UNIVERSITAT DE BARCELONA

Nuevos instrumentos subjetivos y objetivos para evaluar la fase preclínica de la enfermedad de Alzheimer

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Nuevos instrumentos subjetivos y objetivos para evaluar la fase preclínica de la enfermedad de Alzheimer

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INFORME DE LOS DIRECTORES DE LA TESIS

El Dr. José Luis Molinuevo Guix, doctor en Medicina por la Universidad de Barcelona, y la Dra. Lorena Rami González, doctora en Psicología por la Universidad de Barcelona,

CERTIFICAN

Que la memoria titulada *"Nuevos instrumentos subjetivos y objetivos para evaluar la fase preclínica de la enfermedad de Alzheimer",* presentada por Maria Antonella Mollica se ha realizado bajo nuestra supervisión y reúne los requisitos necesarios para ser defendida ante el Tribunal correspondiente para optar al grado de Doctor en Medicina por la Universidad de Barcelona.

Firmado,

José Luis Molinuevo Guix

Unidad de Alzheimer y otros trastornos cognitivos

Servicio de Neurología
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Unidad de Alzheimer y otros trastornos cognitivos

Servicio de Neurología
Hospital Clínico de Barcelona

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El final es el comienzo, y el comienzo es el primer paso,
…y el primer paso es el único paso.

J. Krishnamurti

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I. INTRODUCCIÓN

1. Enfermedad de Alzheimer: neuropatología y caracterización clínica

La enfermedad de Alzheimer es la causa más frecuente de demencia siendo responsable aproximadamente de entre el 60 y el 80 por ciento de los casos (Plassman y cols., 2007). La enfermedad de Alzheimer es una enfermedad neurodegenerativa caracterizada patológicamente por la acumulación cerebral de ovillos neurofibrilares y placas neuríticas, que evoluciona clínicamente generando deterioro cognitivo y síntomas conductuales que afectan a la capacidad para funcionar en la vida diaria.

Los criterios y líneas-guía revisados por el "National Institute on Aging and the Alzheimer's Association" (NIA-AA) publicados en 2011 (Sperling y cols., 2011), proponen que los procesos patológicos cerebrales relacionados con la enfermedad de Alzheimer pueden comenzar 20 años o más antes del inicio de los síntomas clínicos. Siguiendo estos criterios, hoy en día está ampliamente aceptado que existe una larga fase de transición entre el envejecimiento normal (asintomático) y la enfermedad de Alzheimer "clínica". En esta fase la disminución gradual de la función cognitiva se acompaña por la acumulación cerebral de procesos patológicos relacionados con la enfermedad. Cuando la disminución de la función cognitiva llega a ser significativa, se realiza el diagnóstico clínico de deterioro cognitivo leve. Por último, las actividades funcionales de la vida diaria comienzan a deteriorarse en fases más avanzadas, desde el momento en el que se realiza el diagnóstico clínico de demencia asociada a la enfermedad de Alzheimer. Por lo tanto, las personas con deterioro cognitivo leve muestran un deterioro cognitivo más marcado de lo que se esperaría para su edad y nivel de educación, pero esta disminución no interferiría significativamente con las actividades de la vida diaria.

Fundamentalmente, los criterios NIA-AA (Sperling y cols., 2011) actualizan los criterios publicados en 1984 por el "National Institute of Neurological and Communicative Disorders and Stroke" y por el "Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)" (McKhann y cols., 1984) incorporando los biomarcadores, que reflejan los procesos patológicos de la enfermedad. En dependencia del proceso fisiopatológico subyacente que evalúan, estos marcadores se han clasificado en 3

categorías: marcadores de amiloidosis, marcadores de la patología tau y marcadores de neurodegeneración (Jack y cols., 2016). Los marcadores de amiloidosis estarían representados por una reducción de los niveles de la proteína β-amiloide (isoforma 1-42) en el líquido cefalorraquídeo o una mayor retención de los trazadores PET (tomografía por emisión de positrones) de amiloide: estos marcadores evidenciarían en vivo el depósito cerebral de amiloide. Los marcadores de la patología tau (ovillos neurofibrilares) estarían constituidos por los niveles de la proteína tau hiperfosforilada (p-tau) determinados por PET o en líquido cefalorraquídeo. Por otro lado, los marcadores de neurodegeneración estarían representados por un aumento de los niveles de la proteína tau total, por los cambios estructurales objetivados por la resonancia magnética o por el hipometabolismo cerebral de glucosa mediante estudios PET; y serían el reflejo de la disfunción sináptica y la posterior muerte neuronal.

Estos marcadores permiten realizar un diagnóstico precoz y al mismo tiempo más específico, al ser pruebas biológicas que se asocian a cambios patológicos subyacentes a la enfermedad de Alzheimer. En ese sentido, los niveles de proteína tau anormalmente altos en combinación con niveles bajos de β-amiloide se correlacionan con los hallazgos neuropatológicos de la enfermedad de Alzheimer. Así, de acuerdo con los criterios NIA-AA, los individuos con deterioro cognitivo leve y concomitante presencia de niveles anormales de biomarcadores de amiloide y tau tienen una alta probabilidad de que el cuadro clínico sea debido a la enfermedad de Alzheimer (Albert y cols., 2011).

2. Importancia de definir la fase preclínica de la enfermedad de Alzheimer

Los criterios NIA-AA (Sperling y cols., 2011) también han propuesto la existencia de la fase preclínica de la enfermedad de Alzheimer. La fase preclínica se identifica en individuos cognitivamente sanos pero que presentan un biomarcador positivo relacionado con el substrato neuropatológico de la enfermedad. De acuerdo con la "hipótesis de la cascada amiloide" (Jack y cols., 2010) la producción excesiva de la proteína β-amiloide conduciría a la formación de placas seniles que a su vez llevarían,

por su acción tóxica, a la formación de ovillos neurofibrilares y posteriormente a la muerte celular y la aparición de la demencia.

El desarrollo de tratamientos modificadores de la enfermedad, que podrían detener los procesos patológicos de la enfermedad de Alzheimer, se ha convertido en una de las principales prioridades de la investigación médica (Reiman y cols., 2016). Aunque algunos fármacos pueden ralentizar la evolución de los síntomas de la enfermedad de Alzheimer, ningún tratamiento farmacológico disponible en la actualidad puede detener por completo los procesos patológicos que causan la enfermedad. En este contexto, la fase preclínica se ha convertido en un importante foco de investigación ya que se ha postulado que la intervención temprana puede ofrecer la mejor oportunidad de éxito terapéutico. En concreto, los últimos ensayos clínicos han sugerido que los tratamientos anti-amiloide podrían tener un efecto limitado una vez se haya producido la degeneración neuronal, pero han planteado la posibilidad de que este tipo de intervenciones puede tener más probabilidades de lograr una modificación del curso de la enfermedad si se inicia en estadios tempranos, antes de la aparición de los primeros síntomas cognitivos y clínicos asociados a la enfermedad (Akiyama, 2016).

En este marco, es necesaria una comprensión más exhaustiva de las primeras manifestaciones de la enfermedad de Alzheimer para guiar eficientemente la detección temprana de la enfermedad y las futuras intervenciones.

3. Influencia de factores demográficos y genéticos en la manifestación de la patología de la enfermedad de Alzheimer

Hay varios factores que aumentan o reducen el riesgo de los individuos de desarrollar la enfermedad de Alzheimer. En primer lugar, la edad es el factor de riesgo no modificable más importante. A medida que aumenta la edad, también lo hace la probabilidad de tener la enfermedad, con una prevalencia que se estima que puede duplicarse cada 5 años a partir de los 60 años (Hebert y cols., 2013). En segundo lugar, los factores como los años de educación o la reserva cognitiva, pueden reducir la gravedad de los síntomas en individuos que presentan la enfermedad (Rentz y cols., 2010). Asimismo, se ha postulado que los individuos con mayor reserva cognitiva

pueden poseer una mayor capacidad para tolerar los cambios cerebrales relacionados con la enfermedad de Alzheimer, sin exhibir por ellos síntomas clínicos (Stern, 2012).

Por otro lado, la forma más común de la enfermedad de Alzheimer es la forma esporádica (es decir, no determinada por mutaciones genéticas). El mayor factor de riesgo genético conocido para la enfermedad de Alzheimer esporádica es el alelo 4 del genotipo de la apolipoproteína E (ApoE4), presente en entre un 40 y un 65 por ciento de los pacientes que padecen la enfermedad. Esto ha sido confirmado por estudios de asociación a escala de genoma (Lambert y cols., 2013). Está bien documentado que adultos sanos portadores del ApoE4 presentan un mayor riesgo de manifestar deterioro cognitivo asociado a la enfermedad de Alzheimer y que la presencia del ApoE4 modularía los niveles de la proteína β-amiloide en el líquido cefalorraquídeo (Risacher y cols., 2015). Sin embargo, se necesitan nuevos estudios que analicen la influencia del ApoE4 en la relación entre los niveles de amiloide y el rendimiento cognitivo en individuos cognitivamente sanos.

4. Percepción subjetiva de declive cognitivo

4.1. El declive cognitivo subjetivo en la fase preclínica de la enfermedad de Alzheimer

La evaluación de la experiencia subjetiva de declive cognitivo puede llegar a ser muy informativa en la fase preclínica, en la cual los individuos presentan, por definición, funciones cognitivas normales de acuerdo a los instrumentos neuropsicológicos estándar existentes. El declive cognitivo subjetivo daría una visión longitudinal y subjetiva de la función cognitiva que no puede ser capturada por los estudios transversales sobre el rendimiento cognitivo objetivo. Esta es la razón por la cual está creciendo el interés en el declive cognitivo subjetivo como una característica relevante de la enfermedad de Alzheimer preclínica. Sin embargo, a pesar de la importancia de medir el declive cognitivo subjetivo en las fases tempranas de la enfermedad, los resultados de la investigación sobre el declive cognitivo subjetivo no son concluyentes.

En los últimos años se ha sugerido que el declive cognitivo subjetivo puede representar una de las primeras manifestaciones sintomáticas de la enfermedad de

Alzheimer. Hay evidencias emergentes de que existe una asociación entre el declive cognitivo subjetivo y los marcadores de neuroimagen relacionados con la enfermedad, como la pérdida de volumen de la materia gris (Striepens y cols., 2010) y el hipometabolismo cerebral (Mosconi y cols., 2008) en áreas que normalmente se ven afectadas en la enfermedad, y que los individuos con declive cognitivo subjetivo son más propensos a desarrollar en un futuro deterioro cognitivo leve o demencia asociados a la enfermedad de Alzheimer (Jessen y cols., 2011). Otros estudios han propuesto también que la presencia de declive cognitivo subjetivo parece aumentar la probabilidad de presentar biomarcadores de la enfermedad de Alzheimer alterados (Amariglio y cols., 2012). En cambio, otros estudios no han encontrado una asociación entre el declive cognitivo subjetivo y el rendimiento cognitivo objetivo (Hollands y cols., 2015).

Algunos autores han cuestionado la utilidad del concepto de declive cognitivo subjetivo debido a su alta prevalencia en personas mayores (Buckley y cols., 2015) (aparece aproximadamente en entre el 25 al 50 por ciento de esta población), así como por su fuerte relación con el estado de ánimo y la personalidad (Buckley y cols., 2013, Edmond y cols., 2014). Dado que la prevalencia del declive cognitivo subjetivo en la población adulta en general es relativamente alta y puede ser afectada por factores externos, se hace difícil determinar qué quejas podrían indicar un proceso incipiente relacionado con la enfermedad de Alzheimer, frente a otras quejas debidas a patologías neurodegenerativas diferentes de esta enfermedad, o a condiciones psicológicas.

Está ampliamente documentado que una característica común de la demencia asociada a la enfermedad de Alzheimer es la falta de conciencia acerca de los propios déficits o de la propia enfermedad, denominada *anosognosia.* Por otro lado, los estudios sobre los pacientes con deterioro cognitivo leve y la presencia de *anosognosia* discrepan entre ellos: algunos han proporcionado evidencias de que los pacientes con deterioro cognitivo leve presentan un juicio intacto sobre las propias dificultades (Kalbe y cols., 2005), mientras para otros las minimizan presentando niveles bajos de declive cognitivo subjetivo (Roberts y cols., 2009; Galeone y cols., 2011).

