolaou et al., 2010), rechazo y aislamiento social (Rasmussen et al., 2019) y demandas repetidas a los

servicios de salud por las dificultades diagnósticas que erróneamente la clasifican como una de las patologías psiquiátricas conocidas (Wylie et al., 2013).

La DFT afecta la vida de pacientes y cuidadores, por lo que se hace necesario promover y hacer investigación en esta condición en aras de mejorar la caracterización clínica, neurocognitiva y ofrecer mejores estrategias de intervención. En este sentido, uno de los dominios de conocimiento en la DFT que resulta prometedor para la comprensión de la condición, su diagnóstico, seguimiento y pronóstico es el estudio de los síntomas neuropsiquiátricos (SNP) que suelen acompañar la condición. Un mayor estudio sobre las rutas clínicas, neurales y cognitivas de los SNP ayudan a aumentar la comprensión que tenemos sobre la enfermedad y ofrecen nuevas y mejores estrategias de diagnóstico y posibles intervenciones.

Así, en esta tesis se expondrá un grupo de estudios adelantados para comprender las rutas neurales, cognitivas y clínicas de los distintos SNP, que son nucleares en la presentación clínica de la DFT en comparación con otras condiciones neurocognitivas prevalentes, particularmente AD. El estudio sobre la aparición de estos SNP, su variabilidad, momento de aparición e intensidad, su asociación con condiciones clínicas, su impacto cognitivo, funcional y pronóstico, así como también el estudio de las rutas neurales que describen los SNP más prevalentes en la DFT y su relación con procesos cognitivos particulares, resultan relevantes para el desarrollo de esta tesis. De allí la importancia del objetivo propuesto: establecer los correlatos clínicos, cognitivos y de neuroimagen de los SNP, conjugando diversas técnicas, herramientas y análisis de la información.

En el primer estudio presentado reportamos la prevalencia de los SNP en un centro de recepción de trastornos neurocognitivos de alta demanda en la ciudad de Bogotá, Colombia. En este se resalta la necesidad de hacer una búsqueda activa de

un repertorio extenso de SNP para apoyar el diagnóstico de distintos tipos de trastornos neurocognoscitivos (TN) y de rastrear su severidad e impacto en el rendimiento cognitivo y funcional de los pacientes.

En el segundo estudio nos hemos enfocado en la importancia de los SNP como posible factor de riesgo para el deterioro cognoscitivo en pacientes con comorbilidades orgánicas. En particular, evaluamos la presencia de depresión como uno de los síntomas nucleares en el repertorio de SNP, así como la queja subjetiva de memoria en personas con hipertensión arterial y su asociación con una mayor progresión a deterioro cognitivo.

En el tercer estudio hemos evaluado los patrones de atrofia cerebral, el curso clínico y los correlatos cognitivos relacionados con los síntomas de debut tipo SNP clásicos, incluyendo la presencia de apatía y desinhibición en pacientes con DFTvc, haciendo uso de análisis estadísticos complejos como la implementación de máquina de vectores de soporte y análisis factoriales discriminantes.

Para el cuarto estudio, hemos evaluado la presencia, expresión y rutas neurales de distintas emociones sociales y su relación con SNP, procesos de cognición social y de cognición general en pacientes con DFTvc en comparación con pacientes con AD.

En el quinto estudio realizamos un seguimiento longitudinal a dos grupos de pacientes, DFT y EA, para evaluar el impacto funcional y cognitivo que tiene la progresión de los SNP en el curso de la enfermedad, y encontramos un mayor deterioro para ciertos tipos de SNP en cada etiología.

Considerando lo anterior, en nuestra secuencia de producción buscamos resaltar el valor de los SNP como determinantes clínicos y neurocognitivos en la DFT y

subrayamos en igual medida la necesidad de hacer una mejor búsqueda de estos a lo largo de todo el curso de la enfermedad, teniendo en cuenta que tienen un papel predominante como factores de riesgo y de progresión clínica, además de un rol nuclear diagnóstico y pronóstico. Resaltamos, además, el valor del trabajo en equipo y del consenso interdisciplinario, así como la necesaria participación de psiquiatras para un adecuado estudio y exploración de los SNP en el estudio y manejo de la DFT.

Finalmente, este documento recoge en los primeros capítulos, además de las consideraciones éticas, los objetivos, el marco teórico, la hipótesis y metodología generales, aspectos que se amplían y profundizan en el capítulo de resultados y discusión, correspondiente a la presentación de los estudios publicados, para cerrar con el planteamiento de conclusiones y la propuesta de nuevas líneas de investigación.

2. Objetivos

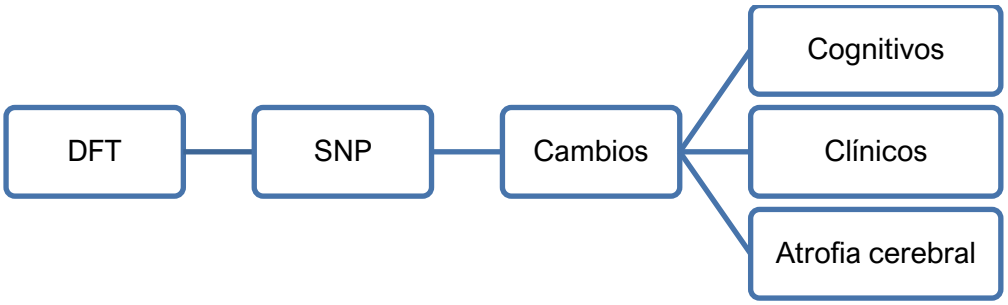
2.1 Objetivo general

Estudiar la relación entre los SNP, la presentación clínica, el funcionamiento cognitivo general, de cognición social y los patrones de atrofia cerebral en pacientes con DFT en distintos momentos del curso de enfermedad.

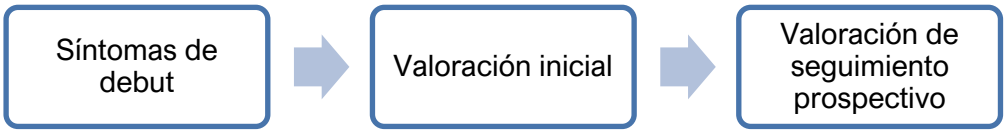
Figura 1. Objetivo general

De manera gráfica, se pretende

Explorar la relación:



En el curso de la enfermedad:



2.2 Objetivos específicos

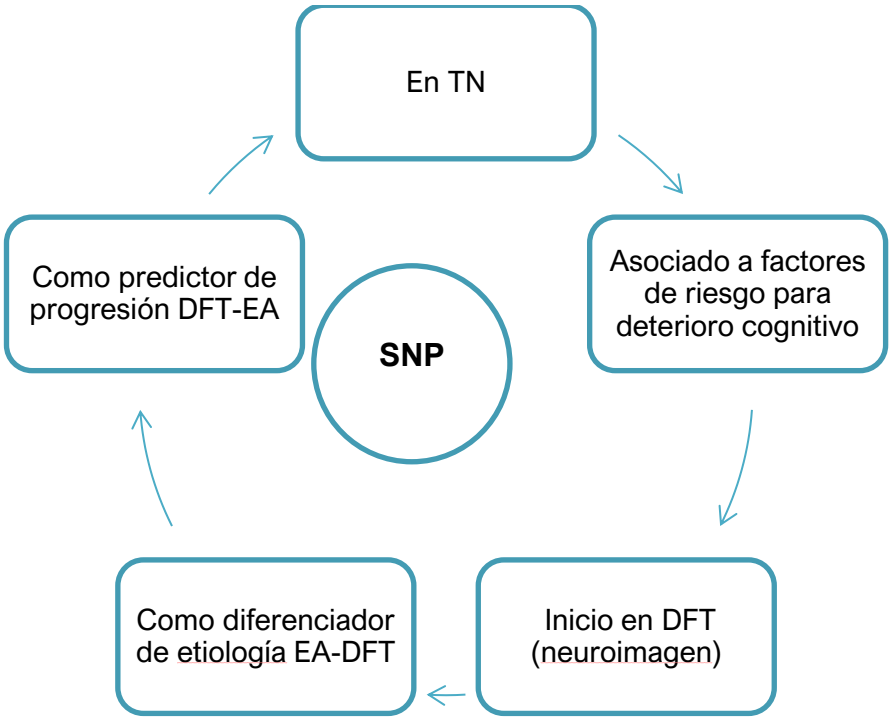
- Identificar los sustratos neurocognitivos de los pacientes con DFT en relación con los SNP en distintas etapas del curso de la enfermedad (debut, valoración inicial y valoración de seguimiento a tres años).

- Determinar el patrón de atrofia de la corteza cerebral medido a través de un análisis de morfometría cerebral basada en voxeles en relación con los SNP y el patrón cognitivo de los pacientes con DFT.

- Determinar la asociación entre perfil clínico de los pacientes con DFT, comorbilidades orgánicas y la presencia de SNP.

Los objetivos específicos se cumplieron a través de los cinco estudios (publicados en revistas internacionales de alto impacto en el campo de investigación de los TN), cuya secuencia aparece en la figura 2, y se exponen en el capítulo 7 “Resultados y discusión”.

Figura 2. Secuencia de producción de los estudios publicados



3. Marco teórico

3.1 Envejecimiento, vejez y trastornos neurocognoscitivos (TN)

En todos los países del mundo, con diferencias debidas a las dinámicas demográficas particulares, se aprecia un envejecimiento poblacional explicado en buena medida por el decremento de las tasas de fecundidad, una mayor esperanza de vida y las políticas de salud pública (saneamiento ambiental, agua potable, seguridad alimentaria). Estas condiciones inciden globalmente en la calidad y mantenimiento de la vida (Chang et al., 2019; He et al., 2016; Wang et al., 2020). Según datos de la Organización Mundial de la Salud (OMS) (2018), entre 2015 y 2050 el porcentaje de personas mayores de 60 años en el mundo se duplicará, pasando del 12 % al 22 %. Este aumento progresivo y sostenido generará nuevas necesidades y servicios, especialmente en lo que compete a la atención en salud.

No todas las personas envejecen igual; este es un proceso individual y multideterminado por condicionantes biológicos, sociales y culturales que da lugar a un envejecimiento que puede ser *patológico, normal o exitoso*, dependiendo del número de patologías que aquejan al sujeto y del impacto de estas en su funcionalidad (Depp et al., 2007; Martin y Sheaff, 2007). Los programas e intervenciones en este campo se orientan cada vez más a lograr ese envejecimiento exitoso, también denominado *activo* o *saludable*. La OMS, en su *Informe mundial sobre el envejecimiento y la salud* (2015), se refiere al *envejecimiento saludable* como el proceso de desarrollar y mantener la capacidad funcional más allá de la ausencia de enfermedad generando bienestar en la vejez, vinculando la capacidad funcional con la capacidad intrínseca. Esta resulta de la combinación de todas las

potencialidades físicas y mentales a utilizar en un momento dado, teniendo en cuenta los recursos de su entorno (OMS, 2015).

A pesar de lo anterior, es claro que existe una serie de problemas de salud característicos de la vejez, usualmente denominados como los grandes síndromes geriátricos, los cuales irán en aumento en la medida en que lo haga el número de personas mayores. Dentro de los síndromes geriátricos se encuentran: la fragilidad, la depresión, la desnutrición, la inestabilidad y caídas, las infecciones, las alteraciones visuales y auditivas y los TN, entre otros (Inouye et al., 2007).

Debido a su magnitud y a la carencia de un tratamiento curativo, los TN provocan una enorme repercusión en la calidad de vida del paciente, la familia y la sociedad y, a diferencia de algunas otras entidades clínicas, alteran de manera gradual la dignidad del propio individuo (Rognstad et al., 2020; Sagbakken et al., 2017). Los TN, antes llamados demencias (aunque es frecuente que ambos términos se utilicen indistintamente), son un grupo de enfermedades relacionadas directamente con la edad y definidas como un síndrome clínico representado por el compromiso de uno o más dominios cognitivos, constatable por parte de pruebas diagnósticas y por parte de personas cercanas al paciente, que afecta la funcionalidad (Sachdev et al., 2014). Uno de los principales desafíos en el ámbito profesional médico es realizar un adecuado diagnóstico de tales trastornos en etapas tempranas, con el fin de reducir, a través de la implementación de las estrategias terapéuticas disponibles, el impacto de estos trastornos en la funcionalidad y la autonomía de los pacientes (Kertesz, 2018; Mendez et al., 2007).

La quinta versión del *Manual de Diagnóstico y Estadístico de Trastornos Mentales (DSM-5)* (American Psychiatric Association [APA], 2013) define los siguientes dominios cognitivos: a) la atención compleja que incluye la atención continua, dividida, selectiva y la velocidad de procesamiento; b) el funcionamiento ejecutivo

comprendido por la capacidad de planeación, toma de decisiones, memoria de trabajo, respuesta a la retroinformación o corrección de errores, inhibición, hábitos predominantes y flexibilidad mental; c) el aprendizaje y la memoria dentro de la que se encuentran la memoria inmediata, memoria reciente (recuerdo libre, recuerdo evocado y memoria de reconocimiento), memoria a muy largo plazo (semántica, autobiográfica) y el aprendizaje implícito; d) el lenguaje expresivo (nombrar cosas, encontrar palabras, fluidez, gramática y sintaxis) y el receptivo; e) las habilidades perceptuales motoras (habilidades de percepción visual, habilidades visoconstructivas, perceptuales motoras, praxis y gnosias). Además, este manual incluye un grupo de procesos cognitivos relacionados con la integración de los estímulos sociales que incluyen el reconocimiento y expresión de emociones y la teoría de la mente (APA, 2013).

La ausencia de un tratamiento curativo para este grupo de trastornos conduce a un énfasis especial en la prevención y el diagnóstico temprano, buscando minimizar sus graves consecuencias. En mayo de 2017, la Asamblea Mundial de la Salud respaldó el “Plan de acción mundial sobre la respuesta de salud pública a la demencia 2017-2025”, enfocado en la reducción de riesgos; el diagnóstico, el tratamiento y la atención; los sistemas de información; el apoyo a los cuidadores; la investigación y la innovación (OMS, 2020).

Según datos reportados por la OMS (2020), la demencia afecta a nivel mundial a unos 50 millones de personas, de las cuales alrededor del 60 % vive en países de ingresos bajos y medios. Cada año se registran cerca de 10 millones de casos nuevos. Calcula la OMS que entre un 5 % y un 8 % de la población general de 60 años o más sufre demencia en un determinado momento y estima que el número total de personas con demencia alcance los 82 millones en 2030 y 152 millones en 2050.

En Colombia, las últimas cifras sobre TN mayor corresponden a la Encuesta Nacional de Salud, Bienestar y Envejecimiento (SABE) (2015), que reportó una prevalencia total de demencia del 9,4 % (IC95%: 7,7-11,4), aumentada notoriamente con la edad, dado que se evidenció que en mayores de 85 años la prevalencia fue de 57,4 % (Ministerio de Salud y Protección Social et al., 2016).

Se han descrito recientemente los factores de riesgo para la presencia de deterioro cognoscitivo como lo revelan dos revisiones recientes de Lancet Commission on Dementia Prevention, Intervention and Care de los años 2017 y 2020. Dentro de los factores de riesgo más relevantes se encuentran: el bajo nivel educativo, la hipertensión, la diabetes, las alteraciones auditivas, el tabaquismo, el consumo de licor excesivo, la obesidad, la depresión, el sedentarismo, un escaso contacto social, el daño cerebral por trauma y la polución ambiental (Livingston et al., 2017; Livingston et al., 2020). La importancia de esta información radica en que los doce factores mencionados son modificables, con un posible impacto en el 40 % de las "demencias" en el mundo, mayor para países de medianos y bajos ingresos. Un factor de riesgo bien conocido para deterioro cognoscitivo es la hipertensión arterial (HTA), la cual se asocia con manifestaciones patológicas de la EA (placas seniles, ovillos neurofibrilares, atrofia hipocampal), con la posibilidad de generar daño cerebral por lesiones isquémicas y terminar de forma manifiesta en una demencia (Skoog y Gustafson, 2006). La presencia de HTA crónica no tratada ha sido vinculada con una variedad de cambios vasculares estructurales y funcionales. Estos cambios alteran la habilidad de autorregulación fisiológica, llevando a isquemia en áreas cerebrales vulnerables, como las que se encargan del control afectivo y del estado de ánimo (Skoog y Gustafson, 2006).

Son escasas las descripciones de factores de riesgo específicos para la DFT. Sin embargo, algunos estudios reportan factores cardiovasculares, entre los que se destaca la diabetes mellitus (Golimstok et al., 2014) y el trauma craneoencefálico

(Rosso et al., 2003). Otros factores de riesgo se han relacionado específicamente con la EA, incluyendo el nivel de actividad cognitiva, el estrés, la hiperhomocistinemia, la hipotensión ortostática, la pérdida de peso después de los 65 años, las alteraciones del sueño, la enfermedad cerebrovascular y la fragilidad (Yu et al., 2020).

3.2 Trastorno neurocognoscitivo mayor (TNM): clasificación y características clínicas

Aunque existen diferentes maneras de categorizar estos trastornos, actualmente se ha optado por utilizar una clasificación etiológica, según la condición médica que puede explicarlos o generarlos. Así, estas enfermedades pueden dividirse en tres grandes grupos: las de causas primarias (o enfermedades neurodegenerativas), como la EA y la DFT, entre otras; las de causas secundarias, como por ejemplo, las generadas por la infección por VIH o por un trauma craneoencefálico; y por último, las de causas vasculares, que varían dependiendo del tipo y localización de la lesión a nivel cerebral (Baio et al., 2018; Ganguli et al., 2011; Sachdev et al., 2014).

Más allá de esta clasificación, la quinta versión del *Manual Diagnóstico y Estadístico de Trastornos Mentales (DSM-5)* (APA, 2013) pone de relieve la comparación del rendimiento de los dominios cognitivos con el nivel anterior, las limitaciones en el desempeño de las actividades cotidianas y la ausencia de otra patología que lo explique. Sugiere identificar las manifestaciones clínicas que lleven a una posible o probable etiología (EA, Parkinson, vascular, taumatismo cerebral u otra); especificar la severidad (si son leves, moderadas —según dificultades las actividades instrumentales o básicas cotidianas— o graves) por su impacto en la funcionalidad que genera dependencia; y finalmente, indicar si hay o no alteraciones de la conducta (Tabla 1).

Tabla 1. Trastorno neurocognitivo mayor (DSM-5)

Evidencias de un declive cognitivo significativo comparado con el nivel previo de rendimiento en uno o más dominios cognitivos (atención compleja, función ejecutiva, aprendizaje y memoria, lenguaje, habilidad perceptual motora o cognición social), basada en: preocupación en el propio individuo, en un informante que le conoce o en el clínico, porque ha habido un declive significativo en una función cognitiva y un deterioro sustancial del rendimiento cognitivo, preferentemente documentado por un test neuropsicológico estandarizado o, en su defecto, por otra evaluación clínica cuantitativa.	
Los déficits cognitivos interfieren con la autonomía del individuo en las actividades cotidianas (es decir, por lo menos necesita asistencia con las actividades instrumentales complejas de la vida diaria, como pagar facturas o cumplir los tratamientos).	
Los déficits cognitivos no ocurren exclusivamente en el contexto de un síndrome confusional.	
Los déficits cognitivos no se explican mejor por otro trastorno mental (por ejemplo, trastorno depresivo mayor, esquizofrenia).	
Especificadores	
Debido a:	
Enfermedad de Alzheimer	Enfermedad por priones
Degeneración del lóbulo frontotemporal	Enfermedad de Parkinson
Enfermedad por cuerpos de Lewy	Enfermedad de Huntington
Enfermedad vascular	Otra afección médica
Traumatismo cerebral	Etiologías múltiples
Consumo de sustancia o medicamento	No especificado
Infección por VIH	
Especificar	
Sin alteración del comportamiento: si el trastorno cognitivo no va acompañado de ninguna alteración del comportamiento clínicamente significativa.	
Con alteración del comportamiento (especificar la alteración): si el trastorno cognitivo va acompañado de una alteración del comportamiento clínicamente significativa (por ejemplo, síntomas psicóticos, alteración del estado de ánimo, agitación, apatía u otros síntomas comportamentales).	
Especificar la gravedad actual	
Leve: dificultades con las actividades instrumentales cotidianas (es decir, tareas del hogar, gestión del dinero).	
Moderado: dificultades con las actividades básicas cotidianas (por ejemplo, comer, vestirse).	
Grave: totalmente dependiente.	

Fuente: APA (2013).

Dentro de los TNM, la DFT y la EA son las dos enfermedades más prevalentes en menores de 65 años. Por su parte, la EA es la más prevalente en toda la población. El interés por la EA data de más tiempo, vinculado quizá con la atención que se ha prestado al fenómeno de envejecimiento: hoy, la EA cuenta con un importante volumen de literatura médica que la configura como un referente para las patologías neurodegenerativas. De hecho, la revisión de Lancet Commission de 2020 (Livingston et al., 2020) en su título alude a la prevención, intervención y cuidado de la demencia de manera general, aunque en el texto se refiere en distintas ocasiones a la EA.

Este referente se aprecia a lo largo de esta tesis. Considerando la prevalencia y la presentación clínica, la EA nos ha servido de modelo de comparación en varios de los estudios de este trabajo

3.2.1 Degeneración frontotemporal (DFT)

La DFT, aunque menos frecuente que la EA, es responsable de un porcentaje importante de las demencias degenerativas: representa 5 a 7 % de las series de autopsias y un 20 % de las muertes en pacientes con demencia antes de los 70 años. Entre el 20 y el 50 % de los casos son familiares. Las mutaciones en las proteínas tau, asociadas a microtúbulos (MAPT), granulina (GRN) y expansión anormal de hexanucleótido del cromosoma 9 (C9orf72), se encuentran en el 60 % de los casos familiares de DFT. Las mutaciones en C9orf72 son las más comunes y representan el 25 %; mutaciones más raras (<5 %) existen en otros genes (Baker et al., 2006; Chen et al., 2017; Convery et al.; Coppola et al., 2012; Ferrari et al., 2014; Gendron et al., 2013; Ghetti et al., 2015; Ghidoni et al., 2006; Hodges y Piguet, 2018; Olszewska et al., 2016; Piguet et al., 2011).

Estudios recientes han logrado importantes avances en la identificación de características clínicas, patológicas y genéticas de este grupo de enfermedades (Hodges y Miller, 2001; Hodges y Piguet, 2018). Actualmente, la DFT es la segunda causa de TN en personas menores de 65 años y la edad media de inicio está entre los 45 y los 65 años, aunque se han reportado casos de aparición más temprana hacia los 30 años y también en la vejez. No hay diferencias en la prevalencia entre hombres y mujeres y la variante comportamental explica alrededor del 60 % del total de los casos (Olney et al., 2017; Devenney et al., 2015; Hodges y Piguet, 2018)

La DFT es considerada como un conjunto de enfermedades con tres grandes variantes clínicas: la variante frontal o comportamental (DFTvc), la demencia

semántica (DS) y la afasia primaria progresiva (APP) (Hodges y Miller 2001; Gorno-Tempini et al., 2011; Rascovsky et al., 2011).

La DFTvc cursa con cambios progresivos en el comportamiento social-afectivo y con un deterioro en funciones cognitivas específicas (Cáceres et al., 2010; Ibañez y Manes, 2012; Rascovsky et al., 2007). Al parecer, en la DFTvc suelen estar relativamente preservados los procesos cognitivos de la memoria episódica, las habilidades visoespaciales, las praxias y los procesos perceptivos (Kipps et al., 2009); sin embargo, se encuentran alterados ciertos procesos de cognición social (alteraciones en el reconocimiento facial, empatía, toma de decisiones, lenguaje figurativo y la teoría de la mente) (Kipps et al., 2009; Possin et al., 2013; Baez et al., 2014), el proceso de toma de decisiones (Gleichgerrcht et al., 2010; Gregory et al., 2002) y las funciones ejecutivas (FE) (Kamminga et al., 2014).

A continuación, en la tabla 2 aparecen los criterios de consenso internacional para la variante de comportamiento DFT (FTDC, por sus iniciales en inglés), para establecer *posible DFTvc*, *probable DFTvc* y *FTDvc con definitiva DLFT patología (degeneración lobar frontotemporal)*, al igual que los criterios de exclusión para DFTvc.

Tabla 2. Criterios diagnósticos DFT (DFTvc)

I. Para el diagnóstico de enfermedad neurodegenerativa
Las siguientes manifestaciones clínicas deben estar presentes para un diagnóstico de DFTvc
A. Deterioro progresivo de la conducta y/o cognición por observación o historia otorgada por informante.
II. Posible FTDvc
Tres de algunos de los siguientes síntomas (A-F). Se requiere que los síntomas sean recurrentes o persistentes, no solo eventos ocasionales.
A. Temprana* desinhibición [uno de los siguientes síntomas (A.1–A.3) debe estar presente]:
A.1. Conducta social inapropiada
A.2. Pérdida de modales o decoro
A.3. Impulsividad o acciones descuidadas
B. Temprana apatía o inercia [uno de los siguientes síntomas (B.1–B.2) debe estar presente]:
B.1. Apatía
B.2. Inercia
C. Temprana pérdida de simpatía o empatía [uno de los siguientes síntomas (C.1–C.2) debe estar presente]:
C.1. Disminución de respuestas hacia sentimientos y necesidades de otros.

C.2. Disminución del interés social, interrelaciones con otros o calidez con otros.
D. Conductas tempranas perseverantes, estereotipadas o compulsivas/ritualísticas (D.3)
[Uno de los siguientes síntomas debe estar presente presente] (D.1-D.3):
D.1. Movimientos repetitivos simples
D.2. Comportamientos ritualísticos o compulsivos complejos
D.3. Lenguaje estereotipado
E. Hiperoralidad o cambios alimenticios**. [Uno de los siguientes síntomas (E.1–E.3) debe estar presente]:
E.1. Alteración de las preferencias alimenticias
E.2. Hiperfagia o aumento del consumo de alimentos, alcohol o cigarrillos
E.3. Exploración oral o ingestión de objetos no comestibles
F. Perfil neuropsicológico: ejecutivo/con relativa preservación de la memoria y funciones visoespaciales
[todos los siguientes (F.1–F.3) deben estar presentes]:
F.1. Déficits en funciones ejecutivas
F.2. Preservación relativa de la memoria episódica
F.3. Conservación relativa de las funciones visoespaciales
III. Probable DFTvc
Todos los siguientes síntomas (A-C) deben estar presentes
A. Cumple criterios para posible DFTvc
B. Deterioro funcional significativo (informado por cuidador o evidenciado en cuestionario de actividades funcionales
C. Neuroimágenes consistentes con FTDvc [Uno de los siguientes (C.1–C.2) debe estar presente]:
C.1. Atrofia frontal y/o atrofia temporal anterior en RNM o TAC
C.2. Frontal y/o hipoperfusión anterior temporal, o hipometabolismo en PET o SPECT
IV. FTDvc con definitiva DLFT patología (degeneración lobar frontotemporal)
Criterio A o B o C debe estar presente.
A. Cumple criterio para posible y probable
B. Evidencia histopatológica de DFT of FTLD en biopsia o *post mortem*
C. Presencia de mutación patogénica conocida
V. Criterios de exclusión para DFTvc
Criterios A y B deben ser negativos. Criterio C puede ser positivo para posible DFTvc, pero negativo para probable DFTvc
A. Perfil o déficits se explican por otros trastornos del sistema nervioso central o desórdenes neurodegenerativos
B. Alteraciones comportamentales son explicadas por enfermedad psiquiátrica
C. Los biomarcadores son indicativos de EA u otro proceso neurodegenerativo

Fuente: Rascovsky et al. (2011).

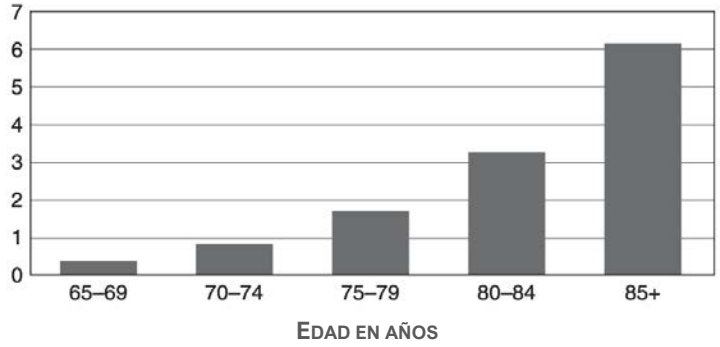
Por su parte, en la demencia semántica aparecen indemnes los elementos fonológicos y sintácticos del lenguaje, pero se pierde el significado de las palabras (Williams et al., 2005), en tanto que en la afasia progresiva primaria ocurren dificultades en la nominación y anormalidades en el discurso: disminución del tamaño de las frases, parafasias fonológicas, alteraciones en la velocidad, articulación, prosodia y errores gramaticales (Snowden et al., 2001).

3.2.2 Enfermedad de Alzheimer (EA)

La EA es la principal etiología de trastorno neurocognoscitivo en el mundo. Explica el 50-70 % de los casos (Alzheimer's Association, 2018), es la que más relación tiene con el envejecimiento y es una de las primeras diez causas de muerte en el mundo (OMS, 2018).

Hoy se calcula que, a escala global, entre el 5 y 7 % de los sujetos mayores de 60 años puede tener una enfermedad neurodegenerativa y, en el caso de la EA, se puede duplicar cada cinco años luego de los 65, sin tener en cuenta para ello otras demencias (Lee y Krishnan 2010; Prince et al., 2013). La figura 3, publicada por Mayeux y Stern (2012), muestra la tasa de incidencia anual (por 100 personas/año) de la EA.

Figura 3. Incidencia anual (por 100 personas/año) de la enfermedad de Alzheimer



Fuente: Mayeux y Stern (2012).

Actualmente, el diagnóstico patológico de la EA requiere la presencia aumentada de placas neuríticas y ovillos neurofibrilares (DeTure y Dickson, 2019; Nelson et al., 2012). Las placas neuríticas están conformadas por un núcleo de proteína amiloide rodeado por astrocitos, microglia y neuritas distróficas. Los ovillos neurofibrilares son la segunda característica histopatológica de la EA: contienen filamentos helicoidales emparejados de proteína tau anormalmente fosforilada, se encuentran

dentro del cuerpo celular y se extienden hacia las dendritas (Cummings y Cole, 2002). Vale anotar que biomarcadores de estos cambios pueden encontrarse incluso en las etapas preclínicas de la enfermedad (López-Álvarez y Agüera-Ortiz, 2015).

Las investigaciones han encontrado varios genes que aumentan el riesgo de padecer EA. El gen con mayor impacto en la EA de aparición tardía es el de la apolipoproteína-e4 (APOE-e4) (Agosta et al., 2009). Es posible desarrollar la enfermedad sin antecedentes familiares; sin embargo, las personas que tienen un familiar de primer grado con EA son más propensos a desarrollarla. En solo un pequeño porcentaje de casos de EA, alrededor del 1 %, se genera la enfermedad como resultado de mutaciones en tres genes específicos: el gen de la proteína precursora de amiloide (APP) y los genes de las proteínas presenilina 1 y presenilina 2 (Alzheimer's Association, 2020). Las personas con síndrome de Down (trisomía 21) tienen un mayor riesgo de sufrir de EA, aparentemente debido a que el cromosoma 21 incluye el gen que codifica para la producción de la APP, lo que provoca consecuentemente un aumento en la producción y acumulación de beta amiloide (Alzheimer's Association, 2020).

La EA es incurable. Tiene un largo periodo preclínico y un curso progresivo caracterizado por la alteración de múltiples funciones cognitivas, incluyendo memoria, pensamiento, orientación, comprensión, cálculo, capacidad de aprendizaje, lenguaje y juicio, sin compromiso del estado de conciencia (Alzheimer's Association, 2020). Las deficiencias de la función cognitiva están comúnmente acompañadas y ocasionalmente precedidas por una alteración en el control afectivo, el comportamiento social o la motivación, que interfieren con el funcionamiento social y laboral (Ballard et al., 2011). Estos hallazgos requieren mayor profundización y es una de las razones que han motivado la línea de investigación de la cual se deriva esta tesis doctoral.

La mayoría de los pacientes con EA no reporta autónomamente pérdida de memoria; a menudo es el cónyuge u otro informante quien lleva el problema al médico (Warren et al., 2012). La dificultad para recordar conversaciones recientes, nombres o eventos es con frecuencia un síntoma clínico temprano; la apatía y la depresión son también comunes en etapas iniciales (Zhao et al., 2016). Los síntomas posteriores incluyen problemas de comunicación, desorientación, confusión, falta de juicio, cambios de comportamiento y, en última instancia, dificultad para hablar, deglutir y caminar. De manera corriente, los pacientes pueden tener dificultades para retener nueva información, gestionar tareas complejas, razonamiento, capacidad espacial y orientación, dificultades semánticas o fonológicas (Alzheimer's Association, 2020). Además, presentan alteraciones afectivas y del comportamiento (Ganguli et al., 2011).

3.3 Trastornos neurocognoscitivos (TN) y los síntomas neuropsiquiatricos (SNP)

Además de las manifestaciones cognitivas y funcionales de los trastornos neurocognitivos, deben considerarse las alteraciones comportamentales, los síntomas psicológicos y afectivos que sumados configuran la categoría de SNP.

En general, los SNP se definen como un grupo heterogéneo de síntomas que afectan diversos dominios del funcionamiento psíquico, incluyendo cambios del afecto o del pensamiento, entre otros (Draper et al., 2015). Los SNP son sumamente frecuentes: entre un 50-80 % de los pacientes con trastorno cognitivo los presenta durante el curso de la enfermedad (Lyketsos et al., 2002), pueden estar presentes a lo largo de esta e incluso surgir con anterioridad a los síntomas cognitivos más característicos. Se ha planteado que los SNP pueden encontrarse en cualquier tipo

de TN y en cualquier estadio de estas enfermedades (Lyketsos et al., 2002; Van der Mussele et al., 2013).

La identificación de los SNP en las personas con TN es cada vez más usual. Por ejemplo, en la EA, una revisión sistemática y un metaanálisis de 48 estudios (2015) publicados entre 1964 y 2014 encontraron como los SNP más frecuentes en las personas mayores de 50 años con TNM debido a EA la apatía (con una prevalencia general del 49 %), seguida de depresión (42 %), agresividad (40 %), ansiedad (39 %), trastorno del sueño (39 %), irritabilidad (36 %), trastorno del apetito (34 %), comportamiento motor aberrante (32 %), ideas delirantes (31 %), desinhibición (17 %) y alucinaciones (16 %); menos común era la euforia (7 %) (Zhao et al., 2016).

Un estudio longitudinal que incluyó 1.430 participantes, con un seguimiento a cinco años, determinó igualmente entre los SNP más comunes la apatía (83 %), la depresión (63 %), la pérdida de apetito (63 %) y el disturbio motor (60 %). También se determinó una gran incidencia y variabilidad de las alteraciones conductuales durante los dos años iniciales, con una posterior meseta en la aparición de los síntomas y una disminución en su severidad (Vik-Mo et al., 2018). En el estudio longitudinal de Steinberg et al. (2003), se estimó que la prevalencia acumulada (18 meses) de SNP en los TN puede alcanzar el 88,6 %. Más aún, se ha señalado que hasta el 97 % de los pacientes presenta al menos uno de esos síntomas durante el curso de la enfermedad, lo cual empeora el pronóstico, pues deteriora globalmente la calidad de vida, la independencia en las actividades de la vida diaria y acelera la progresión de la patología de base (Agüera Morales y Tunez Fiñana, 2011).

Uno de los principales SNP como lo es la depresión ha revelado ser otro factor de riesgo importante para los TN, además de otros factores sociales y biológicos ya descritos (ver 3.1). La depresión es una enfermedad común a lo largo de la vida y su presencia se ha relacionado con la demencia; algunos estudios señalan un

aumento de más del doble en el riesgo de padecer demencia en la vejez (Byers y Yaffe, 2011).

Así, los SNP se han relacionado con peores pronósticos y desenlaces en el curso del TN, mayor presencia de marcadores neuropatológicos, de deterioro cognitivo y daño funcional, avance acelerado de los síntomas e incluso con un incremento de la mortalidad, peor calidad de vida y mayor sobrecarga del cuidador (Ismail et al., 2017; Ismail et al., 2016; Peters et al., 2013; Taragano et al., 2018). Lo anterior debido a que las alteraciones comportamentales suponen un impacto negativo para el paciente y sus cuidadores, superior al de los síntomas propios del deterioro cognitivo (Gitlin et al., 2012). Así mismo, los SNP se asocian con conductas de riesgo (Dillon et al., 2013), con mayores tasas de institucionalización, de hospitalizaciones psiquiátricas (Okura y Langa, 2011) y mayor utilización y costo de los servicios de salud (Schnaider Beeri et al., 2002).

En personas que padecen un deterioro cognitivo leve la presencia de SNP, en comparación con quienes no los presentan, se ha asociado con una mayor probabilidad de progresar a una fase de demencia (Rosenberg et al., 2013). Además, la severidad de los SNP se ha relacionado con el riesgo de deterioro y, a mayor grado de alteración conductual, habrá mayor riesgo de progresión y deterioro (Forrester et al., 2016). La detección temprana de este tipo de síntomas permite instaurar un tratamiento para controlarlos, mejorando la calidad de vida y llegando a impactar en la evolución de estos trastornos.

La valoración de las disfunciones en áreas anatómicas debidas a daño estructural, el análisis del flujo y de los metabolitos cerebrales han permitido establecer asociaciones entre los síntomas y las distintas regiones cerebrales (Sultzer et al., 2003; Craig et al., 1996; Staff et al., 1999). La correlación entre los SNP y los hallazgos neurales ha sido estudiada en los últimos años y ha demostrado que la

atrofia cerebral es responsable de los cambios de la conducta (Williams et al., 2005; Rosen et al., 2005). Consecuentemente, adquiere importancia la contribución de las neuroimágenes en el entendimiento de la patofisiología, diagnóstico y cambio en el manejo de los SNP (Victoroff et al., 2018). La resonancia magnética estructural ha sido de gran utilidad para demostrar la correlación entre los daños estructurales atróficos y los SNP emergentes. También se ha analizado la densidad de la sustancia gris en relación con los síntomas de EA (Bruen et al.2008).

Dentro de los hallazgos de atrofia cortical relacionada con los SNP, se destacan en la DFT la apatía, asociada a atrofia en la corteza cíngulo dorsal anterior, la corteza prefrontal dorsolateral, la cabeza del núcleo caudado izquierdo y el putamen bilaterales y la desinhibición con atrofia en la corteza orbitofrontal medial (Massimo et al., 2009; Zamboni et al., 2008). A su vez, la presencia de depresión y agitación se ha asociado con atrofia en la corteza frontal media izquierda, la ínsula izquierda y la corteza del cíngulo anterior bilateral; la agitación con atrofia en la corteza frontal media izquierda; la conducta motora aberrante y atrofia en la corteza frontal inferior derecha (Hu et al., 2015); los delirios con atrofia en el lóbulo frontal izquierdo, la corteza frontoparietal derecha y el claustro izquierdo (Bruen et al., 2008).

Con relación a las alucinaciones, se ha descrito la relación entre su aparición y la hipoperfusión en la región prefrontal dorsolateral izquierda, el temporal medial izquierdo y el parietal derecho (Lopez et al., 2001). La agresión o agitación ha correlacionado con aumento en la cantidad de ovillos neurofibrilares en el cíngulo anterior y la corteza orbitofrontal (Tekin et al., 2001).

La falta de integridad en las redes frontales subcorticales y los haces de sustancia blanca con un papel importante de cortezas mediales e inferiores, la región anterior del cíngulo y el fascículo arcuato es un hallazgo vinculado a la desinhibición y la apatía en la DFT (Hornberger et al., 2011). Hallazgos similares se han reportado en

EA (Theleritis et al., 2014). La presencia de síntomas psicóticos en la DFT y la EA está vinculada a dificultades con la memoria episódica y de trabajo, pobre lectura de estados internos, desregulación emocional y conclusiones erróneas de la realidad, relacionadas con hipofunción frontal derecha y actividad irregular de áreas temporales mediales (Mendez et al., 2008).

En la DFT, la apatía, la desinhibición y las alteraciones de la empatía son los SNP más prevalentes (Rascovsky et al., 2011; Brodaty et al., 2015) que afectan el avance de la enfermedad (Brodaty et al., 2015; Ranasinghe et al., 2016). Mientras tanto, la depresión y la apatía se han ligado con deterioro cognitivo y mortalidad en la EA (Teng et al., 2007; Karttunen et al., 2011; Ismail et al., 2016; Kaup et al., 2016).