En definitiva, los resultados de la investigación actual sobre el declive cognitivo subjetivo indican que su valor pronóstico y su relación con la enfermedad de Alzheimer siguen siendo pocos claros.

En este contexto, el declive cognitivo subjetivo referido por un informador podría ser una importante fuente de información con respecto a los cambios precoces que ocurren en las fases asintomáticas de la enfermedad de Alzheimer. Algunos estudios longitudinales han argumentado que las preocupaciones sobre el deterioro cognitivo referidas por el informador son mejores predictores del deterioro cognitivo posterior en ancianos cognitivamente sanos en comparación con el declive cognitivo subjetivo referido por el mismo individuo (Rabin y cols., 2012). De manera similar, algunos autores han encontrado una asociación entre el declive en las actividades instrumentales de la vida diaria referido por el informador y los niveles de biomarcadores de la enfermedad de Alzheimer en sujetos cognitivamente sanos o con deterioro cognitivo (Okonkwo y cols., 2010), pero otros no han confirmado dicha asociación (Hollands y cols., 2015). Aunque las quejas referidas por los informadores parecen relevantes para la clasificación clínica de pacientes con la enfermedad de Alzheimer (Harrison y cols., 2015), pocos estudios han utilizado medidas cuantitativas de deterioro cognitivo percibido simultáneamente por el propio individuo y por un informador (Gifford y cols., 2015), o han estudiado la posible discrepancia entre ambas perspectivas (Rattanabannakit y cols., 2016).

4.2. La medición del declive cognitivo subjetivo

La incongruencia encontrada en los estudios que han explorado el declive cognitivo subjetivo en la enfermedad de Alzheimer puede estar ocasionada por la alta variabilidad observada en su medición. De hecho, la medición del declive cognitivo subjetivo puede variar en función del número de preguntas utilizadas (es decir, una sola pregunta frente a múltiples preguntas) o el contenido de las mismas, o en función del término de comparación respecto al cual valorar el propio declive cognitivo subjetivo (o sea, las propias capacidades pasadas o las capacidades de individuos de la misma edad). Dada la variabilidad en los métodos de evaluación, no es de extrañar que las diferentes preguntas de declive cognitivo subjetivo tengan distintas asociaciones

con los factores anteriormente mencionados (biomarcadores de la enfermedad de Alzheimer, factores psicológicos y rendimiento cognitivo). En un intento para reducir esta discrepancia, el grupo internacional *Subjective Cognitive Decline Initiative* (Jessen y cols., 2014) ha propuesto unos criterios para el declive cognitivo subjetivo, y más recientemente se han proporcionado unas recomendaciones concretas para facilitar su uso en investigación (Molinuevo y cols., 2016).

En estos trabajos de consenso se sugiere que el término "declive" refleja mejor el curso temporal del cambio cognitivo asociado a la enfermedad de Alzheimer, en comparación con el término "deterioro" que puede ser de naturaleza crónica y estable. Por otra parte, también se ha argumentado que el declive cognitivo subjetivo percibido en los últimos años podría ser más predictivo de la enfermedad de Alzheimer que el declive cognitivo subjetivo experimentado durante un período más largo, el cual puede manifestarse debido al proceso de envejecimiento normal. Asimismo, se ha propuesto que preguntar sobre la percepción de declive de las funciones "cognitivas", en oposición a preguntar exclusivamente por el declive único de la "memoria", podría ser más sensible a las fases tempranas de la enfermedad de Alzheimer en sus formas de presentación clínica con manifestaciones más heterogéneas. En este sentido, actualmente se acepta que, a pesar de que la patología de la enfermedad de Alzheimer ha sido típicamente asociada con déficits en la memoria, otros aspectos de la cognición, como las funciones ejecutivas, se podrían deteriorar igualmente en algunos sujetos en las fases iniciales de la enfermedad de Alzheimer (Reinvang y cols., 2012).

Teniendo en cuenta estos elementos y reconociendo la importancia de estudiar el declive cognitivo subjetivo de acuerdo con los criterios especificados por el grupo internacional *Subjective Cognitive Decline Initiative*, actualmente hay una clara necesidad de desarrollar herramientas efectivas y capaces de cuantificar el declive cognitivo subjetivo. Estas herramientas deberían incluir una serie de preguntas que aborden cambios que se refieren a un período relativamente corto y a diferentes dominios cognitivos. Además, aunque la confirmación del informador no es un criterio necesario según el *Subjective Cognitive Decline Initiative*, se ha sugerido que la evaluación del declive cognitivo subjetivo se debería realizar con cuestionarios que

incluyan también la opinión de un informador. Por último, puesto que el declive cognitivo subjetivo puede estar determinado en parte por síntomas psicológicos subclínicos (que no cumplen criterios para el trastorno psiquiátrico), se ha recomendado la administración de escalas de ansiedad y depresión con el fin de estudiar la influencia de la sintomatología ansioso-depresiva sobre la percepción subjetiva de declive cognitivo.

5. Rendimiento objetivo en las funciones cognitivo-motoras

5.1. Rendimiento objetivo con tests neuropsicológicos clásicos y computarizados en la fase preclínica de la enfermedad de Alzheimer

Como se ha mencionado anteriormente, en los individuos preclínicos la cognición se mantiene dentro de los límites de la normalidad. Por esta razón, las baterías de pruebas neuropsicológicas no presentan suficiente variabilidad en la población de individuos cognitivamente sanos, de tal manera que es poco probable que sean apropiadas para identificar posibles déficits cognitivos sutiles que puedan manifestarse en esta población. En la apreciación de estas limitaciones, algunos han sugerido que la detección de dificultades sutiles debe basarse en la aplicación de nuevas pruebas cognitivas experimentales (Rentz y cols., 2013). Se ha propuesto que este tipo de pruebas debieran ser lo suficientemente fáciles como para ser entendidas, así como lo suficientemente breves como para no dar lugar a una disminución de la motivación. Estas pruebas tampoco deben generar efecto en la práctica y, además, deben proporcionar mediciones seriadas del rendimiento intra-individual en intervalos de tiempo breves con el fin de detectar cualquier cambio sutil eventual (Rentz y cols., 2013).

En este contexto, las pruebas computarizadas pueden proporcionar medidas más sensibles que las pruebas neuropsicológicas clásicas, que fueron diseñadas para pacientes que ya presentan deterioro cognitivo. Recientemente, se han desarrollado nuevos tests experimentales para explorar el área de la memoria que han demostrado una mayor sensibilidad que las pruebas neuropsicológicas estándares en la identificación de cambios cognitivos en individuos preclínicos (Racine y cols., 2016).

Por consiguiente, la detección de cualquier dificultad cognitiva mediante el uso de nuevas medidas computarizadas podría ser crucial para detectar cambios cognitivos sutiles y caracterizar mejor la fase preclínica de la enfermedad de Alzheimer.

5.2. Evaluación de la coordinación visuomotora

Aunque la enfermedad de Alzheimer se ha asociado típicamente a cambios en la memoria episódica relacionados a su vez con cambios estructurales en las regiones mediales del lóbulo temporal, estudios de neuroimagen funcional han indicado la presencia de anomalías en las áreas de asociación parietal posterior en las fases tempranas de la enfermedad de Alzheimer (Jacobs y cols., 2012). Se sabe que la corteza parietal juega un papel importante en la transformación de la información visuoespacial en acción intencional y que en su conexión con el lóbulo frontal subyacen las funciones visuomotoras (Culham y Valyear, 2006), que comprenden la percepción visual, las relaciones espaciales y la expresión motora de lo percibido.

Estudios longitudinales han sugerido la presencia de un declive cognitivo sutil en las funciones visuomotoras, evaluadas por medio de tests clásicos, en la fase asintomática de la enfermedad de Alzheimer. En concreto, en individuos preclínicos o individuos que posteriormente desarrollan la enfermedad de Alzheimer, se ha documentado una disminución del rendimiento en las pruebas tales como las pruebas “Symbol Digit” y el “Trail Making” (Snitz y cols., 2013, Donohue y cols., 2014). Además, es importante destacar que recientemente ha sido validado el “Preclinical Alzheimer Cognitive Composite” que combina medidas de memoria episódica con la prueba visuomotora “Symbol Digit” (Donohue y cols., 2014). En relación a esto, un estudio reciente ha indicado una mayor disminución de rendimiento en el “Composite” en los participantes preclínicos que en los controles (Lim y cols., 2015).

A pesar de estas evidencias, pocos estudios han investigado, por medio de tests experimentales, la relación entre medidas visuomotoras especificas (es decir, que no requieren la participación de otras funciones cognitivas como las funciones ejecutivas) y variables relacionadas con procesos patológicos de la enfermedad de Alzheimer en las etapas preclínicas. Un trabajo reciente ha identificado la presencia de deterioro

visuomotor temprano en individuos en alto riesgo de desarrollar la enfermedad de Alzheimer (con antecedentes familiares de la enfermedad) en una nueva tarea experimental visuomotora que consiste en transformar la información visual y espacial en respuestas motoras (Hawkins y Sergio, 2014). Los autores han encontrado diferencias entre el grupo de individuos cognitivamente sanos en riesgo de desarrollar la enfermedad de Alzheimer y el grupo de individuos sin riesgo, tanto en el número de errores como en la velocidad de procesamiento visuomotor. Teniendo en cuenta que en este trabajo previo el análisis de biomarcadores no estaba disponible, sería de interés investigar, mediante pruebas experimentales, la relación que puedan tener funciones visuomotoras especificas con la patología de la enfermedad de Alzheimer en la fase preclínica.

5.3. Evaluación del control motor

A su vez, hay un creciente reconocimiento de que la patología asociada a la enfermedad de Alzheimer puede dar lugar a una amplia gama de déficits no solamente cognitivos, sino también motores (Albers y cols., 2015). Siguiendo esta línea de investigación, en los últimos años se ha empezado a delinear la posible relación entre la función motora y el riesgo de desarrollar la enfermedad de Alzheimer. Los estudios longitudinales en adultos, inicialmente cognitivamente sanos, han observado la aparición de deterioro motor (en particular, una disminución en la velocidad de la marcha) en comparación con individuos cognitivamente estables, doce años antes de la aparición de los primeros síntomas cognitivos (Buracchio y cols., 2010). Estos datos sugieren que el deterioro de la función motora podría ser un factor de riesgo para el desarrollo de deterioro cognitivo leve y demencia. Un estudio más reciente también ha encontrado una asociación entre la velocidad de la marcha y los depósitos de amiloide cerebral en sujetos cognitivamente sanos o con deterioro cognitivo leve (del Campo y cols., 2016). No obstante, como comentan los autores, en este estudio las medidas de degeneración neuronal, que es sabido que puede contribuir a la ralentización de la velocidad de la marcha, no han sido investigadas. Por lo tanto, se necesitan nuevas investigaciones para aclarar cómo la velocidad motora se relaciona con los niveles de β-amiloide y tau.

Si bien la marcha ha sido estudiada en investigaciones en fases de demencia asociada a la enfermedad de Alzheimer, el *tapping* manual, otro indicador importante de la función motora, ha recibido poca atención hasta la fecha. De acuerdo con Buracchio y cols. (2010) la presencia de mayor enlentecimiento motor en el *tapping* predeciría el desarrollo de deterioro cognitivo en individuos cognitivamente sanos. Camicioli y cols. (1998) también han observado un declive en la velocidad motora en el *tapping* en pacientes con deterioro cognitivo leve, comparados con controles, pero otro estudio no ha encontrado tales diferencias (Aggarwal y cols., 2006). Esta discrepancia puede deberse a los diferentes paradigmas empleados a lo largo de los estudios. Por ejemplo, las pruebas de *tapping* varían en función del tipo de estímulo usado (es decir, realizar la tarea de manera uniforme según una velocidad predeterminada, al ritmo más rápido que se pueda o a una velocidad "confort") o de la complejidad de la tarea propuesta (o sea, realizar el *tapping* con una sola mano, con múltiples dedos o con las dos manos). Por consiguiente, creemos que el empleo de nuevas pruebas precisas de la función motora, especialmente utilizando métodos cuantitativos fáciles de administrar, sería necesario para poder evaluar los cambios sutiles en la función motora en las fases preclínicas de la enfermedad de Alzheimer.