Ahora, específicamente, la depresión que aparece en la vejez tiene también una alta asociación con la demencia. Sin embargo, debe asumirse de una forma distinta, ya que podría ser una primera manifestación del deterioro cognitivo. Desde hace ya veinte años, Jorm (2000) planteó la necesidad de realizar más estudios para entender el papel de la depresión en esta asociación y enunció estas posibilidades: depresión como un pródromo de la demencia vascular; depresión como una reacción temprana a la percepción de deterioro cognitivo; los efectos de la depresión en el umbral para manifestar la demencia y la depresión como una fuente de daño hipocampal a través de una cascada de glucocorticoides. Dentro de los mecanismos biológicos que relacionan la depresión con la demencia se incluyen enfermedad vascular, un mayor depósito de placas de β-amiloide, cambios inflamatorios y déficits de factores de crecimiento nervioso (Byers y Yaffe, 2011). Estudios recientes continúan mostrando esta asociación tanto para la depresión que ha iniciado años antes del deterioro cognoscitivo como para la depresión de aparición tardía (Holmquist, et al., 2020; Heser et al., 2020).

Las personas mayores con depresión tienen un mayor riesgo de demencia y este se incrementa si los síntomas han estado presentes por mucho tiempo, si los síntomas son graves, cuando hay múltiples comorbilidades y cuando hay cambios cerebrales estructurales (Valkanova et al., 2017). Sin embargo, Almeida et al. (2017) consideran más probable que la depresión sea un marcador de demencia incipiente que un factor de riesgo verdaderamente modificable.

La prevalencia de síntomas psicóticos en la DFT puede llegar a la mitad de los casos, particularmente cuando se presentan mutaciones C9ORF72; en la EA está alrededor de un 20 % (Mendez et al., 2008). Se ha señalado que en la DFT estos síntomas psicóticos complican el diagnóstico (Velakoulis et al., 2009) y en la EA conducen a una progresión acelerada del deterioro cognitivo (Tchalla et al., 2018); sin embargo, no hay claridad acerca de la medida en que los síntomas psicóticos afectan el deterioro cognitivo y funcional en ambas patologías.

Los pacientes con DFT presentan con frecuencia alteraciones en las áreas cerebrales frontal, insular y temporal, las cuales están relacionadas con alteraciones en el comportamiento social y las funciones ejecutivas (Piguet et al., 2011; Rascovsky et al., 2011; Sedeño et al., 2016).

3.3.1 Los síntomas neuropsiquiátricos (SNP) y su correlación neuroanatómica en la degeneración frontotemporal (DFT)

Resulta complejo clarificar el papel de los SNP en la DFT, debido a que, en otras enfermedades neurodegenerativas, las alteraciones comportamentales constituyen el pródromo de la enfermedad y además están presentes durante todo el curso de esta, sumándose a sus expresiones clínicas cognitivas características. En la DFT, los SNP son en esencia la expresión de la enfermedad, probablemente en conjunto con la alteración cognitiva en las funciones ejecutivas. De acuerdo con los dominios

cognitivos planteados por el DSM 5, puede afirmarse que la DFT es una patología en la que se encuentran alterados principalmente la función ejecutiva y distintos dominios de la cognición social, incluyendo el reconocimiento de emociones.

En condiciones normales, la cognición social, las funciones ejecutivas (FE) y la toma de decisiones son interdependientes (Ibanez y Manes, 2012). Las FE permiten regular procesos de cognición social y toma de decisiones a través de la atención selectiva, el control cognitivo y la autorregulación (Possin et al., 2013). El adecuado funcionamiento de estos procesos depende de la actividad de ciertas estructuras como la corteza prefrontal-dorsolateral, la corteza cingulada, la corteza premotora ventral derecha, la corteza parietal inferior, la corteza orbitofrontal, la corteza insular y la amígdala (Eslinger et al., 2011). Diferentes estudios han descrito alteraciones en estas estructuras asociadas a las alteraciones cognitivas descritas en DFTvc (Eslinger et al., 2011; Dopper et al., 2008). Al respecto, investigaciones que han usado volumetría basada en voxeles (VBM) han asociado el perfil de atrofia cortical y subcortical específica en la DFTvc con las alteraciones comportamentales, en la toma de decisiones y en la cognición social (Possin et al., 2013; Muñoz-Ruiz et al., 2012; Kakeda y Korogi, 2010). En particular, estos trabajos informan atrofia cerebral en áreas frontales (corteza orbitofrontal, cingulada anterior, polo frontal) y temporales (porciones del polo temporal anterior) y en la corteza insular en pacientes con DFTvc (Eslinger et al., 2011; Schroeter et al., 2008; Couto et al., 2013).

Por otra parte, la demencia semántica y la afasia primaria progresiva han mostrado distintos correlatos neurocognitivos con respecto a la DFTvc. Estudios con neuroimagen estructural y funcional han propuesto distintos correlatos neurales implicados en la fisiopatología de cada condición. La demencia semántica se ha asociado a una degeneración de la región anterior de los lóbulos temporales; estudios con imágenes o con autopsias han demostrado una afectación importante de los giros temporales inferior y medio (Williams et al., 2005). Los estudios en

pacientes con afasia primaria progresiva indican degeneración en el área perisilviana izquierda (Snowden et al., 2001). En conjunto en las distintas variantes de presentación clínica de la DFT se han descrito alteraciones en la integridad funcional y estructural de la conectividad en las redes frontoamigdalina, frontotemporal y frontoinsular (Eslinger et al., 2013; Torralva et al., 2003).

Según reportes recientes, algunos síntomas pueden predecir la tasa de declinación funcional de la variable comportamental de la demencia frontotemporal, así: una mayor pérdida funcional en sujetos con patrones de atrofia predominantemente frontal y frontotemporal, en comparación con aquellos con patrón de atrofia temporofrontoparietal y temporal. Una edad de inicio mayor, alteraciones neurocognitivas en FE o en procesamiento visoespacial, presencia de síntomas clínicos (desinhibición, agitación, agresión y alteraciones comportamentales nocturnas) pronostican tasa de declinación más rápida (Josephs et al., 2011). La recordación de palabras, comprensión auditiva y de palabras simples, como dominios que están más deteriorados, contribuyen al pronóstico en la afasia primaria progresiva y demencia semántica (Sapolsky et al., 2011).

Dentro de las características más frecuentes en las etapas tempranas de la DFTvc se encuentran la apatía y la desinhibición (Rascovsky et al., 2007; Neary et al., 1998) y se consideran los síntomas conductuales más prevalentes de la DFTvc (Rascovsky et al., 2011). La apatía se refiere a la reducción cuantitativa del comportamiento dirigido por metas voluntario e intencionado (Massimo y Evans, 2014; Levy y Dubois, 2006), debido a una falta de motivación o a la inhabilidad para elaborar un plan dirigido a su logro (Levy y Dubois, 2006). La presentación apática de la DFTvc (DFTvcA) incluye pacientes con ausencia de interés en su entorno y dificultad para la iniciación, planeación y automotivación ante un fin determinado (Levy y Dubois 2006). Por el contrario, la desinhibición implica una reducción de los mecanismos

de control cognitivo, tales como el control inhibitorio (Levy y Dubois, 2006; O'Callaghan et al., 2013; Zamboni et al., 2010; Zamboni et al., 2008).

En la presentación desinhibida de la DFT (DFTvcD) predominan la impulsividad e hiperactividad, a manera de familiaridad indebida, comportamientos desorganizados, irritabilidad y expresiones sexuales (Ridderinkhof et al., 2004); así mismo, alteraciones en el control inhibitorio relacionadas con atrofia en las áreas orbitofrontal (OF), frontal ventromedial y temporal anterior (O'Callaghan et al., 2013; Zamboni et al., 2008). Por su parte, en la versión apática, son evidentes las alteraciones en el comportamiento dirigido por metas, relacionadas con atrofia en el área frontal y los ganglios basales (Zamboni et al., 2008).

3.3.2 Los síntomas neuropsiquiátricos (SNP) como primera manifestación clínica en trastornos neurocognoscitivos (TN)

Es tal la importancia de la alteración comportamental en la historia de los trastornos neurocognitivos y su papel en el diagnóstico temprano, ya que posiblemente sea la primera alteración clínicamente diagnosticable, que ha llevado a la propuesta de una nueva categoría diagnóstica denominada *deterioro comportamental leve (DCL).* Este se ha definido como un síndrome conductual de inicio en la vejez, en ausencia de demencia o de otro trastorno psiquiátrico preciso (Taragano et al., 2009). El riesgo de TN en personas con DCL es alto, incluso comparado con aquellos que sufren deterioro cognitivo leve (Ismail et al., 2016). Al realizar seguimientos longitudinales a pacientes con un DCL, se ha demostrado cómo la conversión a demencia es significativamente mayor en aquellos con SNP tempranos (Elefante et al., 2019; Ismail et al., 2017; Peters et al., 2013; Vik-Mo et al., 2018). Por tanto, la detección precoz de esta sintomatología permitiría un tratamiento oportuno de los síntomas comportamentales, impactando positivamente en la evolución de este

trastorno y favoreciendo la generación de estrategias de seguimiento clínico (Taragano et al., 2018).

3.3.3 Los síntomas neuropsiquiátricos (SNP) como expresión psicopatológica de la cognición social

Cognición social

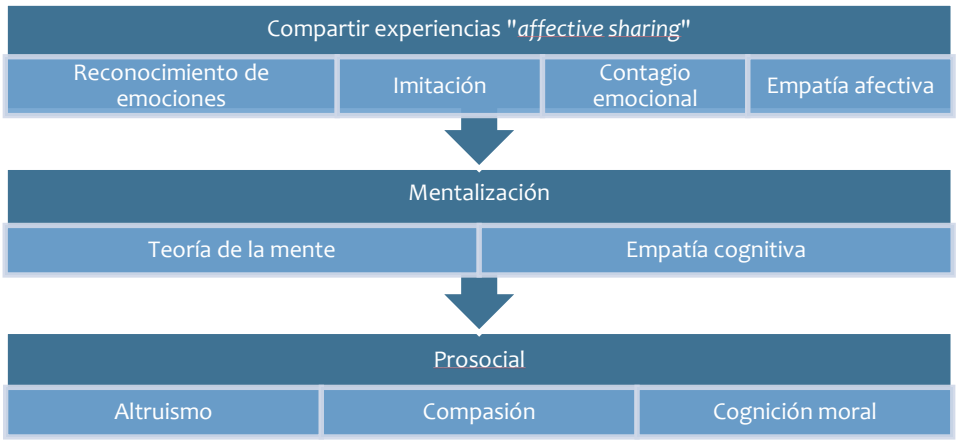
Somos una especie social; ningún componente de nuestra civilización sería posible sin un comportamiento colectivo. Nuestro comportamiento social surge de los mecanismos neurobiológicos y psicológicos compartidos con otras especies de mamíferos (Frith, 2007). La cognición social en los seres humanos hace referencia a los procesos cognitivos y psicológicos que nos permiten reconocer señales sociales y emocionales, hacer inferencias sobre las intenciones, sentimientos y pensamientos de otras personas. Algunos de estos procesos probablemente explican aspectos del comportamiento social humano que son únicos, como nuestra cultura y civilización (Adolphs, 2009).

Cuando se habla de cognición social, se hace referencia a todo el conjunto de facultades utilizado para comprender un estado o una característica en otra persona. Son estas facultades interpersonales, especialmente la habilidad de cooperar y entender a otros, lo que ha apoyado el éxito de nuestra especie. Son estos procesos los que permiten darle sentido a la vida, al entorno, la cultura y las personas que nos rodean por medio de cualquier herramienta cognitiva para comprender e interpretarse a sí mismo, a los otros y al sí mismo en relación con los otros dentro del entorno social (Frith y Frith, 2012).

Durante décadas, distintos modelos de investigación comportamental han examinado dichos procesos y se han desarrollado teorías sobre la naturaleza y

relación entre cada uno de ellos (Gallagher y Varga, 2015). Estos procesos de cognición social incluyen un espectro de procesos cognitivos y comportamientos que abarcan los estados afectivos básicos, automáticos e implícitos; otros procesos más complejos que involucran herramientas cognitivas explícitas; y por último, los modelos relacionados con la cognición moral y el altruismo. Si se habla de empatía, se encuentra por un lado la capacidad de resonar con, compartir o tener en cuenta las emociones de los demás (compartir experiencias), pero, más allá de compartir, también es posible una empatía cognitiva que permite la capacidad de razonar explícitamente y hacer inferencias sobre sus estados mentales (mentalización). Sin embargo, esto no acaba ahí: una última faceta en este modelo es la motivación prosocial para ayudar a otros como resultado del uso de una o varias capacidades de los procesos anteriores que sirven para compartir y/o comprender cognitivamente las emociones que están experimentando los demás (preocupación prosocial) (Zaki y Ochsner, 2012).

Figura 4. Niveles de complejidad de la cognición social



Fuente: Adaptado de Zaki y Ochsner (2012).

Emociones sociales-morales

Las emociones sociales-morales son respuestas adaptativas a situaciones que ofrece el medio, bien sean percibidas de forma amenazante o satisfactoria, y nos

permiten ajustar nuestro comportamiento en respuesta a interacciones sociales con valor moral (Moll et al., 2008). Algunas de estas emociones sociales-morales incluyen la envidia, el gozo por el mal del otro (en alemán se ha acuñado el término *Schadenfreude* para referirse a esta emoción), la culpa o el orgullo, entre otros estados emocionales (Dijk, 2017; Jankowski y Takahashi, 2017; McNamee, 2003). Aunque no se ejecute una acción frente a dichas emociones, pueden generar estados cognitivos y afectivos que vinculen a una persona con ciertos ideales, estilos de pensamiento o costumbres, cuyo objetivo sea el beneficio social y, en muchos casos, pueden ser adoptados por una cultura y guiar una conducta colectiva (Moll et al. 2008).

Algunas estructuras (entre estas la corteza prefrontal ventromedial y orbitofrontal, el lóbulo temporal anterior, circuitos neuronales relacionados con la región de giro temporal superior) han sido vinculadas con diferentes aspectos de la moralidad, incluyendo las emociones sociales-morales. La mayoría de los estudios se basan en alteraciones de la conducta social moral en personas que han tenido lesiones durante el neurodesarrollo o secundarias a una injuria (Kruesi et al., 2004; Allison et al., 2000; Anderson et al., 1999).

La cognición social, como dominio cognitivo incluido en el DSM 5, tendrá entonces expresiones patológicas que generan síntomas que serán distintos a los característicamente mencionados como SNP asociados al deterioro cognitivo, seguramente con una expresión psicopatológica distinta, más sutil, pero podrían seguir siendo considerados en la misma categoría. Las conductas socialmente inapropiadas se reportan con frecuencia en la DFTvc y en las fases prodrómicas de la EA.

La falta de autocontrol, la percepción reducida de las señales sociales, como el reconocimiento de las emociones faciales, el habla sarcástica, la teoría de la mente

deteriorada o la presencia alterada de las emociones sociomorales serán entonces SNP secundarios al trastorno cognitivo (Baez et al., 2018; Baez et al., 2016; Jankowski et al., 2017).

Desmaris et al. (2018) enumeran los siguientes signos de deterioro en la cognición social:

- Pobre percepción social

→ Dificultades para identificar la expresión facial de otros y el lenguaje corporal
→ No reconocer la ira o el aburrimiento en una conversación
→ Contacto visual limitado
→ No comprender el sarcasmo

- Alteración de la teoría de la mente y metacognición

→ Anosognosia
→ Pérdida de perspicacia
→ Incapacidad para inferir lo que otros piensan o sienten
→ Comentarios groseros u ofensivos sin tener en cuenta los sentimientos de los demás

- Reducción de la empatía y el procesamiento emocional

→ Alexitimia
→ Indiferencia
→ Distante, frío
→ Egocentrismo
→ Incapacidad para compartir la alegría o las celebraciones de los demás
→ Reacciones emocionales maladaptativas
→ Reducción de las respuestas afectivas
→ Comportamiento social anormal

→ Arrestos, cargos criminales

→ Pérdida de etiqueta

→ Pérdida del tacto

→ Descuido de la apariencia personal

→ Interrumpir conversaciones

→ Aislamiento social o evitación de contacto social

→ Actos sexuales, agresiones físicas

→ Hablar abiertamente en público de cosas muy personales o privadas

→ Intrusividad

4. Hipótesis general

Los SNP en la DFT determinan el patrón de atrofia cerebral, neural, cognitivo, de cognición social y clínico en distintas etapas de la DFT.

5. Metodología

5.1 Diseños

Esta tesis está elaborada en la modalidad de compendio de artículos. En total se realizaron cinco publicaciones enfocadas en describir el impacto de las alteraciones comportamentales en el transcurrir de la DFT.

El primer artículo, "Alteraciones del comportamiento de pacientes con diagnóstico de trastorno neurocognoscitivo en Bogotá (Colombia)", es un estudio observacional descriptivo de corte retrospectivo. Se revisaron 859 historias clínicas y se obtuvieron 507 historias clínicas con presencia de trastorno cognitivo mayor o leve. Fue publicado en la *Revista Colombiana de Psiquiatría* en el año 2018.

El segundo artículo, "Association of Depressive Symptoms and Subjective Memory Complaints with the Incidence of Cognitive Impairment in Older Adults with High Blood Pressure", es un análisis secundario del Estudio Nacional de Salud y Envejecimiento en México, una cohorte representativa compuesta por individuos con edades mayores de 50 años, con una muestra final de 5.853 personas. Fue publicado en *European Geriatric Medicine* en el año 2019 (factor de impacto de 1.326).

El tercer artículo, "First Symptoms and Neurocognitive Correlates of Behavioral Variant Frontotemporal Dementia", es un estudio observacional de casos y controles en un grupo de controles sanos (n = 30) y dos grupos de pacientes con DFTvc (los cuales presentaron apatía [DFTvca, n = 18] o desinhibición [DFTvcd, n = 16]), en los que evaluamos los correlatos neuropsicológicos, clínicos y

neuroanatómicos (imágenes estructurales 3T) haciendo uso de métodos estadísticos complejos, incluyendo máquinas de soporte vectorial. Fue publicado en *Journal of Alzheimer's Disease* en el año 2016 (factor de impacto 3.731).

El cuarto artículo, "A lesion model of envy and Schadenfreude: legal, deservingness and moral dimensions as revealed by neurodegeneration", es un estudio experimental con 64 participantes de un protocolo en curso, 20 pacientes diagnóstico de DFTvc, 24 pacientes diagnosticados con EA de inicio temprano y 20 sujetos de control sanos. Evaluamos la respuesta frente a la exposición a emociones sociales morales en estos pacientes, sus rutas neurales y cognitivas y la posible asociación con otros SNP. Fue publicado en la revista *Brain* en 2017 (factor de impacto 10.848).

El quinto artículo: *"Neuropsychiatric Symptoms as Predictors of Clinical Course in Neurodegeneration. A Longitudinal Study"* es un estudio longitudinal en un grupo de pacientes con DFT (n = 36) y otro con EA (n = 47) en dos etapas diferentes de la enfermedad (2.5 años). Evaluamos la progresión de los SNP y su influencia en la progresión cognitiva y funcional. Fue publicado en la revista *Frontiers in Aging Neuroscience* en 2019 (factor de impacto 4.362)

La metodología particular, según se indicó, está descrita en profundidad en cada estudio.

5.2 Variables e instrumentos

Los instrumentos utilizados, de acuerdo con las variables establecidas, se describen en cada uno de los artículos.

6. Consideraciones éticas

A lo largo de los estudios se siguieron las directrices nacionales e internacionales del código deontológico y Declaración de Helsinki, así como la normativa legal sobre la confidencialidad de datos tal y como se prevé en la Ley Orgánica 15/1999, del 13 de diciembre, de Protección de Datos de carácter personal (LOPD).

Todos los estudios presentados en esta tesis se acogieron a la Ley 8430 de 1993 de la República de Colombia que define las consideraciones éticas de los estudios de investigación en el país. Todos los estudios de acuerdo con esta normativa fueron considerados como de riesgo mínimo. Además, todos los estudios fueron evaluados y aprobados por el comité de ética de la Pontificia Universidad Javeriana y el Hospital Universitario San Ignacio de Bogotá, Colombia, que siguen las recomendaciones propuestas en la Declaración de Helsinki.

En relación con algunas situaciones éticas particulares que se consideraron en el desarrollo de cada estudio, podemos mencionar que no se presentaron conflictos éticos derivados directamente de los resultados de la investigación. Todas las exploraciones complementarias utilizadas en este proyecto se han descrito como inocuas, incluyendo las pruebas de neuroimagen (resonancia magnética, que no utiliza radiaciones ionizantes ni supone la adición de ningún contraste).

El tratamiento de los sujetos pacientes es el adecuado según los protocolos clínicos asistenciales, independiente al participar o no en el estudio, e idéntico al de otros pacientes en las mismas condiciones que no estuvieron incluidos en el proyecto. Los resultados de las exploraciones tanto en los pacientes como en sus familiares no influyeron en el tratamiento farmacológico ni en el seguimiento del paciente.

Se previó que, en el caso de hallar algún marcador de pronóstico de la DFT con los antecedentes biográficos, la asociación sería demasiado poco específica como para tratarse de material sensible de ser utilizado con fines discriminatorios. En cualquier caso, las exploraciones complementarias en las que se basó uno de los estudios fueron voluntarias y exclusivas de fines científicos y sanitarios, lejos del alcance de otros intereses que pudieran ser discriminatorios.

7. Resultados y discusión

7.1 Estudio 1: Alteraciones del comportamiento de pacientes con diagnóstico de trastorno neurocognoscitivo en Bogotá (Colombia)

ALTERACIONES DEL COMPORTAMIENTO DE PACIENTES CON DIAGNÓSTICO DE TRASTORNO NEUROCOGNOSCITIVO EN BOGOTÁ (COLOMBIA)

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Introducción: El objetivo de este estudio es determinar la frecuencia de alteraciones conductuales (AC) en un grupo de pacientes con diagnóstico de trastorno neurocognoscitivo (TN) valorado durante el año 2015 por clínica de memoria en un centro de evaluación en Bogotá, Colombia.
Material y métodos: Estudio observacional descriptivo y de corte retrospectivo de 507 pacientes con diagnóstico de trastorno neurocognoscitivo, según criterios del DSM-5.
Resultados: A *mujeres* correspondió el 62,72% de la muestra. En los sujetos con trastorno neurocognitivo leve la media de edad en el momento del diagnóstico era 71,04 años y la de aquellos con trastorno neurocognoscitivo mayor, 75,32 años (p<0,001). La etiología más frecuente del trastorno neurocognoscitivo fue la enfermedad de Alzheimer probable, seguida por la degeneración lobar frontotemporal, variante conductual, y el trastorno neurocognoscitivo debido a múltiples etiologías. Las AC se presentan con mayor frecuencia en TN debido a degeneración frontotemporal variante conductual (100%), enfermedad de Alzheimer (77,29%) y vascular (76,19%). Las AC más prevalentes en el grupo evaluado fueron la apatía (50,75%), la irritabilidad (48,45%), la agresividad (16,6%) y la labilidad emocional (14,76%).

PRESENTACIÓN

A partir de la quinta versión del Manual Diagnóstico Asociación Americana de Psiquiatría, el DSM – 5, publicado en 2013, el término de demencia fue sustituido

por el de Trastorno Neurocognoscitivo TN, con dos alternativas: trastorno neurocognoscitivo leve (TNL) y mayor (TNM) [1]. La Organización Mundial de la Salud OMS (2015) ha calculado que dentro de 10 años, 75 millones de personas en el mundo presentarán alguna manifestación de TNM y 20 años después lo harán más de 140 millones [2]. Esas expresiones de alta frecuencia comprometen las áreas cognitivas, funcionales y comportamentales [3] y varían según la etiología [4]. Su pronta detección contribuye a disminuir los costos de la atención en salud [5], las hospitalizaciones en servicios de salud mental [6] y la institucionalización [7].

La *International Psychogeriatric Association* (2015), basada en un consenso de expertos, reemplazó el término de alteraciones conductuales por el de síntomas comportamentales y psicológicos de la demencia, refiriéndolo a perturbaciones del afecto, de la percepción, del contenido del pensamiento y del comportamiento. En particular, incluye dentro de los síntomas comportamentales agresividad, inquietud, agitación, conductas sociales inapropiadas, desinhibición sexual, gritos, vagabundeo, acaparamiento, y dentro de los psicológicos: ansiedad, afecto depresivo, alucinaciones y delirios. A este conjunto de síntomas se les denomina también Síntomas Neuropsiquiátricos (SNP) o Alteraciones conductuales (AC) [8].

Aunque se ha señalado que las AC pueden encontrarse en cualquier tipo de TN y en cualquier estadio de la enfermedad [9-10], y a pesar de la importancia de las AC en el seguimiento y el curso de los TN, los diferentes estudios que han explorado su prevalencia reportan datos disímiles y poco concluyentes en las diferentes muestras analizadas [9-11] con amplias diferencias al describir las prevalencias de AC en los TN. Algunos informan que el 59% de los pacientes con TNL pueden presentar AC [12] otros, que un 50-80% de los pacientes con TN tienen AC durante el curso de su enfermedad [12-13]. Aunque estos reportes proporcionan información importante sobre la presencia de las AC en los TN, su prevalencia en los distintos tipos de TN —incluidos TNL y TNM—está por precisarse.

Independiente de la prevalencia, el impacto de las AC en la calidad de vida y el cuidado de las personas con TN las hace un tema muy importante en el estudio de la población con esa afección.

Las AC poseen un patrón de agrupación variable y surgen, como ya se anotó, en cualquier estadio de la enfermedad e impactan gravemente la funcionalidad de los pacientes [3]; así mismo, tienen consecuencias severas para los cuidadores, mucho más que el propio deterioro cognoscitivo [9]. Entonces, los efectos globales de los AC en la calidad de vida del paciente y en la de sus cuidadores, así como en el sistema de salud, dan cuenta de la importancia de la identificación de estas perturbaciones y orientó el presente estudio en un grupo de pacientes con diagnóstico de TN, diferenciando entre TNL y TNM, que fueron valorados durante el año 2015 en un centro especializado de referencia para trastornos neurocognitivos en Bogotá (Colombia).

METODOLOGÍA

Población. En este estudio, con un diseño observacional descriptivo de corte retrospectivo, se revisaron 859 historias clínicas, suma total de los pacientes valorados en el centro especializado durante el año 2015. Excluyendo las historias de pacientes con enfermedad mental crónica concomitante o trastornos relacionados con consumo de sustancias psicoactivas, y aplicados los criterios del DSM-5 (efectos del déficit cognoscitivo en la funcionalidad y la presencia de una AC significativa clínicamente), se obtuvieron 507 historias clínicas con presencia de TNL y TNM.

Evaluación de casos en Clínica de Memoria. La valoración consignada en la historia de estos pacientes se realizó en la Clínica de Memoria, basada en un protocolo estandarizado interdisciplinario que incluye: geriatría (evaluación completa de la

situación basal del paciente, multimorbilidad, funcionalidad y situación social); psiquiatría (entrevista semiestructurada para determinar AC según la clasificación de la Asociación Internacional de Psicogeriatría (IPA) y el DSM-5 descartando su atribución a un trastorno mental independiente); neurología (examen neurológico, búsqueda factores de riesgo de enfermedad cerebrovascular y presencia de otras enfermedades del sistema nervioso); neuropsicología (aplicación de una batería neuropsicológica completa. Tabla 1. Las descripciones de las pruebas se encuentran en el numeral correspondiente de esta tesis). Con los resultados se realiza una junta interdisciplinaria de toma de decisiones para el diagnóstico y recomendaciones por consenso.

Tabla 1. Batería neuropsicológica

Dominio	Pruebas
Cognición, evaluación general	*Mini Mental State Examination* (MMSE) (15)
Lenguaje	Pruebas de fluidez fonológica y semántica, denominación y comprensión verbal compleja
Dominio visual construccional	Test de copia de la figura de Rey
Funciones ejecutivas	interpretación refranes, series grafomotoras y prueba cribado INECO
Memoria	Prueba de Grober
Atención	Prueba de dígito símbolo
Funcionalidad actividades básicas vida diaria	Escala de Barthel (14)
Tamizaje depresión	Escala de Yesavage (17)
Depresión en demencia	Escala de Cornell (18)

ANÁLISIS

Para el análisis se utilizó el programa STATA (versión 12) para iOS, determinando el nivel de significación estadística en $p < 0,05$. Se partió de un análisis univariable para ajustar y categorizar las variables estableciendo valores extremos y distribución de la muestra. Las variables continuas categóricas se expresaron en frecuencias y porcentajes, y la continuas con las medias ± desviación estándar. Posteriormente se emplearon modelos bivariables para determinar la asociación entre variables dependientes e independientes; se emplearon pruebas de la Chi ^{2}

para las variables categóricas y pruebas de la t de *Studen*t para las variables continuas.

RESULTADOS

El número de mujeres diagnosticadas con TN fue de 318 (62,72%) Vs. 189 (37,27%) hombres y esa diferencia (aunque no significativa p = 0,249) se mantiene con respecto a la gravedad del trastorno. En cuanto a la edad, la media era de 75,32 años para los pacientes con TNM (n= 428) y 71,04 años para los de TNL (n= 79) (p < 0,001).(Tabla 2)

Tabla 2. Descripción de la población (n = 507)

Tabla 1 – Descripción de la población (n = 507)

	TNL (n = 79)	TNM (n = 428)	p
Edad (años)	71,64 ± 0,85	75,32 ± 9,36	< 0,001
Sexo			
Varones	34 (43,04)	155 (36,21)	0,249
Mujeres	45 (56,96)	273 (63,79)	
AC			
No	68 (86,08)	121 (28,27)	< 0,01
Sí	11 (13,92)	307 (71,73)	
Barthel	92,34 ± 15,43	83,07 ± 23,05	< 0,01
MMSE	19,48 ± 4,02	14,78 ± 7,00	< 0,01
Yesavage	8,45 ± 4,68	9 ± 8,45	< 0,01
Cornell	14,69 ± 9,68	15,55 ± 9,24	< 0,01

AC: alteraciones de la conducta; MMSE: *Mini-mental State Examination*; TNL: trastorno neurocognoscitivo leve; TNM: trastorno neurocognoscitivo mayor.
Los valores expresan n (%) o media ± desviación estándar.

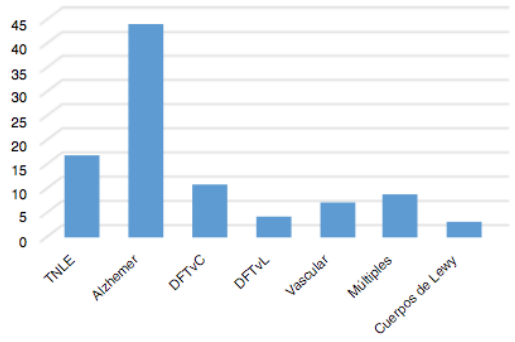

Figura 1 – Etiología de trastorno neurocognoscitivo.
DFTvC: degeneración frontotemporal variante conductual;
DFTvL: degeneración frontotemporal variante lingüística;
TNLE: trastorno neurocognoscitivo leve.

Tomada de: Chimbí-Arias C, et al. Alteraciones del comportamiento de pacientes con diagnóstico de trastorno neurocognoscitivo en Bogotá (Colombia). Rev Colomb Psiquiat. 2018. https://doi.org/10.1016/j.rcp.2018.10.007

Del total, en 182 pacientes (35,89%) no se observaron AC y se manifestaron en 325 (64,10%), anotando que de esos 182 pacientes sin AC casi la mitad (47,80%) tenía un diagnóstico de TNL. Por su parte, del total de pacientes diagnosticados con TNM (401) el 76,30% presentaba AC. En la Tabla 3 se exponen la frecuencia y prevalencia según la etiología.

Tabla 3. Trastorno Neurocognitivo ,
frecuencia y prevalencia de Alteraciones Conductuales (AC)

Etiología TN	Sin AC n=182	Con AC n= 325	Prevalencia (según etiología)
TNL	87 (35,98)	19 (5,84)	17,92
TNM			
Alzheimer	47 (25,82)	160(49,23)	77,29
Múltiples etiologías	20 (10,98)	57 (17,53)	74,02
Degeneración frontotemporal variante conductual DFTvc	0	43 (13,23)	100
Vascular	5(2,74)	16 (4,92)	76,19
Degeneración frontotemporal variante lingüística DFTvl	8 (4,39)	6 (1,84)	42,85
Lewy	3 (1,64)	5 (1,53)	62,50
Otra	9 (4,94)	17(5,23)	65,38
No especificada	3 (1,64)	2 (0,61)	40,00

Tomada de: Chimbí-Arias C, et al. Alteraciones del comportamiento de pacientes con diagnóstico de trastorno neurocognoscitivo en Bogotá (Colombia). Rev Colomb Psiquiat. 2018. https://doi.org/10.1016/j.rcp.2018.10.007

Si bien se encuentran diferencias de acuerdo con la gravedad de su expresión, los AC observados con mayor frecuencia fueron: apatía, irritabilidad, agresividad y labilidad emocional. Irritabilidad y apatía son comunes en los pacientes con TNL y TNM seguidos, en los primeros, por agresividad y, en los segundos, por labilidad emocional, secuencia que caracterizó a la Enfermedad de Alzheimer adicionando paranoia y agresividad. A más de los anteriores, la apatía se asoció con DFTvc, vascular y múltiples etiologías. (Tabla 4).

Tabla 4. Prevalencia de alteraciones de la conducta más frecuentes por etiología del trastorno neurocognoscitivo

AC	TNL (n = 106)	p	TNM (n = 401)	Alzheimer (n = 207)	DFTvC (n = 43)	Múltiples etiologías (n = 77)	Vascular (n = 21)	p
Irritabilidad	12 (11,32)	<0,001	145 (36,15)	85 (41,06)	22 (51,16)	29 (37,66)	4 (19,04)	0,024
Labilidad	2 (1,88)	0,003	45 (11,22)	29 (14)	4 (9,90)	9 (11,68)	4 (19,04)	0,577
Apatía	4 (3,77)	<0,001	159 (39,65)	78 (37,68)	23 (53,48)	32 (41,55)	13 (61,90)	0,436
Paranoia	2 (1,88)	0,003	6 (1,49)	24 (11,59)	10 (23,25)	5 (6,49)	0	0,045
Agresividad	4 (3,77)	0,007	16 (3,99)	24 (11,59)	14 (32,55)	10 (12,98)	2 (9,52)	0,006
Desinhibición	2 (1,88)	0,164	20 (4,98)	3 (1,44)	5 (11,62)	3 (3,89)	3 (14,28)	0,006

AC: alteraciones de la conducta; DFTvC: degeneración frontotemporal variante conductual; TNL: trastorno neurocognoscitivo leve; TNM: trastorno neurocognoscitivo mayor.
Los valores expresan n (%).

DISCUSIÓN

Los hallazgos dan cuenta de que las AC más frecuentes en la población estudiada son apatía, irritabilidad, agresividad y labilidad afectiva, y las que menos parecen son las alucinaciones, psicosis y tristeza son las menos observadas. Es posible que la indagación sistemática que realiza el grupo interdisciplinario permita observar una alta frecuencia de AC vinculada con las diferentes etiologías del TN.

Las AC incluso aparecen en la variante de TNL (13,92%), lo que indica su independencia de la gravedad y la etiología del TN, estos datos son consistentes con los de otros estudios [13]. La Enfermedad de Alzheimer es, en este estudio, la etiología más común del trastorno neurocognoscitivo, luego la degeneración lobar frontotemporal, variante conductual y las múltiples etiologías. Apatía (50,75%), irritabilidad (48,45%), agresividad (16,6%) y labilidad emocional (14,76%) son las AC mas frecuentes, lo son menos, alucinaciones, psicosis y tristeza. Investigaciones informan de un 66% a un 100% presencia de AC en la Enfermedad de Alzheimer, primordialmente apatía, irritabilidad y depresión [24], otros se refieren a hasta un 39%, particularmente agresividad, alteración en la actividad y psicosis [13]. Los resultados de este estudio encontraron que es usual en la población estudiada la labilidad emocional.

Depresión/disforia, apatía, delirio y ansiedad/agresión son comunes en reportes de prevalencia de AC en pacientes con diagnóstico de TNM [19], en pacientes con ese

diagnóstico institucionalizados la prevalencia de las AC alcanza un 92% [20], particularmente apatía, irritabilidad, comportamiento motor aberrante y agitación/agresividad [21], resultados similares en estudios que solo han determinado la presencia o ausencia de demencia [22-23].

Un estudio con 60 pacientes, divididos entre los que tenían demencia multiinfarto y los que tenían enfermedad vascular isquémica subcortical, mostró una prevalencia de AC del 95%, entre estas apatía, alteración en la conducta alimentaria e irritabilidad [25], resultados coincidentes con los del presente estudio, que muestran que las AC en TN de etiología vascular son más del 50% y corresponden a apatía, irritabilidad y labilidad emocional, aunque las alteraciones de la conducta alimentaria no aparecen.

Los cambios en los procesos cognoscitivos, afectivos y de la interacción social en el TN se relacionan con las AC eje de un grupo de perturbaciones neuropsiquiátricas y algunas dparecieran surgir del deterioro en los procesos descritos. Así, perturbaciones en el control inhibitorio y otras funciones ejecutivas (procesos de regulación emocional) podría asociarse con la desinhibición de la conducta, y modificaciones afectivas, cognoscitivas y sociales con síntomas como la apatía y la irritabilidad [29]. Todo ello incide en el curso de los TNM.

Dos aspectos son fundamentales con respecto a la identificación de las AC, primero, su posibilidad diagnóstica y de seguimiento para los pacientes con TN, pues su presencia en sujetos cognoscitivamente normales podría pronosticar su deterioro [27-28], por lo cual se ha propuesto considerar el trastorno conductual leve para identificar cambios incipientes asociados con las enfermedades neurodegenerativas de cualquier etiología [29]. Segundo, la posibilidad de ampliar la investigación acerca del mejor control de la conducta para incidir en la respuesta al tratamiento, el seguimiento y el pronóstico de la enfermedad. Esto podría

contribuir a evitar el aumento de la discapacidad, el deterioro de la calidad de vida del paciente y la sobrecarga de su cuidador, la institucionalización temprana [8] y los costos que conlleva el cuidado de pacientes con demencia [26].

Finalmente, debe anotarse que, la metodología transversal, el origen de la muestra (un centro especializado de referencia) y la evaluación de las AC mediante el consenso clínico y no con base en una escala, constituyen limitaciones del presente estudio, aunque para esta última circunstancia se ha considerado la posibilidad de identificar las AC mediante la observación directa por el equipo médico [8-30].

CONCLUSIONES

Se pretendió, con esta investigación, determinar la frecuencia de AC en un grupo de pacientes con diagnóstico de TN. Los informes de las valoraciones interdisciplinarias por clínica de memoria, permiten afirmar que las AC son una manifestación frecuente en los pacientes con TN en general, y resultan prevalentes en TNL y en las distintas etiologías del TNM según otros estudios. Si bien las AC aparecen primordialmente en el TNM, también se presentan en el TNL, lo que ha llevado a proponer las AC como una forma de identificar cambios tempranos asociados con las enfermedades neurodegenerativas. Esto es particularmente valioso para nuestra población, por cuanto identificadas las AC puede contribuirse a minimizar su impacto en la persona que sufre el TN, en los encargados de su cuidado y en los servicios de salud, a la vez que en la generación y aplicación terapéuticas específicas.

CONFLICTO DE INTERESES

Los autores declaran no tener ningún conflicto de intereses.

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7.2 Estudio 2: Association of Depressive Symptoms and Subjective Memory Complaints with the Incidence of Cognitive Impairment in Older Adults with High Blood Pressure

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RESEARCH PAPER

Association of depressive symptoms and subjective memory complaints with the incidence of cognitive impairment in older adults with high blood pressure

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Key Summary Points

Aim This study aims to uncover the association between frecuent conditions in older persons, according to their blood pressure: memory complaints, depression and incident cognitive impairment.

Findings Individuals with depressive symptoms and/or subjective memory complaints have a higher risk of developing incident cognitive impairment when high blood pressure is present.

Message There are several treatable risk factors, which could be managed through counseling regarding healthy lifestyle habits, including HBP prevention which could importantly impact outcomes in older persons.

Abstract

Purpose High blood pressure is a relevant risk factor for vascular damage, leading to the development of depressive symptoms and dementia in older adults. Moreover, subjective memory complaints are recognized as an early marker of cognitive impairment. However, it has been established that subjective memory complaints could also be a reflection of depressive symptoms. The objective of this paper is to assess the impact of depressive symptoms and subjective memory complaints on the incidence of cognitive impairment in older adults with high blood pressure.

Methods This is a secondary analysis of the Mexican Health and Aging Study, a representative cohort composed by individuals aged ≥ 50 years. Participants with cognitive impairment in 2012 were excluded since the outcome was incident cognitive impairment in 2015. Four groups were created according to depressive symptomatology and subjective memory complaints status; analyses were stratified according to blood pressure status. The odds incident cognitive impairment was estimated through logistic regression models.

Results A total of 6327 participants were included, from which 6.44% developed cognitive impairment. No differences were seen regarding the development of cognitive impairment in participants without high blood pressure. However, increased risk was evident in those with both high blood pressure and depressive symptoms (OR = 2.1, 95% CI 1.09–4.09, $p = 0.026$) as with high blood pressure, depressive symptoms and subjective memory complaints (OR = 1.91, 9% CI 1.4–3.2, $p = 0.001$).

Conclusion Individuals with depressive symptoms and/or subjective memory complaints have a higher risk of developing incident cognitive impairment when high blood pressure is present. Our results suggest that a sequence of events related to altered cerebral vascular dynamics is possible.

Keywords Aged · Depressive symptoms · Cognition disorders · Cognitive impairment · Hypertension · Subjective memory complaint

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Introduction

Older people frequently live with chronic diseases, which interact with economic, cultural, familial and psychological features, particularly in this age group [1]. Moreover, one of the most important age-related challenges faced by both older persons and health professionals is the presence of dementia. The latter is associated with significant functional decline and loss of independence, leading to an increased usage of healthcare services and need for specialized care. It is also important to acknowledge that dementia has a high prevalence at a global scale and is also an increasing issue in Latin America [2–4]. Furthermore, to prevent the progression of disease and further disability, it is imperative to identify modifiable risk factors that are present early or even precede the onset of cognitive symptomatology [4–6].

One of the conditions that are part of the spectrum of problems leading to dementia includes Subjective Memory Complaints (SMC). These may appear in the presence of normal cognitive tests or alongside mild cognitive impairment (MCI), which is defined by subjective and objective cognitive impairment with relatively preserved functioning [7–10]. However, SMC have also been associated with depressive symptoms (DS), not always reflecting symptoms of cognitive disorders [11].

More recently, DS have been described as an early manifestation of dementia since these symptoms could be related to the neuropathology of this disease, for instance, through vascular damage [12]. Furthermore, a well-known risk factor for cognitive impairment is high blood pressure (HBP); which is in line with the path that departs from vascular damage and ends in overt brain damage and dementia [13]. The exact mechanism behind this association is not clear. However, the presence of untreated chronic HBP has been associated with a variety of vascular structural and functional changes. These changes modify the ability of physiological self-regulation, leading to ischemia in vulnerable brain regions, such as those in charge of mood and affective control [13].

Thus, there is likely a mechanistic association between HBP, DS and cognitive impairment (CogI). As previously stated, this link is of major importance due to the potential for early identification, prevention and/or delay of the onset of dementia. This information becomes particularly relevant in Mexico, since high incidences of both HBP and dementia have been noted in the Mexican population [2, 14]. The aim of this work was to assess whether an association exists between DS, SMC and CogI in patients with HBP and without HBP.

Materials and methods

Setting and participants

This is a secondary analysis of the Mexican Health and Aging Study (MHAS), a nation-wide representative cohort of community-dwelling Mexican older adults aged 50 years or older [1, 15]. This study began in 2001 and currently includes information from three follow-up periods (2003, 2012 and 2015). The main objective of the MHAS was to determine which factors have an impact on the aging process in Mexican individuals. Thus, the study comprises a nationally representative sample of urban and rural areas of the 32 states of the country.

Face-to-face interviews were performed by applying a set of questionnaires including topics from different domains, such as sociodemographic characteristics, health-related issues, accessibility and use of healthcare services, cognitive performance, functional status, and financial status. Further information regarding aims and procedures can be found elsewhere [15].

For the purpose of this work, we excluded participants with a past medical history remarkable for previous strokes or psychiatric diseases, as well as those with incomplete data. Participants found to have CogI in 2012 were also excluded from the sample, yielding a total subset of 6327 participants. Nevertheless, 472 participants were lost to follow-up due to absenteeism, difficulties in location or refusal to continue participating. Thus, a final sample of 5853 older persons was analyzed (see Fig. 1).

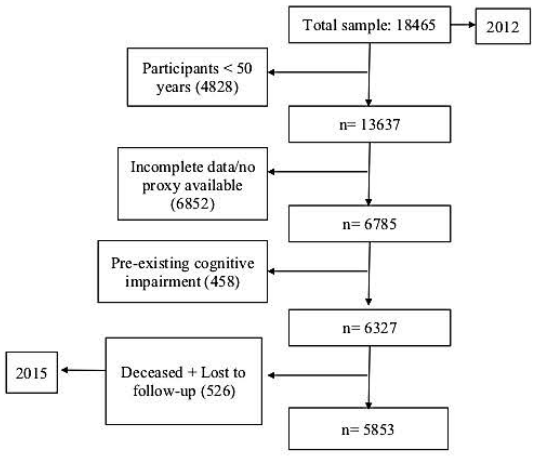

Fig. 1 Flowchart of the study sample

Variables

Dependent variable

The dependent variable was cognitive impairment, which was assessed through the Cross-Cultural Cognitive Examination test (CCCE). This test has a maximum score of 80 points and includes the evaluation of several cognitive domains: (a) primary verbal memory, (b) selective attention; (c) secondary verbal memory; (d) executive function and motor control; (e) visual memory. The CCCE has shown high sensitivity (100%) and specificity (83%) for detection of dementia in a previous publication [18]. Standardization with z scores was used dividing the studied participants in three groups according to years of schooling (0, 1–7 and 7 years or more) and three age categories (60–69, 70–79 and 80 years and above). The cutoff value for CogI was established through normative data generated according to these categories and was set at − 1.5 standard deviations [16, 17].

Independent variable

Depressive symptoms A validated depression questionnaire was used to assess depressive symptoms. The MHAS depression questionnaire has shown to be valid for the detection of clinical depression, with a sensitivity and specificity of 80.7% and 68.7%, respectively. The MHAS screening questionnaire for depression consists of nine items with "yes" or "no" answers: [within the past week, was the respondent: (1) Depressed? (2) Experiencing difficulty performing? (3) Experiencing restless sleep? (4) Happy? (5) Lonely? (6) Enjoying life. (7) Sad? (8) Feeling tired? (9) Energetic?]. The cutoff value for defining depression is any score ≥5 points [18–20].

Subjective memory complaints The presence of SMC was evaluated with the single question: "How would you evaluate your memory in the present?".

The answer options were: excellent, very good, good, fair and poor; and further collapsed into only two groups: no-SMC (Excellent, very good, good) and SMC (fair and poor).

To assess the effect of SMC (with or without DS) on incident CogI, four groups were defined in the baseline assessment (2012).

1. Without SMC/without DS (noSMC/noDS).
2. With SMC/without DS (SMC/noDS).
3. Without SMC/with DS (noSMC/DS).
4. With SMC/with DS (SMC/DS).

High blood pressure Sample was then stratified according to HBP status. This variable was assessed through self-report, with the question: "Have you ever been told by a doctor or medical provider that you have HBP?" If the subject answered yes, they were considered to have HBP.

Confounding variables

Multivariate regression models were adjusted for confounders from different domains, such as sociodemographic (age, sex, marital status, years of schooling); health-related (self-reported vision, stroke, acute myocardial infarction, arthropathy, diabetes mellitus, cancer, chronic pulmonary disease and alcohol use). Importantly, alcohol use was assessed through the CAGE questionnaire [21], an acronym that stands for four yes/no questions: (1) "Have you ever felt you should cut down on your drinking?", (2) "Have people annoyed you by criticizing your drinking?", (3) "Have you ever felt bad or guilty about your drinking?", (4) "Have you ever had a drink as an eye-opener first thing in the morning to steady your nerves or help a hangover?". A total score of 2 or greater was considered clinically significant and a score of 4 was categorized as alcohol dependence [21].

Statistical analysis

Initially, we used a univariate analysis to explore extreme values and normal distribution in order to adjust and categorize variables. Regarding descriptive statistics, frequencies were used for presenting categorical variables, while standard deviations and means were employed for continuous variables. Chi2 test was used for finding differences between groups for categorical variables, and ANOVA was used for continuous variables. Finally, for the multivariate analysis, logistic regression models were fitted to obtain odds ratio (OR) with 95% confidence intervals (CIs) of having incident CogI according to DS/SMC groups (using the group noSMC/noDS as reference). Adjusted and non-adjusted estimates are presented. The statistical level of significance was set at p value < 0.05. Data were analyzed using STATA 14® software.

Ethical issues

The Institutional Review Boards of Ethics Committees of the University of Texas Medical Branch in the United States, the *Instituto Nacional de Estadística y Geografía* and the *Instituto Nacional de Salud Pública* in México approved the study. All study participants signed an informed consent. The study adhered to the ethical guidelines of the Declaration of Helsinki.

Declaration of sources of funding

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Results

At baseline from the 6327 participants, the mean age was 68.59 (±SD 6.78) years, 57.7% ($n=3385$) were female $p<0.001$, 60.57% ($n=3814$) were married $p<0.001$, 43.4% ($n=2760$) had visual deficits, $p<0.001$, 43.83% ($n=2773$) had SMC, 6.89% ($n=436$) had DS and 17.57% ($n=1111$) had both SMC and DS $p=0.474$. The prevalence of HBP was 42.86%. The sample is described in more detail in Table 1.

The 3-year incidence of cognitive impairment was 6.44% ($n=286$); 6.7% ($n=141$) for those with HBP, and 6.03% ($n=145$) in participants without HBP.

The differences in the incidence of CogI were only statistically significant in older persons with HBP. Group 3 + HBP had the greater incidence of CogI corresponding to 9.2% ($n=16$), followed by group 4 + HBP 8.5% ($n=46$), the group 2 + HBP 5.4% ($n=53$) and the group 1 + HBP (reference group) with 3.9% ($n=26$) ($p=0.002$) (Table 1).

Participants with HBP from group 3 (OR = 2.43, 95% CI 1.27–4.64, $p=0.007$) and group 4 (OR = 2.25, 95% CI 1.37–3.69, $p=0.001$) displayed significant associations with the incidence of CogI. After the adjusted analysis, the associations in participants with HBP from the group 3 (OR = 2.11, 95% CI 1.09–4.09, $p=0.026$) and group 4 (OR = 1.91, 95% CI 1.41–3.22, $p=0.001$) remained significant. The analysis performed on subjects without HBP showed no statistically significant associations (Table 2).

Discussion

According to our results, DS were significantly associated with an increase on the 3-year incidence of CogI, only in those participants with HBP. This finding is consistent with several previous studies that have disclosed an important association between development of CogI and early manifestations of dementia such as DS [22–24]. For instance, a meta-analysis recently reported that late-life depression was associated with a significant risk for all-cause dementia,

Table 1 Descriptive sample and bivariate analysis

	Age mean ± SD	Sex (women) *n* (%)	Married *n* (%)	Schooling (years) mean ± SD	Alcohol consumption *n* (%)	Visual deficits *n* (%)	Comorbidities mean ± SD	Total *n* (%)	Incidence of cognitive impairment *n* (%)
No-HBP									
1	67.72 ± 6.59	462 (39.55)	794 (67.98)	6.65 ± 5.24	0.22 ± 0.65	355 (30.39)	0.28 (0.52)	1168 (33.58)	60 (6.37)
2	68.79 ± 7.22	654 (44.58)	964 (65.71)	4.86 ± 3.97	0.25 ± 0.75	702 (47.85)	0.38 (0.61)	1467 (42.18)	60 (5.07)
3	69.09 ± 6.66	107 (55.44)	112 (58.03)	5.11 ± 4.73	0.16 ± 0.56	88 (45.60)	0.4 (0.58)	193 (5.55)	10 (7.14)
4	67.91 ± 6.17	262 (62.53)	250 (59.67)	4.34 ± 3.57	0.21 ± 0.68	244 (58.23)	0.61 (0.73)	419 (12.36)	15 (5.57)
p value	< 0.001	< 0.001	0.003	< 0.001	< 0.001	< 0.001	< 0.001	0.567	0.367
Total	68.37 ± 6.66	1485 (50.52)	2120 (62.84)	5.24 ± 4.37	0.21 ± 0.66	1389 (45.51)	1.67 (0.61)	3247 (93.67)	145 (6.03)
HBP									
1	68.8 ± 6.64	448 (53.46)	541 (64.56)	6.51 ± 4.95	0.17 ± 0.57	257 (30.67)	0.61 ± 0.71	838 (25.42)	26 (3.99)
2	69.07 ± 6.72	761 (58.49)	848 (65.18)	4.85 ± 3.84	0.17 ± 0.61	606 (46.58)	0.62 ± 0.73	1301 (39.47)	53 (5.42)
3	68.59 ± 6.31	175 (72.92)	122 (50.83)	5.12 ± 4.38	0.15 ± 0.56	101 (42.08)	0.93 ± 0.91	240 (7.28)	16 (9.20)
4	68.59 ± 6.29	508 (73.62)	381 (55.22)	3.97 ± 3.38	0.15 ± 0.61	401 (58.12)	0.85 ± 0.82	690 (20.93)	46 (8.57)
p value	0.456	< 0.001	< 0.001	< 0.001	0.573	< 0.001	< 0.001	0.241	0.002
Total	68.7 ± 6.49	1892 (64.62)	1892 (58.94)	5.11 ± 4.13	0.16 ± 0.58	1365 (44.36)	3.01 ± 0.79	3069 (23.27)	141 (6.7)
Total sample									
1	68.17 ± 6.69	911 (45.27)	1335 (66.47)	6.59 ± 5.12	0.21 ± 0.62	613 (30.54)	0.23 ± 0.69	2007 (31.72)	86 (5.40)
2	68.91 ± 6.99	1418 (51.15)	1812 (65.32)	4.86 ± 3.91	0.21 ± 0.69	1310 (47.24)	0.17 ± 0.57	2773 (43.83)	113 (5.22)
3	68.8 ± 6.78	285 (65.26)	234 (53.63)	5.10 ± 4.54	0.15 ± 0.57	190 (43.58)	0.12 ± 0.56	436 (6.89)	26 (8.21)
4	68.4 ± 6.64	771 (69.42)	633 (56.88)	4.12 ± 3.45	0.17 ± 0.64	647 (58.24)	0.18 ± 0.62	1111 (17.57)	61 (6.96)
p value	0.0018	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.474	0.061
Total	68.59 ± 6.78	3385 (57.7)	3814 (60.57)	5.16 ± 4.26	0.185 ± 0.63	2760 (43.40)	0.7 (0.61)	6327 (25)	286 (6.44)

Sample description according to baseline characteristics: Chi2 test used for categorical variables and ANOVA used for continuous variables

HBP High blood pressure, *1* without SMC/without DS, *2* with SMC/without DS, *3* without SMC/with DS, *4* with SMC/with DS

Table 2 Logistic regression model

Study groups	Total			NO-HBP			HBP		
	OR	*p* value	CI	OR	*p*value	CI	OR	*p* value	CI
Unadjusted									
1									
2	0.96	0.81	(0.72–1.28)	0.78	0.19	(0.54–1.13)	1.37	0.19	(0.85–2.22)
3	1.56	0.05	(0.99–2.47)	1.13	0.72	(0.56–2.26)	2.43	0.007	(1.27–4.64)
4	1.31	0.11	(0.93–1.84)	0.68	0.2	(0.38–1.22)	2.25	0.001	(1.37–3.69)
Adjusted									
1									
2	0.86	0.34	(0.64–1.16)	0.69	0.059	(0.47–1.01)	1.29	0.31	(0.79–2.12)
3	1.34	0.21	(0.84–2.13)	1.01	0.97	(0.51–2.04)	2.11	0.03	(1.09–4.09)
4	1.04	0.80	(0.73–1.49)	0.53	0.041	(0.29–0.97)	1.91	0.01	(1.14–3.22)

Logistic regression model which displays the variables when assessed by SMC and DS status. Adjusted by sex, age, number of years in school, marital status, comorbidity, alcoholism, and visual deficits

HBP high blood pressure, *1* without SMC/without DS, *2* with SMC/without DS, *3* without SMC/with DS, *4* with SMC/with DS

vascular dementia and in particular, Alzheimer's Disease [25]. Large community-based studies have shown independent associations between late-life depression, small basal ganglia lesions and white matter abnormalities visualized as hyperintense regions on MRI [24, 26], particularly ischemic lesions in the fronto-striatal region [27], which give rise to the plausible pathway arising from depressive symptoms and leading to CogI in those individuals with vascular risk factors such as HBP.

Moreover, in the Cardiovascular Health Study, the severity of DS independently predicted the diagnosis of MCI 6 years later [28]. Studies have shown that major depression confers a greater relative risk for CogI than the diagnosis of dysthymia or self-reported DS, suggesting a possible dose–response relationship between severity of depressive disease, and risk of cognitive deterioration [29]. Other studies suggest that when depressive and cognitive symptoms appear close in time they likely arise from common neuropathological processes [30]. In this paper, we assess self-report of DS and we show the effect of these over CogI in a period of 3 years. We believe that DS are not cognitive symptoms. Nonetheless, the combination of DS with vascular risk factors such as HBP could predict further cognitive involvement.

Also, studies have shown that the risk for cognitive deterioration and dementia persists latent even after treating depression, which suggests that irreversible vascular damage is the real risk factor and DS just a manifestation [31, 32]. Furthermore, as previously described, untreated chronic HBP has been associated with CogI [6], and even linked to pathological findings related to Alzheimer's disease (AD) [13]. For instance, in the Framingham Heart Study, the first wave of patients had an incidence of dementia of 2.8%, while the second and third waves of patients had incidences of 2.2% and 2%, respectively. It is not entirely clear why the incidence of dementia in this study declined, but it seems to be associated with a healthy lifestyle, control and prevention of HBP [31].

Our study has some limitations; self-report is one of the main issues, leading toward potential memory bias, and under-diagnosis of HBP. It is a secondary analysis from a study not designed specifically for solving our hypothesis. Besides, it was not possible to determine the intensity or duration of DS; thus, we were not able to differentiate between dysthymia and major depression. Also, the treatment status of DS was unknown. Moreover, CCCE is a screening tool; therefore, a diagnosis of overt dementia and subtype thereof was not possible. Regarding HBP, because the MHAS was conducted as a survey, it was not possible to disclose whether HBP was controlled at the time (data regarding blood pressure assessment at the time was not available). In spite of the fact that 70% of the participants were receiving treatment at the time of data collection, having therapy is not equal to be controlled; data in the Latin-American region and other reports in México for uncontrolled hypertension range from 12 to 41% [33, 34]. At certain point, all HBP participants (controlled or not) had been exposed to HBP levels. Thus, the risk for CogI was present. However, uncontrolled participants might have been at greater risk (harmful exposures still present).

Although the treatment of HBP is very useful in the prevention and progression of adverse outcomes, sometimes there is already some degree of damage at the CNS level at the time treatment is started or the blood pressure levels are finally controlled. An ideal scenario should be the prevention of the onset of arterial hypertension [31].

On the other hand, several studies have evidenced a strong dependence of cognitive performance on blood

pressure, pointing to the fact that a low blood pressure or excessive control could lead to neural damage. The latter may be due to decreased cerebral perfusion, an effect that is greater in older persons because of related changes in autoregulatory mechanisms [35–37]. Further studies addressing this issue with wider and comprehensive assessments are still required [38, 39], since exploring even earlier risk factors which could exert a significant influence on risk for future cognitive impairment [40].

On the other hand, this study also has several strengths. It is derived from a representative sample of a Latin-American country, where the evidence in this particular subject is limited and there is a high prevalence of HBP. Populations with a high prevalence of HBP could be reflected in our results. As such, our findings could lead to conclusions relevant from a public health viewpoint. Our results can also be extrapolated to several regions due to limited existing information on this issue, and also due to high rates of Latin American immigrants in other regions which increases applicability elsewhere. We would like to highlight from the results that DS seems to be a predictor for the development of cognitive impairment when a vascular risk factor such as HBP is present. These results appeal for attention since DS are not usually explored in primary care settings, particularly when addressing older adults. However, the presence of DS and psychiatric disease should be assessed in all older patients due to its implications on quality of life, as well as for its probable diagnostic value in early prediction of cognitive impairment. Also, HBP prevention and control could be crucial in preventing vascular damage and CogI progression. This study aims to disclose the importance of taking early actions given the incremental risk for development of CogI.

Thus, we conclude that even if there are no curative treatments for dementia or CogI available at the present time, prevention and delay of their installment are of paramount importance. Also, early targets for potential treatments must be identified. There are several treatable risk factors, which could be managed through counseling regarding healthy lifestyle habits, detection of prodromal symptoms and prevention of cardiovascular risk factors, including HBP which could importantly impact outcomes in older persons [5, 6, 35, 36]. More studies are required to more accurately describe and confirm these findings, leading toward the creation of prevention policies for adequately treating older persons.

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Compliance with ethical standards

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical approval The Institutional Review Boards or Ethics Committees of the University of Texas Medical Branch in the United States, the Instituto Nacional de Estadística y Geografía, the Instituto Nacional de Salud Pública, the Instituto Nacional de Geriatría in Mexico and the Pontificia Universidad Javeriana approved the study. The rights of human participants were protected, the procedures were according to the Helsinki declaration.

Informed consent All patients signed informed consent prior to the assessments.

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7.3 Estudio 3: First Symptoms and Neurocognitive Correlates of Behavioral Variant Frontotemporal Dementia

FIRST SYMPTOMS AND NEUROCOGNITIVE CORRELATES OF BEHAVIORAL VARIANT FRONTOTEMPORAL DEMENTIA

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Running tittle: First symptoms in bvFTD

ABSTRACT

Background: Previous works highlight the neurocognitive differences between apathetic and disinhibited clinical presentations of the behavioral variant frontotemporal dementia (bvFTD). However, little is known regarding how the early presentation (i.e., first symptom) is associated to the neurocognitive correlates of the disease's clinical presentation at future stages of disease.
Objectives: We analyzed the neurocognitive correlates of patients with bvFTD who debuted with apathy or disinhibition as first symptom of disease.
Methods: We evaluated the neuropsychological, clinical and neuroanatomical (3T structural images) correlates in a group of healthy controls (n=30) and two groups of bvFTD patients (presented with apathy [AbvFTD, n=18] or disinhibition [DbvFTD, n=16]). To differentiate groups according to first symptoms, we used multivariate analyses.

Results: The first symptom in patients described the evolution of the disease. AbvFTD and DbvFTD patients showed increased brain atrophy and increased levels of disinhibition and apathy, respectively. Whole brain analyzes in AbvFTD revealed atrophy in the frontal, insular and temporal areas. DbvFTD, in turn, presented atrophy in the prefrontal regions, temporoparietal junction, insula and temporoparietal region. Increased atrophy in DbvFTD patients (compared to AbvFTD) was observed in frontotemporal regions. Multivariate analyses confirmed that a set of brain areas including right orbitofrontal, right dorsolateral prefrontal and left caudate were enough to distinguish the patients' subgroups.
Conclusion: First symptom in bvFTD patients described the neurocognitive impairments after around three years of disease, playing an important role in the early detection, disease tracking, and neuroanatomical specification of bvFTD, as well as in future research on potential disease-modifying treatments.
Keywords: bvFTD, disinhibition, apathy, first symptom, VBM.

INTRODUCTION

The behavioral variant of frontotemporal dementia (bvFTD) is a neurodegenerative disease with early pervasive behavioral dysfunctions affecting social behavior, cognition and personality[1–3]. Among the most frequent features at the early stages of bvFTD are apathy and disinhibition[4,5]. Recent studies have focused on the early detection of bvFTD as it has implications for the differential diagnoses of psychiatric disorders,[2] heritability,[6] therapeutics[7] and the environmental management of patients[8]. Understanding how the first behavioral symptoms shape the neurocognitive profiles of bvFTD is fundamental to early detection.

Although behavioral symptoms in bvFTD can occur variably[9], two distinct presentations termed "apathetic" and "disinhibited" have been largely reported[9,10] and are considered the most prevalent behavioral symptoms of bvFTD[2]. Apathy is the quantitative reduction of self-generated voluntary and purposeful goal-directed behavior (GDB)[10,11] due to either a lack of motivation or the inability to elaborate a plan to achieve a goal[11] . The bvFTD apathetic presentation includes patients who have a lack of interest in their surroundings and difficulty initiating, planning, and self-motivating related to a specific goal[11]. In contrast, disinhibition involves a reduction of mechanisms of cognitive control, such as of inhibitory control[11][12]. BvFTD disinhibited presentation predominantly exhibits with impulsiveness and hyperactivity, typically showing undue familiarity,

disorganized behaviors, irritability, and sexual acting out[13]. Alterations in goal-directed behavior related to atrophy in frontal areas and basal ganglia are involved in apathetic bvFTD[11][14][15]. Conversely, impairment in inhibitory control related to atrophy in the orbitofrontal (OFC), frontal ventromedial and anterior temporal areas are implicated in disinhibited bvFTD[12][14].

Despite the general importance of bvFTD behavioral symptoms[16], no study has specifically focused on how the early presentation of these symptoms shapes the neuropsychological correlates and the disease's pattern of atrophy. Whether the presence of apathetic or disinhibited first symptoms are involved in bvFTD neurocognitive characterization is relevant to the early detection of bvFTD, as well as potential disease-modifying treatments[14]. To our knowledge, this is the first study assessing whether first symptoms are associated to the future neurocognitive profile when patients debut with apathy or disinhibition.

Here, we evaluated the neuropsychological and neuroanatomical correlates (measured at an average of 3 years after the report of the first symptom) in a group of controls and two groups of bvFTD patients (debuting with apathy or disinhibition). We expected a different neurocognitive presentation between groups accordingly to the first symptom. We also expected that a differential pattern of neuropsychological scores in sensitive neuropsychological measures of apathy and disinhibition, as well as dissociable patterns of neuroanatomical signs between both groups, would be observed: specifically, the AbvFTD group's larger atrophy in goal-directed behavior areas (right frontal and basal ganglia regions) the and DbvFTD group's larger atrophy in regions related to in inhibitory control process (ventromedial and OFC). Moreover, specific brain-behavior links within those neurocognitive correlates (sensitive neuropsychological measures and atrophy regions) in each group were anticipated. Finally, with a focus on practical differential diagnosis, we estimated which variables were better able to distinguish groups by

conducting multivariate analyzes including a factorial discriminant analysis and applying a machine learning method.

METHODS AND MATERIALS

Participants

Thirty-four patients recruited from an ongoing protocol[17–19] met the revised criteria for probable bvFTD[4]. See Supplementary section 1 for a detailed description of patient assessment. Thirty control subjects were recruited from a larger pool of volunteers who did not have a history of drug abuse or a family history of neurodegenerative or psychiatric disorders. Controls were recruited and matched one by one with the bvFTD patients, controlling for sex, age and years of education. All participants provided informed written consent, in agreement with the Helsinki declaration. The Ethics Committees of the Pontificia Universidad Javeriana and Institute of Cognitive Neurology approved this study.

First stage of evaluation-Grouping strategy

First, we defined patient groups based on the debut symptom of disease. The debut symptom was established on the basis of family/caregiver reports and clinical history documents. To verify the presence and particularity of the debut symptoms, we only included patients who reported that the reason for the consultation was the discomfort associated to a defined and exclusive first symptom. This criterion was met by 34 out of a total of 41 patients. Seven patients were excluded as they reported that their consultation was not motivated by a main first symptom of apathy or disinhibition. Among those patients, four presented unspecified symptoms, including cognitive alterations. Two other patients were excluded because their consultation did not follow from discomfort associated to its first symptoms. The final

samples included in the study comprised 18 patients who debuted with apathy (AbvFTD), and 16 who debuted with disinhibition (DbvFTD).

Ten external raters with clinical expertise (including five psychiatrists, three neurologists, and two neuropsychologists), blinded to diagnoses, assessed descriptions of first symptoms taking into account a group of clinical categories related to apathy or disinhibition in each case. Similar retrospective approaches have been used in studies exploring the lifetime prevalence of symptoms of mental disorders (see [1][2,3]). To be classified as apathetic, patients had to predominantly present the following symptoms: (a) changes in affectivity, in particular reduced or flattened affect; (b) changes in volition, including difficulty in initiating activities, reduced ability to plan or loss of motivation; or (c) changes in emotional responses, in particular indifference or reduced emotional responses to external events. Instead, to be labeled as disinhibited, patients had to predominantly present with these symptoms: (a) changes in affectivity, including irritability, euphoria, or inappropriate affect; (b) changes in social behavior, including undue familiarity, or breaching of social norms; or (c) changes in motor behavior, including impulsiveness, hyperactivity, disorganized behavior or sexual acting out. These criteria were based on previous studies of clinical signs of apathetic and disinhibited bvFTDs [4–6].

Based on the assessment of raters, patients were assigned to either the AbvFTD or theDbvFTD group. The reliability of the raters' assessments was measured using Cohen's kappa (κ) scores[7][8]. Inter-rater reliability for was $k = 0.93$ for AbvFTD and $k = 0.87$ for DbvFTD; all (κ) scores were significant at $p < 0.001$.

Second milestone of evaluation

Patient groups initially formed following a clinical criterion (namely first-consultation

symptom) were studied around three years after disease debut (DbvFTD mean = 3.3 years SD = 4.1 vs. AbvFTD mean = 3.1 years SD = 4.8). Neurocognitive and neuroanatomical correlates of each group were assessed at this stage. Neurocognitive processes were evaluated with a standardized neuropsychological measures typically used in patients with neurodegenerative diseases. VBM scores were used to assess brain atrophy correlates of patients in each group.

Neuropsychological assessment:

Global cognitive performance was assessed through a comprehensive set of measures, namely, the Frontal Behavioral Inventory (FBI) [30], the INECO Frontal Screening, (IFS) Battery [31], the Montreal Cognitive Assessment (MoCA) [32], and the Mini-Mental State Examination (MMSE)[33].

Neuropsychiatric manifestations including apathy and disinhibition were assessed with the subjective subscales of apathy, executive functions, and disinhibition of the Frontal System Behavioral Scale (FrSBe) [34]. As an additional measure of disinhibition, we also administered the Hayling Test [35]. Other cognitive domains, including attention skills, verbal memory, attentional control, and cognitive control, were assessed with the Digit Symbol task[36], the Boston Naming Test[37], and the Wisconsin Card Sorting Task [38].

The Clinical Dementia Rating (CDR) was used to determine the stage of dementia, as in previous rsearch (see [26,28,29]).

Imaging recordings and Voxel-based morphometry (VBM)

Images for this study were obtained from a Philips Achieva 3T scanner with a 16-channel SENSE antenna. The anatomical and 3D T1-weighted images had the

following parameters: TR = 7.9, TE = 3.8, ACQ matrix 220 x 220 pixels, voxel size 0.5 x 0.5 x 0.5 mm, 310 sections.

Neuroanatomical correlates were analyzed using VBM method. Data processing and analysis were performed with VBM8 in the Statistical Parametric Mapping 8 package (SPM8; Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm) running under Matlab 2012b (The Mathworks, Natick, MA, USA). Each image was inspected for artifacts. All imaging analysis processes were conducted as described in the VBM pipeline (http://www.fil.ion.ucl.ac.uk/~john/misc/VBM) and are briefly summarized as follows. The T1-weighted images were normalized to the same stereotaxic space generated from the complete data set using the DARTEL algorithm that significantly reduces the imprecision of inter-subject registration. Then, the images were segmented into WM and GM and non-brain voxels (CSF, skull). Subsequently, all images were modulated to correct volume changes by Jacobian determinants. Finally, images were smoothed by convolution with an isotropic Gaussian kernel of 8-mm full-width at half maximum for statistical analyses.

Assessment of neuroanatomical markers. Whole-brain and regions of interest (ROI) analyses. To assess atrophy regions as predictors of groups, we have used two procedures: (a) we compared neuroanatomical differences between groups using whole-brain analyses; and (b) we restricted the multidimensionality of data using critical bilateral ROIs involved in bvFTD behavioral symptoms [14,20,21]. All VBM analyses between groups were corrected using FDR at 0.05. VBM procedure for ROIs analyses were conducted using a mask centered in a group of bilateral ROIs reported to be involved in neuropsychiatric symptoms (apathy and disinhibition) of bvFTD. Apathy as symptom of bvFTD is associated with atrophy in prefrontal regions—including bilateral dorso lateral prefrontal cortex (R-L DLPFC), and bilateral Orbito Frontal Cortex (R-L OFC), bilateral anterior cingulate cortex (R-L ACC)—and

basal ganglia, in particular, caudate (Caud) and putamen (Put) [14,20,21]. In contrast, disinhibition in bvFTD is associated with gray matter loss in right medial temporal structures such as right amygdala (R amyg), bilateral hippocampus (R-L Hipp), R-L OFC and R-L ACC[14,20,21].

Assessment of anatomic-clinical relationship

To detect distinctive neurocognitive profiles in each group, we calculated correlations between sensitive neuropsychological measures and atrophy regions in each group via Pearson's correlation coefficient and Sidak correction. VBM scores in ROIs (see Table 2) and standardized scores of neuropsychological measures such as the MMSE, the MoCA, the Frontal Behavioral Inventory, the Frontal System Behavioral Scale (FrSBe) and the Hayling test, among others (see Table 1), were entered as factors. We assumed that an increase in severity of the neuropsychological scores would be associated with decreased tissue density.

Multivariate analyses

To evaluate which neuropsychological and neuroanatomical variables better determine group membership (groups created by first-consultation symptom), we used two methods of binary classification: a factorial discriminant analyses (FDA) and a support vector machine (SVM). Both analyzes provide convergent and confirmatory information that allowed us to (a) specify the contribution of neuropsychological and morphometric measures in differentiating between the apathetic group and the disinhibited group; and (b) look for a possible decision rule for the differential classification between groups based on the minimum relevant neuropsychological and VBM variables. To introduce variables in both methods, we selected only those that reached significant differences between groups after statistical corrections. In each method we used two models. The first model included

both the neuropsychological and anatomical variables that yielded significant differences between groups. A second model included only anatomical variables to avoid considering factors related to apathy and disinhibition, which are directly related to the criteria used to create groups.

Factorial Discriminant Analysis (FDA). FDA is a multivariate statistical procedure that uses a set of explanatory variables to classify patients into different subgroups and allows for the construction of a new variable—namely, the predictive score. This technique was chosen because it is used for classifying subjects into groups on the basis of a battery of measurements, as well as on its parsimonious interpretation [22,23]. Two FDA analyses were performed. In the first FDA we included significant neuropsychological measures and neuroanatomical variables reached significance differences between groups. In a second model we only included significant neuroanatomical variables. The individual predictive score of each significant VBM score (in ROIs) and each significant neuropsychological measure was examined by t-test. This score maximizes the ratio of the variability between the groups to the variability within the groups and therefore patients of different groups have score values as different as possible. The score was used to determine a rule of prediction. Subsequently, to select a best subset of predictor variables, a final stepwise discriminant analysis was performed (at the 5% level and with the “stepwise” option, which is a forward selection allowing elimination; this procedure was applied following previous studies [22]).

Support Vector Machine (SVM). SVM models [24,25][26] were used to evaluate the neuropsychological and anatomical correlates that allow us to determine the group of each patient (AbvFTD and DbvFTD). SVM is a supervised classification algorithm rooted in statistical learning theory [27], where input data are classified into two classes (in this case, AbvFTD and DbvFTD). Conceptually, input vectors are mapped to a higher-dimensional feature space using kernel special functions. Classification

is performed by constructing a hyperplane in the feature space based on a training of data that optimally discriminates between the two groups by maximizing the margin between the two data clusters [27]. We determined the optimal values of two constants: γ, width of the radial basis function, and C, an input parameter for the SVM algorithm, which represents the error/trade-off parameter that adjusts the importance of the separation error in the creation of the separation surface[26].

We implemented two methods to select the variables for the model. First, we entered into the model the same variables used in the FDA analyses –i.e., neuropsychological measures and ROIs that yielded significant differences between groups (AbvFTD vs. DbvFTD) after multiple corrections. Second, to avoid a possible bias mediated by the inclusion of ROIs involved in behavioral symptoms, we performed a SVM model using anatomical variables extracted from whole brain analyses of the contrast AbvFTD vs. healthy controls and those extracted from the contrast DbvFTD vs. healthy controls. Third, we implemented a SVM model using only ROI variables involved in behavioral symptoms (apathy and disinhibition). To perform SVM models the recursive feature elimination method [28], implemented by the selection of attributes in Weka (toolbox InfoGainAttributeEval) was used. This method of classification evaluates the worth of an attribute by measuring the information gain to discriminate information between groups [26][28]. SVM models were implemented by defining a 10-fold cross validation. All experiments were conducted using the Waikato Environment for Knowledge Analysis (WEKA) http://www.cs.waikato.ac.nz/ml/weka suite of ML software [18][28].

Statistical Analyses at second stage measures

Neuropsychological measures

Demographic and neuropsychological data were compared between two groups of patients (AbvFTD, DbvFTD) and a control group using one-way ANOVA and chi square tests for the categorical variables. A one-way ANOVA was used to assess differences in neuropsychological measures between groups of patients (AbvFTD and DbvFTD). Bonferroni post-hoc tests were used (when appropriate) to examine group differences within the neuropsychological measures.

Regions of interest (ROIs) analyses

First, we performed a whole brain analysis using VBM to analyze differences in brain atrophy between the group of patients with AbvFTD and the group of patients with DbvFTD, as well as healthy controls (controlling for global intracranial volume, age, gender and length of disease duration, corrected with FDR at 0.001). In assessing atrophy regions as predictors of groups, we restricted the multidimensionality of data using the critical bilateral ROIs involved in bvFTD behavioral symptoms [14,21,29] (see section 2.2.2.1). Thus, VBM analyses (corrected using FDR at 0.05) between groups were conducted using a mask centered in these reported ROIs.

Assessment of anatomic-clinical relationship

Multiple correlations (Pearson coefficient and Sidak correction) were performed to identify how brain atrophy (VBM scores) correlated with the neuropsychological measures in each group. VBM scores in ROIs (see Table 2) and standardized scores of neuropsychological measures such as the MMSE, the MoCA, the Frontal Behavioral Inventory, the Frontal System Behavioral Scale (FrSBe) and the Hayling test, among others (see Table 1), were entered as factors. We assumed that an increase in severity of the neuropsychological scores would be associated with decreased tissue density.

RESULTS

Clinical, demographic and neuropsychological results

The three groups (AbvFTD, DbvFTD and Controls) were matched for age [F(2, 63) = 1.58, p = .21], gender [X2(1) = 1.11, p = .33], education [F(2, 63) = 1.57, p = .21]. Differences between three groups were observed in MMSE scores [F(2, 63) = 13.54, p = .001]. AbvFTD (Bonferroni p < .001) and DbvFTD (Bonferroni p < .001) patients were outperformed on the MMSE by healthy controls, there being no differences between bvFTD groups (Bonferroni p > .71). Moreover, differences among the groups were also observed in MoCA scores [F(2, 63) = 13.54, p = .001] and in IFS [F(2, 63) = 23.04, p = .0001]. AbvFTD patients and DbvFTD showed lower MoCA and IFS scores than healthy controls (post hoc analyses for AbvFTD vs. Controls and DbvFTD vs. Controls contrasts reached significant values: Bonferroni tests in both contrasts yielded p < 0.001 for MoCA and p < 0.0001 for IFS). No differences were found between bvFTD groups (Bonferroni tests showed p > 0.52 for MoCA and p > 0.89 for IFS) (see Table 1).

We found significant differences between AbvFTD and DbvFTD in apathy and disinhibition measures such as FrSBe scale (DbvFTD=9.7 SD = 4.2 vs. AbvFTD=7.6 SD = 3.5; F(1, 33) = 3.42, p < 0.06) and Hayling test (the number of errors) (DbvFTD=26.2 SD=2.8 vs. AbvFTD=13.4 SD=5.8) [F(1, 33) = 7.54, p < .01]. The AbvFTD group showed worse scores than the DbvFTD group for only the apathy subscore in FrSBe (AbvFTD= 23.3 SD=9.5 vs. DbvFTD=17.8 SD=9.6) [F(1, 33) = 6.55, p < .01]. No other analyzes showed significant differences between the patient groups (for a further description of these analyses see Table 1).

Based on results from neuropsychological measures, and in order to facilitate further analyses, we generated a global score of disinhibition based on scores of both

subjective and objective indexes used to assess disinhibition. FrSBe scores were used as a subjective measure of both apathy and disinhibition following previous procedures [14]. Hayiling Test scores were used to objectively assess disinhibition, as this scale is sensitive to track response initiation and response suppression [12,30] and it has been largely used to assess disinhibition in patients with neurodegenerative diseases (see [20,21]). This global-score approach mirrors procedures used in previous reports of our group (see [18,31]).

VBM results

Whole brain analyses comparing each bvFTD group (AbvFTD and DbvFTD) with healthy controls showed widespread bilateral atrophy predominantly involving the mediofrontal, OFC and anteromedial temporal areas, bilateral insula, and basal ganglia (all FDR 0.001). In particular, the AbvFTD group showed reduced VBM values in R DLPFC, R-L OFC, R-L ACC, R-L Caud. DbvFTD showed reduced VBM values in more areas, including the R DLPFC, R OFC, R-L ACC, L STG, R-L Caud, medial frontal regions (R-L FM) and bilateral insula (R-L Ins). Distribution of atrophy in both groups was consistent with previous VBM studies[14,21,29,32] (see supplementary Figure S1 and Supplementary Table S1).