A pesar de que la literatura previa se ha centrado principalmente en el análisis de la velocidad motora, algunos estudios han sugerido que la variabilidad motora puede también ser un prometedor indicador de procesos patológicos asociados a la enfermedad de Alzheimer. Según Davids y cols. (2006) la variabilidad motora sería una característica inherente del rendimiento motor y se puede definir como las variaciones no intencionadas de movimientos voluntarios. Más concretamente, la variabilidad motora representa las variaciones de velocidad entre movimientos consecutivos, lo que reflejaría la inconsistencia del rendimiento motor. Estudios previos han observado que los individuos con deterioro cognitivo leve, en comparación con adultos sanos, presentan una mayor variabilidad motora durante la marcha (Verghese y cols., 2008), o durante la ejecución de movimientos de *tapping* (Bangert y Balota, 2012). Sin embargo, se necesitan nuevos estudios que analicen la relación de la variabilidad motora con los biomarcadores de la enfermedad de Alzheimer, así como su capacidad para detectar diferencias sutiles entre individuos preclínicos y controles.

Existen controversias sobre la posibilidad de que las alteraciones motoras puedan estar directamente asociadas con la enfermedad de Alzheimer, debido a su falta de especificidad. Individuos de edad avanzada sanos pueden presentar lesiones cerebrales no relacionadas con la enfermedad de Alzheimer que podrían alterar de igual forma la función motora, tales como anomalías vasculares subclínicas (Rosano y cols., 2007). Además, varios factores como la hipertensión, la hipercolesterolemia, la diabetes y el tabaquismo pueden aumentar el riesgo de padecer una enfermedad vascular, y por tanto asociarse a un empeoramiento de la función motora. Se ha descrito que otros factores podrían mejorarla, como por ejemplo un alto nivel de actividad física (Beydoun y cols., 2014). En definitiva, para aclarar la relación entre la patología de la enfermedad de Alzheimer y las funciones motoras en adultos sanos, se requieren nuevos estudios que tengan en cuenta del potencial efecto que estos factores puedan manifestar sobre dicha relación.

Recientemente, la relación entre la función motora y cognitiva ha recibido una atención creciente. La marcha y el *tapping* ya no se consideran actividades motoras automatizadas, como se podría comúnmente pensar, sino que se estima que requieren componentes ejecutivos tales como la atención selectiva, la iniciación y la atención sostenida (Amboni y cols., 2013). De hecho, tanto la generación interna del movimiento como las funciones ejecutivas requieren procesos de toma de decisiones con el fin de seleccionar una acción entre varias posibilidades y mantenerla de acuerdo a los objetivos de la tarea. La relación entre la función motora y cognitiva se ha descrito sobre todo usando el paradigma de "dual-task". En particular se ha observado que, cuando los participantes (adultos sanos) eran instruidos para andar y al mismo tiempo realizar una tarea secundaria de interferencia que requería atención selectiva, el rendimiento motor empeoraba (Yogev-Seligmann y cols., 2008), indicando que la función motora compite con tareas cognitivas para la utilización de recursos atencionales. En esta línea, sería también de interés poder investigar la presencia de posibles asociaciones entre las funciones cognitivas (evaluadas empleando una extensa batería de tests neuropsicológicos) y la función motora, en una población de adultos mayores sanos con o sin patología de la enfermedad de Alzheimer.

6. 6. Declive cognitivo subjetivo y disfunción motora: el "motor cognitive risk syndrome"

Una nueva propuesta de entidad clínica ha surgido recientemente como el "motor cognitive risk síndrome" (Verghese y cols., 2014). Esta entidad se ha definido como la presencia de enlentecimiento motor (marcha lenta) y de quejas cognitivas en individuos sin demencia. Según estos autores las quejas cognitivas y el enlentecimiento motor, considerados conjuntamente, son mejores predictores del desarrollo de la demencia que cualquiera de estos síntomas tomados de forma independiente (Verghese y cols., 2013). El "motor cognitive risk síndrome" parece, pues, dar un valor añadido a la capacidad de identificar a los individuos en riesgo de desarrollar deterioro cognitivo y posterior demencia.

Siguiendo esta línea de investigación y en el reconocimiento de la importancia de la definición de la fase asintomática de la enfermedad de Alzheimer, puede ser de interés el desarrollo de nuevas medidas precisas y sensibles tanto del deterioro cognitivo subjetivo, así como del deterioro objetivo de funciones cognitivo-motoras específicas.

II. HIPÓTESIS Y OBJETIVOS

La presente tesis doctoral se ha centrado en el estudio de la fase preclínica de la enfermedad de Alzheimer y en la identificación de nuevos instrumentos, subjetivos y objetivos, sensibles a disfunciones incipientes relacionadas con los procesos patológicos de la enfermedad de Alzheimer, antes de realizar el diagnóstico clínico de deterioro cognitivo leve.

Hipótesis:

1. La medición del deterioro cognitivo subjetivo permitirá distinguir entre los diferentes estadios de la enfermedad de Alzheimer (desde la fase preclínica a la fase de demencia) y los individuos con enfermedad de Alzheimer preclínica de los individuos sanos.

2. La magnitud del declive cognitivo subjetivo, referido tanto por el propio individuo como por un informador, correlacionará con los niveles de biomarcadores de la enfermedad de Alzheimer (niveles de β-amiloide, tau total y p-tau) en líquido cefalorraquídeo en los distintos estadios de la enfermedad.

3. La magnitud del declive cognitivo subjetivo referido por el informador tendrá una mayor asociación con el rendimiento cognitivo objetivo del individuo, mientras que el referido por el propio individuo estará relacionado con el nivel de ansiedad y depresión.

4. La coordinación visuomotora y el control motor estarán disminuidos en la fase preclínica de la enfermedad de Alzheimer.

5. La coordinación visuomotora y el control motor estarán relacionados con los niveles de biomarcadores de la enfermedad de Alzheimer en el líquido cefalorraquídeo en los diferentes estadios de la enfermedad. La presencia del genotipo ApoE4 no modulará dicha relación.

6. En los participantes cognitivamente sanos, el rendimiento en las pruebas de coordinación visuomotora y de control motor se asociará con el rendimiento en las

pruebas neuropsicológicas clásicas que miden la velocidad psicomotora y las funciones atencionales y ejecutivas.

Objetivos:

1. Evaluar la capacidad del declive cognitivo subjetivo percibido por el propio individuo y por un informador para distinguir entre los diferentes estadios de la enfermedad de Alzheimer (desde la fase preclínica a la fase de demencia) y los individuos con enfermedad de Alzheimer preclínica de los individuos sanos.

2. Investigar la asociación entre la magnitud del declive cognitivo subjetivo, percibido por el propio individuo y por un informador, y los biomarcadores de la enfermedad de Alzheimer (β-amiloide, tau total y p-tau) en líquido cefalorraquídeo en los diferentes estadios de la enfermedad.

3. Explorar la posible relación entre el declive cognitivo subjetivo, tanto del propio individuo como de un informador, con el rendimiento cognitivo objetivo del propio individuo, y con los niveles de ansiedad y depresión de ambos.

4. Estudiar el rendimiento del grupo preclínico con pruebas computarizadas de coordinación visuomotora y de control motor.

5. Evaluar la relación entre la coordinación visuomotora y el control motor y los niveles de biomarcadores de la enfermedad de Alzheimer en líquido cefalorraquídeo en los diferentes estadios de la enfermedad. Evaluar la influencia del genotipo ApoE4 sobre dicha relación.

6. Examinar la relación entre la coordinación visuomotora y el control motor y las funciones cognitivas evaluadas con las pruebas neuropsicológicas estándar en los participantes cognitivamente sanos.

III. METODOLOGÍA

Los materiales y métodos utilizados en la presente tesis se explican con detalle en los apartados correspondientes de cada trabajo de investigación. En este apartado, únicamente se resumen los criterios de inclusión de los participantes, y las principales técnicas y herramientas empleadas. Al final del mismo se discuten, en un breve apartado, algunos aspectos éticos de las investigaciones realizadas.

Diseño:

Los cuatro trabajos que constituyen la presente tesis doctoral son de diseño trasversal y de reclutamiento prospectivo. Los trabajos se han basado en dos cohortes distintas de individuos. El trabajo 1 se ha llevado a cabo en la cohorte 1 y los trabajos 2, 3 y 4 en la cohorte 2.

Muestra:

Cohorte 1: los participantes se han reclutado desde los siguientes centros: CONEX (un centro cívico para personas mayores), Unidad de Alzheimer y otros trastornos cognitivos del Hospital Clínico y Unidad de memoria del Hospital Universitario de San Pau, situados en Barcelona. De esta cohorte deriva el trabajo 1 de la presente tesis.

- **Grupo de voluntarios cognitivamente sanos sin declive cognitivo subjetivo.** Participantes que no presentan quejas cognitivas subjetivas ni acudirían a consulta por ello. Presentan puntuaciones dentro de la normalidad en dos pruebas de *screening* de alta sensibilidad y especificidad para la detección de deterioro cognitivo: *mini-mental state examination* (Folstein y cols., 1975) y *test de alteración de memoria* (Rami y cols., 2007).
- **Grupo de participantes cognitivamente sanos con declive cognitivo subjetivo.** Participantes que acuden a una consulta en una unidad especializada por presentar quejas cognitivas subjetivas. Presentan puntuaciones dentro de la normalidad en todas las pruebas de la batería neuropsicológica estándar.
- **Grupo de pacientes con deterioro cognitivo leve**. Pacientes que presentan deterioro en al menos un dominio cognitivo y, al mismo tiempo, mantienen preservadas las actividades instrumentales de la vida diaria de acuerdo con el

cuestionario de actividad funcional de Pfeffer (puntuación < 6) (Pfeffer y cols, 1982). Presentan una puntuación de 3 en la *escala de deterioro global* (Reisberg y cols., 1982).

- **Grupo de pacientes con enfermedad de Alzheimer (criterios NINCDS-ADRDA)**. Pacientes diagnosticados en base a los criterios NINCDS-ADRDA (McKhann y cols., 1984) de enfermedad de Alzheimer inicial. Presentan deterioro cognitivo moderado (puntuaciones alteradas en más de una prueba de la batería neuropsicológica estándar), una puntuación alterada en el *cuestionario de actividad funcional* (Pfeffer y cols, 1982) y una puntuación de 4 en la *escala de deterioro global* (Reisberg y cols., 1982).

El informante de cada participante ha completado la parte II del cuestionario de declive cognitivo subjetivo.

Los criterios de exclusión para todos los participantes fueron los siguientes: ausencia de condición médica grave, enfermedades psiquiátricas, sistémicas o neurológicas (diferentes de la demencia asociada a la enfermedad de Alzheimer).

Cohorte 2. Los participantes se han reclutado desde los siguientes centros: Unidad de Alzheimer y otros trastornos cognitivos del Hospital Clínico, Unidad de memoria del Hospital Universitario de San Pau, situados en Barcelona; y Fundación CITA Alzheimer de San Sebastián. De esta cohorte derivan 3 de los estudios de la presente tesis.

- **Grupo de individuos con enfermedad de Alzheimer en fase preclínica**. Participantes con cognición normal que presentan puntuaciones dentro de la normalidad en todas las pruebas de la batería neuropsicológica y un perfil alterado de biomarcadores de la enfermedad de Alzheimer (ver apartado “estudio de biomarcadores en líquido cefalorraquídeo”).
- **Grupo control**. Participantes cognitivamente sanos que presentan puntuaciones dentro de la normalidad en todas las pruebas de la batería neuropsicológica estándar y que además presentan un perfil normal de biomarcadores de la enfermedad de Alzheimer (ver apartado “estudio de biomarcadores en líquido cefalorraquídeo”).