Whole brain analyses

Whole brain analyses comparing each bvFTD group (AbvFTD and DbvFTD) with healthy controls showed widespread bilateral atrophy predominantly involving the mediofrontal, OFC and anteromedial temporal areas, bilateral insula, and basal ganglia (all FDR 0.001). In particular, the AbvFTD group showed reduced VBM values in R DLPFC, R-L OFC, R-L ACC, R-L Caud. DbvFTD showed reduced VBM values in more areas, including the R DLPFC, R OFC, R-L ACC, L STG, R-L Caud, medial frontal regions (R-L FM) and bilateral insula (R-L Ins). Distribution of atrophy in both groups was consistent with previous VBM studies[14,21,29,32] (see

Supplementary Figure S1 and Supplementary Table S1).

Additional whole-brain analyses comparing AbvTFD and DbvFTD groups showed differences in the brain atrophy pattern according to type of contrast. The AbvFTD > DbvFTD contrast showed major atrophy for the apathetic group in a collection of areas including the R DLPFC, Left precuneus, Right Angular Gyrus, L Caudate (FDR 0.05). Instead, the DbvFTD > AbvFTD contrast reflected major brain atrophy for the disinhibited group in a set of areas including R-L OFC, R FM, R DLPFC, L STG, R-L ACC, and Left and Right Temporal Middle (R-L Temp M)(FDR 0.05) (see Supplementary Figure1 panel C).

ROIs differences between groups

Reduced VBM values in DbvFTD (DbvFTD>AbvFTD contrast) were found in the R OFC, right dorso lateral prefrontal cortex (R Dlpfc), left caudate (L Caud), left superior temporal gyrus (L STG) and left ACC (all $p<0.01$) (see Table 2 and Figure 1A). Using the opposite comparison (AbvFTD>DbvFTD), analyzes did not show significant differences.

To assess which areas were involved in generating both symptoms, VBM results were then reanalyzed covarying for the disinhibition score in AbvFTD and for apathy score in DbvFTD. In AbvFTD, reduced VBM values in R DLPFC and L Caud were preserved after covarying for the disinhibition score (FDR 0.01). In DbvFTD, reduced VBM scores in the L STG, R FM and R OFC were preserved after covarying for the apathy score (FDR 0.01). VBM scores of R Caud, L ACC and bilateral insula were overlapped in both groups after covarying for apathy and disinhibition scores.

Correlations between neuropsychological measures and ROIs in each group

Different patterns of correlations (Pearson, Sidak corrected) between neuropsychological measures and brain atrophy in each group (AbvFTD and DbvFTD) were detected (figure 1B-C). Among AbvFTD, we found a negative correlation between the score of apathy and voxel values of L Caud ($r2=-0.53$, $p<0.01$) and R DLPFC ($r2=-0.48$, $p>0.05$), as well as positive correlations among atrophy areas (R DLPFC and R ACC: $r2=0.40$ $p< 0.05$; R OFC and R FM; $r2= 0.44$, $p<0.05$). Among DbvFTD, the global score of disinhibition was inversely correlated with R OFC ($r2=-0.54$, $p<0.01$), R DLPFC ($r2=-0.4$, $p>0.05$) and L ACC ($r2=-0.51$, $p<0.05$). In addition, a negative correlation between apathy score and L Caud ($r2=-0.49$, $p<0.05$) was observed. Finally, in this group, positive correlations were also observed between R OFC and R DLPFC ($r2=0.46$, $p< 0.05$) and between R DLPFC and L ACC ($r2=0.51$, $p<0.01$). No other correlations were significant.

Multivariate analyses

After identifying the neuropsychological variables and ROIs that showed a significant difference between groups, we included them as predictors in an FDA analysis and SVM model to assess the group classification of each patient. As neuropsychological measures, the global scores of disinhibition and apathy were included as predictors[33],[34]. Brain regions with significant differences between groups were: R OFC, R DLPFC, L Caud, L STG and L ACC.

FDA

An FDA was performed on the reported variables (2 neuropsychological measures and 4 ROIs). All variables showed a substantial separation between groups in terms of means of the discriminant score ($r2$ ratio > 0.74). Among the 34 patients, 33 (97%) were correctly classified. To select a best subset of predictor variables, a final stepwise discriminant analysis was performed (at level 5%). After the stepwise

discriminant analysis, the following five predictor-variables were retained: Global score of apathy and disinhibition, R OFC, DLPFC and L caud. A second FDA was performed on these five remaining variables. Using this FDA among the 34 patients, 32 (94.1%) were correctly classified. The FDA used an individual predictive score of each significant VBM score and each significant neuropsychological measure based on the results of a t-test. We used this score to determine a prediction rule following a previous procedure[22]. The prediction rule was calculated as follows:

S= 2.68(Global score of disinhibition) – 2.78* (score of apathy) + 2.56*(R Ofc) + 2.08* (R Dlpfc) + 2.72*(L Caud)*

Following the S score, the next rule was derived: if S<0, then it belongs to the AbvFTD group. In contrast, if S>0, it belongs to the DbvFTD group. Using this decision rule, 100% (18/18) of the AbvFTD group and 88% (14/16) of the DbvFTD group were classified in the correct group (94.1%). Figure 1D shows that a subset of five variables seemed to be relevant in determining the group of each patient.

SVM

The SVM model included the global score of disinhibition and the score of apathy, and significant areas between groups, namely in the R OFC, R DLPFC and L Caud, reached a sensitivity of 84.8%, an index of specificity of 80% and a precision index of 81.6% for differentiating between the groups.

To control the multidimensionality of analyses, we used an SVM model examining reduced features (measures) with the method of recursive feature elimination (RFE) using the selection of attributes in Weka[28]. This method assesses the worth of an attribute using an SVM classifier, and the features are ranked by the square of the weight assigned by the SVM. Following the rank proposed by this method, the four initial variables were selected as predictors; the first two attributes were two atrophy

regions (R OFC and L Caud), and the two-second scores of apathy and disinhibition. An SVM model with these four variables reached a sensitivity of 83%, an index of specificity of 84% and a precision index of 81% for differentiating between the groups (see Figure 1E and Supplementary Figure 2).

We ran two additional SVM models. The first one included anatomical variables extracted from whole-brain analyses of two contrasts (i.e., AbvFTD vs. healthy controls and DbvFTD vs. healthy controls). Following the rank proposed by the recursive feature elimination (RFE) method, the first eight attributes (brain areas) obtained by the model were: R Temporal M, Left Precuneus, L Caudate, R ACC, R OFC, L ACC, L STG, R FM. The SVM model using these attributes reached a sensitivity of 70%, and index of specificity of 68%, and a precision index of 67%. The last SVM model was performed only with the VBM scores of ROI areas that yielded between-group differences (namely R OFC, R DLPFC, L Caud, L STG and L ACC areas). Following the RFE method, the first three attributes (brain areas) were L Caud, R DLPFC and R OFC. An SVM model with these three brain areas reached a sensitivity of 72.9%, an index of specificity of 71.8%, and a precision index of 72.1% for differentiating between the groups (see Figure 1E and Supplementary Figure2).

DISCUSSION

In this study, we evaluated how the first symptoms determine clinical and neuroanatomical profiles of bvFTD. The first symptom (apathetic or disinhibited) was related to bvFTD's neurocognitive characterization. After an average of 3 years of presentation of the first symptom (DbvFTD mean = 3.3 years SD = 4.1 vs. AbvFTD mean = 3.1 years SD =4.8), the patients who debuted with apathy (AbvFTD) presented higher apathy scores and the patients in the DbvFTD group exhibited higher disinhibition scores. Neuroanatomical signs revealed increased atrophy of DbvFTD compared with AbvFTD in several frontal, striatal and temporal regions

(figure 1A). Convergent multivariate analyzes (FDA and SVM) confirmed that apathy, disinhibition and related brain structures were able to determine the group with high accuracy (figure 1D-E). These findings highlight the relevance of bvFTD's first symptoms to the neurocognitive characterization and clinical course.

The first symptom determined the disease presentation, as shown by the results in neuropsychological measures assessed after around three years from the onset of disease (DbvFTD mean = 3.3 years SD = 4.1 vs. AbvFTD mean = 3.1 years SD = 4.8). Although the patient groups did not show differences in global cognitive performance, they differed in sensitive measures to detect symptoms of apathy and disinhibition in bvFTD, including FrSBe and Hayling test (considered objective measures of apathy and disinhibition[35][33][34]). Even if apathetic and disinhibited presentations can be simultaneously present in the course of FTD disease[16], in our sample, the groups seem to preserve the clinical profile with which they began, independent of duration of disease progression. Previous studies have suggested that behavioral symptoms might persist across time and may occur simultaneously in advanced stages of the disease[9,16]. To our knowledge, this is the first report showing the persistence of an initial symptom and its relevance in shaping disease presentation.

Previous work has shown specific neural correlates for the apathetic and disinhibited presentations (regardless of which was the initial symptom). BvFTD clinical presentation of apathy has been linked to atrophy of the frontal lobes and striatum[14,15]. More specifically, ACC has been associated with difficulty in initiating activities[36], DLPFC appears to contribute to the generation of higher-level planning and organization[37], and OFC has been implicated in motivation[38]. In contrast, disinhibited bvFTD presentation has been associated with alterations in cognitive and inhibitory control related to atrophy in OFC and ventromedial areas [14,21,29,32]. Our findings corroborate these findings. Whole brain analyzes in

AbvFTD revealed reduced VBM values in DLPFC, OFC, ACC, insular and superior temporal areas, among others. Whole brain analyzes in DbvFTD revealed brain atrophy in the OFC, DLPFC, FM regions, tempoparietal junction (TPJ), bilateral ACC, insular and temporal parietal regions, among others (Supplementary Figure S1 and Supplementary Table S1).

To our knowledge, this is the first evidence (indexed with both whole brain and ROIs analysis) of the DbvFTD group exhibiting a larger pattern of brain atrophy (R OFC, R DLPFC, L Caud, L STG and L ACC, figure 1A) than AbvFTD after 3 years of evolution (approximation to length of disease duration at time of second stage of evaluation in both groups). Neuropsychiatric symptoms (in particular apathy and disinhibition) tend to increase over the time[9,16]. However, there are no studies reporting the extent to which the first behavioral symptom shapes the brain atrophy pattern and the linical profile. Arguably, disinhibition symptoms occur as a consequence of brain atrophy in a large and more diversified set of brain areas, which are implicated in cognitive control and inhibitory processes[12,21]. By contrast, a smaller group of brain areas are related to apathy[11,14]. Thus, brain atrophy in some of these areas would be enough to produce and sustain symptoms of apathy. Future research should be conducted to assess the extent to which the course of neuropsychiatric symptoms and treatments used to control those symptoms might contribute to the brain atrophy process.

Importantly, the differential atrophy between groups mapped onto the behavioral symptoms is measured by neuropsychological scales. In the DbvFTD group, disinhibition measures were negatively correlated with higher brain atrophy in R DLPFC, L Cau and R OFC, as previously reported[21]. In AbvFTD, apathy was negatively correlated with atrophy of R DLPF, also reported previously [14] (see figure 1B-C). Positive correlations in both groups between VBM scores of near brain areas were also observed, suggesting a consistent pattern of atrophy between near

and structurally connected regions, as reported in Alzheimer's disease[39,40]. Together, the pattern of correlations in each group supports the existence of an independent path of presentation of disease according to the first symptom.

Given the multidimensionality of the results, we used convergent multivariate analyses to determine which variables were more sensitive to distinguish differences between groups. An FDA including scores of apathy, disinhibition and relevant brain areas (R DLPFC, R OFC, and L Caud) yielded an accurate classification, confirmed by SVM classification. The usage of methods that prioritize features with a higher weight are timely in bvFTD research[9]. The SVM model, with reduced features and data training, allows us to improve the neurodegenerative diagnosis by identifying the most relevant features, usually blind to classical statistical analyzes[22],[41]. SVM results with reduced features yielded four variables in the following order: the R OFC, the L Caud, the score of apathy and the global score of disinhibition. It is noteworthy that in our sample of patients, the brain atrophy variables presented a higher discriminant value than the neuropsychological variables. It is possible that the brain areas selected as attributes have more discriminant weight than other areas because they are more implicated in one of the two behavioral profiles (apathy or with disinhibition). In fact, R OFC has been more frequently related to the disinhibited profile[20,42], and the atrophy in L Cau has been more frequently associated with the apathetic profile[11,14,15]. This result (together with the FDA data) confirms the influence of first symptoms, given that both measures track apathy and disinhibition with high reliability in bvFTD patients[41,43]. Thus, classification results suggest that both patient groups presented a predominant (disinhibited or apathetic) pattern of brain-behavioral affectation rather than a mixed pattern.

Our results show that atrophy in R Caud, L ACC and bilateral insula seem to be involved in both groups of patients. These areas have been implicated in both apathy and disinhibition [4,18,25]. Our findings add evidence on how first symptoms are

associated to neurocognitive alterations involved in both symptoms. Although we have found evidence of a differential neurocognitive pattern between apathy and disinhibition, our results also support the view that both symptoms share neural mechanisms [17,24]

FTD patients usually present a mixed pattern of neuropsychiatric symptoms throughout the course of disease [3,4,9,16,44]. However, no studies have shown that the initial symptom will necessarily remain the dominant symptom in later disease stages. This exploration is required to improve the comprehension of how neuropsychiatric symptoms are presented in FTD. In our study, some patients had a mixed presentation of clinical features (high scores in both subjective and objective apathy and disinhibition measures), together with an overlap in neuroanatomical markers of each group. Although our results are compatible with the presence of mixed clinical profiles in bvFTD, significant differences in measures used to track apathy and disinhibition and between-group differences in brain atrophy patterns support the idea of a persistence of the debut symptom and its relevance as the predominant clinical alteration around three years after disease onset –an effect unreported to date.

While recently revised diagnostic criteria for bvFTD indicate that patients with possible bvFTD may exhibit early presentation of at least three behavioral/cognitive symptoms including apathy, disinhibition, and empathy impairment, among others [2], in our sample 34 out of 41 patients reported that the reason for consultation was the discomfort associated to a defined and exclusive first symptom. In our sample, only four patients described the presence of combination of behavioral symptoms. Although our results suggest that those patients who debuted with an exclusive symptom might present this feature as dominant in another stages of disease, this does not preclude the existence of mixed clinical presentations of FTD. We acknowledge that our results do not allow exploring the neurocognitive correlates of

patients who debuted with a combination of behavioral symptoms. This question should be explored in future research.

Furthermore, further research should be conducted to assess neuropsychological and anatomical correlates in the earliest stages. Given that behavioral symptoms in bvFTD seem to be manifestations of impairments in a large group of neurocognitive mechanisms, additional investigations should be conducted to explore which particular cognitive processes are impaired by each symptom and in each stage of the disease. Considering the particular case of apathy, we have assessed apathy via a subjective clinical approach which lacks the multidimensionality of cognitive-clinical frameworks following previous reports [14,45]. Bearing in mind that the presence of apathy depends on alterations of different cognitive processes, including planning, motivation, and goal-directed behavior, among others, future studies should be conducted to assess more fine-grained aspects of apathy in FTD patients following multimodal approaches.

Prima facie, our results could seem affected by circularity. However, we would like to clarify that this is not the case. First, while clinical presentation of BvFTD is usually mixed, we show that first symptoms leave different long-lasting traces which trigger differences in disease presentation even three years after disease onset (approximation to length of disease duration at time of second stage of evaluation in both groups). Also, our analysis did not just consider neuropsychological indexes of apathy and disinhibition. Rather, we contemplated different levels of analysis, as we included the first clinical description debuting with apathy and disinhibition, then provided anatomical evidence, and finally offered neuropsychological confirmation of apathy and disinhibition. In brief, the anatomical patterns we observed discriminated patients with high scores of apathy in AbvFTD (apathy debut) and high scores of disinhibition in DbvFTD (disinhibition debut). This last result suggests that an early dominant symptom is concordant with the ulterior clinical presentation in

bvFTD. Furthermore, our results go beyond the apathy/disinhibition dimensions by showing a distinctive pattern of brain atrophy. In fact, atrophy patterns on their own (without neuropsychological measures of apathy/disinhibition) afforded accurate classification of both groups (see Results). In addition, note that it was not our goal to assess whether clinical marks of apathy and disinhibition correlate with brain atrophy. Instead, we explored whether initial symptoms are associated to different atrophy patterns. All these arguments seem to dispel concerns about circularity.

Co-occurrence of behavioral symptoms and mixed presentations are typical in bvFTD [16-18]. Nevertheless, our results highlighted the importance of evaluating each symptom in particular. Specifically, they suggest that behavioral presentation in bvFTD might be heterogeneous and likely even characterized by the presence of one dominant behavioral symptom. Furthermore, the study of behavioral symptoms in FTD following a multidimensional/clinical approach is relevant and aligns with an emerging literature on the existence of subtypes of clinical phenotypes in different types of neuropsychiatric conditions [26] and neurodegenerative diseases [27], including bvFTD [10, 23, 28-32]. This approach allows exploring the behavioral symptoms in bvFTD looking for fine-grained profiles rather than considering general, unspecific clinical presentations. Moreover, this approach might have a translational impact, as clinicians might emphasize treatment for the dominant symptom. Thus, we call for further research using longitudinal approaches to better understand whether the course of disease changes when patients debut with a particular symptom, and whether such an initial profile impacts disease progression and treatment options.

Although our study showed a differential neurocognitive profile each patient group, it does not indicate to what extent these differences are due to how the disease started. That being said, we acknowledge that retrospective analyses have intrinsic limitations. How neurocognitive patterns in both groups could be related to

additional factors is beyond the scope of this report. A different design would be needed to address this issue. In particular, longitudinal studies might provide evidence on the particular relationship between debut symptoms and disease trajectories and progression in bvFTD.

CONCLUSION

Together, the results suggest that clinical dimensions at early stages have a crucial impact in bvFTD neurocognitive presentation. The clinical subdivision of bvFTD based on the first symptom appears to be useful in tracking the predominant behavioral manifestations and their neurocognitive correlates. This is especially relevant given that current probable vbFTD criteria assign the same weight to the presence of apathy, disinhibition and other symptoms (e.g., empathy or ritualistic behavior). Along this line, studies that explore the extent to which an early pharmacological intervention on first symptoms can modify the neurocognitive presentation and prognosis of bvFTD might provide crucial information to cope with the global impact of the disease.

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HSMG: Principal Investigator and Corresponding Author, performed statistical

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AI: Principal Investigator and Corresponding Author, obtained the grant for the research program and drafted the manuscript.

PR: contributed with analysis of data and revision of manuscript.

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FIGURE AND LEGENDS

Figure 1. Panel A depicts the significant areas that better discriminate between the apathetic (AbvFTD) and disinhibited groups (DbvFTD). Panel B and C show the matrices of correlations in each group: (A) apathetic group and (B) disinhibited group. We used significant variables between groups, including the neuropsychological measures and significant neuroanatomical scores as factors. Panel D shows the discriminant canonical function (FDA analysis) using six variables, including global score of disinhibition, score of apathy, R OFC, L Caud, R STG and L ACC. This function is able to reach a discriminant power of 94.4%. Panel E shows a representation of classification using an SVM model with reduced features that was able to discriminate between groups with a precision index of 81%. The model postulated that R OFC, L Caud, score of apathy and global score of disinhibition would be the better attributes to distinguish group membership. Here, we used a 3D-graph to facilitate the visualization, presenting the first three attributes selected by the SVM model (for a better visualization of SVM data, see Supplementary Figure 2).

Table 1. Demographic and neuropsychological assessments in patients according to first symptoms AbvFTD vs. DbvFTD

		Controls (n = 30)	AbvFTD (n = 18)	DbvFTD (n = 16)	P value	P value
		Mean /SD	Mean /SD	Mean /SD	Controls vs. bvFTD	AbvFTD vs. DbvFTD
Demographics	Age (years)	60.1 (6.55)	58.0 (7.43)	57.0 (8.64)	N.S.	N.S.
	Gender (F.M)	14.16	8.10	8.8	N.S.	N.S.
	Education (years)	13.22 (4.8)	13.68 (4.3)	14.67 (3.7)	N.S.	N.S.
	Age of disease progression	NE	3.1 (4.8)	3.3 (4.1)	NE	N.S.
	MMSE	27.4 (2.1)	22.7 (6.5)**	23.7 (4.5)**	<0.01	N.S.
	MoCA	26.2 (3.1)	17.2 (6.7)**	17.1 (6.1)**	<0.01	N.S.
	CDR	NE	1.5 (0.8)	1.5 (0.6)	NE	N.S
Neuropsychological assessment	IFS Total Score	27.2 (1.9)	13.4 (5.8)	12.6 (5.8)	N.S	N.S.
	Phonological Fluency	NE	9.39 (6,3)	9.5 (5.3)	NE	N.S.
	Hayling Test	NE	13.4 (5.8)	26.2 (2.8)	NE	<0.01
	Frontal behavior inventory (FBI)	NE	23.3 (9.6)	23.1 (13.9)	NE	N.S.
	FrSBe total*	NE	48.4(31.4)	47.8 (27.7)	NE	N.S.
	FrSBe apathy score*	NE	23.3 (9.5)	17.8 (9.6)	NE	<0.01
	FrSBe disinhibition score*	NE	7.6(7.5)	9.7 (8.2)	NE	<0.01
	FrSBe executive functions score	NE	25.5 (13.7)	27.2 (9.7)	NE	N.S.
	Wisconsin Card Sorting Test	NE	22.9 (9.6)	22.9 (8.9)	NE	N.S.

*To obtain an index of progression of FrSBe scores, we calculated the actual score subtracting the present score from the previous score

**Significant differences compared to controls.

N.S Differences were not significant.

NE Non assessed

Table 2. VBM differences between DbvFTD>AbvFTD groups in selected ROIs.

Brain region	*X*	*Y*	*Z*	Cluster *k*	Peak *p* (FDR-cor)	Peak *t*	Peak *z*
R Frontal Sup Medial (R Dlpfc)	52,5	9,9	24,3	547	<0.01	283.65	6.67
R Middle Frontal Gyrus (R Dlpfc)	49,4	12,9	17,6	938	0.02	229.31	6.82

R Frontal Sup (R Dlpfc)	62,5	19,9	14,3	699	0.03	244.76	6.00
R Frontal Sup Orb (R Ofc)	39,6	61,2	0,8	449	<0.01	400.52	7.05
R Frontal Mid Orb (R Ofc)	29,6	69,3	0,9	263	<0.01	531.48	6.60
L Anterior Cingulate (L Acc)	-1,8	30,6	24,3	388	0.04	209.10	5.62
L Caudate (L Caud)	-8,1	12,6	-1,5	780	<0.0	380.97	6.45
L Superior Temporal Gyrus (L Stg)	-34,2	9,9	-24,3	377	0.04	191.87	5.22
L Temporal Mid (L Stg)	-37,8	10,8	-24,2	241	0.02	200.87	5.81

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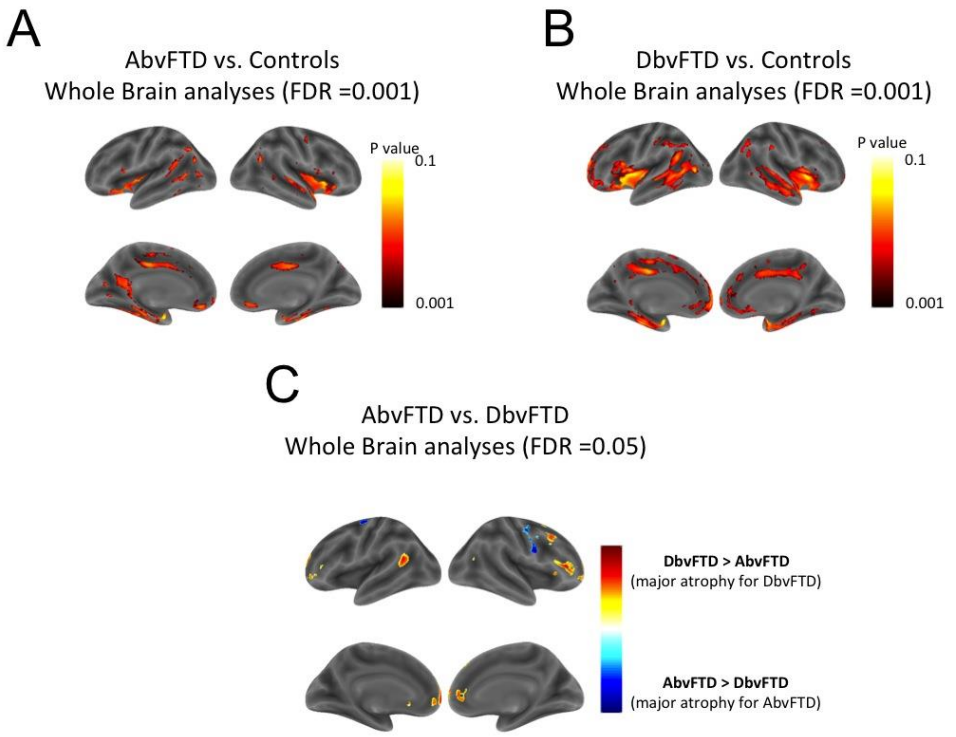
SUPPLEMENTARY DATA:

FIRST SYMPTOMS AND NEUROCOGNITIVE CORRELATES OF BEHAVIORAL VARIANT FRONTOTEMPORAL DEMENTIA

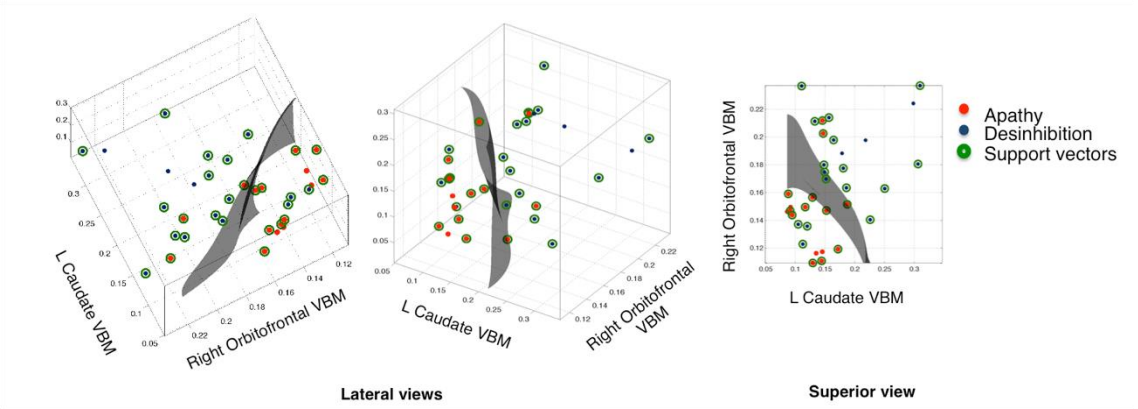
PATIENT DIAGNOSIS AND CHARACTERIZATION

Diagnosis was made by a group of bvFTD experts. Patients underwent a standard examination from an ongoing research protocol[1–3] that included neurological, neuropsychiatric and neuropsychological assessments and a routine MRI. All patients were in the early stages of the disease and did not meet the criteria for specific psychiatric disorders. All patients had mild disease (MMSE ≥ 20) to minimize potential confounding factors related to severe cognitive impairment. Patients presenting primarily with language deficits were excluded. Caregivers reported how and when the initial symptoms of the disease in the patients occurred. Patients presented with prominent changes in personality and social behavior as verified by caregivers.

SUPPLEMENTARY FIGURES

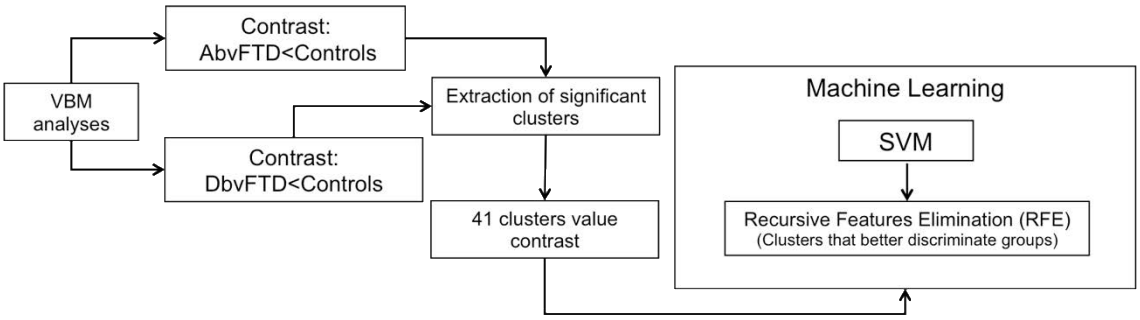


Supplementary Figure 1. Panel A shows the profile of atrophy in the group of patients who debuted with apathy (i.e., AbvFTD). Whole-brain analyses revealed reduced VBM values in DLPFC, OFC, ACC, insular and superior temporal areas, among others. Panel B shows the profile of atrophy in the disinhibition group (i.e., DbvFTD). Whole-brain analyses revealed brain atrophy in the OFC, DLPFC, medial frontal regions, as well as the TPJ, bilateral ACC, and insular areas, among others (see Supplementary Table S1). For both groups of patients, a whole-brain analysis was performed controlling for age, length of disease duration, gender and global brain volume, which was corrected with false discovery rate (FDR) at 0.001. Panel C shows the profile of brain atrophy between AbvFTD vs DbvFTD using whole-brain analyses. Two contrasts are shown: (a) DbvFTD > AbvFTD (areas colored in red) and (b) AbvFTD > DbvFTD (areas colored in blue).



Supplementary Figure 2 Graph shows different sides of a 3D-graph to facilitate the visualization of the

representation of classification using an SVM model with reduced (see Fig 1 Panel E in the main text). Here, presenting the two of better attributes to discriminate groups selected by the SVM model.



Supplementary Figure 3. The graph schematizes the procedure used to select brain areas included in the machine-learning model (SVM), based on results of whole-brain analyses. We selected a group of significant clusters combining results from two contrasts: (a) AbvFTD < controls and (b) DbvFTD < Controls. To determine which clusters discriminate between groups of patients (AbvFTD and DbvFTD), we established a rank based on the Recursive Features Elimination procedure (RFE) (see Methods and Results section in the main text).

SUPPLEMENTARY TABLES

Supplementary Table S-1. VBM results of whole brain atrophy for (A) AbvFTD group (n=18) and (B) DbvFTD group (n=16).

(A) VBM MAIN EFFECT in AbvFTD group (n=18)[*]

Region of Interest ROIs	Coordinates x, y, z {mm}	Cluster size	Peak T	Peak Z
Amygdala Right	-22 -7 -15	3131	10.41	7.24
			7.16	5.73
			6.46	5.34
Putamen Right	27 -6 -15	4281	9.69	6.95
			8.31	6.33
			7.96	6.16
Fusiform Left	-38 -22 -26	192	7.79	6.07
			7.34	5.83
Angular Gyrus Left	-54 -64 24	682	7.65	6
			6.93	5.6
			6.37	5.28
Insula Left	-38 -1 7	281	7.48	5.91
			6.18	5.17
Cingulum Mid Left	-2 3 45	1247	6.92	5.6
			6.66	5.45
			6.64	5.44
		131	6.6	5.42
		116	6.52	5.37
			5.38	4.65
Hippocampus Right	16 -33 1	163	6.48	5.34

			6.27	5.22
Temporal Sup Right	58 -15 -11	482	6.39	5.29
Frontal Med Orb Left	-3 38 -15	334	6.27	5.22
			5.49	4.72
Precuneus Left	-6 -48 9	120	6.19	5.17
			5.44	4.69
Caudate Left	-12 14 4	40	6.17	5.16
Putamen Left	-15 8 13	23	6.15	5.14
Temporal Inf Left	-54 -67 -11	43	6.05	5.09
		19	5.93	5.01
		18	5.88	4.98
Temporal Mid Right	62 -43 7	33	5.81	4.94
		16	5.6	4.8
		20	5.42	4.68
Precuneus Left	-4 -63 12	42	5.28	4.59
Frontal Orb Right	-28 60 3	162	4.9	4.32
Dorsolateral Frontal Right	-2 3 45	3863	6.92	5.6
Dorsolateral Frontal Left	-2 3 45	3863	6.92	5.6

*p < 0.001, FDR corrected α = 0.2;

(B) VBM MAIN EFFECT in DbvFTD group (n=16)*

Region of Interest ROIs	Coordinates x, y, z {mm}	Cluster size	Peak T	Peak Z
Putamen Right	27 -7 -14	59557	11.72	7.53
			10.39	7.07
			9.86	6.86
Temporal Mid Left	-52 -72 10	8947	9.91	6.88
			8.26	6.18
			7.44	5.78
		60	5.89	4.92
SupraMarginal Right	62 -30 42	452	5.38	4.59
			4.84	4.23
			4.07	3.68
Lingual Right	27 -57 -9	391	5.37	4.59
Frontal Sup Orb Right	24 58 -3	400	5.14	4.44
Dorsolateral prefrontal Right	51 39 1	112	4.94	4.3
			4.04	3.65
Precuneus Left	-26 -52 66	126	4.81	4.21
			4.63	4.09
Frontal Sup Right	21 47 25	38	4.71	4.14
			4.1	3.7
Frontal Mid Right	28 30 42	124	4.7	4.14
			3.91	3.55
Precuneus Right	0 -64 46	217	4.58	4.05
			4.53	4.01
			4.09	3.69
Frontal Sup Left	-6 11 60	315	4.54	4.02
Precuneus Left	14 -67 60	159	4.51	4

			4.22	3.79
			4.1	3.7
Frontal Sup Left	-24 26 49	225	4.51	4
Temporal Sup Right	62 -13 9	122	4.5	4
			4.1	3.7
Cuneus Left	-6 -67 21	285	4.47	3.97
			4.16	3.74
		44	4.4	3.92
Temporal Inf Left	45 12 31	82	4.31	3.85
Temporal Pole Sup Left	-24 2 57	48	4.21	3.78
		36	4.17	3.75

*p < 0.001, FDR corrected α = 0.2;

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7.4 Estudio 4: A Lesion Model of Envy and Schadenfreude: Legal, Deservingness and Moral Dimensions as Revealed by Neurodegeneration

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A lesion model of envy and *Schadenfreude*: legal, deservingness and moral dimensions as revealed by neurodegeneration

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The study of moral emotions (i.e. *Schadenfreude* and envy) is critical to understand the ecological complexity of everyday interactions between cognitive, affective, and social cognition processes. Most previous studies in this area have used correlational imaging techniques and framed *Schadenfreude* and envy as unified and monolithic emotional domains. Here, we profit from a relevant neurodegeneration model to disentangle the brain regions engaged in three dimensions of *Schadenfreude* and envy: deservingness, morality, and legality. We tested a group of patients with behavioural variant frontotemporal dementia (bvFTD), patients with Alzheimer's disease, as a contrastive neurodegeneration model, and healthy controls on a novel task highlighting each of these dimensions in scenarios eliciting *Schadenfreude* and envy. Compared with the Alzheimer's disease and control groups, patients with bvFTD obtained significantly higher scores on all dimensions for both emotions. Correlational analyses revealed an association between envy and *Schadenfreude* scores and greater deficits in social cognition, inhibitory control, and behaviour disturbances in bvFTD patients. Brain anatomy findings (restricted to bvFTD and controls) confirmed the partially dissociable nature of the moral emotions' experiences and highlighted the importance of socio-moral brain areas in processing those emotions. In all subjects, an association emerged between *Schadenfreude* and the ventral striatum, and between envy and the anterior cingulate cortex. In addition, the results supported an association between scores for moral and legal transgression and the morphology of areas implicated in emotional appraisal, including the amygdala and the parahippocampus. By contrast, bvFTD patients exhibited a negative association between increased *Schadenfreude* and envy across dimensions and critical regions supporting social-value rewards and social-moral processes (dorsolateral prefrontal cortex, angular gyrus and precuneus). Together, this study provides lesion-based evidence for the multidimensional nature of the emotional experiences of envy and *Schadenfreude*. Our results offer new insights into the mechanisms subsuming complex emotions and moral cognition in neurodegeneration. Moreover, this study presents the exacerbation of envy and *Schadenfreude* as a new potential hallmark of bvFTD that could impact in diagnosis and progression.

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Keywords: dementia; social cognition; brain atrophy; frontotemporal dementia

Abbreviations: ACC = anterior cingulate cortex; bvFTD = behavioural variant frontotemporal dementia; DLPFC = dorsolateral prefrontal cortex; IFS = INECO Frontal Screening; MoCA = Montreal Cognitive Assessment; RMET = Reading the Mind in the Eyes Test; VBM = voxel-based morphometry

Introduction

The emerging cognitive neuroscience of moral emotions, such as *Schadenfreude* (a German word implying pleasure for others' misfortunes) and envy (Takahashi *et al.*, 2009; Jankowski and Takahashi, 2014) have opened a window for comprehending ecological affective processes (Fontenelle *et al.*, 2015). So far, this field has mainly relied on correlational imaging studies, largely neglecting the contributions of the lesion model approach, which helps to reveal direct links between brain regions and fine-grained cognitive functions. Active tasks in neuroimaging and electromagnetic studies provide only indirect evidence of brain-behaviour associations (Linden, 2012). The lesion model (Rorden and Karnath, 2004; Shahid *et al.*, 2017) and, in particular, the neurodegenerative lesion model (Irish *et al.*, 2012; García-Cordero *et al.*, 2016; Melloni *et al.*, 2016; O'Callaghan *et al.*, 2016; Ibanez *et al.*, 2017), reveals the critical areas, which directly relate to performance in a specific domain. Here we profit from this methodological strategy to shed new light on the neural correlates of both emotion types and their key dimensions.

Emotions constitute an adaptive mechanism supporting the regulation of one's own acts and the assessment of others' behaviours (Haidt, 2003; Adolfi *et al.*, 2016). Moral emotions, in particular, seem to be mediated by culturally defined conventions that are critical for group organization and cohesiveness (Haidt, 2003; Tangney *et al.*, 2007). Contrary to basic emotions, these are linked to the welfare of social groups (Moll *et al.*, 2003; Moll and de Oliveira-Souza, 2007), as they encourage or inhibit behaviours depending on their social acceptability (Ortony *et al.*, 1990). Moral emotions seem to modulate how humans assess which behaviours are social and morally acceptable. According to Haidt (2003), moral emotions are shaped under the influence of two factors: elicitors and action tendencies. Elicitors range from the behaviour of others to events affecting them and their evaluations of own actions. As regards social action tendencies, moral emotions are experienced when we are motivated to deploy other-targeted actions, modulating social order and welfare. For Haidt (2003), envy and *Schadenfreude* appear to integrate another category as they involve no pro-social action tendencies (Haidt, 2003). Similar to the self-conscious family of emotions, which arise from a discrepancy between one's ideal self and current self (Ortony *et al.*, 1990), *Schadenfreude* and envy imply a discrepancy between one's current status and the status of another person (Ortony *et al.*, 1990). Thus, social comparison is crucial for describing all types of moral emotions. New approaches in the study of moral emotions have described *Schadenfreude* and envy as counter-empathy (Cikara and Fiske, 2013) or fortune of others' emotions (Shamay-Tsoory *et al.*, 2014).

Schadenfreude (to gloat), refers to the perceiver's experience of pleasure at another's misfortune (van Dijk *et al.*, 2006; Dvash *et al.*, 2010*b*; Jankowski and Takahashi, 2014). Envy, on the other hand, is defined as displeasure associated with another's success. These emotions have been shown to involve a critical interplay between social, moral, and affective processes (Takahashi *et al.*, 2009; Dvash *et al.*, 2010*b*; Jankowski and Takahashi, 2014), highlighting the complexity of their organization. At the neuroanatomical level, *Schadenfreude* has been associated with activity in ventral striatum, as assessed with functional MRI (Takahashi *et al.*, 2009; Cikara and Fiske, 2013; Jankowski and Takahashi, 2014). By contrast, envy has been associated with activation of temporal regions as well as the anterior and medial cingulate cortices (ACC and MCC, respectively) (Takahashi *et al.*, 2009; Cikara and Fiske, 2013; Jankowski and Takahashi, 2014). Despite the above advances, the literature on moral emotions still faces two caveats: the assumption of monolithic conceptions of the constructs and the lack of lesion studies to address the issue.