- **Grupo de pacientes con enfermedad de Alzheimer (criterios NIA-AA).** Pacientes diagnosticados según los criterios NIA-AA (Sperling y cols., 2011) de enfermedad de Alzheimer, con deterioro cognitivo leve o moderado (puntuación alterada en al menos una prueba de la batería neuropsicológica estándar), con una puntuación de 3 o 4 en la *escala de deterioro global* y con niveles tanto de β-amiloide como de tau total o p-tau alterados.

Todos los participantes de esta cohorte se han, además, clasificado en base a la presencia o ausencia de al menos 1 alelo ApoE4 (definidos como portadores del ApoE4).

Los criterios de exclusión para todos los participantes fueron los siguientes: ausencia de condición médica grave, enfermedades psiquiátricas, sistémicas o neurológicas (diferentes de la demencia asociada a la enfermedad de Alzheimer).

Recogida de datos

Los sujetos de la cohorte 1 han participado en la validación del cuestionario de declive cognitivo subjetivo. A todos ellos se les han administrado los tests de *screening* cognitivo y un cuestionario para medir el estado de ánimo. Los sujetos de la cohorte 2 han participado en los estudios 2, 3 y 4 con el objetivo de identificar disfunciones cognitivas y motoras precoces en el grupo preclínico, por medio de nuevas medidas de rendimiento subjetivo y objetivo. A todos ellos se les ha determinado el genotipo de la ApoE y el análisis de biomarcadores de la enfermedad de Alzheimer en líquido cefalorraquídeo.

Cuestionario de declive cognitivo subjetivo

El cuestionario de declive cognitivo subjetivo se ha administrado a todos los sujetos y sus informadores que han participado en el trabajo 1 (estudio de validación del cuestionario) y en el trabajo 3, para poder cuantificar los cambios cognitivos percibidos durante los últimos dos años. El cuestionario consta de dos partes: la parte I se refiere a la percepción del declive cognitivo por parte del sujeto y la parte II representa la percepción del informador. Antes de responder a las 24 preguntas del cuestionario, se

han administrado tres preguntas de metacognición sobre las funciones cognitivas generales: 1) *¿Percibe usted dificultades cognitivas o de memoria?*, 2) *¿Consultaría a un médico por estos problemas?* y 3) *¿Su memoria ha empeorado en los últimos dos años?*

Cada parte del cuestionario (I y II) consta a su vez de tres segmentos que evalúan tres dominios cognitivos diferentes: memoria (11 ítems), lenguaje (6 ítems) y funciones ejecutivas (7 ítems).

Evaluación psicológica

La escala hospitalaria de ansiedad y depresión (Zigmond y Snaith, 1983) se ha administrado a los sujetos y a sus informadores que responden al cuestionario de declive cognitivo subjetivo, con el fin de estudiar la influencia de la sintomatología ansioso-depresiva de sujetos e informadores sobre el declive cognitivo subjetivo.

Tarea de coordinación visuomotora

La tarea de coordinación visuomotora se ha administrado a los participantes del trabajo 2. La tarea evalúa la coordinación visuomotora y la atención espacial. Las sesiones experimentales se llevan a cabo en una habitación tranquila, con los participantes sentados delante de la pantalla del ordenador a una distancia de unos 60 cm. La tarea se compone de 4 bloques (el primero y el tercero se ejecutan con la mano derecha y el segundo y el cuarto con la mano izquierda) y cada bloque consta de 20 ensayos. La tarea consiste en presionar con el dedo índice una de las 5 teclas situadas en un teclado modificado de un ordenador que imita la ubicación del los estímulos visuales que aparecen en 5 posibles posiciones en la pantalla del ordenador. Las variables de interés son: el tiempo de respuesta (media del tiempo empleado en responder a cada estímulo, calculado en milisegundos), el número de errores (número de respuestas en las que se presiona una tecla equivocada) y el número de omisiones (número de veces que no se produce una respuesta).

Tarea de control motor

La prueba de control motor o *finger tapping* se ha diseñado para medir las habilidades motoras (no coordinadas) en el trabajo 4. Se compone de 6 bloques idénticos. Las sesiones experimentales se llevan a cabo en una habitación tranquila, con los participantes sentados delante de la pantalla del ordenador a una distancia de unos 60 cm, con sus manos mirando hacia abajo y sus dedos extendidos sobre la mesa. La tarea consiste en presionar con el dedo índice la tecla de respuesta (barra espaciadora) en un teclado de un ordenador cuantas más veces sea posible durante 10 segundos. Se pide a los participantes que inicien la prueba con el dedo índice de la mano derecha, y se les permite descansar durante 30 segundos entre cada bloque. Los dedos índices de la mano derecha e izquierda se alternan en cada bloque. Las variables de interés son la frecuencia de los movimientos consecutivos (número total de movimientos) y la variabilidad intra-individual (variaciones en el tiempo de respuesta entre dichos movimientos). La variabilidad se obtiene a través del coeficiente de variación (desviación estándar/media del tiempo de respuesta). Mayor variabilidad indica mayor inconsistencia en el rendimiento.

Evaluación neuropsicológica

En los grupos de sujetos cognitivamente normales se ha administrado una valoración cognitiva completa de 1 hora de duración. Se han utilizado los siguientes tests neuropsicológicos: *recuerdo libre y selectivamente facilitado* (Grober y Buschke, 1987), *fluencia verbal semántica*, *denominación* de Boston (Kaplan y cols., 1983), *localización de números y de decisión de objetivos* de la batería *visual object and space perception* (Warrington y James, 1986), *symbol digit modalities test* (Smith, 1982), *trail making test* partes A y B (Reitan y Wolfson, 1985), *interferencia palabra-color* de Stroop (Golden, 1978). En los pacientes con deterioro cognitivo leve o moderado se ha administrado un subgrupo de la batería neuropsicológica, incluyendo los tests de *recuerdo libre y selectivamente facilitado*, *fluencia semántica, localización de números y trail making test* parte A. Para la evaluación del rendimiento en todos los tests se han aplicado los datos normativos existentes para la población española (Peña-Casanova y cols., 1997).

Determinación del genotipo del gen de la apolipoproteína E

En todos los sujetos de la cohorte 2 se ha determinado el genotipo de la apolipoproteína E (ApoE) a partir del método de la amplificación del material genético a través de PCR, digestión enzimática (HhaI) seguida de la migración electroforética y lectura espectrométrica de las bandas resultantes.

Estudio de biomarcadores en líquido cefalorraquídeo

En todos los sujetos de la cohorte 2 se han cuantificado los niveles de biomarcadores en el líquido cefalorraquídeo (proteínas β-amiloide, tau total y p-tau). Se han utilizado kits comerciales de ELISA (Fujirebio-Europe). Se han considerado alterados unos niveles de β-amiloide < 550 pg/ml, niveles de tau total > 450 pg/ml y niveles de p-tau > 75 pg/ml (Antonell y cols., 2011; van Harten y cols., 2013).

El análisis estadístico de los resultados

El análisis estadístico de los resultados se ha llevado a cabo con el Statistical Package Social Sciences. Las características demográficas, biológicas y genéticas de cada grupo se han analizado por medio de análisis de varianza o t-test para variables continuas, o a través del test x^2 o del test de Fisher para variables categóricas. En el trabajo 1, con el objetivo de determinar la validez y fiabilidad del cuestionario de declive cognitivo subjetivo, se han realizado los siguientes análisis: el coeficiente Alfa de Cronbach para determinar la consistencia interna, el análisis de varianza para evaluar la validez discriminante y el análisis factorial con el fin de averiguar si existe una estructura dimensional en el cuestionario. Para los trabajos 2, 3 y 4 las diferencias entre grupos en la batería neuropsicológica y en las nuevas medidas subjetivas y objetivas (cuestionario de declive cognitivo subjetivo, test de coordinación visuomotora y test de control motor) se han analizado por medio de t-tests, análisis de varianza y análisis de covarianza (controlando por los efectos de las variables demográficas). Las posibles asociaciones entre los biomarcadores de la enfermedad de Alzheimer y las nuevas medidas subjetivas y objetivas se han examinado mediante los análisis de correlación o los análisis de regresión lineal múltiples.

Aspectos éticos

Este proyecto de tesis doctoral ha recibido la aprobación del Comité Ético de Investigación del Hospital Clínico. Todos los sujetos que han aceptado participar en los 4 estudios han firmado el consentimiento informado correspondiente antes de ser incluidos, siendo libres de salir del estudio en cualquier momento. Los participantes han aceptado ser sometidos a las siguientes pruebas:

Evaluación neuropsicológica y psicológica. Las exploraciones neuropsicológicas y la administración de cuestionarios psicológicos son procedimientos habituales en la práctica clínica.

Estudio de biomarcadores. Para cuantificar los niveles de biomarcadores en líquido cefalorraquídeo se realiza una punción lumbar. Los posibles efectos secundarios de la punción lumbar son el dolor en el punto de punción durante el procedimiento y la cefalea post-punción lumbar, que se maneja con unas horas de reposo en cama, ingesta abundante de líquidos y analgésicos convencionales. Para evitar complicaciones severas como los hematomas intrarraquídeos, a pesar de tratarse de reacciones extremadamente raras, se excluyen del estudio a todos los pacientes que presenten problemas de coagulación o que tomen medicación anticoagulante. Asimismo, se solicita consentimiento explícito para el almacenamiento y conservación de estas muestras biológicas extraídas una vez finalizado el estudio.

IV. RESULTADOS

Trabajo 1

The Subjective Cognitive Decline Questionnaire (SCD-Q): a validation study

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The Subjective Cognitive Decline Questionnaire (SCD-Q): A Validation Study

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Abstract.
Background: Subjective cognitive decline (SCD) is gaining importance as a focus of investigation, but adequate tools are needed for its quantification.
Objective: To develop and validate a questionnaire to quantify SCD, termed the Subjective Cognitive Decline Questionnaire (SCD-Q).
Methods: 124 controls (CTR), 144 individuals with SCD, 83 mild cognitive impairment subjects, 46 Alzheimer's disease patients, and 397 informants were included. The SCD-Q contains: part I, named MyCog, which is answered by the subject; and part II, TheirCog, which includes the same questions and is answered by the informant or caregiver. The 24 SCD-Q items assess the perceived subjective decline in memory, language, and executive functions in the last two years.
Results: The MyCog scores of controls differed significantly from those of the other groups ($p < 0.05$) and there were significant differences in TheirCog scores between all groups. The optimal TheirCog cut-off score for discriminating between individuals with and without cognitive impairment was 7/24 (sensitivity 85%, specificity 80%). MyCog scores correlated significantly with anxiety and depression ($r = 0.29$, $r = 0.43$, $p < 0.005$), but no correlations were found with neuropsychological tests. TheirCog scores correlated significantly with most of the neuropsychological tests ($p < 0.05$). Informants' depression and anxiety influenced TheirCog scores in controls and SCD groups.
Conclusion: Self-perceived cognitive decline, measured by the SCD-Q part I (MyCog), discriminated SCD from CTR. Part II (TheirCog) was strongly related to subjects' objective cognitive performance, and discriminated between subjects with or without cognitive impairment. The SCD-Q is a useful tool to measure self-perceived cognitive decline incorporating the decliner and the informant perspective.

Keywords: Alzheimer's disease, cognition, diagnosis, memory, test

INTRODUCTION

In the attempts to define the earliest symptoms of the Alzheimer's disease (AD) continuum, self-perceived cognitive decline represents an increasingly important focus of research [1–4]. There is now a clear need to develop instruments able to quantify subjective

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cognitive decline (SCD). Although many neuroimaging studies [5–9] and cognitive studies [10, 11] have been conducted in populations with subjective memory complaints, the prognosis of the condition remains unclear. Furthermore, several relevant clinical issues must be investigated before complaints can be classified and quantified inside the cognitive impairment continuum. In the last few years, SCD has been considered to be clinically more relevant than subjective memory complaints, which may depend on the subject's psychological condition [12–14]. Many questionnaires have been designed to evaluate memory complaints, but few quantify SCD; and those that do assess it, it is over a time period longer than 10 years, in which case the decline may simply be due to aging [15–19]. Recently, the working group of the subjective cognitive decline initiative (SCD-I) reached a consensus on terminology and on a conceptual framework for research on SCD in AD [20]. A set of SCD features was presented, which according to current knowledge, increases the likelihood of the presence of preclinical AD in individuals with SCD. After revising the literature, we concluded that the onset of SCD within a few years might be more predictive of cognitive decline and AD than the presence of SCD for several years [20]. In this regard, a short period may be a better reflection of the perceived cognitive decline that may have relevance to predict future cognitive impairment, since a longer one may be meaningless and a shorter one may still be able to change and could be influenced by counter current situations [21–23]. There is now a clear need to develop instruments able to quantify SCD, in order to rate the subjective cognitive perceived change on cognition during the previous two years. Using a time reference can be of help to the individual to focus and therefore to measure their self-perceived cognitive changes.

On the other hand, although informants' reports are extremely relevant to clinical classification, few studies have included questionnaires to measure cognitive decline perceived simultaneously by decliners and by their relatives or informants [24, 25]. In a recent study of non-demented, community-dwelling older individuals, Slavin et al. [26] found that informants were more accurate than subjects in endorsing a cognitive complaint when objective impairment was present. In addition, some studies have shown that informants' reports were more highly correlated with neuropsychological performance than self-complaints [26, 27], and predict diagnostic conversion in non-demented older adults [28–30]. As a result, it would be very useful to apply the same SCD questionnaire both to decliners and to their informants in order to fully characterize cognitive subjective decline. Other questionnaires like the Everyday Cognition Scale have been designed to assess cognitively mediated functional abilities in older adults with normal cognition, mild cognitive impairment (MCI), or AD; however, no validation studies have been carried out in a subjective cognitive complaint group [30]. In addition, although subjective cognitive reports have been consistently associated with depression and anxiety symptoms [12, 14], studies determining the effect of informants' psychological variables are needed.

Another interesting task in the field of subjective decline is to determine the profiles of subjects who are likely to seek help from clinicians and those who are not. Some studies report that only a minority of older people with cognitive decline seek help (the clinical population) [31, 32], and that the prevalence of memory impairment identified in community surveys is over twice that reported by general practice registrations [33]. The differences between SCD subjects who seek help and those who do not seek help have not yet been studied. Distinguishing between these two groups may help us to understand why some healthy subjects seek help for cognitive problems and to establish whether there is a relationship between seeking help and personality traits. Previous studies have consistently reported that memory complaints are more strongly associated with psychological variables (depression, anxiety, and personality) than with cognitive function or the presence of genuine impairment [12–14]. Further studies are needed to determine whether the propensity to seek help is also influenced by subjects' emotional and personality variables.

The aim of the present study was to design and validate the Subjective Cognitive Decline Questionnaire (SCD-Q) to quantify the perceived subjective cognitive decline over the last two years. The SCD-Q comprises 24 items administered in parallel to subjects with SCD and to their informants. In addition to assessing the questionnaire's validity and reliability, we explored the psychological and demographic determinants in both groups by comparing the relationship between cognitive status and their scores on the SCD-Q.

MATERIAL AND METHODS

Design of the SCD-Q (Annex 1 and 2: English version, Annex 3 and 4: Spanish version)

An initial pool of 60 items was assembled by surveying possible questions intended to identify cognitive

decline in everyday life and by reviewing the literature. An expert consensus panel consisting of three neurologists and three neuropsychologists selected the items for the SCD-Q, condensing them from 60 to 40 items. In a pilot study, the first version (40 items) was tested in independent samples including 194 subjects: 86 SCD subjects, 31 healthy controls, 57 MCI, and 20 AD subjects. After the pilot study, 24 items were selected for the final version of the questionnaire. Items were selected using appropriate statistical methods, mainly through discrimination analyses of the items, comparing groups of subjects with or without cognitive impairment. The final version of the questionnaire consisted of 24 items assessing decline in several cognitively demanding domains including memory tasks (11 items), language tasks (6 items), and executive function tasks (7 items). To enhance the feasibility and reliability of each item, the subject's responses to each question were restricted to either yes or no. Subjects answer "yes" to a question only when they perceived a decline. The total score for each part of the questionnaire ranged from 0 to 24 points, with higher scores indicating greater perceived cognitive change over the past two years. Although the time frame of two years was chosen arbitrarily, previous literature reports indicate that the onset of SCD within a few years may be more predictive of AD and cognitive decline than the presence of SCD for several years [21–23].

The SCD-Q was administered to subjects with SCD and to their informants. The questionnaire has two parts: Part I represents subjects' perceptions of their cognitive decline (MyCog, an abbreviation of "My Cognition"), and part II, which was self-administered, represents informants' perceptions (TheirCog, an abbreviation of "Their Cognition"). Subjects and informants were asked to rate the subjects' cognitive changes in everyday functioning over the last two years.

Before answering the 24 items of the questionnaire, respondents answered three relevant questions regarding their metacognition of general cognitive functions: 1) "Do you perceive memory or cognitive difficulties?", 2) "Would you ask a doctor about these difficulties?', and 3) "In the last two years, has your cognition or memory declined?"

Validation of the SCD-Q

Subjects

A total of 794 subjects completed the present study between October 2012 and June 2013. All participants were fully informed of the procedure and purpose of the study, and were assured that the results would be treated confidentially. Subjects with any neurological diagnosis, serious or unstable medical condition, or with a diagnosis of major psychiatric disorder including schizophrenia and major depressive severe somatic disease or substance abuse were excluded. The ethical committee for clinical research at the Hospital Clinic of Barcelona approved the study.

One hundred and twenty-four cognitively healthy controls were recruited from Conex, a senior center in Barcelona. Students on the neuropsychology master's degree program at Sant Pau University Hospital also recruited cognitively healthy volunteers among their relatives. Control subjects (CTR) were defined as volunteers presenting no cognitive decline and with normal scores on two screening tests with good sensitivity and specificity for cognitive impairment detection (Mini-Mental State Examination (MMSE) [34], and Memory Alteration Test (M@T) [35]). The age range in the control group was from 45 to 90 years.

One hundred and forty-four individuals with SCD were identified on the basis of self-reports. This group was further divided into:

- A clinical subjective cognitive decline (SCD-C) group ($n = 82$) including subjects who consulted a memory unit for their cognitive decline, presenting, as the CTR group, normal scores on the two screening tests. In addition, this group did not show any impairment in a neuropsychological battery testing for memory, language, and executive functions. No objective deficits in cognitive domains were found. For the neuropsychological tests, cognitive deficits were defined as a score of 1.5 SDs or more below the mean of healthy controls, matched for age and education.
- A population subjective decline (SCD-P) group ($n = 62$) comprising volunteers with normal cognition who obtained normal scores on the MMSE and M@T screening tests, and who answered "yes" to the question "Do you perceive memory or cognitive difficulties?" Although they perceived decline, they had not consulted a memory unit. Two screening tests were used, and subjects scoring below the cut-off for cognitive impairment were removed.
- A mild cognitive impairment (MCI) group ($n = 83$) comprising subjects with cognitive impairment on at least one test (1.5 SD below the control mean score, adjusted for age and educational level) of one cognitive domain (memory, attention, language, praxis, visuoperceptive,

and/or visuospatial ability). 40.7% were pure amnestic MCI patients, 50.8% were amnestic multi-domain, and 8.5% were non-amnestic MCI patients. These patients presented no significant changes in the instrumental activities of daily living according to Pfeffer's Functional Activity Questionnaire [36] and did not meet criteria for dementia.

- An AD group ($n=46$) comprising patients diagnosed with AD on the basis of the NINCDS-ADRDA criteria and mild stage defined as a score of 4 on the Global Deterioration Scale (GDS) [37]. All clinical subjects and patients were recruited from two clinical centers in Barcelona: the Alzheimer's Disease and Other Cognitive Disorders Unit at the Hospital Clinic, and the Memory Unit at Sant Pau University Hospital.

Three hundred and ninety-seven informants participated in the study. There was one informant for each healthy volunteer and SCD subject included, and one informant for each MCI and AD patient included. Informants were relatives of the healthy volunteers and SCD subjects, and caregivers of the MCI and AD patients. Most of the informants who accompanied the subject/patient to the appointment completed the SCD-Q during the visit. If the subject came alone, the questionnaire was returned by post. In the case of caregivers, 60.2% were the subject's partner and 34% were the subject's son or daughter. No cognitive screening tests were applied to informants.

Procedures: Cognition and psychological assessment

Regarding the inclusion criteria, all subjects underwent the same battery of tests to define the presence or absence of cognitive impairment, the MMSE and M@T, which present an excellent area under the curve to distinguish normal cognition from both MCI and dementia. The two-hour battery was administered to a subgroup of subjects with SCD to define the relation of the SCD-Q with other traditionally used neuropsychological tests and to MCI and AD patients to confirm their decline.

Neuropsychological Assessment (See Neuropsychological Assessment details in the Supplementary material): All the clinical groups (SCD, MCI, and AD) were administered a two-hour comprehensive neuropsychological battery by a trained neuropsychologist to assess memory, language, praxis, visual perception, and frontal functions. All neuropsychological scores were adjusted for age and educational level. Neuropsychological normative data were collected previously from a sample of healthy older individuals from Spain [38, 39].

Depression and Personality Questionnaires: Depression was measured in all subjects using the GDS [40] and/or the Hospital Anxiety and Depression Scale (HADS) [41]. The Neuroticism scale from the Eysenck's Revised Personality Questionnaire (EPQ-R) [42] was administered to measure neuroticism personality traits in healthy cognitive subjects. Due to its complexity, the EPQ-R could not be administered to MCI and AD patients. These questionnaires were completed at the time of the visit or were taken home to be self-completed and returned by post. The GDS and HADS questionnaires were also administered to relatives who answered the TheirCog questionnaire, in order to study the influence of informants' mood on the TheirCog results.

Data analysis

Statistical analyses were performed with the SPSS package for Windows (V.17.0). Reliability was tested using the Cronbach alpha score for the total MyCog-TheirCog items and for all individual items less one item at a time to examine whether the reliability of the questionnaire dropped when the item was excluded. Factor analysis was used to determine the construct validity of MyCog and TheirCog and to establish whether they consisted of global or several factors. Internal validity was examined using total-item correlations, and correlations of each individual MyCog-TheirCog item with the total score using the Pearson correlation coefficient. Descriptive statistics were generated for the sample. ANOVA and independent samples, and *post-hoc* test (Scheffé test) were conducted to examine differences in MyCog and TheirCog scores. Student's *t-tests* were used to test differences between MyCog and TheirCog in all the study groups. Discriminant validity was examined by receiver operating curves (ROC) in order to calculate the sensitivity and specificity of the MyCog and TheirCog items to discriminate CTR from the SCD groups and patients (MCI and AD) from healthy subjects (CTR) respectively. The SCD-C group was not included in order to test the cut-off obtained in this group after the analysis. Concurrent validity was examined by correlating scores on the MyCog and TheirCog items with scores on all neuropsychological tests. Associations between MyCog and TheirCog items with psychological, neuropsychological, and demographic variables were assessed by Pearson's

Table 1
Demographic, psychological, cognitive, and SCD-Q data results in the study groups (ANOVA and *post-hoc* tests-Scheffé test)