First, *Schadenfreude* and envy are most often treated as monolithic phenomena (van Dijk *et al.*, 2006; Takahashi *et al.*, 2009). However, research on various other emotion types have revealed partially dissociable dimensions

(Portmann, 2000; Chester *et al.*, 2013). Indeed, *Schadenfreude* or envy can be differently triggered by a broad spectrum of behaviours and affective scenarios (Portmann, 2000). Previous studies have shown that envy and *Schadenfreude* have different modulators, including (i) the inferred desirability of an outcome for a target (Haidt, 2003; Tangney *et al.*, 2007; Takahashi *et al.*, 2009; Jankowski and Takahashi, 2014); (ii) target likeability (Haidt, 2003; Tangney *et al.*, 2007; Takahashi *et al.*, 2009; Jankowski and Takahashi, 2014); (iii) inferred target deservedness (Feather and Sherman, 2002; van Dijk *et al.*, 2005; Smith and Kim, 2007; Dvash *et al.*, 2010*a*; Chester *et al.*, 2013; Ben-Ze'ev, 2014; van Dijk and Ouwerkerk, 2014; Zaki *et al.*, 2015); and (iv) subject's perception of justice and fairness in others' outcomes (Feather and Sherman, 2002; Smith, 2009; Dvash *et al.*, 2010*a*; Jankowski and Takahashi, 2014; Shamay-Tsoory *et al.*, 2014; van Dijk and Ouwerkerk, 2014; Yoder and Decety, 2014; Najle, 2015; Portmann, 2017). The situations used to trigger envy and *Schadenfreude* in our study are in part supported by some of these factors. In particular, deservingness situations trigger moral emotions with modulating factors such as target likeability and inferred target deservedness. In contrast, moral and legal situations evoke envy and *Schadenfreude* by modifying the subjects' perception of justice and fairness in outcomes reached by a receptor.

Deservingness, morality, and legality concepts are all intertwined notions able to modulate experiences of *Schadenfreude* (van Dijk and Ouwerkerk, 2014) and envy (Smith and Kim, 2007; Chester *et al.*, 2013). Considering that these emotions respond to the disagreement between one's current situation and that of another person, different sources and modulators can be identified for these emotions, including deduced target deservedness (Feather and Sherman, 2002; van Dijk *et al.*, 2005; Smith and Kim, 2007; Dvash *et al.*, 2010*a*; Chester *et al.*, 2013; Ben-Ze'ev, 2014; van Dijk and Ouwerkerk, 2014; Zaki *et al.*, 2015) and the perception of fairness in others' outcomes (Feather and Sherman, 2002; Smith, 2009; Dvash *et al.*, 2010*a*; Jankowski and Takahashi, 2014; Shamay-Tsoory *et al.*, 2014; van Dijk and Ouwerkerk, 2014; Yoder and Decety, 2014; Najle, 2015; Portmann, 2017). Along these lines, different approaches ranging from social psychology (Ortony *et al.*, 1990; Portmann, 2002; Ben-Ze'ev, 2014), to sociology (Plutchik, 1980; Fiske, 1992) and philosophy (de Spinoza, 1883) and, more recently, research in the field of social cognitive neuroscience (van Dijk *et al.*, 2005; Takahashi *et al.*, 2009; Dvash *et al.*, 2010*a*; Chester *et al.*, 2013; Cikara and Fiske, 2013; Fiske and Taylor, 2013), indicate that *Schadenfreude* and envy are complex and non-unified emotional experiences modulated by different factors, including the interplay between high and low order affective and cognitive mechanisms (Chester *et al.*, 2013; Jankowski and Takahashi, 2014).

Also, building on Schopenhauer's (1788–1860) account of *Schadenfreude* as a most obscure expression of human emotionality, this emotion can be considered to possess a component of maliciousness, even if the outcome is deserved. However, *Schadenfreude* may also rely on notions of justice (van Dijk *et al.*, 2006; Ben-Ze'ev, 2014), and moral or legal analyses can exonerate the pleasure experienced in presence of others' misfortunes. Enjoying the misfortune of someone who has violated a legal code or moral norm may be considered as a well-intentioned emotion, as it would reflect a reaction to fairness (van Dijk *et al.*, 2006; Ben-Ze'ev, 2014). Although both situations involve *Schadenfreude*, they clearly differ in their affective implications. Likewise, previous studies suggest that envy can be elicited either when someone gets an undeserved outcome or when someone is rewarded despite moral or legal transgressions (Portmann, 2000; Ben-Ze'ev, 2014; van Dijk and Ouwerkerk, 2014).

From a neurobiological perspective, abundant evidence indicates that morality is not a wholly unified faculty, but a collection of dissociable neurocognitive processes depending on the type of transgression being judged (Parkinson *et al.*, 2011; Hayashi *et al.*, 2014; Sinnott-Armstrong, 2016). Although different moral situations can share some neurocognitive mechanisms, they also exhibit dissociable neural pathways. For instance, processing of different moral situations, including disgust and moral transgressions, share neurocognitive processes as all of them are related to activity of the ACC, the medial prefrontal cortex, and the temporoparietal junction. However, these situations also have dissociable neural activations, as moral transgressions are more related to activity of the amygdala and the parahippocampus, whereas disgust is more associated to the activity of the posterior cingulate cortex and the dorsolateral prefrontal cortex (Parkinson *et al.*, 2011; Hayashi *et al.*, 2014; Sinnott-Armstrong, 2016). Our study aims to delve deeper into perspective by analysing the emotional responses associated with envy and *Schadenfreude* as dissociable experiences rather than as unified, monolithic constructs. We use the term 'monolithic' to refer to different situations than can elicit a same emotional response. For instance, although all dimensions of moral emotions can elicit pleasure or displeasure, each of them is typical of different situations (moral, legal or deservedness). This approach could offer new options in the study of envy and *Schadenfreude* by providing evidence on how they can be modulated by situations that differ in their nature.

Thus, at least three distinct dimensions of *Schadenfreude* and envy can be identified as more or less prominent depending on the situation: deservingness (the degree to which an actor deserves the outcome he experienced), morality (the degree to which an actor gets a different outcome than he/she could expected involving a moral precept violation), and legality (the degree to which an actor gets a different outcome than he/she could expected involving a legal precept violation). While each of these dimensions involves different cognitive and affective foundations and may thus rely on partially different neural mechanisms, such fine-grained associations have not yet been assessed.

Against this background, we conducted the first lesion-model study on the correlates of these dimensions for both *Schadenfreude* and envy. Specifically, we focused on the behavioural variant of frontotemporal dementia (bvFTD), a relevant neurodegenerative lesion model featuring selective atrophy of the main pathways associated with envy (the ACC and temporal areas) and *Schadenfreude* (the fronto-striatal network). This complex clinical syndrome is characterized by social cognition deficits and marked behavioural changes that impair social interaction (Piguet *et al.*, 2011; Ibañez and Manes, 2012; Seeley *et al.*, 2012; Ibanez *et al.*, 2014, 2017). More particularly, bvFTD have been associated with alterations in social and moral cognition, including reduced empathic concern for others' suffering (Eslinger *et al.*, 2011*a*; Baez *et al.*, 2014*c*, 2016*b*; Melloni *et al.*, 2014), diminished prosocial sentiments (Moll *et al.*, 2011), and reduced long-term cooperative behaviours (Melloni *et al.*, 2016; Ibanez *et al.*, 2017). Furthermore, patients with bvFTD show altered moral judgements, displaying more utilitarian judgements in the face of moral dilemmas (Baez *et al.*, 2014*a*, 2016*a*). A similar pattern has been also observed in extreme criminal terrorists (Baez *et al.*, 2017*b*). Finally, these patients have been shown to display increased antisocial and criminal behaviour (de Oliveira-Souza *et al.*, 2008; Liljegren *et al.*, 2015), as well as a relatively high incidence of legal violations (Mendez, 2010). In sum, bvFTD offers a relevant lesion model to assess the specific neural correlates of the different dimensions operative in the experience of *Schadenfreude* and envy.

To this end, we created a novel task tapping the dimensions of deservingness, morality, and legality in moral emotions, and administered it to patients with bvFTD, matched healthy controls, and patients with early stage Alzheimer's disease—another form of dementia offering a contrastive neurodegenerative model. Our task features situations whose characters are involved in fortunate and unfortunate events evoking envy and *Schadenfreude*, respectively. Crucially, each emotion type involved a subset of scenarios dominated by feelings of deservingness, morality, or legality. In addition, neutral situations were added to test task comprehension and attentional engagement.

We propose two sets of hypotheses at behavioural and neurocognitive levels. First, we expected a specific pattern of responses regarding the dimensions of moral emotions. Previous studies have shown that situations where justice notions are disrupted (and which feature severe violations of social codes) involve increased discomfort and heightened emotional responses (Tangney *et al.*, 2007; Yoder and Decety, 2014). Thus, for *Schadenfreude* and envy, healthy controls can be expected to show more emotional responses in situations with prominent moral and legal components compared to deservingness situations. Second, given that patients with bvFTD present disruptions of social skills, moral cognition, disinhibited behaviours, and altered affective states, they were expected to experience exacerbated degrees of envy and *Schadenfreude* relative to the other two groups. Also, since these patients usually exhibit low sensitivity to follow moral and legal codes (Mendez *et al.*, 2005; Mendez, 2010; Baez *et al.*, 2014*a*, 2016*a*), and usually present counter-empathy behaviours (Moll *et al.*, 2011), we expected bvFTD patients to exhibit higher scores across all dimensions (deservingness, moral or legal) in both emotion types. Thus, in those patients, a general (non-selective) increase of emotional responses can be predicted, irrespective of whether they are elicited by deservingness or moral-legal scenarios. Regarding neuroanatomy (assessed with voxel-based morphometry, VBM), we expected to find differential pathways implicated in *Schadenfreude* (striatum) and envy (ACC). In bvFTD patients, atrophy of frontotemporal regions subserving social cognition, cognitive control, and behavioural regulation (Ibañez and Manes, 2012; Seeley *et al.*, 2012; Sedeno *et al.*, 2017) should be associated with enhanced experiences of both emotion types. Furthermore, atrophy of regions involved in judging third-party and personal moral and legal situations (Buckholtz *et al.*, 2008), such as the ACC and angular gyrus, which are impaired in bvFTD and associated with moral deficits and illegal behaviour in this condition (Mendez, 2010; Baez *et al.*, 2016*b*), should also be associated with envy.

Materials and methods

Participants

We recruited 64 participants from an ongoing protocol (Couto *et al.*, 2013; Baez *et al.*, 2014*c*, 2016*a*, 2017*c*; García-Cordero *et al.*, 2016; Melloni *et al.*, 2016; Santamaria-Garcia *et al.*, 2016; Sedeno *et al.*, 2016), namely, 20 patients that met revised criteria for probable bvFTD (Rascovsky *et al.*, 2011), 24 patients diagnosed with early onset Alzheimer's disease (McKhann *et al.*, 2011), and 20 healthy control subjects. All patients were assessed by a multidisciplinary group of experts, including two neurologists (A.L., C.H.C.), three psychiatrists (J.M.S., G.O., H.S.), and two geriatricians (J.F.M., S.H.). Groups did not differ significantly in terms of age, gender, or years of education (Table 1). Patients and controls were included if they had no history of major neurological or psychiatric illnesses (other than bvFTD or Alzheimer's disease, in the case of patients) or alcohol/drug abuse. Patients and healthy controls were included in the study if they had no general language deficits, including semantic and comprehension alterations (see additional test below). All participants provided written informed consent in agreement with the Declaration of Helsinki. The study was approved by the Institution's Ethics and Research Committee.

Neuropsychological tests

General cognitive state

Participants' general cognitive state was assessed with the Montreal Cognitive Assessment (MOCA) (Nasreddine *et al.*, 2005), and their executive skills were evaluated with a frontal battery including the INECO Frontal Screening (IFS) test

Table 1 Demographic and neuropsychological data for all three groups

	Controls ($n = 20$)	BvFTD ($n = 20$)	Alzheimer's disease ($n = 24$)	*P*-value	*P*-value
	Mean /SD	Mean /SD	Mean /SD	Controls versus bvFTD	BvFTD versus Alzheimer's disease
Demographics					
Age (years)	61.1 (7.98)	58.9 (6.35)	63.1 (5.64)	N.S.	N.S.
Gender (F:M)	11:9	9:11	13:11	N.S.	N.S.
Education (years)	13.32 (4.9)	14.81 (4.3)	13.88 (5.6)	N.S.	N.S.
Years since disease onset	NA	3.1 (2.2)	3.9 (1.9)	NA	N.S.
MMSE	27.4 (2.1)	21.6 (4.5)**	20.7 (4.8)**	<0.01	N.S.
General cognitive assessment					
MoCA	26.2 (3.1)	19.2 (6.7)**	22.1 (6.1)**	<0.01	N.S.
Total IFS score	24.2 (2.9)	16.9 (5.4)	19.1 (5.9)	N.S	N.S.
Inhibitory cognitive control measure					
Hayling test	9.4 (2.1)	16.4 (2.8)	14.8 (3.1)	<0.01	<0.05
Behavioural changes					
FrSBE (Frontal System Behavioural Scale) total*	NA	48.4 (31.1)	37.9 (27.7)	NA	<0.01
Social cognitive measure					
RMET	0.88(0.10)	0.51 (0.16)**	0.69 (0.12)**	<0.01	<0.05

*To obtain an index of progression of Frontal System Behavioural Scale (FrSBE) scores, we subtracted the present score from the previous score.
**Differences compared to controls.
N.S = differences were not significant; NA = not assessed.

(Torralva *et al.*, 2009). The IFS is a 30-point scale that has been shown to successfully detect executive dysfunction in patients with neurological and psychiatric diseases (Torralva *et al.*, 2009; Baez *et al.*, 2014*b*). This test includes the following eight subtests: (i) motor programming (Luria series, 'fist, edge, palm'); (ii) conflicting instructions (hitting the table once when the administrator hits it twice, or hitting it twice when the administrator hits it only once); (iii) motor inhibitory control; (iv) numerical working memory (backward digit span); (v) verbal working memory (months backwards); (vi) spatial working memory (modified Corsi tapping test); (vii) abstraction capacity (inferring the meaning of proverbs); and (viii) verbal inhibitory control (modified Hayling test).

As a complementary measure of inhibitory control, we used the complete version of the Hayling test (Perez-Perez *et al.*, 2016). This scale tracks response initiation and response suppression (Hornberger *et al.*, 2010; Perez-Perez *et al.*, 2016) and has been largely used to assess disinhibition in patients with neurodegenerative diseases (Torralva *et al.*, 2009; Hornberger *et al.*, 2010). Higher scores on the Hayling test are thought to reflect difficulties in inhibitory control (Torralva *et al.*, 2009; Hornberger *et al.*, 2010).

Neuropsychiatric manifestations, including apathy and disinhibition, were assessed with the subjective subscales of apathy, executive functions, and disinhibition of the Frontal System Behavioural Scale, which tracks the degree of behavioural changes since disease onset (Carvalho *et al.*, 2013) and is usually reported as the percentage of changes of behavioural disturbances between free stages of disease and current stages (Carvalho *et al.*, 2013; Santamaria-Garcia *et al.*, 2016).

Theory of mind skills were assessed with the Reading the Mind in the Eyes Test (RMET) (Baron-Cohen *et al.*, 1997), which is also sensitive for the assessment of bvFTD and patients with Alzheimer's disease (Gregory *et al.*, 2002; Couto *et al.*, 2013; Baez *et al.*, 2014*a*). This is a computerized and validated test consisting of 36 pictures of the eye region of a face. Participants are asked to choose which of four words best describes what the person in each photograph is thinking or feeling.

Language assessment

Language subscale in the Montreal Cognitive Assessment

We analysed the scores in the language subscale from the MoCA to assess general language performance among the groups. This subscale has a maximum possible score of 3 points out of a total of 30 in the MoCA. Results of this task revealed non-significant differences between groups [$F(2,82) = 1.76$, $P = 0.11$]. Mean values of the ratings for this subscale were 2 [standard deviation (SD) = 0.8] for bvFTD patients, 2.3 (SD = 0.6) for patients with Alzheimer's disease, and 2.6 (SD = 0.4) for healthy controls.

Picture naming task

To rule out semantic deficits, we administered a well-established picture-naming task (Snodgrass and Feenan, 1990; Sanfeliu and Fernandez, 1996) based on 60 black-and-white pictures depicting three categories of living things (animals, birds, and fruit) and three categories of artefacts (household items, tools, and vehicles). Subjects were required to name with a single spoken word a picture included in an array of other pictures within a same category. Results of this task revealed non-significant differences between groups [$F(2,82) = 2.16$, $P = 0.09$]. Mean values of the ratings for picture naming test in bvFTD group, Alzheimer's disease group and healthy controls were 53.7 (SD = 5.6), 56.4 (SD = 4.7), and 58.8 (SD = 2.8), respectively.

Experimental task

For the current study we created a novel task based on previous studies from our own group and others (Takahashi *et al.*, 2009; Baez *et al.*, 2016*c*, 2017*d*). We designed 40 situations to evoke different types of pleasant (*Schadenfreude*, $n = 15$) or unpleasant (envy, $n = 15$) emotional experiences, as well as emotionally neutral scenarios ($n = 10$) for control purposes. The situations eliciting each emotion type included five scenarios dominated by deservingness, five dominated by morality, and five dominated by legality. For *Schadenfreude*, we used situations that evoke pleasure due to feelings of deservingness (e.g. a liar is excluded from his or her group of friends), morality (e.g. a subject is found guilty and punished for faking a physical disability), and legality (e.g. a subject is punished for not paying for public transportation). Moreover, we included five neutral situations (e.g. a person turns on the light in the house when it gets dark). Likewise, for envy, we created situations evoking displeasure related to feelings of deservingness (e.g. a young man got a better test score for being the son of a professor), morality (e.g. someone avoids waiting at the bank by simulating a physical disability), and legality (e.g. a politician takes a vacation using taxpayers' money). As for the *Schadenfreude* situations, we also included five neutral situations for the envy condition.

Situations associated with each dimension in each type of emotion were validated through a survey completed by 81 subjects (39 females), with a mean age of 39 years, (SD = 4), and an average of 12.6 years of education (SD = 2.2). In this validation study, participants scored a group of deservingness situations, a group of moral situations, and a group of legal situations according to their degree of deservedness, morality, and legality. Results confirmed that each group of situations effectively tracked the expected dimension for each moral emotion (*Schadenfreude* and envy). The deservingness situations obtained the highest deservingness scores, the moral situations obtained the highest moral content scores, and the legal situations obtained the highest legality scores (Fig. 1 and Supplementary material).

In addition, an additional group of 39 extra subjects (details in the Supplementary material) validated the emotional profile of the situations of each dimension in each type of emotion (*Schadenfreude* and envy). Participants rated deservingness, moral, and legal situations according to their capacity to evoke different emotions. Mainly, we assessed the degree in which situations were able to evoke envy and *Schadenfreude* emotions, but also, as a control measure, we assessed to what extent the situations evoked other socio-moral emotions, such as pride and guilt. Thus, for *Schadenfreude*, the participants were required to score the situations according to how intensely they evoked (i) pleasure; (ii) *Schadenfreude* (as Spanish lacks a single word to name this experience, we translated it as: '*La satisfacción por lo que le ha ocurrido al sujeto de la situación*'; in English: 'How much satisfaction do you feel for the protagonist's outcome'); and (iii) pride. The participants also rated the envy situations in terms of how much these situations evoked (i) displeasure; (ii) envy; and (iii) guilt. Both pride and guilt emotions were used as control socio-moral emotions (Jankowski and Takahashi, 2014). Results confirmed that each group of situations effectively tracked the expected emotion (*Schadenfreude*/envy). Although the situations also evoked other socio-moral emotions, such as pride/guilt, the scores for those emotions were significantly lower than for envy/*Schadenfreude* and for more general emotional responses, namely displeasure/pleasure (Supplementary material and Supplementary Fig. 1).

Task procedure

First, each participant was shown a real-life photograph and a description of two target characters matched to the participant in age and gender (based on data obtained in a brief interview before the task). The situations for each type of emotion occurred to the character presented before each block. Based on the results from the validation study, situations were organized in two blocks. In the first block (envy), participants evaluated situations that evoked dimensions of envy and, in the second block, they evaluated situations that evoked dimensions of *Schadenfreude*. Envy situations were presented first, in line with previous evidence suggesting that the degree of envy predicts *Schadenfreude* responses (Takahashi *et al.*, 2009; Jankowski and Takahashi, 2014). In each block, participants read five situations for each dimension. Within each block, we also included five situations describing five neutral events (e.g. a person washes clothes on weekends). Situations in each block were presented in pseudorandomized order.

Each situation was presented for 3 s. After reading each situation, participants reported the intensity of their 'displeasure' (for the envy block) or 'pleasure' (for the *Schadenfreude* block) regarding the character's situation. This stage lasted ~3 s (Fig. 2). All participants provided their responses using 9-point Likert scales, with 1 meaning 'low emotional intensity' and 9 meaning 'high emotional intensity'. In line with previous research on empathy and moral processing (Baez *et al.*, 2014*a*, *c*, 2016*c*; Patil and Silani, 2014; Carr *et al.*, 2015), the scales were always accompanied by simple words indicating low and high pleasure/unpleasantness, thus minimizing memory-related confounds while reducing attentional demands and improving comprehension. This procedure has been reported in multiple neuropsychiatric conditions (Brown and Cohen, 2010; Ibanez *et al.*, 2012; Baez *et al.*, 2015, 2016*a*, *c*), including neurodegenerative diseases such as bvFTD (Zamboni *et al.*, 2010; Eslinger *et al.*, 2012; Cohen *et al.*, 2016) and patients with Alzheimer's disease (Lai *et al.*, 2008; Tsoucalas *et al.*, 2015).

In our task, participants were asked to report their *Schadenfreude* and envy in terms of pleasure/displeasure given that these are the main overarching states elicited by each of those emotions. Previous studies have defined envy as: 'an *unpleasant*, often painful emotion characterized by feelings of inferiority, hostility, and resentment caused by an awareness of a desired attribute by another person or group of persons' (van Dijk *et al.*, 2006; Smith and Kim, 2007; Smith, 2009; Takahashi *et al.*, 2009; Dvash *et al.*, 2010*b*; Jankowski and Takahashi, 2014). Also, *Schadenfreude* has been formally defined as the pleasure derived from the misfortune of others, involving 'the expression of pleasure or self-satisfaction at another's failure' (van Dijk *et al.*, 2006; Dvash *et al.*, 2010*b*; Jankowski and Takahashi, 2014). Thus, we have used the terms 'pleasure' and 'displeasure' highlighting the critical emotional responses elicited by specific scenarios of envy and *Schadenfreude*. Also, explicit manifestations of envy and *Schadenfreude* are socially penalized (van Dijk *et al.*, 2006; Dvash *et al.*, 2010*b*; Jankowski and Takahashi, 2014) and,

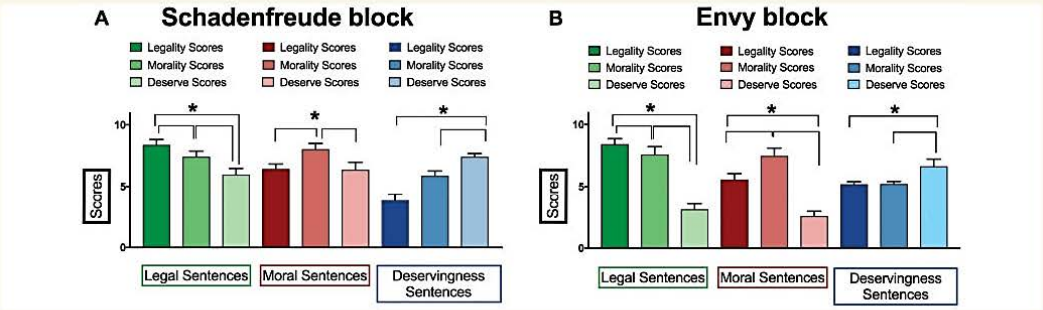

Figure 1 Scores for deservingness, morality, and legality for each group of situations (deservingness, moral, and legal) of each moral emotion (envy and *Schadenfreude*). Situations dominated by deservingness, morality, and legality are identified in green, red, and blue, respectively. (**A**) Scores for the *Schadenfreude* block; (**B**) scores for the envy block.

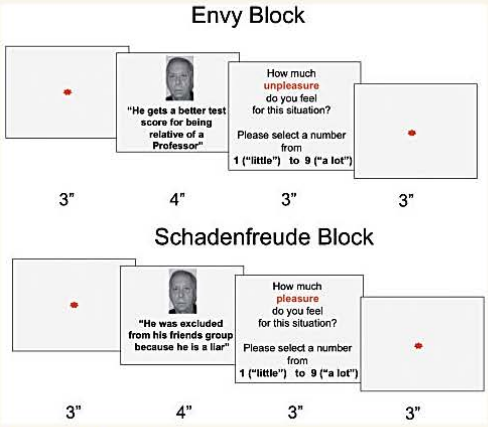

Figure 2 General task procedure. The *upper* panel shows a trial in the envy block and the bottom panel shows a trial in the *Schadenfreude* block. Participants first took part in the envy block and then performed the *Schadenfreude* block. In each block, participants read five situations (each lasting 3 s) in each dimension including a group of five neutral situations. In total, participants read 20 situations from each block, which were presented in randomized order. Next, participants reported the intensity of their 'displeasure' (for the envy block) or their 'pleasure' (for the *Schadenfreude* block) regarding the character's situation using a 9-point Likert scale with 1 meaning low, and 9 meaning high intensities.

hence, subjects might report lower levels of these emotions due to social desirability. Thus, our procedure circumvents such biases by avoiding explicit questions to explore social situations and inquiring into pleasure/displeasure, in line with previous methodological recommendations for exploring social and affective cognitive processes (Berkman *et al.*, 2014). In fact, asking about levels of pleasure/displeasure is the standard procedure reported in previous studies of envy and *Schadenfreude* (Takahashi *et al.*, 2009; Baez *et al.*, 2016*c*, 2017*d*). We have adopted this design to make our results comparable with those of previous relevant literature. Note, also, that the terms 'pleasure' and 'displeasure' are easier to understand and thus more reliable than 'envy' and '*Schadenfreude*' as verbally cued measures. This is of critical relevance when assessing patients with such disorders as bvFTD and Alzheimer's disease.

Task comprehension assessment

Before the emotion task, bvFTD and Alzheimer's disease patients performed a pilot study involving situations with positive, negative, and neutral outcomes affecting a third person. Patients were asked to determine the type of valence (fortunate versus unfortunate) of each situation, which allowed us to assess general comprehension of situations while discarding potentially random response patterns. Relative to neutral situations, positive and negative situations were assigned higher and lower scores by both patient samples. These results suggest that patients discriminated the emotional valence of each situation type, showing that their performance was not biased by general comprehension difficulties (for details, see Supplementary material).

Data analysis

Demographic and cognitive state data were compared among groups using ANOVA and Tukey's honest significant difference *post hoc* tests. Chi square tests were applied to analyse categorical variables. Differences between types of emotion (envy, *Schadenfreude*, neutral) in each group (bvFTD patients, Alzheimer's disease patients, healthy controls) were first analysed using a 3 × 3 mixed repeated measures ANOVA. If any interaction among types of emotion and group was found, a second level of analysis was implemented for each emotion separately (*Schadenfreude*, envy, and neutral) and subsequently analysed with a one-way ANOVA using dimension (deservingness, morality, legality) as the within-subject factor and group (bvFTD patients, Alzheimer's disease patients, healthy controls) as the between-subjects factor. To control for the effect of general cognitive status on the experimental tasks, we applied ANCOVA tests independently adjusted for

total scores on the MoCA and the IFS batteries. In addition, we ran extra analyses controlling results on the experimental task for inhibitory control and theory of mind measures (Hayling test and RMET, respectively). As in other reports of neurodegenerative conditions from our group (Baez *et al.*, 2014*c*; García-Cordero *et al.*, 2016), we report only those effects that remained significant following covariation. Tukey's HSD *post hoc* tests were used when appropriate. Effect sizes were calculated through the partial eta squared (η^2) ratio.

Moreover, correlation analyses were used to explore the relationship between individual differences in disease presentation (regarding inhibitory control, theory of mind, and behavioural changes) and moral emotions (envy and *Schadenfreude*) in each group (bvFTD, Alzheimer's disease, healthy controls). A global score of envy (mean of deservingness, morality, and legality dimensions) and a global score of *Schadenfreude* were created to facilitate the analysis of the relationship between each moral emotion and the cognitive-behavioural measures. We also conducted correlational analyses with the scores for each dimension of both moral emotions.

Imaging recordings and voxel-based morphometry

Recordings were restricted to bvFTD and healthy control groups. Structural brain images were obtained using a Philips Achieva 3T scanner with a 16-channel SENSE antenna. The anatomical and 3D T_1-weighted images had the following parameters: repetition time = 7.9 ms, echo time = 3.8 ms, ACQ matrix 220 × 220 pixels, voxel size 0.5 × 0.5 × 0.5 mm, 310 sections. Neuroanatomical correlates were analysed using VBM (Ashburner and Friston, 2000). Data processing and analysis were performed with VBM8 on the Statistical Parametric Mapping 8 package (SPM8; Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm), running under Matlab 2012 (MATLAB and Statistics Toolbox Release 2012b, The MathWorks, Inc., Natick, MA, USA). All imaging analysis steps were conducted as described in the VBM pipeline (http://www.fil.ion.ucl.ac.uk/~john/misc/VBM), as follows. The T_1-weighted images were normalized to the same stereotaxic space generated from the complete dataset using the DARTEL algorithm, which significantly reduces the imprecision of inter-subject recordings. The images were then segmented into white matter, and grey matter, and non-brain voxels (CSF). Subsequently, all images were modulated to correct volume changes by Jacobian determinants. Finally, images were smoothed by convolution with an isotropic 8-mm full-width Gaussian kernel at half maximum for statistical analyses.

First, we performed a whole-brain analysis using VBM to assess differences in brain atrophy between the group of patients with bvFTD and healthy controls (controlling for global intracranial volume, age, gender, and length of disease duration) (Supplementary Fig. 2). The statistical threshold for whole-brain analysis was defined as $P < 0.001$ (extent threshold = 50 voxels). In addition, to investigate potential, the association between brain areas and moral emotions, we performed a more restrictive analysis using a mask including the brain regions significantly associated with socio-moral cognitive processes and moral emotions (*Schadenfreude* and envy) (Supplementary Fig. 3). Then, using this mask, we performed multiple regression analyses for each group using topological false discovery rate (FDR) for correction, at a threshold of $P < 0.05$ (Figs 5 and 6). The topological FDR was used following previous studies that suggest that this procedure is more sensitive than voxel-wise FDR (Chumbley *et al.*, 2010).

In assessing regions of atrophy as predictors of group performance in the experimental task, and following previous studies (Couto *et al.*, 2013; Baez *et al.*, 2016*a*), we restricted the data's multidimensionality using an extended mask that included the brain areas reported to be involved in social-moral cognition and moral emotions. The group of brain areas composing the mask was corroborated using the Neurosynth database (http://www.neurosynth.org). This meta-analytic database aggregates activation from thousands of previous functional MRI studies (Yarkoni *et al.*, 2011). This technique has been used to define main brain areas related to cognitive processes even in studies using imaging methods, including VBM (Vendetti and Bunge, 2014; Fermin *et al.*, 2016; Allen *et al.*, 2017). In Neurosynth online system we introduced as keywords: 'moral' and 'social cognition'. Afterwards, we downloaded the mask for both terms and integrated the brain areas selected in a single unified mask. This mask, following the Neurosynth database, includes a default correction for brain multiple comparisons using a FDR criterion of $P = 0.01$. In addition, we included basal ganglia in this mask considering its role in processing moral emotions, in particular *Shadenfreude* (Takahashi *et al.*, 2009). Furthermore, we also included bilateral frontal lobe as these brain areas are involved in inhibitory control (Collette *et al.*, 2001; Nathaniel-James and Frith, 2002; Roca *et al.*, 2010; Volle *et al.*, 2011) and are related to regulation of moral emotions (Koechlin, 2011; Rudebeck *et al.*, 2013). Therefore, we used an extended and unified mask including brain areas derived of two Neurosynth keywords (moral and social cognition), the basal ganglia, and frontal lobes. The final unified mask was smoothed with a standard $\sigma = 4$ mm isotropic Gaussian kernel (corresponding to full-width at half-maximum = 9.4 mm) following a procedure used in previous studies (Radua *et al.*, 2014; Scarpazza *et al.*, 2015).

In this study we used a mask that includes the ventromedial prefrontal cortex (VMPFC), the dorsolateral prefrontal cortex (DLPFC), the cingulate cortex (the anterior and posterior portions), the bilateral insula, the temporal lobes, bilateral angular gyrus, the superior and medial temporal gyri, the precuneus, the amygdala, the hippocampus, and the parahippocampus (socio-moral areas) (Moll *et al.*, 2008; Pievani *et al.*, 2011; Bzdok *et al.*, 2012; Ibañez and Manes, 2012; Chiong *et al.*, 2013; Baez *et al.*, 2016*a*; Santamaria-Garcia *et al.*, 2016; Sedeno *et al.*, 2016), areas involved in inhibitory control (in particular the frontal lobe) (Collette *et al.*, 2001; Nathaniel-James and Frith, 2002; Roca *et al.*, 2010; Eslinger *et al.*, 2011*b*; Volle *et al.*, 2011), and regions involved in moral emotions, including the anterior cingulate cortex and the ventral and dorsal striatum (Takahashi *et al.*, 2009; Dvash *et al.*, 2010*a*; Jankowski and Takahashi, 2014; Shamay-Tsoory *et al.*, 2014; van Dijk and Ouwerkerk, 2014; Baez *et al.*, 2016*c*, 2017*d*) (Supplementary Fig. 3). Considering that the different dimensions of *Schadenfreude* and envy (deservingness, moral and legal) could encompass different complex cognitive-affective and social constructs, we also analysed the brain-behaviour correlations using a whole-brain analysis to reveal other brain areas involved in processing specific dimensions of moral emotions (Supplementary Fig. 4).

Brain–behaviour associations

To detect distinctive neurocognitive correlates of moral emotions, we performed a two-step analysis based on regression models between moral emotion measures and brain volume. The VBM regression models were run for of each dimension of moral emotions independently. This procedure was applied to analyse which brain areas were exclusively associated to each dimension and which areas exhibited overlap between dimensions. We did not run all variables together in order to avoid collinearity.

First, both bvFTD patients and controls were included in a single set (all subjects) to increase behavioural variance and statistical power (Sollberger *et al.*, 2009; Irish *et al.*, 2014*a*; O'Callaghan *et al.*, 2016). This procedure has been also previously reported in studies exploring the structural correlates of social cognition in bvFTD (Melloni *et al.*, 2016; Sedeno *et al.*, 2016). In a second stage, aimed to assess the specific association between brain atrophy and potentially abnormal moral emotion performance, we conducted the same analysis only on bvFTD patients. Thus, we compared VBM findings first in a grouped set (all subjects) and later in the bvFTD group only. This two-step procedure addresses two critical requisites of the present study. First, as shown by previous studies (Irish *et al.*, 2012, 2014*b*; Kumfor *et al.*, 2013; Melloni *et al.*, 2016), the report of combined results between patients and healthy controls aims to tackle individual differences in VBM analyses while improving statistical power by increasing sample size, stability of VBM results, and consistency of the anatomical correlates of the cognitive measure analysed. Second, the study of a cognitive measure exclusively in bvFTD allows exploring which areas are critical for a particular cognitive process (Rorden and Karnath, 2004; García-Cordero *et al.*, 2016; Melloni *et al.*, 2016; Shahid *et al.*, 2017).

Results

General cognitive state and performance on cognitive control, behavioural, and social cognition measures

As expected, bvFTD patients were outperformed by controls on the IFS and the MoCA tests, but they did not differ significantly from patients with Alzheimer's disease (Table 1). BvFTD patients also obtained significantly lower scores than both other groups on the inhibitory control measure (Hayling B, Table 1). Furthermore, the Frontal System Behavioural Scale revealed that patients with bvFTD had significantly greater behavioural impairments than patients with Alzheimer's disease (Table 1). Finally, patients with bvFTD were also significantly more impaired than the other two groups on a social cognition measure (RMET), while patients with Alzheimer's disease performed worse than healthy controls (Table 1).

Moral emotions

An ANOVA between type of emotion (envy, *Schadenfreude*, neutral) and group (bvFTD, Alzheimer's disease, healthy controls) revealed a main effect of type of emotion [$F(2,82) = 43.51$, $P < 0.0001$, $\eta^2 = 0.43$]. In all groups, *Schadenfreude* ($P < 0.01$) and envy ($P < 0.01$) situations were given higher scores than neutral situations. Also, we observed an interaction of group × type of emotion [$F(4,82) = 13.51$, $P < 0.001$, $\eta^2 = 0.19$]. This result allowed us to perform additional ANOVAs over each emotion type.

Schadenfreude

The ANOVA showed a main effect of dimension [$F(2,82) = 14.53$, $P < 0.001$, $\eta^2 = 0.13$], as deservingness showed lower scores than morality and legality. In addition analyses showed an interaction between dimension and group [$F(4,82) = 12.28$, $P < 0.01$, $\eta^2 = 0.22$]. *Post hoc* analyses (Tukey HSD, mean square = 12.5, $df = 2$) revealed higher scores across all three dimensions of *Schadenfreude* in bvFTD patients (Fig. 3A) than in patients with Alzheimer's disease (deservingness, $P = 0.001$; morality, $P = 0.03$; legality, $P = 0.004$) and healthy controls (deservingness, $P = 0.04$; morality, $P = 0.04$; legality, $P = 0.05$). No differences were observed between patients with Alzheimer's disease and healthy controls (deservingness, $P = 0.31$; morality, $P = 0.24$; legality, $P = 0.12$).

Envy

Envy scores were analysed using the same factors reported above for *Schadenfreude*. The analyses showed a main effect of dimension [$F(2,82) = 23.53$, $P < 0.0001$, $\eta^2 = 0.39$], as deservingness situations had lower scores than morality and legality; and an interaction between dimension and group [$F(4,82) = 22.38$, $P < 0.0001$, $\eta^2 = 0.52$]. *Post hoc* analyses of this last interaction (Tukey HSD, mean square = 12.5, $df = 2$) showed that bvFTD patients assigned higher scores for envy in the legal, moral and deservingness dimensions (Fig. 3B) than patients with Alzheimer's disease (deservingness, $P = 0.001$; morality, $P = 0.03$; legality, $P = 0.011$) and healthy controls (deservingness, $P = 0.05$; morality, $P = 0.043$; legality, $P = 0.031$). No differences were observed on any dimension between patients with Alzheimer's disease and healthy controls (deservingness, $P = 0.17$; morality, $P = 0.31$; legality, $P = 0.27$).

Neutral situations

No significant between-group differences emerged in the ratings for neutral situations [$F(2,82) = 0.89$, $P = 0.41$, $\eta^2 = 0.001$] (Fig. 3C).

Consistency of behavioural results among groups

Relative to controls, bvFTD and Alzheimer's disease patients evinced less consistent (i.e. more varied) scores across situations in both moral emotions (Supplementary

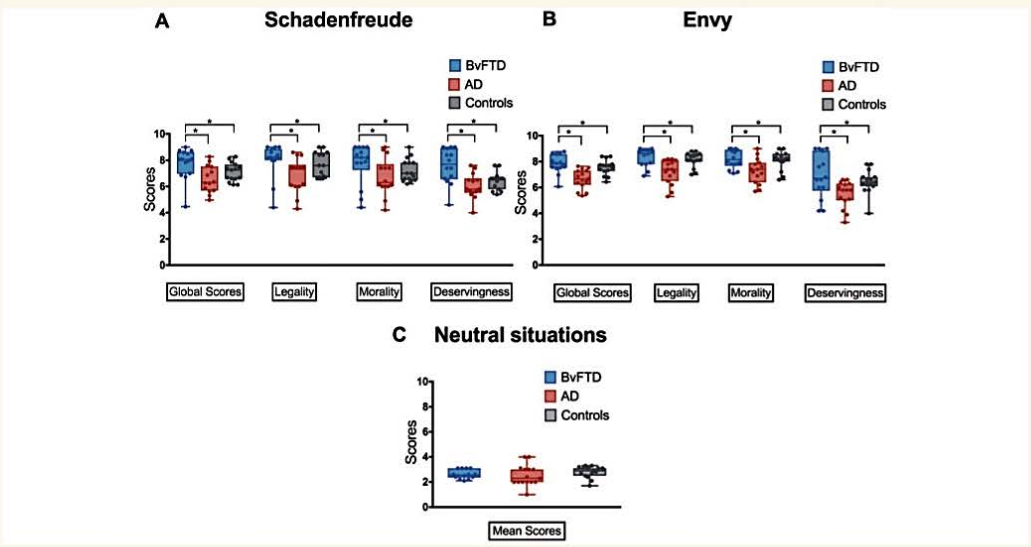

Figure 3 Dimensions of moral emotions in each group. (**A**) *Schadenfreude* results by group. (**B**) Envy results for each dimension by group. (**C**) Results for the neutral condition in each group. The whisker box plot depicts scores of each dimension in each group and the range of responses (depicted by dots) in each group. Each group was represented by different colours: bvFTD in blue; Alzheimer's disease (AD) in red, controls in grey. Asterisks depict significant differences at $P < 0.01$.

material). Nevertheless, no difference emerged between both patient groups.