Groups	Controls ($n=124$)	SCD-P ($N=62$)	SCD-C ($n=82$)	MCI ($n=83$)	AD ($n=46$)	F	$p<0.05$
Age	60.2 ± 9.2	56.8 ± 10.4	67.0 ± 8.9	70.5 ± 9.2	74.5 ± 8.8	40.2	CTR, SCD-P<SCD-C, MCI, AD SCD-C<AD
Education (y)	12.5 ± 3.8	11.1 ± 3.5	10.7 ± 4.3	10.7 ± 4.5	10.2 ± 4.9	4	SCD-C, MCI, AD<CTR
Female (%)	66 (59%)	33 (58%)	58 (71%)	39 (49%)	29 (64%)		non-significant
MMSE	28.9 ± 1.2	28.9 ± 1.2	27.8 ± 1.9	27.1 ± 2.4	22.9 ± 3.2	76	AD<CTR, SCD-P, SCD-C, MCI MCI<CTR, SCD-P SCD-C<CTR, SCD-P
M@T	46.6 ± 2.8	45.9 ± 3	45.2 ± 3.3	37.1 ± 7.2	26.9 ± 5.9	139.7	AD<CTR, SCD-P, SCD-C, MCI MCI<CTR, SCD-P, SCD-C
SCD-Q (MyCog)	3.5 ± 2.8	9.1 ± 5.1	12 ± 5.8	12.5 ± 6.2	9.3 ± 5.3	55.5	CTR<SCD-P, SCD-C, MCI, AD SCD-P<SCD-C, MCI AD<SCD-C, MCI
SCD-Q (TheirCog)	3.2 ± 3.7	5 ± 4.5	6.8 ± 5.3	11.7 ± 5.9	17.2 ± 5.5	88.5	CTR<SCD-C, MCI, AD SCD-P, SCD-C<MCI, AD MCI<AD
HAD-A (MyCog)	5.8 ± 2.9	8 ± 3.7	7.2 ± 3.5	6.8 ± 4.6	6.6 ± 4.6	3.5	CTR<SCD-P
HAD-D (MyCog)	2.9 ± 2.5	4.9 ± 3.3	5 ± 3.7	4.7 ± 4	3.2 ± 2.8	6.8	CTR<SCD-P, SCD-C, MCI
EPQ-R (MyCog)	7.4 ± 4.7	9.5 ± 5	11.3 ± 5.6	n.a.	n.a.	4.8	CTR<SCD-C
GDS (MyCog)	5.4 ± 4.7	10.3 ± 8.5	10.4 ± 6.1	12.4 ± 7.8	10.6 ± 7	5.2	CTR<SCD-C, MCI
HAD-A (TheirCog)	5.8 ± 3.2	7.1 ± 4.1	6.9 ± 4.4	7 ± 3.5	5.6 ± 3.3	2.1	non-significant
HAD-D (TheirCog)	3.5 ± 3.4	4.5 ± 4.2	4 ± 3.5	3.8 ± 2.7	3.2 ± 2.8	0.9	non-significant

SCD-C, clinical subjective cognitive decline group; SCD-P, population subjective cognitive decline group; MCI, mild cognitive impairment patients; AD, Alzheimer's disease patients; MMSE, Mini-Mental State Examination; M@T, Memory Alteration Test; HAD-A, Hospital Anxiety and Depression Scale–Anxiety; HAD-D, Hospital Anxiety and Depression Scale-Depression; EPQ-R, Revised Personality Questionnaire of Eysenck–neuroticism scale; GDS, Geriatric Depression Scale; n.a., non applicable.

correlation coefficients, considering $p<0.005$ as significant in order to avoid false positive associations. Logistic regression for the binary variable (presence or absence of cognitive impairment) was used to analyse the ability of SCD-Q, age, and psychological variables to predict cognitive impairment.

RESULTS

Demographic characteristics

Demographic and cognitive data are shown in Table 1. ANOVA did not show differences between groups in terms of gender or level of education. However, significant differences were found for age ($p<0.001$). The Scheffé test (*post-hoc* analysis) found differences between CTR and the other groups, and between SCD-P and the other groups.

Convergent validity

In order to assess convergent validity, we correlated the 24 items of part I (MyCog) with question c) referring to cognition or memory decline in the last two years. The Pearson's correlation coefficient was highly significant ($r=0.56$; $p<0.001$). Answers to part II (TheirCog) also showed a significant Pearson's correlation with question c): ($r=0.68$; $p<0.001$).

Internal consistency reliability

Cronbach alpha scores of 0.90 and 0.93 were obtained for MyCog and TheirCog respectively, with Cronbach's alpha scores for individual items versus the rest ranging from 0.89 to 0.90 in MyCog and 0.92 to 0.94 in TheirCog, suggesting that each item made an important contribution to the MyCog and TheirCog scales. All MyCog and TheirCog items correlated significantly with the total score; a corrected total-item correlation greater than $r=0.3$ suggested that each item had discriminative capacity.

Factor analysis

The application of principal component analysis (PCA) to the 24 MyCog items revealed the presence of five components explaining 30.7%, 5.2%, 4.7%, 4.3% and 4.3% of the variance respectively. The correlation matrix revealed the presence of many coefficients of 0.3 and above and the factorability of the correlation matrix was confirmed (Kaiser-Meyer-Olkin value = 0.94; Bartlett's Test of Sphericity < 0.001). PCA of the 24 TheirCog items revealed similar outcomes were found, with three components explaining 37.8%, 5.9% and 4.6% of the variance respectively. Furthermore, a scree plot revealed a clear break after the first component in MyCog-TheirCog question-

naires, suggesting that the MyCog-TheirCog items were assessing only one underlying dimension or factor.

Discriminant validity and comparisons between groups

ANOVA analyses of MyCog and TheirCog resulted statistically significant among all the groups of the study. The Scheffé test (*post-hoc* analysis) showed statistically significant difference in the MyCog scores between CTR and the other groups ($p < 0.001$) (see Table 1), and within the clinical population between SCD-P and SCD-C ($p < 0.005$) and between SCD-P and MCI ($p < 0.001$), but not between SCD-C and MCI ($p < 0.96$). The Scheffé test (*post-hoc* analysis) also showed statistically significant differences in TheirCog scores ($p < 0.001$) between controls and SCD-C, MCI, and AD groups, but not between CTR and SCD-P or between the two SCD groups (see Supplementary Table 1). Student's *t*-test showed that AD patients presented significantly lower scores in MyCog than in TheirCog ($p < 0.001$). Moreover, Student's *t*-test showed that SCD-P and SCD-C presented significantly higher scores in MyCog than in TheirCog ($p < 0.001$). No statistical differences were detected between MyCog and TheirCog in the CTR and MCI groups. Figure 1 shows MyCog and TheirCog scores differences (Student's *t*-test) in each study group.

ROC was also used in order to calculate the sensitivity and specificity of MyCog to discriminate SCD-C from CTR. The optimal cut-off score was 7/24, with a sensitivity of 83% and a specificity of 87% (AUC: 0.91). Discriminant validity was examined by ROC analysis in order to calculate the sensitivity and specificity of the TheirCog for discriminating between subjects with cognitive impairment (MCI and AD) and those without (CTR and SCD-P). The SCD-C group was deliberately excluded from this analysis, in order to test the cut-off obtained in this group in an independent analysis. The optimal TheirCog cut-off score for determining "cognitive impairment" was 7/24 with a sensitivity of 85% and a specificity of 80% (AUC: 0.91). The cut-off of 6/24 presented better sensitivity (90%) but poorer specificity (72%). We then compared the cognitive tests scores in the SCD-C group, dichotomizing the population through the "TheirCog" cut-off previously obtained for cognitive impairment. We found significant differences in the following neuropsychological test scores ($p < 0.05$): MMSE, Semantic fluency, Total Digits, Trail Making Test-A (TMT) part A and part B. There was also a trend towards significance in total recall on the Free and Cued Selective Reminding Test (FCSRT) ($p < 0.05$).

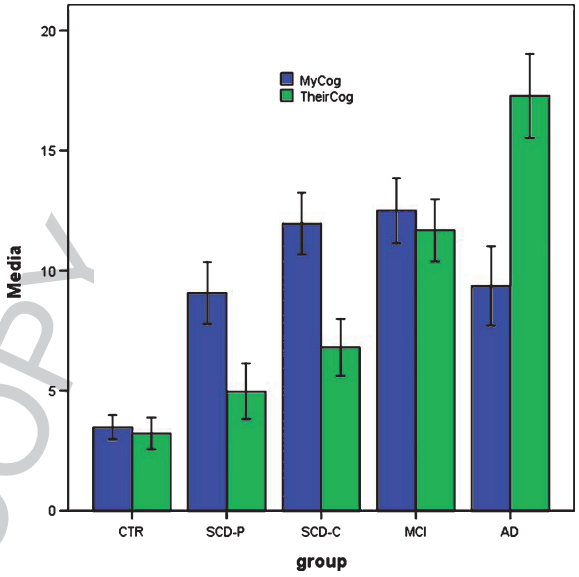

Fig. 1. MyCog and TheirCog scores differences in each study group. Student's *t*-test showed that AD patients presented significantly lower scores in MyCog than in TheirCog ($p < 0.001$). Student's *t*-test, showed that SCD-P and SCD-C presented significantly higher scores in MyCog than in TheirCog ($p < 0.001$). No statistical differences were detected between MyCog and TheirCog in the CTR and MCI groups.

We assessed the ability of TheirCog and MyCog, anxiety and depression measures, and subject's age to predict "objective cognitive impairment" by means of binary logical regression. The full model containing all predictors was statistically significant, $\chi^2(7,258) = 127.36$, $p < 0.001$, indicating that the model was able to distinguish between subjects with objective cognitive impairment and cognitively healthy subjects. The model as a whole explained between 39% and 59% of the variance, and classified 86% of cases. The independent variables that made a statistically significant contribution to the model were TheirCog ($p < 0.001$) and age ($p < 0.001$).

Interaction with psychological variables

Taking all the groups together, the Pearson's correlation coefficient showed that MyCog scores were significantly correlated with subject's anxiety measured by HADS-A ($r = 0.29$, $p < 0.005$) and with subject's depression measured by HADS-D ($r = 0.43$, $p < 0.005$); TheirCog scores were only significantly correlated with informants' HADS-A ($r = 0.23$, $p < 0.005$).

In the SCD-C group, the Pearson's correlation coefficient showed that subjective complaints (MyCog) presented a strong positive correlation with the anxiety scale (HADS-A) ($r = 0.41$, $p < 0.005$), depression scale (HADS-D) ($r = 0.55$, $p < 0.005$), and EPQ-N ($r = 0.52$, $p < 0.005$). There was also a strong positive correlation between informants' HAD-D/HAD-A and TheirCog in the SCD-C group ($r = 0.40$ and $r = 0.41$ respectively; $p < 0.005$).

In the MCI and AD groups, MyCog scores presented significant correlations (Pearson's correlation coefficient) with the HADS-D depression scale ($r = 0.40$ and $r = 0.56$, respectively, $p < 0.005$). No significant associations between TheirCog and informants' psychological scores (HAD-D or HAD-A) were found in the MCI or AD group.

We found significant correlations between TheirCog and informants' HADS-A ($r = 0.35$, $p < 0.005$) in the CTR group. No significant associations between MyCog and TheirCog with psychological variables were found in the SCD-P group.

Relationship with demographic characteristics

We did not find any association between age or education and subjective decline measured by MyCog. Age and education were significantly correlated with TheirCog (Pearson's correlation coefficient), but partial correlations (adjusting for the MMSE) were not significant. There was a significantly higher number of younger individuals (age below 60 years old) in the SCD from the general population group (SCD-P) than in the SCD from clinical memory unit groups (SCD-C) ($\chi^2 = 36.8$; $p < 0.001$). 75.8% of SCD-P subjects were under age 60, compared with only 24.7% of SCD-C subjects.

There was no difference between male and female participants in the degree of self-complaints (MyCog scores) in the full sample. The subgroup analysis (Student's *t*-test) showed that male CTR presented more complaints than females in terms of MyCog mean scores (4.2 versus 3.1, $p < 0.05$), but no gender differences were found in the other groups.

Concurrent validity

No correlations were found between neuropsychological tests and MyCog scores, taking all cases together and each group separately. However, significant correlations (Pearson's correlation coefficient) were found between neuropsychological tests and TheirCog scores, in all the study groups ($p < 0.005$). TheirCog presented significant correlations with screening tests (M@T and MMSE; $r = -0.53$ and $r = -0.44$), all subtests of the FCSRT ($r = -0.38$ and $r = -0.45$), visual memory from the CERAD battery ($r = -0.44$), total digit Span from the WAIS III (digit test) ($r = -0.50$), Boston Naming Test ($r = -0.39$), semantic fluency ($r = -0.40$), VOSP-incomplete letters ($r = -0.27$), TMT-A ($r = -0.41$), and Phonemic verbal fluency-FAS ($r = -0.41$). In the SCD-C group, TheirCog scores presented significant correlations ($p < 0.005$) with Total digit test ($n = 52$; $r = -0.40$, $p < 0.005$), TMT-A ($r = 0.36$, $p < 0.005$), and a trend toward significance with TMT-B ($n = 26$; $r = 0.53$; $p < 0.006$).

DISCUSSION

The SCD-Q, a new questionnaire for quantifying SCD, proved useful for discriminating among all the groups with different degrees of cognitive impairment, from healthy controls to dementia. MyCog was useful for quantifying self-cognitive decline in CTR and SCD populations, and made it possible to discriminate SCD-C from SCD-P and SCD-P from CTR. Moreover informants' reports, measured by part II (TheirCog) allowed us to classify all the groups along the AD continuum: CTR, SCD-C, MCI, and AD, discriminating between subjects with or without cognitive impairment. Both parts of the SCD-Q, MyCog and TheirCog, were reliable and had robust internal validity.

The results of this study suggest that MyCog is useful for quantifying self-cognitive decline, and made it possible to discriminate SCD-C from SCD-P and from CTR. The MyCog results were not associated with cognitive performance in SCD-C, SCD-P, or CTR. However, MyCog scores were strongly associated with psychological and personality measures. These results indicate that individual psychology may play an important role in how subjects feel about their cognition and may influence their likelihood of reporting decline, as reported previously [43]. Previous studies have found little or no correlation between self-cognitive complaints and cognitive performance or decline, concluding that self-cognitive complaints are more strongly associated with psychological variables than with cognitive function or the presence of genuine impairment [12–14, 26, 44, 45]. Interestingly, although there was a trend toward higher neuroticism scale scores in the SCD-C group than in the SCD-P, there were no differences in depression and anxiety scales between these groups. However, the association between MyCog and psychological tests was significantly higher in the SCD-C group, who seek help

for their cognitive complaints at clinical memory units, while no association was found between psychological variables and self-complaints in the SCD-P. Therefore it seems that the seeking help behaviour in the SCD-C group was significantly influenced by personality and psychological variables. These results may be related to the fact that self-complaints represent a psychological symptom in some subjects in the SCD-C rather than an objective cognitive impairment. Other studies have suggested that personality traits may play an important role in the perception of one's own cognition and in the decision to seek help [46].

Although MyCog was able to differentiate the SCD groups from the CTR group, it did not discriminate SCD groups from MCI or AD, possibly because SCD, MCI, and AD groups presented similar levels of perceived decline. Moreover, the distribution of the MyCog scores in the MCI and AD groups indicated that, although some subjects showed poor insight into their cognitive impairment (i.e., low MyCog scores), others with higher MyCog scores were able to maintain metacognitive functions even in the dementia phase. As has been reported previously, in some subjects the meta-memory function may be maintained at early AD stages [47], which suggests that awareness of deficit may vary greatly across individuals. However, most of our AD patients presented significantly lower scores in MyCog than in TheirCog, indicating that although some AD subjects presented insight, most perceived less cognitive impairment than did their informants (TheirCog). The same pattern was found in some (though not all) MCI patients. Biomarkers were not available in this study; therefore our MCI group was heterogeneous, and probably included subjects in whom AD was the cause of the condition and others in whom it was not the cause.

Informants' reports, measured by part II (TheirCog), allowed us to classify all the groups along the AD continuum: CTR, SCD-C, MCI, and AD. TheirCog scores increased along the entire spectrum from CTR to AD patients. Interestingly, TheirCog scores were significantly higher in the SCD-C group than in CTR, but significantly lower than in MCI or AD. As consistently reported in the literature, the dementia process is progressively associated with poor insight into cognitive difficulties [48], and so informants' reports are highly relevant along the disease continuum. In fact the informant's report is one of the requisites for fulfilling AD clinical criteria and it is essential for assessing the effect of new pharmacological therapies. In our analysis, TheirCog scores and subjects' age were significant predictors of subjects' cognitive performance, but MyCog or psychological variables were not. These findings corroborate those of previous longitudinal studies in which informants' reports were associated with worse performance on memory tests and hence an increased risk of cognitive impairment and progression to dementia, thus facilitating identification of very early neurodegenerative decline [3, 24–27, 49, 50]. Slavin et al. [26] found that informants were more accurate than subjects in endorsing a cognitive complaint when objective impairment was present. Also recently, Gifford et al. [29] reported that complaints made both by subjects and by their relatives were most predictive of MCI diagnosis outcome in non-demented older adults, highlighting the need to obtain corroboration from informants in order to enhance prognosis and to distinguish underlying pathological processes from normal cognitive aging.

In our study, the optimal TheirCog cut-off score for discriminating cognitively impaired subjects (MCI and AD) from cognitively healthy subjects (CTR) was 7 out of 24. This score presented good specificity and sensitivity (80% and 85%, respectively) for detecting cognitive impairment. Interestingly, using this cut-off to assess the TheirCog scores in the SCD-C sample, we found significant differences in some of the neuropsychological test scores. SCD-C TheirCog scores showed a significant association with some subjects' executive test scores like digit span or trail making tests, indicating that, in some cases, informants' reports of cognitive dysfunction may be associated with mild executive dysfunction in the pre-MCI stages. In fact, increased prefrontal cortex activation compared to controls during an encoding task has been described in subjective cognitive impairment [51]. Therefore, the relationship found between TheirCog and cognition in the SCD-C groups may be clinically relevant and the TheirCog scores (part II of SCD-Q) may help clinicians to predict certain cognitive outcomes in this population. Altogether, the TheirCog descriptive and discriminant characteristics support the potential use of this scale not only in memory clinics, but it could be useful in primary care to identify subjects to be referred to memory clinics.

Another interesting result found in this study was the strong positive correlation between TheirCog and the informants' anxiety and depression levels in the SCD-C group, and between TheirCog and informants' anxiety in the CTR group. There were no associations between TheirCog and informants' psychological variables in MCI or AD groups. No other studies have assessed the relationship between informants' psychological variables and the reports they provide. Taking

into account the psychological influences on the SCD-Q (MyCog and TheirCog scores) in the SCD-C group, it seems that not only the subject's personality and psychological profile plays a role in the seeking help behaviour but the informant's depression and anxiety status may also be involved. These results indicate that although informants' reports seem to be more closely related to objective measures than self-complaints in the AD continuum, some brief psychological screening tests are recommended in studies in which informants' reports are extremely relevant, for instance, in certain pharmacological trials.

In this study we included a population with an age range from 45 to 90 years in order to investigate the association between age and cognitive complaints in a healthy community-based sample. Our results showed that MyCog and TheirCog scores were not influenced by age in this group. Although the raw scores did not differ significantly between young and old people in this group, there was a trend toward answering yes to the question "Do you believe you have cognitive or memory problems?" in the younger group (45 to 65 years old). However, the SCD-C group was significantly older than the SCD-P group. This may be because young people are less likely to be referred to clinicians, or because people associate AD with age and complaints are attributed more importance when subjects are at the oldest ages. In a prevalence study, Montejo et al. [52] found that memory complaints increase with age: 24% of subjects between 65 and 69 years made memory complaints, and 57% of those aged over 90.

The main limitation of this study was that we only had cross-sectional data. Therefore although the information on cognitive changes obtained with the SCD-Q referred to the perceived change over the previous two years, it could not be contrasted with a real cognitive measure of their change. Another limitation was that we were not able to obtain complete neuropsychological assessment for CTR and for most of the SCD-P group. And no cognitive screening tests were carried out in informants. A further limitation was that biomarkers were not included. Future longitudinal studies with biomarkers to define their predictive capacity in this population are needed. These studies will be useful to define as a function of the biomarkers and previous family history the different timeframes for SCD-subjects to develop MCI, taking into account that some studies have described that MCI conversion of subjects with subjective complaints is significantly higher than in CTR subjects without complaints [2, 29]. Also, no other subjective questionnaires about functionality were used in this study. Further work is needed to study the SCD-Q's concurrent validity with similar questionnaires about subjective complaints. Finally, another limitation is that the time reference for the questionnaire was chosen arbitrarily, although based on the evidence that the onset of SCD within a few years may be more predictive of AD and cognitive decline than the presence of SCD for several years [21–23].

In summary, the most important advantage provided by the SCD-Q is the possibility to quantify decline as reported by the subject and the informant at different degrees of cognitive impairment. Part I (MyCog) was useful to identify SCD groups and was also able to discriminate between individuals with SCD who had sought help at memory units and those who had not. Part II (TheirCog), the informant's report, was associated more with the subject's objective cognitive performance and provided good cognitive impairment discrimination. The SCD-Q emerges as a useful tool for measuring self-perceived cognitive decline incorporating the decliner and the informant perspective.

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SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-132027.

ANNEX

Annex 1. Subjective Cognitive Decline Questionnaire (SCD-Q).
Part 1: Assessment of My Cognitive Decline (MyCog).

Name:
Age:
Date:

a) Do you perceive memory or cognitive difficulties?"	YES	NO
b) Would you ask a doctor about these difficulties?	YES	NO
c) In the last two years, has your cognition or memory declined?	YES	NO

Below is a list of activities. Please answer YES if you believe you perform them WORSE than roughly two years ago.

1. I find it harder to learn new telephone numbers.	YES	NO
2. I find it harder to find personal possessions (keys, telephone, utensils, etc.).	YES	NO
3. I find it harder to describe the plots of films.	YES	NO
4. I find it harder to remember doctor's appointments.	YES	NO
5. I find it harder to follow the plot of a book.	YES	NO
6. I'm worse at recalling the details of a recent family event.	YES	NO
7. I find it harder to remember the result of a recent sporting event.	YES	NO
8. I find it harder to remember sums of money (payments or debts).	YES	NO
9. I find it harder to remember the details of a conversation.	YES	NO
10. I find it harder to remember things without using strategies (lists, diary, etc.).	YES	NO
11. I find it harder to remember the details of recent news.	YES	NO
12. I find it harder to remember famous people's names.	YES	NO
13. I find it harder to remember the names of people I've met recently.	YES	NO
14. I find it harder to remember street and city names.	YES	NO
15. I'm worse at finding the word I want to use in a conversation.	YES	NO
16. I find it harder to understand things the first time someone says them.	YES	NO
17. I find it harder to remember the names of places I've visited recently.	YES	NO
18. I find it harder to concentrate on what I am doing.	YES	NO
19. I'm worse at planning things that aren't part of my daily routine (travel, excursions, etc.).	YES	NO
20. I find it harder to use electronic devices.	YES	NO
21. I find it harder to start new or different things	YES	NO
22. I find it harder to start conversations.	YES	NO
23. I find it harder to do mental arithmetic.	YES	NO
24. I find it harder to do more than one thing at once without getting agitated.	YES	NO
TOTAL "YES"		

Annex 2. Subjective Cognitive Decline Questionnaire (SCD-Q)
PART II: Assessment of Her/His Cognitive Decline (TheirCog)

Name:
Age:
Date:

***Read the questions below and circle* YES *or* NO.**

a) Do you percieve he/she has cognitive or memory difficulties?	YES	NO
b) Would you advise him/her to ask a doctor about these cognitive difficulties?	YES	NO
c) In the last two years, has he/she experienced cognitive or memory decline?	YES	NO

Below is a list of activities. Please answer YES if you believe he/she performs them WORSE than roughly two years ago.