Correlation analyses between moral emotions and cognitive-behavioural measures

Correlational analyses revealed that in bvFTD patients, the stronger experience of *Schadenfreude* (Fig. 4A), the least inhibitory control (Hayling test, $r^2 = 0.39$, $P < 0.05$), the greatest behavioural changes (Frontal System Behavioural Scale, $r^2 = 0.44$, $P < 0.01$), and the lowest theory of mind skills (RMET, $r^2 = -0.27$, $P < 0.05$). Similarly, higher envy was associated with reduced inhibitory control (Frontal System Behavioural Scale, $r^2 = 0.39$, $P < 0.05$; Fig. 4B) and theory of mind skills (RMET, $r^2 = -0.31$, $P < 0.05$). Correlational analyses for each specific dimension of *Schadenfreude* and envy did not reach significance (all *P*-values > 0.32). No associations were found in patients with Alzheimer's disease (all *P*-values > 0.24) or healthy controls (all *P*-values > 0.31).

Reanalysis of scores on the *Schadenfreude*, envy, and neutral situations with cognitive measures as covariates

Group differences in *Schadenfreude* [$F(2,82) = 5.34$, $P < 0.001$, $\eta^2 = 0.11$] and envy [$F(2,82) = 2.28$, $P < 0.05$, $\eta^2 = 0.07$] remained significant after adjusting for MoCA. Similarly, differences in *Schadenfreude* [$F(2,102) = 2.86$, $P < .05$, $\eta^2 = 0.06$], and envy [$F(2,102) = 3.18$, $P < 0.05$, $\eta^2 = 0.07$] were preserved after covarying for Hayling scores. Finally, differences between groups in *Schadenfreude* [$F(1,59) < 7.1$, $P < 0.01$, $\eta^2 = 0.11$] and envy [$F(1,59) = 3.46$, $P < 0.05$, $\eta^2 = 0.04$] were also preserved after covarying for RMET scores.

Atrophy in bvFTD patients: VBM results

Whole-brain analyses comparing the bvFTD group with healthy controls showed widespread bilateral atrophy predominantly involving the medial frontal cortex (MFC), the orbitofrontal cortex (OFC), the anteromedial temporal areas, the ACC, the bilateral insula, the basal ganglia, the right DLPFC, and bilateral medial frontal regions ($P = 0.001$, uncorrected) (Supplementary Fig. 1). Atrophy distribution was consistent with that reported in previous VBM studies (Rosen *et al.*, 2002; Kipps *et al.*, 2009; Seeley *et al.*, 2009; Whitwell *et al.*, 2009; Santamaria-Garcia *et al.*, 2016; Baez *et al.*, 2017*c*).

Structural neuroimaging of *Schadenfreude* and envy

Here we report the regression analyses ($P < 0.05$, FDR corrected) between each emotion (envy and *Schadenfreude*) for each dimension (deservingness, morality, and legality) and grey matter volume in all subjects (first step) and in bvFTD patients only (second step).

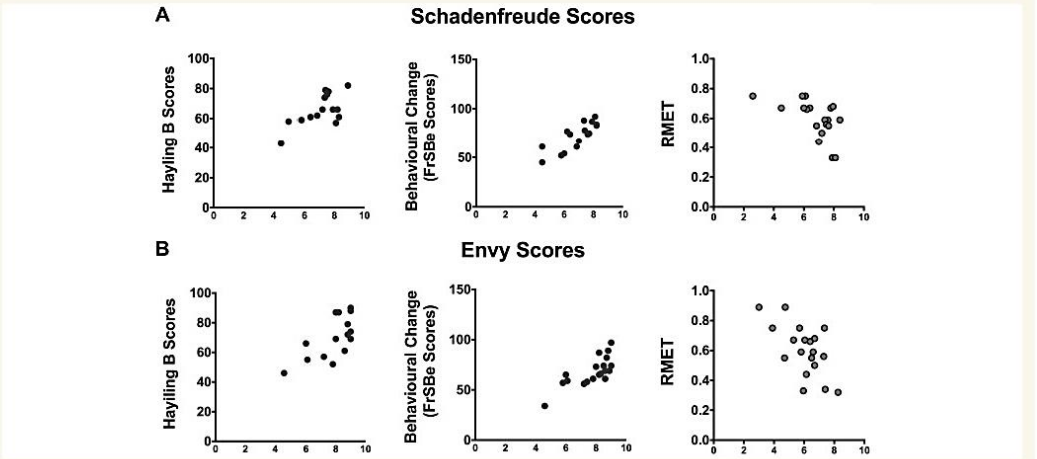

Figure 4 Correlations between moral emotions and individual bvFTD profiles. (**A**) Positive correlations between *Schadenfreude* scores and behavioural measures (behavioural changes tracked by FrSBE, inhibitory control tracked by the Hayling B test and social cognition tracked by RMET). (**B**) The same results are depicted for these behavioural scores and envy. FrSBe = Frontal System Behavioural Scale.

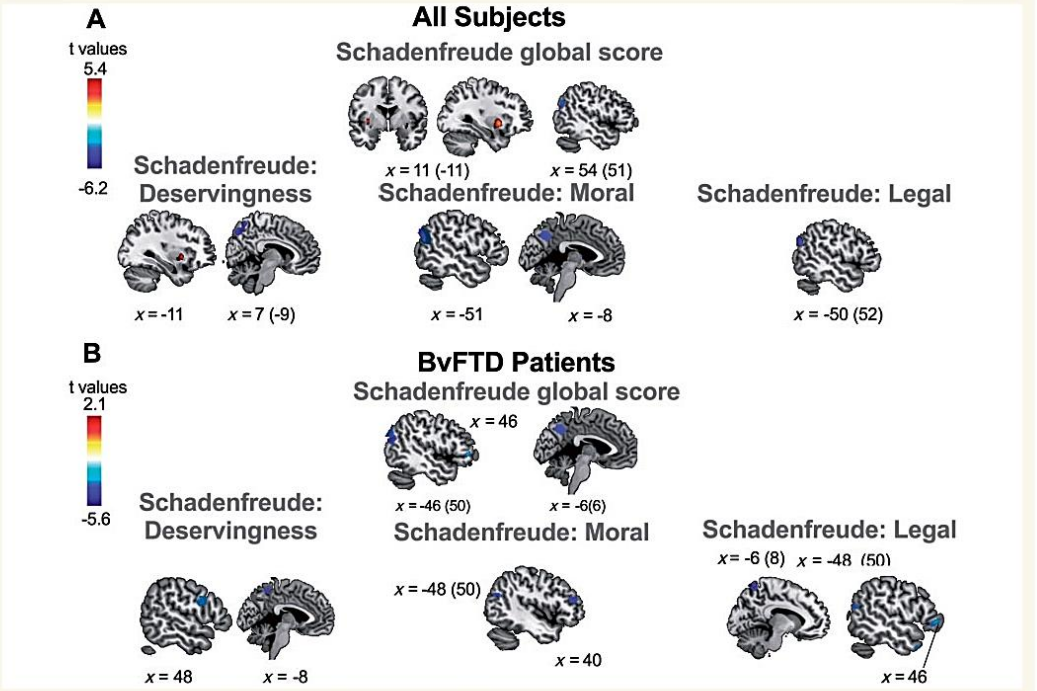

Figure 5 VBM analyses and *Schadenfreude* dimensions. VBM regression analyses within the brain areas associated with the social cognition network and moral emotion areas and the scores for each sub-dimension of *Schadenfreude*. (**A**) VBM analysis in all subjects. (**B**) VBM analysis in bvFTD patients only (in both cases, $P < 0.05$, FDR corrected).

Table 2 Association between grey matter volume and scores for each dimension of *Schadenfreude* and envy (FDR corrected at $P < 0.05$)

Moral emotion by group analyses	Brain regions (+) (−)	Coordinates x, y, z {mm}	Cluster size	Peak T
Grouped *Schadenfreude* Mean	Bilateral angular gyrus (−)	51 (−54)* 62 23	332	5.65
	Right − left putamen (+)	28 (−27)* −6 −15	281	5.69
	Right − left Caudate (+)	10 −12 14 4	133	5.43
Grouped *Schadenfreude* (deservingness dimension)	Bilateral precuneus	7 (−) 48 9	223	5.49
	Right putamen (+)	28 −6 −15	281	5.39
	Right caudate (+)	10 14 4	133	5.43
Grouped *Schadenfreude* (moral dimension)	Bilateral angular gyrus (−)	−54 −64 24	382	5.43
	Bilateral precuneus (−)	10 (−12)* 14 4	133	5.43
	Bilateral angular gyrus (−)	52 (−54)* −64 24	822	6.16
Grouped *Schadenfreude* (legal dimension)	Right frontal pole (−)	46 47 25	236	5.32
BvFTD *Schadenfreude* Mean	Bilateral precuneus (−)	6(−6) −63 47	510	5.13
	Bilateral angular gyrus (−)	−46 (50)* −64 24	232	5.44
	Right DLPFC (−)	46 39 1	242	5.11
BvFTD *Schadenfreude* (deservingness dimension)	Bilateral precuneus (−)	10 (−12) 14 4	222	4.38
BvFTD *Schadenfreude* (deservingness dimension)	Right frontal pole (−)	40 47 25	433	5.76
	Bilateral angular gyrus (−)	50 (−48)* −64 24	394	5.23
	Right frontal pole (−)	46 42 2	638	5.33
BvFTD *Schadenfreude* (legal dimension)	Bilateral precuneus (−)	8(−6) −48 9	523	5.44
	Bilateral angular gyrus (−)	50 (−48)* −64 24	682	5.56
	Right ACC (+)	2 3 45	457	5.42
Grouped envy Mean	Bilateral amygdala (+)	30 (−21)* −6 −15	134	5.43
	Bilateral hippocampus (+)	16 (−19) −33 1	101	4.48
	Right ACC (+)	12 6 45	503	5.77
Grouped envy (deservingness dimension)	Right DLPFC (−)	−51 39 1	346	5.66
	Right ACC (+)	11 3 45	468	5.44
Grouped envy (moral dimension)	Bilateral amygdala (+)	22 (−24)*−6 −15	381	5.88
	Bilateral hippocampus (+)	16 (−19) −33 1	103	5.89
	Right ACC (+)	2 3 45	378	5.24
Grouped envy (legal dimension)	Precuneus	−6 53 −30	328	4.32
	Bilateral amygdala (+)	16 (−14)*−6 −15	317	4.12
	Bilateral hippocampus (+)	18 (−21) −33 1	564	4.09
BvFTD envy Mean	Bilateral precuneus (−)	8 (−6) −56 39	127	4.57
BvFTD envy (deservingness dimension)	Right DLPFC (−)	−51 39 1	206	4.16
BvFTD envy (deservingness dimension)	Bilateral precuneus (−)	−5 (6) −48 9	323	3.94
	Bilateral precuneus (−)	8 −6 −48 9	447	8.66
BvFTD envy (legal dimension)	Right ventromedial prefrontal cortex (−)	12 (−17)*−6 −15	210	4.43

*Left x-axis coordinates (MNI space).
(+) Positive associations between moral emotion scores and grey matter volume.
(−) Negative associations between moral emotion scores and grey matter volume.

The global score for *Schadenfreude* was positively associated with grey matter volume in the bilateral ventral striatum and negatively associated with the volume of the bilateral angular gyrus. *Schadenfreude* scores for the deservingness dimension were positively associated with grey matter in the dorsal striatum (left caudate and putamen) and negatively correlated to bilateral precuneus. Scores for moral *Schadenfreude* were negatively associated with the left angular gyrus and left precuneus. Legal *Schadenfreude* scores were negatively associated with bilateral angular gyrus (Fig. 5A and Table 2).

The global score for envy was positively associated with grey matter volume in the right ACC and with the volume of the bilateral amygdala and parahippocampus. Deservingness envy scores were positively associated with grey matter volume in the right ACC and negatively associated with the right DLPFC. In addition, moral and legal envy were positively associated with grey matter in the

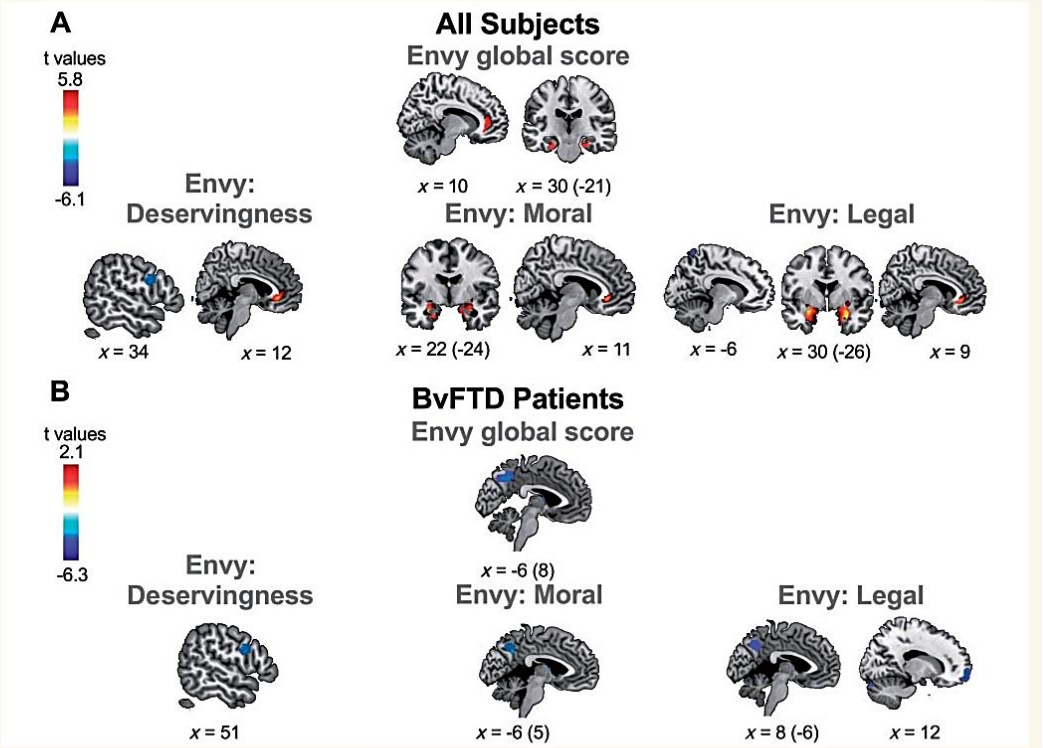

Figure 6 VBM analyses and envy. VBM regression analyses within the brain areas associated with the social cognition network and moral emotion areas and the scores for each sub-dimension of envy. (**A**) VBM analysis in all subjects. (**B**) VBM analysis in bvFTD patients only (in both cases, $P < 0.05$, FDR corrected).

right ACC and with the volume of the bilateral amygdala and parahippocampus (Fig. 6A and Table 2).

BvFTD patients

An exacerbated experience of *Schadenfreude* was associated with atrophy of the left angular gyrus and and precuneus. Increased *Schadenfreude* for the deservingness dimension was negatively associated with atrophy of the right DLPFC and the left precuneus. Enhanced moral *Schadenfreude* was negatively associated with the bilateral angular gyrus, and right frontal pole. Legal *Schadenfreude* scores were negatively associated with the bilateral angular gyrus, bilateral precuneus, and right frontal pole (Fig. 5B and Table 2).

Increased envy was correlated with reduced grey matter volume in the bilateral precuneus. Scores for the deservingness dimension of envy were negatively associated with grey matter volume of the right DLPFC. Moral envy scores were negatively associated with the volume of the right precuneus. Legal envy was negatively associated with the volume of the right DLPFC and the right precuneus (Fig. 6B and Table 2).

The brain–behaviour association in patients with bvFTD remained similar even using a more general volumetric analysis (whole-brain analysis, Supplementary Fig. 4). This analysis revealed negative correlations between *Schadenfreude* and envy dimensions and a set of areas including the precuneus, the angular gyrus, the dorsolateral prefrontal cortex, and the frontal pole. In addition, using this analysis we observed an additional association between legal scores of *Schadenfreude* and the left superior parietal lobe (Brodmann area 7). Furthermore, regarding envy scores, (global score, moral, and legal dimensions), a positive association was observed with the bilateral amygdala and the parahippocampus. Also, other associations were observed beyond the regions included in the mask. Schadenfreude was associated with bilateral sensory association areas (deservingness, moral, and legal dimensions), the superior temporal lobe (global score), and the posterior cingulate cortex (legal dimension). In the same line, envy

was associated with the superior parietal lobe (global score), the left frontal area (deservingness dimension), sensory association areas (moral and legal dimensions), and the right supplementary motor area (legal dimension) (Supplementary Fig. 4 and Supplementary Table 1.

Analysis of envy and *Schadenfreude* dimensions controlling by inhibitory control and theory of mind

For mean scores of *Schadenfreude*, only the association between the mean scores and atrophy of the precuneus remain significant after covarying for Hayling test and RMET scores. The negative association between *Schadenfreude* for the deservingness dimension and atrophy of the precuneus and DLPFC was preserved after controlling for such two measures. For moral *Schadenfreude*, only the negative association with atrophy of the angular gyrus survived the correction analyses, as the negative association with dorsolateral prefrontal cortex disappeared. Legal *Schadenfreude* scores remained associated with atrophy of the precuneus and the angular gyrus. As in the case of moral *Schadenfreude*, the negative association with frontal areas disappeared after covarying for RMET and Hayling scores (Supplementary Fig. 5 and Supplementary Table 2).

Increased envy remained negatively associated with reduced grey matter volume in the precuneus after correction for Hayling and RMET measures. The negative association between DLPFC and deservingness envy was preserved after covarying with Hayling and RMET scores. Moral envy scores remained negatively associated with the volume of the right precuneus after controlling for Hayling and RMET scores, too. The same was true for legal envy, although the negative association between this dimension and the ventromedial prefrontal cortex disappeared after covariation (Supplementary Fig. 5 and Supplementary Table 2).

Discussion

This study relied on a neurodegenerative lesion model (bvFTD) to offer the first examination of the neuroanatomical signatures of three key dimensions of *Schadenfreude* and envy (deservingness, legality, and morality).

Results supported our behavioural hypothesis. Healthy controls showed more emotional responses in situations with prominent moral and legal components compared to deservingness situations. Similarly, bvFTD patients experienced exacerbated degrees of envy and *Schadenfreude* relative to the other two groups. Results also provide support for the partially differentiated but overlapped dimensions of moral emotions (Hamann, 2012; Lindquist *et al.*, 2012, 2013). These contextual differences in emotional responses between domains (deservingness, moral and legal) were supported by several findings. First, although the type of situations seem to elicit different degrees of emotional responses, all of them elicit pleasure in the context of *Schadenfreude* and displeasure in the context of envy situations. Second, those situations showed only partially dissociable brain patterns. Third, they seem to be related to different cognitive processes, as shown by correlations between moral emotion scores and scores in the theory of mind task and the Hayling test.

Regarding the neuroanatomical hypothesis, present results confirmed the critical role of the striatum in *Schadenfreude* and of the ACC in envy, while showing additional involvement of temporo-parietal regions related to social and moral cognition processes. Our results also provide evidence of a convergent pathway for the legal and moral dimensions, but not for deservingness, which involves parietal regions in the case of *Schadenfreude* and anterior temporal regions for envy.

Moral dimensions across groups

Relative to patients with Alzheimer's disease and healthy controls, patients with bvFTD had increased scores for all dimensions of envy and *Schadenfreude*. Moreover, an increased experience of *Schadenfreude* and envy in bvFTD was associated with alterations in social cognition, executive functions, and behavioural disturbances reported in those patients. Specific analyses revealed that the legal and moral dimensions elicited higher scores than the deservingness dimension in all groups. These results suggest that envy and *Schadenfreude* are multi-dimensional emotions, in agreement with the notion that they can be elicited by a broad spectrum of social situations, dominated by feelings of deservingness but also (and especially) by notions of justice linked to moral and legal conventions (Shamay-Tsoory *et al.*, 2007; Kipps *et al.*, 2009; Jankowski and Takahashi, 2014). Judgements of moral and legal rightness recruit high emotional resources and require more pacing between cognitive and emotional processes (Moll *et al.*, 2003; Moll and de Oliveira-Souza, 2007). Such processes are highly rooted in our cognitive systems and require special moral assessment, punishment evaluation, and semantic knowledge of a particular action (Moll *et al.*, 2003; Moll and de Oliveira-Souza, 2007).

Our results are consistent with these previous findings, as they show enhanced emotional experience for fortunate or unfortunate situations that occur to other individual in both the moral and legal dimensions. Interestingly, our results also show that even in bvFTD patients, who exhibit various executive, emotional, and socio-cognitive alterations, judgements over morality and legality invoke higher emotional responses compared to deservingness (Supplementary material). Given the social and moral transgression in bvFTD (de Oliveira-Souza *et al.*, 2008; Mendez, 2010; Baez *et al.*, 2014*a*, 2016*a*; Liljegren *et al.*, 2015), exacerbated emotional responses can be expected in these patients irrespective of the type of situations presented to elicit displeasure/envy.

The source of displeasure and envy facing moral and legal situations seems to be different from the source of displeasure for the purer deservingness situations. For

moral and legal situations, displeasure and envy are probably associated to implicit inequity produced by an apparent success that the receptor achieves by avoiding sanctions in punishable situations. By contrast, for deservingness situations, the source of displeasure and envy are directly related to the receptor's success in obtaining a desirable outcome. Thus, by exploring those differential dimensions of moral emotions, we have shown that scenarios featuring moral, legal, and deservingness situations can trigger different processes related to envy. Our design does not allow clarifying whether the displeasure reported in all envy scenarios (including deservingness, moral, and legal situations), is generated by the degree of desirability of each situation a priori, or by the third-party outcome described in each situation. Future studies should explore these questions and assess to what extent an undesirable situation modulates moral emotions and evokes other emotional responses.

Structural brain signatures of experiencing moral emotions in all subjects

First, through a combined analysis between bvFTD patients and healthy controls, we aimed to tackle individual differences in VBM analyses. The VBM analyses in all subjects showed that global *Schadenfreude* scores were positively associated with the volume of the striatum, confirming functional MRI evidence (Takahashi *et al.*, 2009; Jankowski and Takahashi, 2014). In addition, our analyses showed that brain signatures of *Schadenfreude* go beyond the striatum, as reduced grey matter volume of the bilateral angular gyrus was negatively associated with the moral and legal *Schadenfreude* dimensions. By contrast deservingness was related with the right caudate and putamen but also with bilateral precuneus. The angular gyrus has been reported as a crucial area involved in moral judgements (Moll *et al.*, 2005) and in the processing of third-party moral and legal judgements (Raine and Yang, 2006). In addition, regarding to precuneus, previous studies have associated this area to mentalizing abilities and socially valued decision-making processes (Bzdok *et al.*, 2012; Schlaffke *et al.*, 2015; Niemi *et al.*, 2017). The precuneus has been reported as impaired in bvFTD patients (Ibañez and Manes, 2012; Devenney *et al.*, 2014; Baez *et al.*, 2017*c*). Thus, *Schadenfreude* would not only involve reward-related regions, but also more extended networks indexing moral and legal dimensions of this emotion.

Regarding envy, we provide the first lesion-based evidence of a positive association with the volume of the right ACC in all subjects, as previously reported with functional MRI (Takahashi *et al.*, 2009; Cikara and Fiske, 2013; Jankowski and Takahashi, 2014). This region is modulated by threat of self-concept, similar to cognitive dissonance (Moll *et al.*, 2005), or social pain (similar to social exclusion) (van Veen *et al.*, 2009). In addition, the grouped analysis showed an association between bilateral the parahippocampus and amygdala with the moral and legal dimensions (deservingness was negatively associated with the right DLPFC). Both regions (parahippocampus and amygdala) are engaged in emotional appraisal (Levenson *et al.*, 2014) and during unfair social comparisons (Jankowski and Takahashi, 2014; O'Callaghan *et al.*, 2016). The amygdala seems to be a critical region for the early detection of the basic mosaic of moral evaluation [i.e. intention to harm (Hesse *et al.*, 2016)]. Furthermore, previous studies have reported abnormal amygdala volume in subjects who engage in antisocial behaviours (Raine and Yang, 2006; Yang *et al.*, 2009). In this report, envy scores were obtained by asking subjects about the level of displeasure they feel in deservingness, moral, and legal situations. The positive correlation between the volume of the amygdala/parahippocampus and scores of envy facing moral and legal situations fits well with previous studies reporting associations between the volume of the amygdala/paralimbic cortex and self-reported displeasure in emotion tasks (Vicario *et al.*, 2017).

Neurocognitive correlates of moral dimensions in bvFTD

We also analysed results from the bvFTD group alone, which afforded a lesion model to explore which areas are critical for the cognitive process targeted in our task. Most of the brain-behaviour correlations for envy and *Schadenfreude* in bvFTD patients remain significant after covarying for Hayling and RMET scores (Supplementary Fig. 5 and Supplementary material). These results suggest that exacerbation in moral emotions in bvFTD is not a simple manifestation of social and behavioural disturbances, but rather a new expression of the social and affective deregulation in bvFTD. Moreover, the whole brain analyses in bvFTD confirmed a similar pattern of associations plus additional relevant regions (Supplementary material).

Schadenfreude

In bvFTD patients, the increased experience of *Schadenfreude* was associated with reduced volume in the bilateral angular gyrus and precuneus, and in the right frontal pole. Furthermore, as in the grouped analyses, we found a dissociable pattern between *Schadenfreude* dimensions. Deservingness showed a negative association with volume of the right DLPFC and the precuneus. These regions subserve social decision-making, moral cognition and mentalizing skills (Lieberman, 2007) and are disrupted in bvFTD (Kipps *et al.*, 2009). Thus, higher experience of *Schadenfreude* in situations of deservingness would be related to disrupted social decision-making and moral-mediated behaviours.

Higher scores for the moral dimension were associated with a volume reduction of the bilateral angular gyrus, and the right frontal pole, while increased legal scores were

associated with reduced volume of the bilateral angular gyrus, the right precuneus and the right frontal pole. These structures are activated during processing of emotionally salient stimuli and moral judgements (Moll *et al.*, 2005), and are related to social cognition impairments in bvFTD (Bertoux *et al.*, 2012; Ibañez and Manes, 2012; Couto *et al.*, 2013; Bertoux *et al.*, 2014; Baez *et al.*, 2016*a*). In fact *Schadenfreude* implies implicit self-other comparison of mental states (Shamay-Tsoory *et al.*, 2007). In bvFTD, an impaired long-term self-other's perspective integration is observed (Melloni *et al.*, 2016). Accordingly, higher *Schadenfreude* scores in patients with atrophy in those social cognition regions support the gap between *Schadenfreude* and mentalizing skills (this interpretation is also supported by the negative correlation found between *Schadenfreude* and theory of mind).

Envy

BvFTD patients presented a negative association between envy and bilateral precuneus. In addition, a dissociable brain pattern was found between envy dimensions in this group. Scores for envy situations dominated by deservingness score (as in the case of *Schadenfreude*) were negatively associated with the DLPFC, further supporting the converging role of this area in high level social cognition in bvFTD. The envy elicited in the moral dimension in bvFTD patients was associated with volume reduction the precuneus, a region related to the interplay between mentalizing abilities and social decision-making (Bzdok *et al.*, 2012), and affected in bvFTD (Ibañez and Manes, 2012). Feelings of envy associated with mentalizing involve precuneus engagement for immoral and illegal scenarios (Yamada *et al.*, 2012; Baez *et al.*, 2016*a*). Finally, scores for the legal dimension of envy were negatively associated with volume in the right VMPFC and the right precuneus. The VMPFC is engaged in scenarios with possible negative social consequences (Moll *et al.*, 2005; Shamay-Tsoory *et al.*, 2007). Arguably, reduced volume of this area in bvFTD may be associated to high scores for legal contexts, as these kinds of situations arguably recruit more emotional and cognitive resources.

The relevance of studying moral dimensions in bvFTD

Most of the reported anatomical pathways of *Schadenfreude* (ventral striatum, DLPFC, and frontal pole), and envy (ACC, prefrontal cortex, the parahippocampus, and the amygdala) correspond to targets of atrophy in bvFTD, namely, fronto-temporal (Piguet *et al.*, 2011; Tosun *et al.*, 2012; Sedeno *et al.*, 2016) and striatal regions (Pan *et al.*, 2012; Bertoux *et al.*, 2015). Also, other relevant structures, such as the posterior cingulate cortex, medial temporal lobe, and parietal regions, has been associated with this condition (Supplementary material).

Our results pave the way for comprehending the interplay between more complex and ecological emotions and other cognitive processes affected in bvFTD. First, the increase in moral emotions, also considered as counter-empathy emotions, aligns with previous studies showing disruptions in social and morally determined behaviours, such as impairments in affective sharing (Eslinger *et al.*, 2011*a*; Kumfor *et al.*, 2013; Baez *et al.*, 2014*c*, 2016*b*; Melloni *et al.*, 2014; Kamminga *et al.*, 2015; Sturm *et al.*, 2015; Van den Stock *et al.*, 2015; Hutchings *et al.*, 2017), alterations in perspective taking and the more cognitive sides of empathy (Baez *et al.*, 2014*c*, 2016*b*; Dermody *et al.*, 2016; Ibanez *et al.*, 2016; O'Callaghan *et al.*, 2016; Ibanez *et al.*, 2017; O'Callaghan and Hornberger, 2017), and diminished motivation for prosocial behaviours (Moll *et al.*, 2011; O'Callaghan *et al.*, 2016), alongside of a disruption in processing moral judgements (Baez *et al.*, 2014*a*, 2016*a*) and an increase in immoral and illegal behaviours (de Oliveira-Souza *et al.*, 2008; Mendez, 2010; Liljegren *et al.*, 2015). The impaired moral emotions in bvFTD observed in the present results can be related to affective deregulation; to the relationship between basic emotion impairments and moral cognition; or to behavioural disturbances in these patients (Supplementary material).

Moreover, recent studies on bvFTD have shown that patients exhibit deficits in integrating self-perspectives with those of others and rewarding benefits (Melloni *et al.*, 2016; O'Callaghan *et al.*, 2016; Ibanez *et al.*, 2017). These impairments are associated with impairments in frontotemporal structures. The integration of self-preferences with the outcomes of another person seems to be a crucial aspect of the *Schadenfreude* and envy (Jankowski and Takahashi, 2014; Fontenelle *et al.*, 2015). Deficits in assessing self and other perspectives in bvFTD might abnormally enhance moral emotions irrespective of their positive/pleasant valence (as in the case of *Schadenfreude*) or negative displeasing valence (as in the case of envy).

Previous authors have suggested that although compliance with basic social norms can be maintained in bvFTD, more complex normative behaviours (prosociality or behaviour modulation in function of social information) that require integration of social contextual information are usually disrupted in this condition (O'Callaghan *et al.*, 2016; Baez *et al.*, 2017*a*). Thus, higher emotional scores for both *Schadenfreude* and envy seen in bvFTD patients could be related to impulsive behaviours, such that patients fail to integrate the implicit social information present in emotional situations with different social normative challenges.

Nonetheless, our results suggest that the exacerbation in moral emotions in all categories in bvFTD is not fully explained by social cognitive and executive deficits. In fact, responses in moral emotions in bvFTD patients remain preserved after controlling for inhibitory (Hayling test) and social cognitive measures (RMET). The exacerbation of moral emotions in bvFTD seems to be a partially

independent and new hallmark of the disruption of social, behavioural, and affective processes in bvFTD.

Taken together, the above alterations seem related to deficits in the integration of social contextual information seen in bvFTD, arguably due to deficits in the frontal-temporo-insular network (Ibañez and Manes, 2012; Baez *et al.*, 2017*a*). The bvFTD emerges as a relevant lesion model tapping into the 'mystery of frontal lobes' (Burgess *et al.*, 2009): patients provide accurate responses to abstract, isolated and decontextualized cognitive tasks, but they typically fail in more ecological paradigms demanding a combination of cognitive, affective, and social processes (Ibañez and Manes, 2012; Melloni *et al.*, 2014; Baez *et al.*, 2017*a*). Such social contextual deficits would lie at the core of the behavioural, socio-moral, and emotional impairments observed in bvFTD. Future studies should further explore the links between specific compromise of the social context network and moral emotions.

Limitations and further assessments

Our study has some limitations. First, diagnosis in our patient sample was based on established clinical assessments, but it lacked pathological confirmation. However, such confirmation is not required for diagnosis at the probable level, as shown in several studies (Rascovsky *et al.*, 2011; Chiong *et al.*, 2016; García-Cordero *et al.*, 2016; Melloni *et al.*, 2016; Sedeno *et al.*, 2016; Ahmed *et al.*, 2017). Moreover, we have followed international standards (Knopman and Roberts, 2011; Piguet *et al.*, 2011; Rascovsky *et al.*, 2011), as diagnosis was performed in a memory clinic after deliberative consensus by a highly experienced group composed of geriatricians, neurologists, neuropsychologists, and psychiatrists (Baez *et al.*, 2014*a*, 2016*b*; García-Cordero *et al.*, 2016; Melloni *et al.*, 2016; Sedeno *et al.*, 2017). In particular, all diagnoses were performed following criteria by (Rascovsky *et al.*, 2011), for probable bvFTD patients, and international criteria (McKhann *et al.*, 2011), for patients with Alzheimer's disease.

Second, our approach did not allow us to assess the relationship between envy and *Schadenfreude* dimensions with other cognitive processes, including reward processing, and other social cognitive processes such as emotional sharing (e.g. empathy). Further studies should explore the particular relationship between dimensions of moral emotions and their relationship with cognitive processes including social reward and socio-cognitive skills (including perspective taking and affective sharing), moral judgement, and cognitive control among other processes.

Third, we compared the behavioural responses of bvFTD patients to moral emotions relative to those of a contrastive lesion model (Alzheimer's disease), to control for task comprehension problems associated with neurodegeneration. Future studies should explore the brain correlates of processing those emotions in Alzheimer's disease (as well as other neurodegenerative conditions) to fully comprehend the role of other brain areas usually impaired across neurodegenerative conditions. Although our study did not include VBM analysis of patients with Alzheimer's disease, several reasons attest to the validity of the neurocognitive pattern observed in bvFTD (Supplementary material). Despite these considerations, future studies should evaluate the degree of atrophy specificity by comparing bvFTD with other conditions, such as Alzheimer's disease, other forms of FTD, and Huntington's disease (another neurodegenerative condition associated with moral emotion impairments (Baez *et al.*, 2017*d*).

Finally, we only found correlations between global scores of moral emotions and measures tracking social, cognitive, and behavioural impairments in bvFTD. Since this relationship was only reported with global scores, we do not know to what extent performance on each sub-dimension of envy and *Schadenfreude* is related to other cognitive and behavioural dimensions in bvFTD. Further studies should explore the extent to which the deservingness and moral-legal dimensions are related to specific cognitive and behavioural processes. The relationship between recognition and third-party evaluation of moral and legal situations and social cognitive processes (including empathy, emotion perception, and social decision-making) represents a promising avenue for future research.

Conclusions

Classical theoretical approaches have hinted at the multidimensional nature to the moral emotions of envy and *Schadenfreude*. Those earlier theories suggested that moral emotions are complex cognitive and affective states that, depending on the circumstances, may be considered the worst evil emotions (Schopenhauer 1788–1860) or, alternatively, good-natured emotions based on principles of fairness (Nietzsche 1844–1900). Together, our results provide unprecedented evidence of an exacerbated experience of moral emotions in bvFTD, while reinforcing the multidimensional nature of envy and *Schadenfreude*. Our results highlight the importance of analysing new and more ecological moral emotions in this population, with a view to examining relevant interactions between cognitive, moral, and emotional processes. In addition, our study reveals a new behavioural profile in bvFTD, which may help clinicians identify patients with neurocognitive disorders with mixed cognitive and behavioural alterations.

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Supplementary material

Supplementary material is available at *Brain* online.

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7.5 Estudio 5: Neuropsychiatric Symptoms as Predictors of Clinical Course in Neurodegeneration. A Longitudinal Study

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Neuropsychiatric Symptoms as Predictors of Clinical Course in Neurodegeneration. A Longitudinal Study

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Background: To study the extent to which neuropsychiatric symptoms (NPS) influence the cognitive and functional decline in frontotemporal degeneration (FTD) and Alzheimer's disease (AD).

Methods: We assessed the progression of NPS and their influence on cognitive and functional progression in a group of FTD (n = 36) and AD patients (n = 47) at two different stages of the disease (2.5 years). A standardized scale was used to assess NPS—the Columbia University Scale for Psychopathology in Alzheimer's Disease (CUSPAD)—which tracks different symptoms including depression, psychotic symptoms, as well as sleep and conduct problems. In addition, in a subsample of patients (AD n = 14 and FTD n = 14), we analyzed another group of NPS by using the Neuropsychiatric Inventory (NPI). Cognitive declines were tracked by using the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE), while functionality was tracked by using the Lawton scale and the Barthel Index.

Results: The presence of NPS impacts cognitive and functional decline in both groups of patients 2.5 years after disease onset. However, we observed a dissociable profile of the affectation of NPS in each group. In the AD group, results indicate that the progression of depressive symptoms and sleep problems predict cognitive and functional decline. In contrast, the progression of a mixed group of NPS, including conduct problems and delusions, predicts cognitive and functional decline in FTD.

Conclusion: The presence of NPS has a critical impact on the prediction of cognitive decline in FTD and AD patients after 2.5 years of disease progression. Our results demonstrate the importance of assessing different types of NPS in neurodegenerative disorders which, in turn, predict disease progression. Future studies should assess the role of NPS in predicting different neurocognitive pathways and in neurodegeneration.

Keywords: frontotemporal dementia, Alzheimer's disease, behavioral disturbances, depression, cohort studies, assessment of cognitive disorders/dementia

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INTRODUCTION

Frontotemporal degeneration (FTD) and Alzheimer's disease (AD) are prevalent neurodegenerative diseases which generate alterations in different cognitive and behavioral processes and have a considerable impact on the functionality of patients (Piguet et al., 2011; Livingston et al., 2017).

It is usual for patients with FTD to present alterations in the frontal, insular, and temporal brain areas, which are related to alterations in social behavior and executive functions (Piguet et al., 2011; Rascovsky et al., 2011; Sedeño et al., 2016). In turn, cognitive, language, and praxis alterations in AD have been associated with progressive atrophy in parieto-temporal areas (Dubois et al., 2014).

Both AD and FTD tend to exhibit neuropsychiatric symptoms (NPS; Ismail et al., 2016), which are considered relevant indexes for the determination of disease severity and progression (Teng et al., 2007; Peters et al., 2015). Depression and apathy have been associated with cognitive decline and mortality in AD (Teng et al., 2007; Karttunen et al., 2011; Ismail et al., 2016; Kaup et al., 2016), whereas in FTD, apathy, disinhibition and empathy impairments are the most prevalent NPS (Rascovsky et al., 2011; Brodaty et al., 2015) that impact disease progression (Brodaty et al., 2015; Ranasinghe et al., 2016). Previous studies have shown different neurocognitive progression according to the major type of symptom in FTD (Santamaría-García et al., 2016). A broad range of NPS in both AD and FTD has been described including delusions and sensory-perceptual alterations (hallucinations and illusions; Rubin et al., 1988; Van Dam et al., 2016; Gossink et al., 2017), as well as conduct problems (Santamaría-García et al., 2016; Van Dam et al., 2016), depressive and anxiety symptoms (Brodaty et al., 2015; Sellami et al., 2018), sleep problems (Mander et al., 2016; Merrilees et al., 2014) and eating changes (Ahmed et al., 2015; Ringman et al., 2015). Regarding the psychotic symptoms (including delusions and sensory-perceptive alterations such as hallucinations and illusions), previous studies have reported that those symptoms can appear in both AD and FTD. Previous studies have estimated the prevalence of psychotic symptoms in AD reached 20% and around 10% in FTD, mainly presented in patients with C9ORF72 mutations (Mendez et al., 2008). Psychotic symptoms presented in AD and FTD are associated with difficulties in episodic and working memory, poor reading of internal feelings, emotional dysregulation and inaccurate conclusions on reality associated with right frontal hypofunction and impaired activity of medial temporal areas (Mendez et al., 2008). Although the presence of psychotic symptoms has been associated with diagnosis difficulties in FTD (Velakoulis et al., 2009) and rapid cognitive decline in AD (Tchalla et al., 2018), to date, it is unknown to what extent the presence of those symptoms can impact cognitive and functionality decline in both AD and FTD.

Although previous studies have assessed the presence of different NPS in neurodegenerative disorders, to our knowledge, this is the first study assessing to what extent their presence at early stages of disease impacts the course of disease in AD and FTD.

Particularly, we study aimed to determine to what extent the presence of different types of NPS (including behavioral, affective and psychotic symptoms among others) at early stages of disease progression, predict the cognitive and functional disease progression in AD ($n = 47$) and FTD ($n = 36$) patients. Considering previous studies, we expected that depression, rather than other behavioral symptoms, has a predictive role of cognitive and functional progression in AD, but not in FTD. Conversely, we expected that the conduct problems, rather than depression, would be predictive of cognitive and functional deterioration in FTD.

MATERIALS AND METHODS

Participants

Patients recruited to this study were divided into two groups. The first group included 36 patients who fulfilled the revised criteria for probable FTD (Rascovsky et al., 2011) and presented with prominent changes in personality and social behavior as verified by caregivers. They were recruited from the Bogotá FTD Cohort (BOGFTD), largely reported in previous studies (Baez et al., 2014a,b; Santamaría-García et al., 2016, 2017). The second group included 47 patients diagnosed with AD who were included in this study after meeting criteria outlined in McKhann et al. (2011). Patients were recruited from the Memory Clinic of the Intellectus Memory and Cognition Center, at the Hospital San Ignacio in Bogotá (Colombia). Patients underwent a standard examination battery, including neurological, neuropsychiatric, and neuropsychological assessments by geriatricians, psychiatrists, neurologists, and neuropsychologists. All patients were in the early/mild stages of the disease and did not meet the criteria for specific psychiatric disorders. Patients presenting primarily with language deficits or a history of drug abuse, or a family history of neurodegenerative or psychiatric disorders were excluded from the study.

Initial Clinical Considerations in AD and FTD Patients

AD Patients

Most of the AD patients debuted with symptoms at 68.6 years and diagnosis was made on average 1.2 years after onset of symptoms (SD 0.4 years). Most of the participants debuted with cognitive symptoms consisting of episodic memory alterations (79.5%), language difficulties (43.1%) and disorientation (18.2%). A group of patients also coursed with depression (38.8%), anxiety (11, 1%), irritability (19.2%) and insomnia (12.1%).

Additionally, a group of AD patients received medications before diagnosis, including selective serotonin reuptake inhibitors (SSRIs; 12.6%), antipsychotic agents (19.4%), cholinergic agents (rivastigmine, donepezil and galantamine; 13.4%), benzodiazepines (1.5%) and GABA-A agonists (zopiclone and eszopiclone; 1.3%).

FTD Patients

Most of the AD patients debuted with symptoms at 60.7 years and were diagnosed 1.1 years after debut symptoms on

average (SD 0.6 years). Most of the participants debuted with behavioral symptoms featured by apathy (25.9%), disinhibition (34.5%), delusions (1.9%), depression (18.5%) and anxiety (11.1%). Furthermore, 18.1% of patients coursed with attention impairments, 15.6% with language difficulties and 27. 8% with working memory impairments. A group of FTD patients received pharmacological treatments before diagnosis was made, from them 17.9% received selective serotonin reuptake inhibitors (SSRIs), 14.1% antipsychotic agents, 0.8% benzodiazepines, 0.9% valproate and 0.6% carbamazepine.

Assessment Milestones

Patient groups (FTD and AD) were assessed at two stages of the disease progression. Patients were assessed by the same group of specialists at both stages. All enrolled patients had the same diagnosis in the first and second stages of assessment. In the first stage, patients were assessed at the time of diagnosis. The second assessment took place 2.5 years after the first (FTD mean = 2.4 years, SD = 1.2 vs. AD mean = 2.6 years, SD = 1.1). In each stage, patients in both groups were assessed with neurocognitive measures, as well as with measures of NPS (see below). As reported in previous studies (Baez et al., 2014b; Sedeño et al., 2017), we observed differences in the age at disease onset (see **Table 1**).

Cognitive Assessment

Global cognitive performance was assessed in two stages through a comprehensive set of measures, using the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005; Freitas et al., 2012; Delgado et al., 2017) and the Mini-Mental State Examination (MMSE; Folstein et al., 1983). The MoCA scale has a sensitivity above 87% and a specificity of 90% with a cut-off point of 26, and a sensitivity of 87% and a specificity of 87% with a cut-off lower than 18 points. It is composed of 19 items that evaluate eight cognitive domains, including executive skills, denomination, memory, attention, language, abstraction, deferred memory and orientation (Nasreddine et al., 2005; Pedraza et al., 2016). The MMSE is a classical instrument for assessing cognitive domains, including verbal memory, working memory, language, and visuospatial functions. A score of 24 points has a sensitivity above 88.3% and a specificity close to 87% for detecting cognitive impairment in patients with neurodegeneration (Folstein et al., 1975, 1983).

Assessment of Instrumental Functionality

The Lawton scale is an instrument for assessing the instrumental activities of daily living (Lawton and Brody, 1969). This instrument has been used to assess the clinical progression of dementia with respect to functional commitment. It contains eight items that assess functionality, including the ability to use the phone, go shopping, prepare food, perform household care and laundry, use of public transportation, as well as medication and money management, with an internal consistency measured by a Cronbach's alpha coefficient of 0.94 (Lawton and Brody, 1969; Vergara et al., 2012). The Lawton scale is an instrument previously reported for assessing functionality in neurodegenerative disorders (Cornelis et al., 2017).

Assessment of Physical Functionality

In addition, we used the Barthel index (Mahoney and Barthel, 1965), which was introduced as a way to measure the impairments of patients in their neuromuscular and musculoskeletal function, placing a strong focus on the spared activity of inferior extremities. The index is an ordinal scale comprising 10 activities of daily living, including sphincter control. The original Barthel index was scored in steps of five points to give a maximum total score of 100. The Lawton scale is an instrument previously reported for assessing functionality in neurodegenerative disorders including FTD and AD (Merrilees et al., 2013; Liljegren et al., 2015).

Assessment of Neuropsychiatric Symptoms (NPS)

The assessment of NPS, including delusions, sensory-perceptive alterations (hallucinations and illusions), conduct problems, sleep problems, depression, anxiety, and changes in eating patterns, was conducted at two stages using the Columbia University Scale for Psychopathology in Alzheimer's Disease (CUSPAD; Devanand et al., 1992; Suárez-González et al., 2013). CUSPAD is a quick and easy to use standardized instrument that provides information regarding neurodegenerative psychopathology. Classical reports calculated that this instrument has a high reliability (k = 0.74). This scale has been reported in studies assessing psychopathology in AD (Zahodne et al., 2015) and other neurodegenerative conditions (Suárez-González et al., 2013). In addition, it is an instrument that has shown high sensitivity for detecting psychosis (Cohen-Mansfield and Golander, 2011) as well as depressive symptoms, sleep disturbances, eating changes and disinhibited conducts in

TABLE 1 | Socio-demographic description of patients diagnosed with Alzheimer's disease (AD) and frontotemporal degeneration (FTD).

Gender	AD (n = 47)		FTD (n = 36)	
Male	20 (42.6%)		18 (50%)	
Female	27 (57.4%)		18 (50%)	
Variables	**Mean (SD)**	**Median**	**Mean (SD)**	**Median**
Age at time 1 (years)	72.1 (7.3)	72	64.1 (6.4)	63.4
Age at time 2 (years)	74.9 (6.2)	75	67.6 (6.9)	65
Age difference (years)	2.6 (1.1)	2	2.4 (1.2)	2
Educational level (years)	13.6 (4.9)	14	14.4 (5.2)	15
Age at disease onset (years)	68.3 (6.9)	69	61.2 (6.6)	60

Note: SD, standard deviation; AD, Alzheimer's disease; FTD, frontotemporal dementia.

patients with neurocognitive disorders (Suárez-González et al., 2013; Zahodne et al., 2015).

The Neuropsychiatric Inventory (NPI)

A subsample of patients in AD group (n = 14) and FTD group (n = 14) were assessed using the NPI scale. This scale was used as a second measure to track behavioral disturbances in disease progression of neurodegenerative disorders. The NPI (Cummins, 1997) consists of a selection of NPS and a measure of severity of each symptom. The caregiver rates each of the 12 symptoms as present or absent during the current month and, if some of those symptoms are present, they provide a measure of severity (which is tracked using a Likert scale between 1 and 3 points, with 1 being mild severity). The 12 symptoms on the NPI include behavioral/conduct symptoms (aberrant motor behavior, disinhibition, apathy), emotional-mood symptoms (euphoria, anxiety, depression, irritability), disruptive/psychotic symptoms (agitation, delusions, hallucinations) and other types of symptoms (nighttime behaviors, appetite and eating behavior disturbances). This instrument has been previously reported as efficient and reliable in tracking behavioral alterations in different neuropsychiatric disorders (Ismail et al., 2013, 2016) and neurocognitive disorders (Lai, 2014; Nowrangi et al., 2015; Ismail et al., 2016).

Data Analysis

Demographic and neuropsychological data for the two groups of patients (FTD and AD) were compared using one-way analysis of variance (ANOVA) and chi square tests for the categorical variables. Where indicated, Tukey's *post hoc* tests were used to examine group differences within neuropsychological measures.

Analyses of Longitudinal Progression Measures and Predictive Factors

To calculate the degree of change in cognitive functioning and instrumental and physical functionality between the first and second stage of assessment, two progression indexes for cognitive performance ΔMoCA (MoCA score at stage 1 − MoCA score at stage 2) and ΔMMSE (ΔMMSE = MMSE score at stage 1 − MMSE score at stage 2) were obtained. Following the same procedure, we obtained progression indexes for functionality, ΔLawton and ΔBarthel.

In order to assess the extent to which changes in NPS predict a change in cognitive or instrumental measures in both groups, we ran independent regression models in each group using each of the above-mentioned progression indexes (i.e., ΔMMSE, ΔMoCA, ΔLawton and ΔBarthel) as dependent variables. Behavioral indexes tracked with CUSPAD (including a global score of CUSPAD obtained from sum total of each symptom of the scale) were included as independent variables in each model in order to assess whether progression in one type of symptom predicts cognitive and functional progression. To account for differences in educational level in the groups, we applied a covariance analysis to the regression models, adjusted independently for years of education (see **Table 1**). Effect sizes were calculated through partial eta-squared (η^2). A group of similar analyses was run using the NPI scores and individual scores of each type of symptom as measures to track a broad group of behavioral disturbances in a subsample of subjects in each group (see "Instrument" section for more information on the subsample of subjects who were studied using the NPI measure). All statistical analyses were run using SPSS package version 21.0.

Disease Progression

Previous studies have suggested that subjects who have a fall of more of four MMSE points per-year have rapidly progressive cognitive deterioration (Doody et al., 2001, 2005). Based on this approach, we have subdivided the sample of each group (AD and FTD) into subgroups according to the level of cognitive deterioration. Thus, in each clinical group, we assessed the presence of subjects with expectable deterioration (subjects with a fall of less than four MMSE points per year) and a group with subjects with fast deterioration (subjects with a fall of more than four MMSE points per year). Additionally, we assessed the presence of subjects without any level of deterioration (subjects in whom the MMSE did not change or even improved). In each of the groups, we analyzed the relationship between the presence of NPS at the early stages of the disease and cognitive and functional decline. Additionally, we performed a one-way ANOVA to analyze the magnitude of NPS between subgroups of disease progression in two groups of patients (FTD and AD).

Mediation Analyses

We also assessed whether demographic factors (age of disease onset and disease time), medical comorbidities (presence or absence of comorbidities) and the usage of medications before diagnosis mediated the association between cognitive (ΔMoCA, ΔMMSE) and functional decline (ΔLawton, ΔBarthel) and scores of NPS tracked by CUSPAD. In addition, we assessed to what extent the cognitive decline measures mediate effects on functional decline measures and *vice versa*. To this end, we ran an independent mediation analysis for each regression model of cognitive and functional decline measures.

RESULTS

Results in cognitive, behavioral, and instrumental functionality measures in two stages of assessment are reported in **Table 2** (see descriptive analyses in **Table 2**). FTD and AD groups differed in age at disease onset ($F_{(1,82)}$ = 13.12, $p < 0.001$) as AD were older than FTD patients [AD = 68.6 years (SD = 8.2 years) and FTD = 60.7 years (SD = 7.5 years)]. Furthermore, FTD patients reached higher levels of formal education than AD patients [($F_{(1,82)}$ = 11.54, $p < 0.001$; AD = 11.2 years (SD = 5.5 years) and FTD = 14.8 years (SD = 6.2)]. No gender differences were found ($X^2_{(1)}$ = 0.58, p = 0.62).

First Stage of Assessment

Analyses did not reveal differences between FTD and AD groups in MoCA scores ($F_{(1,82)}$ = 0.65, p = 0.81; MoCA FTD = 17.3, SD = 5.8, AD = 17.6, SD = 5.4) nor in MMSE scores ($F_{(1,82)}$ = 0.88, p = 0.37; MMSE FTD = 23.1, SD = 4.9; AD = 22.9, SD = 4.8). With respect to functionality and instrumental measures, no differences were found between groups in the Lawton scale

TABLE 2 | Cognitive performance.

Scales	Mean	SD
(A) AD patients (*n* = 47)		
Cognitive measures		
MMSE, time 1	22.9	4.8
MMSE, time 2	19.8	5.7
MoCA, time 1	17.6	5.4
MoCA, time 2	13.1	6.1
Functionality measures		
Total Lawton, time 1	33.6	10.6
Total Lawton, time 2	24.2	9.2
Barthel Index, time 1	95.4	9.8
Barthel Index, time 2	87.8	9.9
Neuropsychiatric symptoms		
CUSPAD, time 1		
Delusions	1.4	1.1
Hallucination	0.1	0.05
Illusion	0.2	0.06
Conduct problems	1.4	1.1
Depression	2.1	0.9
Sleep problems	1.8	1.2
Eating changes	0.5	0.07
CUSPAD, time 2		
Delusions	1.5	1.4
Hallucination	0.2	0.1
Illusion	0.1	0.04
Conduct problems	1.7	1.1
Depression	1.8	0.7
Sleep problems	1.1	0.6
Eating changes	0.7	0.1
(B) FTD patients (*n* = 36)		
Cognitive measures		
MMSE, time 1	23.1	4.9
MMSE, time 2	15.6	7.5
MoCA, time 1	17.3	5.8
MoCA, time 2	12.5	5.4
Functionality measures		
Total Lawton, time 1	34.5	7.9
Total Lawton, time 2	27.6	7.6
Barthel Index, time 1	94.2	7.8
Barthel Index, time 2	87.2	7.1
Neuropsychiatric symptoms		
CUSPAD, time 1		
Delusions	1.9	0.8
Hallucination	0.4	0.03
Illusion	0.3	0.07
Conduct problems	2.5	1.4
Depression	1.5	0.7
Sleep problems	1.2	1.3
Eating changes	2.1	0.7
CUSPAD, time 2		
Delusions	1.8	1.1
Hallucination	0.3	0.2
Illusion	0.2	0.09
Conduct problems	2.6	0.8
Depression	1.1	0.8
Sleep problems	0.7	0.1
Eating changes	1.2	1.1

Basic and instrumental functionality and neuropsychiatric symptoms in patients with AD and FTD. Note: SD, standard deviation; AD, Alzheimer's disease; FTD, frontotemporal dementia; CUSPAD, Columbia University Scale for Psychopathology in Alzheimer's Disease; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

($F_{(1,82)} = 0.95$, $p = 0.33$; Lawton FTD = 34.5, SD = 7.9; AD = 33.6, SD = 1.6) nor in Barthel index ($F_{(1,82)} = 2.11$, $p = 0.13$; Barthel FTD = 94.2, SD = 7.8; AD = 95.4, SD = 9.8). Regarding behavioral measures, analyses showed greater scores in the global score of CUSPAD in the FTD compared to AD ($F_{(1,82)} = 3.95$, $p < 0.05$, $\eta^2 = 0.06$). In addition, the FTD group compared with the AD group showed higher scores in conduct problems ($F_{(1,82)} = 4.22$, $p < 0.05$, $\eta^2 = 0.06$) and in eating change measures ($F_{(1,82)} = 3.99$, $p < 0.05$, $\eta^2 = 0.06$). In contrast, the AD group had higher scores in sleep problems than in the FTD group ($F_{(1,82)} = 3.15$, $p < 0.05$, $\eta^2 = 0.06$). No other comparisons reached significant values.

Second Stage of Assessment

Analyses revealed minor MoCA and MMSE scores in FTD compared with the AD group [for MoCA ($F_{(1,82)} = 2.93$, $p < 0.05$, $\eta^2 = 0.06$; MoCA FTD = 12.5, SD = 5.4; AD = 13.1, SD = 6.1)], and for MMSE ($F_{(1,82)} = 2.76$, $p = 0.05$, $\eta^2 = 0.05$; MMSE FTD = 15.6, SD = 7.5; AD = 19.8, SD = 5.7). In addition, the AD group showed greater impairment in functionality than the FTD group as measured with the Lawton scale ($F_{(1,82)} = 2.75$, $p < 0.05$, $\eta^2 = 0.05$; Lawton FTD = 27.6, SD = 7.6; AD = 24.2, SD = 9.2). No differences were observed in the Barthel index ($F_{(1,82)} = 1.92$, $p = 0.16$; Barthel FTD = 87.2, SD = 7.1; AD = 87.8, SD = 9.9). With respect to behavioral measures, analyses showed higher scores in depressive symptoms in the AD group compared with the FTD group ($F_{(1,82)} = 3.76$, $p < 0.05$, $\eta^2 = 0.06$). In addition, results showed higher scores for eating changes in the FTD group when compared with the AD group ($F_{(1,82)} = 3.94$, $p < 0.05$, $\eta^2 = 0.06$) and higher conduct problems ($F_{(1,82)} = 2.98$, $p < 0.05$, $\eta^2 = 0.06$). No other comparisons reached significant values.

Progression Indexes

A progression index for each cognitive (ΔMMSE, ΔMoCA) and functional measure (ΔLawton and ΔBarthel) was created as described above. Analyses between groups revealed greater cognitive progression in FTD compared with the AD group [ΔMoCA ($F_{(1,82)} = 3.43$, $p < 0.05$, $\eta^2 = 0.06$) and ΔMMSE ($F_{(1,82)} = 2.69$, $p < 0.05$, $\eta^2 = 0.06$)]. In addition, we observed a major functional progression in AD compared with the FTD group [for ΔLawton ($F_{(1,82)} = 2.42$, $p < 0.05$, $\eta^2 = 0.06$)], and no differences when we analyzed progression between groups in ΔBarthel ($F_{(1,82)} = 0.25$, $p = 0.51$).

Neuropsychiatric Symptoms and Progression in Cognitive and Functional Measures

AD Group

Analyses Using CUSPAD Scale

We ran an independent regression model using ΔMoCA as dependent measure and the CUSPAD scores at the first stage of assessment (scores for delusions, hallucinations, illusions, alterations, conduct problems, depressive and anxiety symptoms, sleep problems and eating changes) as independent measures. This model reached significant values ($F_{(1,46)} = 4.21$, $p < 0.05$, $R^2 = 0.19$), showing that the variability in ΔMoCA was explained by the presence of depression and the score for sleep alterations. No significant effects were observed when exploring the score for other CUSPAD domains (see **Table 3** for a further description of results). A similar regression model with ΔMMSE as a dependent measure of cognitive progression also reached significant values

TABLE 3 | Independent regression model of cognitive progression (ΔMoCA and ΔMMSE) and functional physical and instrumental progression (ΔBarthel and ΔLawton, respectively) through groups of symptoms of behavior disturbance with CUSPAD at first stage in patients with AD and FTD.

Regression model	Global	Delusions	Hallucinations	Illusions	Depression	Conduct *p.*	Sleep *p.*	Eating *p.*
(A) AD patients								
ΔMoCA	$\beta = 0.82$	$\beta = 0.29$	$\beta = 0.01$	$\beta = 0.23$	$\beta = 0.48$	$\beta = 0.16$	$\beta = 0.45$	$\beta = 0.12$
($F_{(1,46)} = 4.21$, $p < 0.05$,	**$P = <0.01$**	$P = 0.19$	$P = 0.93$	$P = 0.22$	**$P = <0.05$**	$P = 0.31$	**$P = <0.05$**	$P = 0.34$
$R^2 = 0.19$)	$\eta^2 = 0.12$	$\eta^2 = 0.05$	$\eta^2 = 0.01$	$\eta^2 = 0.05$	$\eta^2 = 0.09$	$\eta^2 = 0.01$	$\eta^2 = 0.09$	$\eta^2 = 0.02$
ΔMMSE	$\beta = 0.26$	$\beta = 0.25$	$\beta = 0.12$	$\beta = 0.19$	$\beta = 0.36$	$\beta = 0.04$	$\beta = 0.22$	$\beta = 0.16$
($F_{(1,46)} = 3.59$, $p < 0.05$,	$P = 0.11$	$P = 0.12$	$P = 0.49$	$P = 0.19$	**$P = <0.05$**	$P = 0.98$	$P = 0.13$	$P = 0.31$
$R^2 = 0.09$)	$\eta^2 = 0.04$	$\eta^2 = 0.01$	$\eta^2 = 0.05$	$\eta^2 = 0.05$	$\eta^2 = 0.02$	$\eta^2 = 0.03$	$\eta^2 = 0.05$	$\eta^2 = 0.05$
ΔLawton	$\beta = 0.11$	$\beta = 0.29$	$\beta = 0.26$	$\beta = 0.13$	$\beta = 0.33$	$\beta = 0.10$	$\beta = 0.18$	$\beta = 0.21$
($F_{(1,46)} = 3.71$, $p < 0.05$,	$P = 0.58$	$P = 0.09$	$P = 0.15$	$P = 0.34$	**$P = <0.05$**	$P = 0.54$	$P = 0.38$	$P = 0.12$
$R^2 = 0.07$)	$\eta^2 = 0.05$	$\eta^2 = 0.06$	$\eta^2 = 0.05$	$\eta^2 = 0.05$	$\eta^2 = 0.07$	$\eta^2 = 0.01$	$\eta^2 = 0.05$	$\eta^2 = 0.05$
ΔBarthel	$\beta = 0.39$	$\beta = 0.25$	$\beta = 0.23$	$\beta = 0.16$	$\beta = 0.45$	$\beta = 0.21$	$\beta = 0.24$	$\beta = 0.03$
($F_{(1,46)} = 0.72$, $p = 0.51$,	**$P = <0.05$**	$P = 0.19$	$P = 0.20$	$P = 0.21$	**$P = <0.05$**	$P = 0.23$	$P = 0.09$	$P = 0.81$
$R^2 = 0.03$)	$\eta^2 = 0.09$	$\eta^2 = 0.05$	$\eta^2 = 0.05$	$\eta^2 = 0.05$	$\eta^2 = 0.12$	$\eta^2 = 0.05$	$\eta^2 = 0.06$	$\eta^2 = 0.05$
(B) FTD patients								
ΔMoCA	$\beta = 0.36$	$\beta = 0.32$	$\beta = 0.11$	$\beta = 0.03$	$\beta = 0.078$	$\beta = 0.42$	$\beta = 0.14$	$\beta = 0.091$
($F_{(1,35)} = 7.28$, $p < 0.001$,	**$P = <0.05$**	**$P = <0.05$**	$P = 0.12$	$P = 0.56$	$P = 0.31$	**$P = <0.001$**	$P = 0.11$	$P = 0.25$
$R^2 = 0.31$)	$\eta^2 = 0.12$	$\eta^2 = 0.11$	$\eta^2 = 0.04$	$\eta^2 = 0.02$	$\eta^2 = 0.04$	$\eta^2 = 0.13$	$\eta^2 = 0.04$	$\eta^2 = 0.03$
ΔMMSE	$\beta = 0.19$	$\beta = 0.15$	$\beta = 0.08$	$\beta = 0.05$	$\beta = 0.04$	$\beta = 0.18$	$\beta = 0.11$	$\beta = 0.09$
($F_{(1,35)} = 4.41$, $p < 0.05$,	**$P = <0.05$**	$P = 0.11$	$P = 0.22$	$P = 0.61$	$P = 0.78$	$P = 0.09$	$P = 0.11$	$P = 0.26$
$R^2 = 0.12$)	$\eta^2 = 0.06$	$\eta^2 = 0.05$	$\eta^2 = 0.05$	$\eta^2 = 0.02$	$\eta^2 = 0.04$	$\eta^2 = 0.06$	$\eta^2 = 0.05$	$\eta^2 = 0.05$
ΔLawton	$\beta = 0.91$	$\beta = 0.47$	$\beta = 0.02$	$\beta = 0.04$	$\beta = 0.21$	$\beta = 0.31$	$\beta = 0.04$	$\beta = 0.38$
($F_{(1,35)} = 3.12$, $p < 0.05$,	**$P = <0.001$**	**$P = <0.05$**	$P = 0.89$	$P = 0.81$	$P = 0.22$	**$P = <0.05$**	$P = 0.81$	**$P = <0.05$**
$R^2 = 0.06$)	$\eta^2 = 0.16$	$\eta^2 = 0.06$	$\eta^2 = 0.05$	$\eta^2 = 0.04$	$\eta^2 = 0.05$	$\eta^2 = 0.09$	$\eta^2 = 0.03$	$\eta^2 = 0.11$
ΔBarthel	$\beta = 0.39$	$\beta = 0.11$	$\beta = 0.17$	$\beta = 0.03$	$\beta = 0.22$	$\beta = 0.41$	$\beta = 0.25$	$\beta = 0.21$
($F_{(1,35)} = 0.98$, $p = 0.47$,	$P = 0.23$	$P = 0.54$	$P = 0.49$	$P = 0.88$	$P = 0.49$	$P = 0.11$	$P = 0.28$	$P = 0.33$
$R^2 = 0.03$)	$\eta^2 = 0.06$	$\eta^2 = 0.16$	$\eta^2 = 0.02$	$\eta^2 = 0.01$	$\eta^2 = 0.02$	$\eta^2 = 0.06$	$\eta^2 = 0.05$	$\eta^2 = 0.05$

Note: AD, Alzheimer's disease; FTD, frontotemporal dementia; CUSPAD, Columbia University Scale for Psychopathology in Alzheimer's Disease; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

($F_{(1,46)} = 3.59$, $p < 0.05$, $R^2 = 0.09$). In this case, only the score for depression explained the variability of ΔMMSE (**Table 3A**).

A second group of regression models was run, including ΔLawton and ΔBarthel as dependent measures of functional and instrumental progression and the CUSPAD total scores, and scores in each symptom at first stage as independent measures. The model on ΔLawton reached significant values ($F_{(1,46)} = 3.71$, $p < 0.05$, $R^2 = 0.07$), showing that the variability in ΔLawton was explained by the score for depression and the scores for sleep problems. The regression model with ΔBarthel as a dependent measure of functional physical progression and using the same independent measures did not reach significant values ($F_{(1,46)} = 0.72$, $p = 0.51$, $R^2 = 0.03$; see **Table 3A**).

Analyses Using NPI

In a subsample of subjects ($n = 14$), we used an extra scale for tracking NPS in order to analyze the role of a broad group of behavioral symptoms in predicting cognitive and functional progression in AD patients. We ran an independent regression model using ΔMoCA as a measure of cognitive progression, and as independent measures we included the total score of NPI, and the scores in each group of symptoms of NPI at the first stage (delusions, hallucinations, euphoria, depression, anxiety, aggression, apathy, disinhibition, irritability, motor disturbance, eating changes, sleep problems). This model reached significant values ($F_{(1,13)} = 3.14$, $p < 0.05$, $R^2 = 0.41$), showing that the variability of ΔMoCA was explained by the score of depression and the score for sleep disorders. No significant effects were observed when exploring the score for other NPI domains (see **Table 4B**). A similar regression model with ΔMMSE as a dependent measure of cognitive progression and the same independent measures did not reach significant values ($F_{(1,13)} = 1.19$, $p = 0.09$, $R^2 = 0.21$). The regression models with ΔLawton as functional instrumental progression measure ($F_{(1,13)} = 1.25$, $p = 0.55$, $R^2 = 0.28$) and ΔBarthel as functional physical progression measure ($F_{(1,13)} = 0.97$, $p = 0.60$, $R^2 = 0.24$) did not reach significant values (see **Table 4A**).

FTD Group

Analyses Using CUSPAD Scale

We ran an independent regression model using ΔMoCA as a measure of cognitive progression, and as independent measures we included the total score of CUSPAD and the scores in each group of symptoms of CUSPAD at the first stage. This model reached significant values ($F_{(1,35)} = 7.28$, $p < 0.001$, $R^2 = 0.31$), showing that the variability, ΔMoCA was explained by the global scores for CUSPAD, the score for delusions, the score for conduct problems and the score for eating changes (see **Table 3** for a further description of results). A similar regression model with ΔMMSE as dependent measure of cognitive progression and

TABLE 4 | Significant Independent regression model of cognitive progression through groups of symptoms of behavior disturbance with NPI at first and second stage in patients with AD and FTD.

Regression model	Global	Del.	Hal.	Euph.	Dep.	Anx.	Agg.	Apa.	Dis.	Irr.	Mot. D.	Eat. C.	Ste. P.
(A) AD patients (*n* = 14)													
ΔMoCA ($F_{(1,13)} = 3.14$, $p < 0.05$, $R^2 = 0.41$)	$\beta = 0.32$ $P = 0.10$ $\eta^2 = 0.06$	$\beta = 0.09$ $P = 0.69$ $\eta^2 = 0.04$	$\beta = 0.19$ $P = 0.59$ $\eta^2 = 0.04$	$\beta = 0.08$ $P = 0.65$ $\eta^2 = 0.03$	$\beta = 0.44$ $P < 0.05$ $\eta^2 = 0.07$	$\beta = 0.11$ $P = 0.63$ $\eta^2 = 0.04$	$\beta = 0.04$ $P = 0.82$ $\eta^2 = 0.03$	$\beta = 0.23$ $P = 0.22$ $\eta^2 = 0.05$	$\beta = 0.19$ $P = 0.59$ $\eta^2 = 0.04$	$\beta = 0.31$ $P = 0.11$ $\eta^2 = 0.06$	$\beta = 0.08$ $P = 0.65$ $\eta^2 = 0.03$	$\beta = 0.24$ $P = 0.21$ $\eta^2 = 0.05$	$\beta = 0.40$ $\mathbf{P = < 0.05}$ $\eta^2 = 0.06$)
(B) FTD patients (*n* = 14)													
ΔMoCA ($F_{(1,13)} = 2.41$, $p < 0.05$, $R^2 = 0.39$)	$\beta = 0.15$ $P = 0.41$ $\eta^2 = 0.05$	$\beta = 0.47$ $\mathbf{P = < 0.05}$ $\eta^2 = 0.07$	$\beta = 0.21$ $P = 0.39$ $\eta^2 = 0.05$	$\beta = 0.09$ $P = 0.72$ $\eta^2 = 0.03$	$\beta = 0.11$ $P = 0.47$ $\eta^2 = 0.04$	$\beta = 0.04$ $P = 0.89$ $\eta^2 = 0.02$	$\beta = 0.17$ $P = 0.42$ $\eta^2 = 0.05$	$\beta = 0.43$ $\mathbf{P = < 0.05}$ $\eta^2 = 0.05$	$\beta = 0.48$ $\mathbf{P = < 0.05}$ $\eta^2 = 0.08$	$\beta = 0.19$ $P = 0.31$ $\eta^2 = 0.02$	$\beta = 0.12$ $P = 0.47$ $\eta^2 = 0.02$	$\beta = 0.24$ $P = 0.26$ $\eta^2 = 0.02$	$\beta = 0.22$ $P = 0.39$ $\eta^2 = 0.05$
ΔMMSE ($F_{(1,13)} = 2.19$, $p < 0.05$, $R^2 = 0.30$)	$\beta = 0.23$ $P = 0.39$ $\eta^2 = 0.05$	$\beta = 0.56$ $\mathbf{P = <0.05}$ $\eta^2 = 0.06$	$\beta = 0.03$ $P = 0.87$ $\eta^2 = 0.03$	$\beta = 0.26$ $P = 0.11$ $\eta^2 = 0.04$	$\beta = 0.29$ $P = 0.18$ $\eta^2 = 0.05$	$\beta = 0.04$ $P = 0.83$ $\eta^2 = 0.03$	$\beta = 0.26$ $P = 0.11$ $\eta^2 = 0.04$	$\beta = 0.25$ $P = 0.12$ $\eta^2 = 0.04$	$\beta = 0.48$ $\mathbf{P<0.05}$ $\eta^2 = 0.06$	$\beta = 0.26$ $P = 0.11$ $\eta^2 = 0.04$	$\beta = 0.21$ $P = 0.42$ $\eta^2 = 0.04$	$\beta = 0.11$ $P = 0.69$ $\eta^2 = 0.04$	$\beta = 0.38$ $P = 0.21$ $\eta^2 = 0.05$

Note: AD, Alzheimer's disease; FTD, frontotemporal dementia; NPI, neuropsychiatric inventory; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; Del., delusions; Hal., hallucinations; Euph., euphoria; Dep., depression; Anx., anxiety; Agg., aggression; Apa., apathy; Dis., disinhibition; Irr., irritability; Mot. D., motor disturbance; Eat. C., eating changes; Ste. P., sleep problems.

the same independent measures also reached significant values ($F_{(1,35)} = 4.41$, $p < 0.05$, $R^2 = 0.12$; see **Table 3B**). In this case, only the global score of CUSPAD explained the ΔMMSE variability. The regression model with ΔLawton as dependent measure of functional and instrumental progression and CUSPAD scores as independent measures reached significant values ($F_{(1,35)} = 3.12$, $p < 0.05$, $R^2 = 0.06$), showing that the global score of CUSPAD and the scores for conduct problems explained the ΔLawton variability. The regression model with ΔBarthel did not reach significant values ($F_{(1,35)} = 0.98$, $p = 0.47$, $R^2 = 0.03$; see **Table 3B**).

Analyses Using NPI

In a subsample of FTD patients (n = 14), we assessed to what extent a broad group of behavioral symptoms predicted cognitive and functional progression using the NPI measure. The independent regression model using ΔMoCA as a measure of cognitive progression, and the total score of NPI, and the scores in each group of symptoms of NPI at the first stage as independent measures reached significant values ($F_{(1,13)} = 2.41$, $p < 0.05$, $R^2 = 0.39$). In particular, this model showed that the variability of ΔMoCA was explained by the score of delusions, the score for disinhibition and the score for apathy. No significant effects were observed when exploring other NPI domains (see **Table 4B**).

A similar regression model with ΔMMSE as dependent measure of cognitive progression and the same independent measures also reached significant values ($F_{(1,14)} = 2.19$, $p < 0.05$, $R^2 = 0.30$). In this case, the score of delusion and the disinhibition explained the ΔMMSE variability. No significant effects were observed when exploring other NPI domains. The regression models with ΔLawton as functional instrumental progression measure ($F_{(1,13)} = 0.85$, $p = 0.65$, $R^2 = 0.18$) and ΔBarthel as functional physical progression measure ($F_{(1,13)} = 0.93$, $p = 0.57$, $R^2 = 0.18$) did not reach significant values (see **Table 4B**).

Regression Analyses According to the Subgroups of Disease Progression

AD Group

Among the 47 AD patients, a total of three patients did not show deterioration (6.3% of the total of the sample), a group of 38 patients showed an expectable deterioration (85.1% of the total of the sample), and four patients showed fast deterioration (8.5% of the total of the sample).

The analyses of NPS in AD subgroups only revealed differences in the depression scores at the first stage of assessment ($F_{(1,46)} = 6.56$, $p < 0.01$). No differences were observed when we analyzed the other symptoms (all p values above 0.3). A *post hoc* analysis (Tukey's HSD, MS = 81.24, df = 46) revealed that patients who did not show deterioration presented minor depression scores compared to patients with expectable deterioration ($p < 0.01$) and patients with fast deterioration ($p < 0.01$). Additionally, patients with fast deterioration had major depression scores compared to expectable deterioration patients ($p < 0.01$).

We ran new independent regression models only in the group of patients who presented the expectable deterioration (n = 38) to analyze the predictive role of NPS on cognitive

and functional decline in the group of patients with expectable deterioration. The regression models on this group revealed a similar pattern of results to the regression models ran with the total number of patients. In particular, the model reached significant values ($F_{(1,37)} = 3.21$, $p < 0.05$, $R^2 = 0.09$), and showed that the variability of ΔMoCA was explained by the score for depression ($\beta = 0.39$, $p < 0.05$, $\eta^2 = 0.06$), the score for sleep problems ($\beta = 0.35$, $p < 0.05$, $\eta^2 = 0.06$) and the global score of CUSPAD ($\beta = 0.55$, $p < 0.05$, $\eta^2 = 0.06$). The regression model of the ΔLawton also reached significant values ($F_{(1,37)} = 2.99$, $p < 0.05$, $R^2 = 0.06$) and revealed that the score for depression ($\beta = 0.31$, $p < 0.05$, $\eta^2 = 0.06$) and the scores for sleep problems ($\beta = 0.29$, $p < 0.05$, $\eta^2 = 0.06$) explained the variability of ΔLawton. The model of ΔBarthel did not reach significant values ($F_{(1,37)} = 0.72$, $p = 0.51$, $R^2 = 0.03$). We avoided running the regression model of ΔMMSE, considering that MMSE scores were used to categorize the subgroups of disease progression and then generate circularity.

FTD Group

Among the 36 FTD patients, three patients did not show deterioration (8.3% of the total of the sample), a group of 29 patients showed an expectable deterioration (80.5% of the total of the sample) and four patients showed fast deterioration (11.1% of the total of the sample). The analyses of NPS in FTD subgroups only revealed differences in the conduct problems scores at the first stage of assessment ($F_{(1,35)} = 9.98$, $p < 0.01$). No differences were observed when we analyzed other CUSPAD symptoms (all p values above 0.1). A *post hoc* analysis (Tukey's HSD, MS = 81.24, $df = 46$) revealed that patients who did not show deterioration presented minor conduct problem scores compared to expectable deterioration patients ($p < 0.001$) and fast deterioration patients ($p < 0.0001$). Additionally, patients with fast deterioration had major conduct problem scores compared to expectable deterioration patients ($p < 0.05$).

Following the same procedure used in the AD group, we ran new independent regression models only in the group of patients who presented the expectable deterioration ($n = 29$). As occurred in the AD group, the regression models on this group revealed a similar pattern of results to the regression models ran with the total number of patients. In particular, the model reached significant values ($F_{(1,28)} = 8.95$, $p < 0.001$, $R^2 = 0.33$) and showed that the global scores for CUSPAD, the score for delusions ($\beta = 0.44$, $p < 0.05$, $\eta^2 = 0.06$), the score for conduct problems ($\beta = 0.48$, $p < 0.05$, $\eta^2 = 0.06$) and the score for eating changes ($\beta = 0.42$, $p < 0.05$, $\eta^2 = 0.06$) explained the variability of ΔMoCA. The regression model of the ΔLawton also reached significant values ($F_{(1,28)} = 3.12$, $p < 0.05$, $R^2 = 0.06$) and revealed that the score for delusion ($\beta = 0.45$, $p < 0.05$, $\eta^2 = 0.06$), the scores for conduct problems ($\beta = 0.49$, $p < 0.05$, $\eta^2 = 0.06$) the score for eating changes ($\beta = 0.39$, $p < 0.05$, $\eta^2 = 0.06$) and the global score of CUSPAD ($\beta = 0.62$, $p < 0.01$, $\eta^2 = 0.09$) explained the variability of ΔLawton. The model of ΔBarthel did not reach significant values ΔBarthel ($F_{(1,28)} = 1.28$, $p = 0.29$, $R^2 = 0.05$). We did not run the model of ΔMMSE to avoid circularity considering that this measure was used to divide the subgroups of disease progression.

Mediation Analyses

AD Group

We ran independent mediation analyses to track the impact of demographical factors and medical comorbidities in the association between cognitive (ΔMoCA, ΔMMSE)-functional decline measures (ΔLawton, ΔBarthel) and NPS (tracked by CUSPAD). The regression model between ΔMoCA (dependent variable) and scores of CUSPAD ($F_{(1,46)} = 4.11$, $p < 0.05$, $R^2 = 0.19$) showed to be mediated by medical comorbidities, age of disease, onset time of disease, ΔLawton and ΔBarthel considering that the model remained significant although the F score decreased ($F_{(1,46)} = 2.19$, $p < 0.05$, $R^2 = 0.05$). The mediation analyses also revealed that comorbidities ($\beta = 0.27$, $p < 0.05$, $\eta^2 = 0.06$), age of disease onset ($\beta = 0.29$, $p < 0.05$, $\eta^2 = 0.06$) disease time ($\beta = 0.49$, $p < 0.01$, $\eta^2 = 0.07$), ΔLawton ($\beta = 0.52$, $p < 0.01$, $\eta^2 = 0.07$) and ΔBarthel ($\beta = 0.56$, $p < 0.01$, $\eta^2 = 0.07$), explained the variance of the dependent measure ΔMoCA. However, no significant mediation effects were found when analyzing the usage of medications before diagnosis ($\beta = 0.11$, $p = 0.26$, $\eta^2 = 0.02$).

A similar mediation analysis was run with the regression model of ΔMMSE ($F_{(1,46)} = 3.59$, $p < 0.05$, $R^2 = 0.09$) and revealed a partial mediation (the regression remained significant although the F index decreased) of comorbidities, age of disease onset and disease time ($F_{(1,46)} = 2.32$, $p < 0.05$, $R^2 = 0.06$). The mediation analyses also revealed that comorbidities ($\beta = 0.26$, $p < 0.05$, $\eta^2 = 0.06$), the age of disease onset ($\beta = 0.31$, $p < 0.05$, $\eta^2 = 0.06$), disease time ($\beta = 0.41$, $p < 0.05$, $\eta^2 = 0.06$), ΔLawton ($\beta = 0.58$, $p < 0.01$, $\eta^2 = 0.07$) and ΔBarthel ($\beta = 0.32$, $p < 0.05$, $\eta^2 = 0.06$), explained the variability of ΔMMSE. The usage of medications before diagnosis did not reach significant mediation effect ($\beta = 0.003$, $p = 0.93$, $\eta^2 = 0.01$).

The mediation analyses on regression model of ΔLawton ($F_{(1,46)} = 2.24$, $p < 0.05$, $R^2 = 0.07$) also revealed a partial mediation of comorbidities, age of disease onset and disease time as revealed by the reduction of F scores in the model ($F_{(1,46)} = 2.69$, $p < 0.05$, $R^2 = 0.07$). The mediation analyses also revealed that the presence of comorbidities ($\beta = 0.29$, $p < 0.05$, $\eta^2 = 0.06$), the age of disease onset ($\beta = 0.34$, $p < 0.05$, $\eta^2 = 0.06$), the disease time ($\beta = 0.31$, $p < 0.05$, $\eta^2 = 0.06$), ΔMoCA ($\beta = 0.65$, $p < 0.01$, $\eta^2 = 0.07$) and ΔMMSE ($\beta = 0.53$, $p < 0.01$, $\eta^2 = 0.07$), explained the variability of ΔLawton. The usage of medications before diagnosis did not reach significant mediation effects ($\beta = 0.005$, $p = 0.98$, $\eta^2 = 0.01$).

The model of ΔBarthel was initially non-significant ($F_{(1,46)} = 0.72$, $p = 0.51$, $R^2 = 0.03$). The mediation analyses did not reveal mediation effects of comorbidities age of disease onset, disease time and the usage of medication before diagnosis as the model remained non-significant after the inclusion of comorbidities age of disease onset, disease time and cognitive decline measures (ΔMMSE and ΔMoCA; $F_{(1,46)} = 1.72$, $p = 0.08$, $R^2 = 0.03$).

FTD Group

The mediation analyses on models of cognitive decline measures [ΔMoCA ($F_{(1,35)} = 7.28$, $p < 0.001$, $R^2 = 0.31$) and ΔMMSE ($F_{(1,35)} = 4.41$, $p < 0.05$, $R^2 = 0.12$)] revealed only a partial

mediation of comorbidities, age of disease onset, disease time and functional decline measures (ΔLawton, and ΔBarthel), as showed by reductions in F scores [ΔMoCA ($F_{(1,35)}$ = 2.67, $p < 0.05$, $R^2 = 0.31$); and ΔMMSE ($F_{(1,35)}$ = 2.44, $p < 0.05$, $R^2 = 0.12$)]. The analyses revealed that comorbidities [ΔMoCA ($\beta = 0.33$, $p < 0.05$, $\eta^2 = 0.06$) and ΔMMSE ($\beta = 0.37$, $p < 0.05$, $\eta^2 = 0.06$)], disease time [ΔMoCA ($\beta = 0.44$, $p < 0.05$, $\eta^2 = 0.06$) and ΔMMSE ($\beta = 0.46$, $p < 0.05$, $\eta^2 = 0.06$)] and ΔLawton [ΔMoCA ($\beta = 0.37$, $p < 0.05$, $\eta^2 = 0.06$) and ΔMMSE ($\beta = 0.39$, $p < 0.05$, $\eta^2 = 0.06$)] explained the variability of both cognitive decline measures. The analyses on the mediation effect of age of disease onset [ΔMoCA ($\beta = 0.05$, $p = 0.53$, $\eta^2 = 0.05$) and ΔMMSE ($\beta = 0.16$, $p = 0.17$, $\eta^2 = 0.05$)], Barthel [ΔMoCA ($\beta = 0.12$, $p = 0.22$, $\eta^2 = 0.04$) and ΔMMSE ($\beta = 0.08$, $p = 0.34$, $\eta^2 = 0.05$)] and the usage of medication [ΔMoCA ($\beta = 0.06$, $p = 0.92$, $\eta^2 = 0.01$) and ΔMMSE ($\beta = 0.12$, $p = 0.64$, $\eta^2 = 0.01$)] did not reach significant effects.

The mediation analyses on the model of ΔLawton ($F_{(1,35)}$ = 2.89, $p < 0.05$, $R^2 = 0.06$) revealed only partial mediation effects due to comorbidities, age of disease onset and disease time as the regression models showed reductions in F score (ΔLawton ($F_{(1,35)}$ = 2.22, $p < 0.05$, $R^2 = 0.06$). The mediation analyses showed that the disease time ($\beta = 0.44$, $p < 0.05$, $\eta^2 = 0.06$), ΔMoCA ($\beta = 0.34$, $p < 0.05$, $\eta^2 = 0.06$) and ΔMMSE ($\beta = 0.31$, $p < 0.05$, $\eta^2 = 0.06$) explained the variability of ΔLawton. Additionally, analyses revealed that no comorbidities ($\beta = 0.13$, $p = 0.34$, $\eta^2 = 0.04$), no age of disease onset ($\beta = 0.11$, $p = 0.39$, $\eta^2 = 0.04$) and no usage of medication before diagnosis ($\beta = 0.07$, $p = 0.78$, $\eta^2 = 0.01$) reached significant beta values to explain the variability of ΔLawton.

The mediation analyses on ΔBarthel did not reveal mediation effects as the initial model between CUSPAD scores and ΔBarthel showed to be non-significant ($F_{(1,35)}$ = 0.98, $p = 0.47$, $R^2 = 0.03$) and remained non-significant after the inclusion of comorbidities, age of disease onset, disease time, cognitive decline measures and the usage of medications before diagnosis ($F_{(1,35)}$ = 0.44, $p = 0.71$, $R^2 = 0.01$).

DISCUSSION

In this study, we have evaluated the role of the presence of NPS in predicting cognitive and functional decline in AD and FTD. Our results indicate that during the initial stages of disease, NPS affect in particular and differentiated ways, the cognitive and functional disease progression for each type of neurocognitive disorder. In the case of AD, the results show that the presence of depressive symptoms as well as sleep problems had a higher predictive value for cognitive alterations than other NPS. In addition, the scores for depressive symptoms predict functional and instrumental progression. Conversely, the results from the FTD group showed that the global scores of behavioral alterations tracked by CUSPAD, the scores of delusions, conduct problems and eating changes at early stages of assessment had a higher predictive value for cognitive and functional progression. Together, our results highlighted the importance of tracking since early stages of disease assessment the presence of different types of NPS, as those symptoms directly impact disease course.

In our study, the sample of subjects in each group coursed with an expectable pattern of disease progression (patients who had a fall of around four MMSE points per-year). In the AD and FTD groups, more than 80% of cases presented an expectable pattern of deterioration.

Crucially, our results showed that subgroups of patients according to the degree of disease progression also differed in the magnitude of NPS symptoms at early stages of assessment. In particular, in the AD group, the patients with fast and expectable deterioration presented at early stages of assessment major depressive scores compared to patients without deterioration. In the same line, the FTD patients with fast deterioration and expectable deterioration showed major scores of conduct problems compared to patients with deterioration at early stages of assessment. However, our results are far from being conclusive as we have few patients in the subgroup of fast deterioration and the group without deterioration. Future studies should explore the differences in NPS in subgroups of disease progression by including more patients in each subgroup. The Independent regression analyses only in the subgroup of patients with expectable deterioration revealed a similar pattern of results as those observed in the total of sample in each group. This pattern confirms that the results were reliable, and results were not due to out of range effects in subjects with atypical disease course.

Additionally, the impact of NPS at first stage of assessment on cognitive and functional decline was corroborated by a group of extra analyses performed in a subsample of AD and FTD patients. By using the NPI (Cummins, 1997), a sensible instrument to track a broad spectrum of behavioral alterations (affective changes, psychotic symptoms, anxiety symptoms, behavioral control alterations, apathy, sleep disorders, eating changes and motor disturbances among others), we confirmed that the early behavioral alterations predict cognitive and functional decline. In agreement with the results found using the CUSPAD scores, we observed that depression and sleep disorders tracked by NPI predict cognitive decline in AD. This pattern of results affirms the preeminence of affective and somatic symptoms in predicting a poor disease course in AD. Besides, in FTD, the presence of delusions, apathy and disinhibition tracked by NPI predict cognitive decline. Crucially, with the usage of NPI, we were able to track two nuclear symptoms for FTD diagnosis (Zamboni et al., 2008; Rascovsky et al., 2011). Our results showed that apart from being crucial for diagnosis, those symptoms also have a role in determining the disease course.

In agreement with previous studies, our results revealed mediation effects of demographical factors (in particular age of disease onset and disease time; Borroni et al., 2008; Choi et al., 2016) and comorbidities (Kansal et al., 2016; Eldholm et al., 2018) on the association between NPS and cognitive and functional decline in both groups. However, the described pattern of results in regression models remained significant after mediation analyses, suggesting that the relationship between early NPI and cognitive and functional decline are not completely explained by comorbidities and demographical factors. In addition, our results showed a mutual mediation effect of cognitive and functional decline measures supporting previous studies revealing that

both cognitive and functional measures are interdependent (Cornelis et al., 2017).

Concerning the potential factors that could mediate the association between NPI and cognitive and functional decline measures, our study presents some limitations. First, although we found no mediation effects on cognitive and functional disease progression related to the usage of medications before diagnosis, we did not include further analysis on the impact of pharmacological and non-pharmacological interventions to alleviate NPS during the first and second stages of assessment on the cognitive-functional progression. Previous studies have shown that pharmacological interventions, rehabilitation plans and person-centered interventions could impact disease progression in both AD and FTD (Atri, 2011; Fazio et al., 2018). Future studies should assess to what extent different pharmacological interventions could reduce the disease progression in both AD and FTD. Second, we did not further assess the mediation effect of different types of comorbidities on cognitive and functional decline in neurodegenerative disorders. Previous studies have shown a strong impact of vascular complications on cognitive and functional decline (Sena et al., 2015; Janota et al., 2016). Future studies should control for both AD and FTD the impact of comorbidities in generating and maintaining the NPI and to what extent a combination of those factors accelerate the disease progression.

Previous studies have demonstrated the importance of depression in determining the progression towards a major neurocognitive disorder (Brendel et al., 2015; Zahodne et al., 2015; Kaup et al., 2016). A meta-analysis of 12 studies published in 2013 (Gao et al., 2013) showed that depression was a major risk factor for incidence of dementia (including AD, vascular dementia and any dementia) and Mild cognitive impairment (MCI). Our study adds new information on the role of different types of NPS as predictors of the course of AD. The presence of sleep problems predicted a worsening cognitive function in AD patients. Our results are in line with these studies, and also indicate that sleep alterations at the first stages of disease could also predict functionality impairments (Palmer et al., 2018). Furthermore, when depressive symptoms and sleep problems are present during the first stages of AD, they are predictive of major impairments in instrumental functionality 2.5 years into disease progression, which differs from other studies (Hallikainen et al., 2018) in which delusions, agitation, and aberrant motor behavior at the time of diagnosis predicted later AD progression.

In addition, we demonstrate that the presence of depressive symptoms in AD is associated with worse cognitive prognosis (Teng et al., 2007). This is important, since it suggests that specific monitoring of depression should have a greater value in predicting deterioration in AD. Our findings differ from a previous study (Peters et al., 2015), where NPS were predictors of greater progression to severe neurocognitive disorder and death, and affective symptoms were associated with death only (Rabins et al., 2013). In addition, it also differs from other studies where psychotic symptoms, agitated behavior, and aberrant motor behavior were associated with rapid disease progression (Buccione et al., 2007; Hallikainen et al., 2018). The presence of at least mild or one clinically significant NPS at baseline (compared with no symptoms) predicted both severe dementia and death (Rabins et al., 2013; Rosenberg et al., 2013), but this was not discriminated by NPS, as it was done in our study.

Other studies have commented on having at least mild or one clinically significant NPS at baseline (compared with no symptoms) and predicted both severe dementia and death (Peters et al., 2015; Rabins et al., 2013; Rosenberg et al., 2013), but this was not discriminated by NPS as was done in our study.

Using FDG PET, it is possible to determine that individuals with basic mild cognitive impairment with depressive symptoms have a higher load of B-amyloid with hypermetabolism in brain areas compared to non-depressive individuals (Ng et al., 2017). This could be related to the presence of active inflammation, resulting in a high-risk group for greater progression to a major neurocognitive disorder (Brendel et al., 2015).

This could be related to the presence of active inflammation, resulting in a high-risk group for greater progression to a major neurocognitive disorder (Brendel et al., 2015). One study reported that patients with depression in AD had more medial temporal lobe atrophy (MTA) than patients with AD without depression (Dhikav et al., 2014), and a post-mortem study revealed that AD patients with a history of depression had more neuritic plaques and neurofibrillary tangles in the hippocampus than those without a history of depression (Rapp et al., 2008). Therefore, in patients with neurocognitive disorders, depression could cause greater accumulation of β-amyloid, atrophy and inflammation leading to further deterioration, as demonstrated by our findings. Therefore, in patients with neurocognitive disorders, depression could cause greater accumulation of β-amyloid and inflammation, leading to further deterioration, as demonstrated by our findings. However, given that patients with depression experience alteration in volition and motivation, it is not clear whether progression is biased by depressive symptoms; in other words, it is not clear to what extent alterations and cognitive and functional progression are explained by the fact that these patients have depressive symptoms. Future studies should explore this further. Although there is no consensus on the interaction between cognition and affective symptoms in AD (Wilson et al., 2002; Rapp et al., 2011), previous studies suggest that depression does affect progression at least in patients with mild cognitive impairment (Kaup et al., 2016). Our results agree with earlier findings that revealed the role of depression in predicting cognitive declining. Thus, emotional and affective reactions associated with the neuropathological changes may manifest as an affective syndrome, signaling an impending decline in functional abilities (Palmer et al., 2018). Our findings implied that depression treatment might be applied to prevent or delay the occurrence and development of AD in patients with MCI.

However, given that patients with depression experience alteration in volition and motivation, it is not clear whether progression is biased by depressive symptoms; in other words, it is not clear to what extent alterations and cognitive and functional progression are explained by the fact that these patients have depressive symptoms. Future studies should explore this further. Although there is no consensus on the interaction between cognition and affective symptoms in AD,

previous studies suggest that depression does affect progression at least in patients with MCI (Kaup et al., 2016). Our results are in agreement with earlier findings that revealed the role of depression in predicting cognitive declining. However, in our study, the presence of depressive symptoms also impacts the functionality. Although it is possible that functional impairments are directly related to cognitive decline, the role of depressive symptoms in explaining impairments in functionality could also be associated with the fact that depressive symptoms also affect volitional and motor skills, which are necessary for functional autonomy. Altogether, our results show that it is of vital importance to assess depressive symptoms more carefully in patients with AD. Our findings support the necessity for new studies that evaluate whether an intervention on depression can modify the cognitive course of the underlying condition.

Previous studies have reported a high prevalence of sleep alterations in different neurodegenerative disorders (Mander et al., 2016). In fact, a possible association between behavioral pathways that include sleep alterations and neuropathological changes was recently demonstrated (Ehrenberg et al., 2018). Sleep-wake disturbances have been associated with the formation of amyloid plaques, and with the accumulation of the amyloid-β (Aβ) peptide (Lim et al., 2014). Our results are in line with these studies, and also indicate that sleep alterations at the first stages of disease could also predict functionality impairments (Palmer et al., 2018).

The presence of higher global scores in the scale tracking different types of NPS (CUSPAD), along with conduct problems and delusions predicts a worsened progression of the cognitive state and functionality in the FTD group. The role of NPS in FTD has shown to be nuclear and constituted of an accurate diagnosis for a behavioral variant of FTD, but also in linguistic variants (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). Conduct problems, in particular those related to apathy and disinhibition, are present from the very early stages of disease and many times in prodromes (Bott et al., 2014). In addition, it has recently been reported that the type of the first symptom in FTD, in particular the predominant presence of apathy or disinhibition, is related to a particular pattern of neurocognitive impairment (Santamaría-García et al., 2016). In this study, we add new data on the role of NPS in FTD by showing that the progression of a mixed group of NPS (general alteration of NPS and particularly, the presence of conduct problems) leads to a worse cognitive and functional prognosis.

Contrary to what we observed in AD, depression is not a strong predictor for cognitive and functional progression in FTD. Poor control of behavior in general could be explained by a pattern of classic neurocognitive alterations in FTD, characterized by alterations in key structures for behavioral regulation, including frontal, temporal, and insular structures (Ibañez and Manes, 2012; Baez et al., 2017). These findings could also suggest that NPS are another face of the neurocognitive degeneration seen in FTD. In this sense, a progression of cognitive, functional, and behavioral alterations in FTD is generated by classic neurocognitive changes in this condition. Another explanation to be explored in future studies is whether the presence of NPS generates a worsening of the cognitive and functional profile in FTD. This scenario would agree with disease progression studies in FTD that show an increase and mixed pattern of NPS, and an association between NPS and prognosis in this condition. Therefore, a broader exploration of the role of NPS in cognitive function in FTD, particularly whether NPS worsen the course of the disease or they are simply a consequence of the general frontotemporal neurocognitive alteration observed in FTD, is needed.

Furthermore, we observed that the presence of delusions is predictive of cognitive impairment in FTD. Although the presence of psychotic symptoms is more prevalent in neurocognitive disorders associated with Lewy Bodies (Cagnin et al., 2013; Gossink et al., 2017; Pezzoli et al., 2017), previous studies have also reported that FTD patients could be affected by delusions (Gossink et al., 2017). Delusions are especially pertinent as they are less widely recognized as harbingers of structural brain disease and more likely to lead to psychiatric misdiagnosis. Delusion mechanisms are likely to involve neural networks in the frontal and temporal lobes that are particularly vulnerable in FTD (Omar et al., 2011). Our results also reveal that a major presence of delusions could be a bio-behavioral predictor of cognitive decline in FTD (Mendez et al., 2008).

Finally, results in the FTD group also demonstrate that the presence of eating changes at the first stage of disease predicts cognitive and functional impairments in these patients. Eating abnormalities including appetite changes, increased carbohydrate craving, and changes in food preference are present in up to 60% of patients with frontotemporal dementia (FTD), and are one of the core symptoms required for the diagnosis of behavioral variant FTD (bvFTD; Rascovsky et al., 2011; Ahmed et al., 2015, 2018). Arguably, eating behavior alterations in FTD could be explained by altered frontal and temporal lobe volume, as well as impairments in networks linking those structures to the striatum and orbitofrontal cortices (Ahmed et al., 2018). Crucially, the impairments in these fronto-temporal and insular networks are at the core of behavioral and cognitive alterations in FTD. Our results indicate that the presence of eating changes at the first stages of disease could be a sensitive bio-behavior marker of cognitive and functional impairment in FTD.

Conduct problems and delusions are related to changes in frontotemporal and insular networks (Ibañez and Manes, 2012), and one might argue that eating changes could be considered as initial clinical footprints of the classical neurocognitive impairment pathway reported in FTD.

Our findings support the need for further studies exploring the differential role of various types of symptoms in predicting cognitive and functional changes in neurocognitive disorders. In particular, it is important to elucidate the role of apathy, disinhibition and irritability in predicting the general course of the disease progression, with the presence of particular pathways of neural atrophy and cognitive impairments of neurocognitive disorders. Similarly, it is essential to refine techniques for the observation and measurement of NPS during the diagnostic process, as well as in the follow-up of neurocognitive disorders. To this effect, it is necessary to include information provided by family members, companions, and caregivers, as well as the assessment of NPS clinicians, in order to improve symptom

evaluation. Taken together, our results highlight the need to better and more closely monitor NPS in neurocognitive disorders, along with studies that can determine if the presence of NPS can have a generative (causal) role in cognitive alterations. If so, new studies should also consider whether an effective treatment of behavioral disturbances would change the clinical course of these conditions.

Our results might be elucidating several aspects of the same problem. It is well known that changes in behavior are associated with changes in cognition and functionality. In some cases, cognitive alterations are found in patients without behavioral alterations and may be a predictive factor. Despite this, our study shows that behavioral progression is a determining factor that should be monitored and evaluated when analyzing the progression of neurocognitive disorders.

Therefore, NPS are much more than specifiers in neurocognitive disorders and are likely to play a central role in neurodegenerative diseases. The results of our study also support further studies to establish whether there are neurocognitive biomarkers associated with the progression of NPS in neurocognitive disorders and to evaluate the impact that adequate treatment and control of NPS can have on the functional and cognitive progression of these pathologies.

Analyses in the subsample of AD patients assessed with NPI revealed that depressive but not anxiety symptoms significantly predict cognitive decline. This pattern of results is in agreement with results reported with the CUSPAD. Contrary to the CUSPAD, the NPI is more selective in tracking particular types of symptoms. Although in our study the assessment with NPI revealed significant predictor effects for depressive symptoms, it is unclear to what extent the negative results for other behavioral symptoms are due to a restricted number of subjects assessed with this instrument. Future studies should assess the impact of behavioral symptoms on cognitive and functional decline by using different types of measures able to track a broader profile of behavioral, affective and cognitive symptoms.

In addition, it would be useful to assess the predictive role on cognitive and functional decline in neurodegeneration of other cognitive and psychological factors, including the copying styles, problem solving skills and personality traits, which have beeb shown to be relevant factors in predicting disease course in neurodegenerative disorders (Irish et al., 2012a,b; D'Iorio et al., 2018).

In this study, we have tried to fully analyze to what extent a broad group of behavioral symptoms could impact different cognitive and functional decline measures. A potential limitation of our study is that we have tested different regression models with a considerable number of predictors and outcomes. Evidently, the presence of a major number of factors and levels of analyses could increase error rates and false positive effects. However, we considered that there are some attenuators for this issue. First, we were interested in assessing the impact of NPS on disease progression following an approach that did not follow any *a priori* assumptions on NPS associated to disease progression. In this sense, the inclusion of variables of levels of analyses were needed to maintain the independence of assumptions in this topic. Second, we have tried to control the effects of multidimensionality and false positives by using effect sizes and *post hoc* analyses of each contrast when it was appropriate. Future studies should assess the multidimensionality of behavioral alterations in disease progression of AD and FTD by using another statistical approach including multidimensional reduction following principal component analyses or machine learning methods.

CONCLUSION

In this study, we demonstrate that the progression of behavioral disturbances is a determining factor in predicting functional and cognitive deterioration in patients. In particular, we observed that the presence of general behavioral alterations, delusions and eating changes predicts functional and cognitive impairment in FTD. In contrast, in patients with AD, the progression of depression as well as sleep changes are two crucial behavioral alterations that predict changes in the course of the condition. Taken together, our results highlight the importance of detecting and monitoring NPS in patients with different types of neurocognitive disorders.

ETHICS STATEMENT

Participants in this study provided verbal informed consent to be enrolled in this study. All patient caregivers provided written informed consent according with the Helsinki declaration. This study was approved by The Ethics Committee of the Pontificia Universidad Javeriana and the Hospital Universitario San Ignacio in Bogotá (Colombia). Additionally, we ran a secondary analysis of the information obtained in clinical records of patients. In particular, we assessed the scores of the results of NPI from that clinical records. All information obtained of the clinical records were treated ensuring confidentiality and privacy of identification information.

AUTHOR CONTRIBUTIONS

JSE and HS-G participated in design and conceptualization of the study, data acquisition, analysis and interpretation of the data, writing and revision of the manuscript. JB and ÁP participated in the data acquisition, data analysis and revision of the manuscript. DM, PR and VP-S participated in the design and conceptualization of the study and provided revisions of the manuscript. All authors contributed equally in the preparation of the manuscript. The manuscript was approved by all coauthors.

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8. Discusión

La línea de investigación que sustentó esta tesis se desarrolló a través de los cinco estudios expuestos en el capítulo anterior siguiendo el curso o historia de la enfermedad y el papel de los SNP. La variedad de los diseños metodológicos facilitó abordajes cada vez más complejos y precisos, debido a la multidimensionalidad de las técnicas de recolección de la información, de evaluación y de análisis, integrando las dimensiones neuropsicológicas, neuropsiquiátricas y neuroanatómicas, con técnicas e instrumentos diversos. Cada estudio consultó los avances más recientes, mediante una juiciosa revisión bibliográfica y, a su vez, logró resultados originales y novedosos que contribuyen a ampliar el conocimiento acerca del tema objeto de la tesis y sugieren opciones para darle continuidad a los esfuerzos investigativos.

En el primer estudio, se partió de identificar en pacientes colombianos el tipo y frecuencia de los síntomas neuropsiquiátricos (o alteraciones conductuales) y su etiología y se encontró una alta prevalencia en los diferentes subtipos como consecuencia de la búsqueda activa de estos. A diferencia de lo descrito en la literatura, encontramos que los SNP están presentes en el total de los pacientes con degeneración frontotemporal variante conductual, seguida por el 77,29 % en la enfermedad de Alzheimer. Además, encontramos una alta presencia de labilidad emocional en TN. Los datos son de especial valor, debido al papel que pueden cumplir estas alteraciones en el diagnóstico y en el seguimiento de la progresión del TN, así como en la disminución del impacto negativo en la vida de las personas con TN, en la de sus cuidadores y en el sistema de salud.

En el segundo estudio, se determinó en qué medida la presencia de depresión como representante de los síntomas neuropsiquiátricos y la queja subjetiva de memoria

podrían constituirse como factores de riesgo para deterioro neurocognoscitivo en pacientes con comorbilidades orgánicas. En particular, los síntomas depresivos parecen ser un predictor de desarrollo de deterioro cognoscitivo en presencia de hipertensión arterial. Se destaca la amplia muestra analizada (datos correspondientes a 5.853 personas mayores), representativa de un país latinoamericano. Estos hallazgos le conceden un espacio importante a la prevención y a la detección temprana y conducen a conclusiones de interés en salud pública.

En el tercer estudio, se establecieron las rutas neurales, cognitivas y clínicas en pacientes que debutaron con distintos tipos de SNP incluyendo la apatía y la desinhibición en el contexto de la DFTvc. Los hallazgos de este estudio permiten proponer claramente una subdivisión clínica nueva que debe ser considerada, basada en el tipo de SNP, generando así distintas variantes clínicas y neurocognitivas en DFT, incluyendo una variante conductual de *apatía* de la DFT y una variante de *desinhibición* de la DFT.

En el cuarto estudio, la cognición social ofreció nuevas luces para el diagnóstico de la DFTvc, con la construcción y aplicación en tres grupos (pacientes con DFTvc, EA y controles sanos) de una herramienta original para evocar emociones sociales-morales, incluyendo envidia y *Schadenfreude.* Los hallazgos de este estudio revelaron un aumento en la expresión de envidia y *Schadenfreude* en pacientes con DFT en comparación con pacientes con EA y controles sanos. Más aun, este estudio reveló los patrones neurales estructurales, cognitivos y clínicos de la experiencia de estas emociones sociales-morales en el grupo de pacientes descrito y su asociación con otros procesos de cognición social y la presencia de SNP, incluyendo la apatía y la desinhibición. La exacerbación de esas emociones sociales-morales aparece como una impronta distintiva de la DFTvc, una nueva expresión de la desregulación social y afectiva que podría impactar en el diagnóstico y la progresión de la enfermedad. Así mismo, se demostró una multidimensionalidad neurocognitiva en

la evocación de la envidia y el *Schadenfreude* que resultan modificadas en consecuencia de la presencia de TN.

En el quinto estudio, más allá de lo consignado en la literatura describiendo la presencia de los SNP en las enfermedades neurodegenerativas, se logró avanzar en el conocimiento al evaluar, por primera vez, cómo la presencia de distintos tipos de SNP (conductuales, afectivos y psicóticos, entre otros), durante las etapas tempranas de la enfermedad en pacientes con DFT y EA, predice la progresión cognitiva y funcional de manera diferenciada en cada enfermedad neurocognitiva. Para la DFT, los mayores valores predictivos corresponden a alteraciones conductuales, delirios y cambios en la alimentación; para la EA, la presencia de síntomas depresivos y las alteraciones del sueño. Estos resultados resaltan la necesidad del seguimiento de los diferentes tipos de SNP, dado su impacto directo en el curso de la enfermedad y en su manejo.

La discusión y conclusiones generales de los estudios se resumen enseguida.

Estudio 1

Los SNP, también denominados *alteraciones conductuales (AC)* (International Psychogeriatric Association, 2015), son una manifestación frecuente en los pacientes con TN incluyendo el trastorno neurocognoscitivo leve (TNL). Estas AC constituyen una forma de identificar cambios tempranos asociados con las enfermedades neurodegenerativas, cumplen una función diagnóstica y de seguimiento para estos pacientes e incluso apoyan la evaluación sobre la progresión de cambios cognitivos y funcionales en sujetos cognoscitivamente normales (Geda et al., 2014; Ismail et al., 2016). Las alteraciones más comunes descritas en la literatura son apatía, irritabilidad, comportamiento motor aberrante y agitación/agresividad (Steinberg et al., 2008; García-Alberca et al., 2010),

consistente con los hallazgos del estudio 1. Las AC se presentan con mayor frecuencia en TN, debido a degeneración frontotemporal variante conductual (100 %), enfermedad de Alzheimer (77,29 %) y vascular (76,19 %). Las AC más prevalentes en el grupo evaluado fueron la apatía (50,75 %), la irritabilidad (48,45 %), la agresividad (16,6 %) y la labilidad emocional (14,76 %). Sin embargo, se observó una particularidad en la población colombiana analizada y es una mayor prevalencia de la labilidad emocional. La etiología más frecuente de TN fue la EA probable, seguida por la DFTvc y el TN debido a múltiples etiologías.

El impacto de estos cambios comportamentales se aprecia en la persona que sufre el trastorno al generar rechazo y aislamiento en los familiares (que, en Colombia, al igual que en otros países, son los principales y exclusivos cuidadores), en la sociedad en general y en el sistema de salud por las continuas demandas de atención. La identificación de SNP puede sustentar el desarrollo y la implementación de estrategias de tratamiento y manejo específicas para disminuir tales impactos.

Los hallazgos de este estudio hacen un llamado a generar nuevas investigaciones destinadas a evaluar la presencia de SNP con instrumentos estandarizados y explorar las asociaciones entre factores demográficos y cognoscitivos con los cambios en la prevalencia de SNP en los distintos tipos de TN, toda vez que el manejo y control de estas alteraciones podrían modificar el curso progresivo de la enfermedad e incidir en el pronóstico, el seguimiento y las respuestas a las intervenciones terapéuticas.

Estudio 2

Las personas mayores de 60 años con síntomas depresivos (SD) y/o quejas subjetivas de memoria (QSM), que sufren hipertensión arterial (HTA), tienen un riesgo mayor de deterioro cognoscitivo. Esta afirmación pudo comprobarse en el

estudio 2, mediante el análisis de los datos de una amplia muestra poblacional (5.853 personas mayores), representativa de un país latinoamericano (Wong et al., 2017). Algunos estudios señalan una fuerte dependencia del desempeño cognoscitivo con la presión arterial, pues la presión arterial baja o su control excesivo pueden generar daño neuronal debido al incremento de la perfusión cerebral. Los cambios en los mecanismos autorregulatorios de las personas mayores potencian esos efectos (McLeod y Jain, 2017; Cipolla, 2009).

De otra parte, las QSM se han vinculado con síntomas depresivos (SD), los cuales son una manifestación temprana de demencia, explicado por el daño vascular base de la neuropatología de esta enfermedad (Geda et al., 2014). De allí la importancia de explorar los SD especialmente en los adultos mayores.

La prevención y retardar su inicio son fundamentales en el caso de la demencia y del deterioro cognoscitivo. Esto puede alcanzarse modificando ciertos factores de riesgo con la adopción de estilos de vida saludable, detección de síntomas prodrómicos y prevención de factores de riesgo cardiovascular, incluyendo la HTA, lo cual podría impactar de forma importante los desenlaces en las personas mayores (Frankish y Horton, 2017; Taragano, 2009; McLeod y Jain, 2017; Cipolla, 2009).

Son necesarios nuevos estudios con evaluaciones más amplias y comprensivas para precisar y confirmar estos hallazgos, identificar factores de riesgo aún más precoces y dianas tempranas para potenciales tratamientos.

Estudio 3

Las dimensiones clínicas en las primeras etapas de la enfermedad tienen un impacto crucial en la presentación neurocognitiva de la DFTvc, preservando el perfil clínico con el que se inició, independientemente de la duración de la progresión de la

enfermedad. La subdivisión clínica de DFTvc basada en el primer síntoma, sería útil para rastrear las manifestaciones conductuales predominantes y sus correlatos neurocognitivos, cuestionando la tendencia actual de asignar el mismo peso a la presencia de apatía, desinhibición y otros síntomas (por ejemplo, empatía o comportamiento ritualista).

Adicionalmente, los resultados arrojaron una primera evidencia de un patrón distintivo de atrofia cerebral (integrando ambos análisis de cerebro completo y regiones de interés), después de tres años de evolución de la enfermedad, así: mayor atrofia cerebral y niveles aumentados de desinhibición y apatía, respectivamente en los pacientes con DFTvcA y DFTvcD; atrofia en las áreas frontales, insulares y temporales en pacientes con DFTvcA, y atrofia de las regiones prefrontales, unión temporoparietal, ínsula y región temporoparietal en los de DFTvcD (análisis de cerebro completo); también, un aumento de la atrofia en las regiones frontotemporales en pacientes con DFTvcD en comparación con los pacientes con DFTvcA; se confirmó que un conjunto de áreas cerebrales, incluyendo la orbitofrontal derecha, prefrontal dorsolateral derecha, y el caudado izquierdo permiten distinguir los subgrupos de pacientes.

Se requieren estudios longitudinales para aportar evidencia de la relación particular entre los síntomas de inicio y la trayectoria y progresión de la enfermedad en la DFTvc, evaluando los correlatos neuropsicológicos y anatómicos en las etapas más tempranas buscando establecer que procesos cognitivos específicos se encuentran alterados por cada síntoma en cada etapa de la enfermedad. Igualmente, para comprender si el curso de la enfermedad cambia de acuerdo con un síntoma específico y si la intervención farmacológica precoz sobre los primeros síntomas puede modificar la presentación neurocognitiva, el pronóstico y el proceso de atrofia cerebral en la DFTvc.

Estudio 4

Este estudio reveló una exacerbación de las emociones morales de *Schadenfreude* (placer por las desgracias de los demás) y envidia (molestia por los logros de otro) en la DFTvc. Este hallazgo constituye así un nuevo sello clínico de esa patología que podría impactar en el diagnóstico y la progresión de la enfermedad. El análisis de los datos de controles sanos, pacientes con DFT y con EA con respecto a esas emociones y a sus facetas primordiales (merecimiento, moralidad y legalidad), mostraron respuestas aumentadas en envidia y *Schadenfreude* en los primeros ante componentes morales y legales en los pacientes DFTvc. En estos últimos, la indagación de las áreas neurales críticas en el proceso cognitivo con un modelo de lesión puso en evidencia los correlatos neurocognitivos de cada una de las expresiones emocionales descritas en pacientes con distintos perfiles de atrofia. La exacerbación de las emociones sociales-morales en DFTvc son una nueva expresión de la desregulación social y afectiva en pacientes con DFT y no la simple manifestación de perturbaciones sociales y conductuales, como lo revelaron los resultados controlados por distintas covariables incluyendo evaluación de SNP, medidas de cognición ejecutiva y otras medidas de cognición general.

Los resultados del estudio acerca de las emociones sociales-morales ofrecen nuevos conocimientos sobre los mecanismos neurodegenerativos que subyacen a las emociones complejas y a la cognición social y moral, destacando una relación entre el deterioro de esas emociones en la DFTvc, con desregulación afectiva, nexos entre impedimentos emocionales básicos y alteraciones del comportamiento. La mayoría de las vías anatómicas descritas de *Schadenfreude* y envidia corresponden a la atrofia en DFTvc, es decir, atrofia frontotemporal e insular (Piguet et al., 2011; Tosun et al., 2012; Sedeno et al., 2016) y regiones estriatales (Pan et al., 2012; Bertoux et al., 2015), así mismo corteza cingulada posterior, lóbulo temporal medial y regiones parietales. Específicamente, en *Schadenfreude* la mayor

experiencia se asoció con volumen reducido en la circunvolución angular bilateral, precuneus y polo frontal derecho.

Además, el que todos los grupos obtuvieran mayores puntajes en las dimensiones moral y legal en contraste con la de merecimiento comprueba la multidimensionalidad de *Schadenfreude* y envidia, que pueden ser generadas por situaciones variadas en las cuales predominan sentimientos de merecimiento, pero especialmente por nociones de justicia ligados a pautas morales y legales (Shamay-Tsoory et al., 2007; Kipps et al., 2009; Jankowski y Takahashi, 2014), incluso los pacientes con DFTvc. En esa línea, es conveniente indagar más a fondo los vínculos entre el compromiso específico de la red del contexto social y las emociones morales.

Estudio 5

La presencia de SNP durante las etapas iniciales de la DFT y la EA son cruciales en la predicción del deterioro cognitivo de esos pacientes, debido a que afectan la progresión cognitiva y funcional de forma diferenciada y particular en cada tipo de enfermedad neurocognitiva. Estos hallazgos resaltan la necesidad de monitorizar los SNP de una forma mejor y más estrecha en las enfermedades neurocognitivas desde etapas tempranas de progresión de los TN.

En la DFT, los problemas conductuales, delirios y alteraciones en la alimentación (cambios en el apetito, en la preferencia de comidas y ansias aumentadas de carbohidratos) en etapas tempranas predicen mejor la progresión cognitiva y funcional. Un elemento nuevo es que la progresión de un grupo mixto de SNP (alteraciones generales de SNP, específicamente la presencia de problemas conductuales) lleva a un peor pronóstico funcional y cognitivo.

En el caso de la EA, la presencia de síntomas depresivos, al igual que las alteraciones del sueño, tuvieron un valor predictivo más alto que otros SNP para alteraciones cognitivas, subrayando que los síntomas depresivos también impactaron la funcionalidad al afectar las habilidades volitivas y motoras, necesarias para la autonomía funcional. Un dato novedoso es que los problemas del sueño predijeron un empeoramiento de la función cognitiva en la EA, en consonancia con estudios que indican que las alteraciones del sueño en las primeras etapas de la enfermedad también podrían predecir alteraciones funcionales (Palmer et al., 2018).

Con respecto a la progresión de la enfermedad, cada grupo exhibió un patrón de deterioro esperable (caída de alrededor de cuatro puntos en el MMSE al año); los subgrupos de pacientes establecidos según diferentes grados de progresión de la enfermedad variaron en la magnitud de SNP en etapas tempranas de la evaluación. En EA, los pacientes con deterioro rápido y esperable presentaron puntajes de depresión más altos que aquellos sin deterioro y, en DFT, los pacientes con deterioro rápido y esperable presentaron puntuaciones más altas de problemas conductuales que aquellos sin deterioro.

Lo anterior señala el camino para ampliar el conocimiento sobre el impacto de los SNP en el rendimiento cognitivo y funcional en distintos tipos de TN. En este sentido, se hace necesario usar diferentes tipos de medidas, incluyendo información proporcionada por los familiares, cuidadores, compañeros y la de distintos profesionales y buscar un perfil más amplio de SNP que incluya evaluación de cambios conductuales, afectivos y cognitivos y su papel en el deterioro cognitivo y funcional en la neurodegeneración. De igual manera, se hace necesario continuar con la exploración de las diferentes rutas neurocognitivas asociadas a cada tipo de SNP, revelando de esta manera patrones diferenciales del curso de la enfermedad a nivel neural. Esto permitiría evaluar el impacto del tratamiento adecuado y del

control de los SNP en el curso clínico y la progresión cognitiva y funcional de estas enfermedades.

9. Conclusiones

En síntesis, los hallazgos de esta tesis permiten avanzar en el conocimiento sobre el rol que tienen los SNP en las enfermedades neurodegenerativas, específicamente en la DFT, y en la EA, resaltando la función decisiva que dichos síntomas tienen para determinar rutas neurales, cognitivas y clínicas en distintas etapas de la historia de las condiciones neurodegenerativas.

Contrariamente a la descripción general que se hace de los SNP, nuestros hallazgos llaman al estudio individualizado de cada SNP. Dicho estudio y evaluación desde etapas tempranas de progresión de las condiciones neurodegenerativas parecen tener impactos en la comprensión clínica de la enfermedad y parecen revelar posibles nuevas rutas de tratamiento.

Los SNP durante las etapas iniciales de la DFT y la EA son cruciales en la predicción del deterioro cognitivo de los pacientes con TN, debido a que afectan la progresión cognitiva, clínica orgánica y funcional de la enfermedad de manera diferenciada y específica.

Todo esto permite señalar la utilidad de una subdivisión clínica de la DFT basada en los SNP y enfatizar la importancia de su identificación y seguimiento longitudinal. De manera similar, es necesario continuar el estudio de los SNP, pues parecen determinar resultados cognitivos particulares en pacientes con condiciones orgánicas comórbidas.

Finalmente, los resultados abren oportunidades de investigación relacionadas con un campo en constante desarrollo como lo es el de la cognición social,

particularmente el de las emociones sociales-morales, sus distintas dimensiones y los nexos cognitivos, afectivos y los mecanismos neurodegenerativos que subyacen a las emociones complejas y a la cognición social y moral.

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