1. Finds it harder to learn new telephone numbers.	YES	NO
2. Finds it harder to find personal possessions (keys, telephone, utensils, etc.).	YES	NO
3. Finds it harder to describe the plots of films.	YES	NO
4. Finds it harder to remember doctor's appointments.	YES	NO
5. Finds it harder to follow the plot of a book.	YES	NO

6. Worse at recalling the details of a recent family event.	YES	NO
7. Finds it harder to remember the result of a recent sporting event.	YES	NO
8. Finds it harder to remember sums of money (payments or debts).	YES	NO
9. Finds it harder to remember the details of a conversation.	YES	NO
10. Finds it harder to remember things without using strategies (lists, diary, etc.).	YES	NO
11. Finds it harder to remember the details of recent news.	YES	NO
12. Finds it harder to remember famous people's names.	YES	NO
13. Finds it harder to remember the names of people I've met recently.	YES	NO
14. Finds it harder to remember street and city names.	YES	NO
15. Worse at finding the word I want to use in a conversation.	YES	NO
16. Finds it harder to understand things the first time someone says them.	YES	NO
17. Finds it harder to remember the names of places I've visited recently.	YES	NO
18. Finds it harder to concentrate on what I am doing.	YES	NO
19. Worse at planning things that aren't part of my daily routine (travel, excursions, etc.).	YES	NO
20. Finds it harder to use electronic devices.	YES	NO
21. Finds it harder to start new or different things.	YES	NO
22. Finds it harder to start conversations.	YES	NO
23. Finds it harder to do mental arithmetic.	YES	NO
24. Finds it harder to do more than one thing at once without getting agitated.	YES	NO
TOTAL "YES"		

Annex 3. Evaluación de Mis Cambios Cognitivos (MICOG)

Nombre:
Edad:
Fecha:

a) ¿Cree que tiene problemas cognitivos o de memoria?	Si	NO
b) ¿Consultaría a un médico por estos problemas?	Si	NO
c) ¿Su cognición o memoria ha empeorado en los últimos 2 años?	Si	NO

A continuación se exponen una serie de actividades. Por favor responda Si, si cree que las hace PEOR que hace aproximadamente dos años.

1. Aprende peor nuevos números de teléfono.	Si	NO
2. Encuentra peor objetos personales (llaves, teléfono, utensilios, etc.).	Si	NO
3. Recuerda peor el argumento de películas.	Si	NO
4. Recuerda peor citas de médicos.	Si	NO
5. Recuerda peor el hilo de una novela.	Si	NO
6. Recuerda peor los detalles sobre acontecimientos familiares recientes.	Si	NO
7. Recuerda peor el resultado de competiciones deportivas recientes.	Si	NO
8. Recuerda peor cantidades de dinero (pagos o deudas).	Si	NO
9. Recuerda peor detalles de conversaciones recientes.	Si	NO
10. Recuerda peor información sin uso de estrategias (listas, agenda, etc.).	Si	NO
11. Recuerda peor los detalles de noticias recientes.	Si	NO
12. Recuerda peor el nombre de personas famosas.	Si	NO
13. Recuerda peor el nombre de personas conocidas recientemente.	Si	NO
14. Recuerda peor los nombres de calles o ciudades.	Si	NO
15. Encuentra con más dificultad la palabra que quiere usar en conversaciones.	Si	NO
16. Entiende peor a la primera lo que le dicen.	Si	NO
17. Recuerda peor el nombre de lugares visitados recientemente.	Si	NO
18. Se concentra peor en lo que está haciendo.	Si	NO
19. Planifica peor las actividades fuera de la rutina (viaje, excursión, etc.).	Si	NO
20. Maneja peor los aparatos electrónicos.	Si	NO
21. Le cuesta más empezar cosas nuevas o diferentes.	Si	NO
22. Le cuesta más iniciar conversaciones.	Si	NO
23. Calcula peor mentalmente.	Si	NO

24. Hace peor más de una cosa al mismo tiempo sin ponerse nervioso	Si	NO
TOTAL Si		

Annex 4. Evaluación de los Cambios Cognitivos de su Familiar (SUCOG)

a) ¿Cree que su familiar tiene problemas cognitivos o de memoria?	Si	NO
b) ¿Le aconsejaría consultar a un médico por estos problemas?	Si	NO
c) ¿Su cognición o memoria ha empeorado en los últimos 2 años?	Si	NO

A continuación se exponen una serie de actividades. Por favor responda Si, si cree que las hace PEOR que hace aproximadamente dos años.

1. Aprende peor nuevos números de teléfono.	Si	NO
2. Encuentra peor objetos personales (llaves, teléfono, utensilios, etc.).	Si	NO
3. Recuerda peor el argumento de películas.	Si	NO
4. Recuerda peor citas de médicos.	Si	NO
5. Recuerda peor el hilo de una novela.	Si	NO
6. Recuerda peor los detalles sobre acontecimientos familiares recientes.	Si	NO
7. Recuerda peor el resultado de competiciones deportivas recientes.	Si	NO
8. Recuerda peor cantidades de dinero (pagos o deudas).	Si	NO
9. Recuerda peor detalles de conversaciones recientes.	Si	NO
10. Recuerda peor información sin uso de estrategias (listas, agenda, etc.).	Si	NO
11. Recuerda peor los detalles de noticias recientes.	Si	NO
12. Recuerda peor el nombre de personas famosas.	Si	NO
13. Recuerda peor el nombre de personas conocidas recientemente.	Si	NO
14. Recuerda peor los nombres de calles o ciudades.	Si	NO
15. Encuentra con más dificultad la palabra que quiere usar en conversaciones.	Si	NO
16. Entiende peor a la primera lo que le dicen.	Si	NO
17. Recuerda peor el nombre de lugares visitados recientemente.	Si	NO
18. Se concentra peor en lo que está haciendo.	Si	NO
19. Planifica peor las actividades fuera de la rutina (viaje, excursión, etc.).	Si	NO
20. Maneja peor los aparatos electrónicos.	Si	NO
21. Le cuesta más empezar cosas nuevas o diferentes.	Si	NO
22. Le cuesta más iniciar conversaciones.	Si	NO
23. Calcula peor mentalmente.	Si	NO
24. Hace peor más de una cosa al mismo tiempo sin ponerse nervioso.	Si	NO
TOTAL Si		

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Trabajo 2

Informants' perception of subjective cognitive decline helps to discriminate preclinical Alzheimer's disease from normal aging

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Informants' Perception of Subjective Cognitive Decline Helps to Discriminate Preclinical Alzheimer's Disease from Normal Aging

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Abstract.
Background: Self-reported and informant-reported subjective cognitive decline (SCD) may be useful in the detection of preclinical Alzheimer's disease (Pre-AD) and cognitive impairment related to abnormal amyloid-β ($A\beta_{42}$) levels.
Objectives: a) To compare the Subjective Cognitive Decline Questionnaire (SCD-Q) ratings between Pre-AD subjects and cognitively healthy controls, b) to study the association of SCD-Q scores with levels of AD biomarkers in cognitively healthy and cognitively impaired subjects, and c) to compare SCD-Q ratings in cognitively impaired subjects with or without abnormal $A\beta_{42}$.
Methods: Two hundred and seventeen participants (111 subjects; 106 informants) answered the SCD-Q. All subjects underwent a lumbar puncture to determine levels of $A\beta_{42}$ and tau, and an extensive neuropsychological battery. Healthy subjects were classified as Controls (CTR) or Pre-AD according to the absence or the presence of abnormal $A\beta_{42}$, and those with cognitive impairment (CI) into Non-amyloid (NonAB-CI) or Amyloid (AB-CI) impairment.
Results: Informants' SCD-Q scores were significantly higher in the Pre-AD group than in the CTR group ($F = 6.75$; $p = 0.01$). No significant differences were found in self-ratings. In the cognitively impaired groups, there were no significant differences in the SCD-Q ratings. In the whole sample, informants' ratings of SCD-Q correlated with $A\beta_{42}$ ($r = -0.21$; $p = 0.02$) and tau levels ($r = 0.28$; $p = 0.00$).
Conclusions: Higher informants' ratings of SCD-Q differentiated Pre-AD subjects from CTR. Informants' ratings of SCD-Q correlated weakly with cerebrospinal fluid AD biomarkers.

Keywords: Amyloid-β, preclinical Alzheimer's disease, subjective cognitive decline, tau proteins

INTRODUCTION

The identification of sensitive clinical markers of preclinical AD (Pre-AD), characterized by the presence of abnormal AD biomarkers in the absence of objective cognitive impairment [1], is crucial for the design of secondary prevention trials. In recent years, the assessment of subjective cognitive decline (SCD) has attracted increasing interest in the context of Pre-AD, and has suggested that SCD may represent the first symptomatic manifestation of AD [2–4].

Despite the potential relevance of the condition in the Pre-AD stage of the disease, the results of research into SCD are still inconclusive [4–7]. Some studies have shown that SCD healthy subjects present atro-

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phy and hypometabolism in areas that are typically affected in AD [8–10] and are more likely to develop incident mild cognitive impairment or dementia due to AD [2, 11, 12]. A series of studies have also suggested that the presence of SCD increases the likelihood of biomarker evidence for AD [3, 4]. However, other studies have not found an association between SCD and objective cognitive performance or cognitive decline [13–15], and some authors have questioned the usefulness of the concept of SCD because of its high prevalence in the elderly and its strong relationship with psychological variables [16–18]. Thus, the prognostic value of SCD still remains unclear [19].

Another unresolved issue is the relative value of self- and informant-reported SCD. Some longitudinal studies have found that informants' assessments of SCD are a better predictor of subsequent decline in cognitively healthy elderly than self-reported SCD [6, 7, 20]. However, other studies found no association between informants' reported SCD and subsequent cognitive decline [5]. Similarly, some studies have found an association between informants' SCD reports and AD biomarker levels in cognitively healthy and cognitively impaired subjects [21, 22] but other studies have not [23].

The divergence found in the studies exploring SCD and AD may be due to the high variability observed in the conceptualization and measurement of SCD [3, 4]. In an attempt to reduce this inconsistency, the international Subjective Cognitive Decline Initiative (SCD-I) work group proposed specific features for SCD to be used in the research field [3]. They suggested that subjective "*decline*" might better reflect the progressive nature of cognitive deterioration in AD than subjective "*impairment*". Furthermore, the SCD-I also proposed that SCD reported in the last few years might be more predictive of AD than SCD experimented over a longer period. Finally, it was proposed that asking about perceived "*cognitive*" decline as opposed to restricting the question to "*memory*" decline would be more sensitive to early AD in its heterogeneous forms of manifestation.

Following the criteria specified by the SCD-I, and acknowledging the importance of quantifying the SCD with new comprehensive instruments, we validated the Subjective Cognitive Decline Questionnaire (SCD-Q) [19]. The SCD-Q is designed to quantify subjects' and informants' reported SCD over the last two years. In our validation study, we found that subjects' SCD-Q scores were not associated with cognitive performance in the cognitively healthy, but were strongly related to psychological and personality measures. On the other hand, we found that informants' SCD-Q scores were significant predictors of subjects' cognitive performance and allowed the differentiation of all the groups along the AD continuum: controls, SCD, mild cognitive impairment, and AD [19].

Some studies report that patients with cognitive impairment (CI) often neglect their SCD [24, 25], while other studies provide evidence for intact self-judgment of abilities in patients with CI [26]. This discrepancy may be explained by the fact that these latter studies did not consider the pathological confirmation of the disease [27]. In this regard, a recent study has suggested that anosognosia is related to amyloid-β ($A\beta_{42}$) levels in the cognitively impaired [28].

The present study's objectives are: a) to assess the capacity of self-reports and informant-reports for discriminating Pre-AD subjects from controls, and b) to investigate the association between self-reports and informant-reports of SCD with cerebrospinal fluid (CSF) biomarkers of AD. In addition, the study aims to explore possible significant differences in SCD ratings between amyloid-related and non-amyloid-related CI. Based on previous results, our study hypotheses are the following: a) informants' reports will discriminate Pre-AD from controls better than self-reports, b) informants' reports, but not subjects' reports, will be associated with AD biomarkers, and c) self-reports of SCD will be significantly higher in non-amyloid-related CI than in amyloid-related CI.

MATERIAL AND METHODS

Subjects

Two hundred and seventeen participants (111 subjects and 106 informants) completed the present study between 2012 and 2014. All participants were recruited through convenience sampling at the memory clinics of Hospital Clinic and Hospital de la Santa Creu i Sant Pau, in Barcelona, Spain. Some of the participants came to the memory clinics seeking medical assistance, while others who came to the clinics as companions of patients took part in the study as volunteers. The ethics committee approved the study, and all participants signed informed consent before undergoing a neuropsychological assessment and a lumbar puncture.

The study included subjects aged 50 or more, with or without cognitive impairment, who agreed to participate. The following exclusion criteria were applied: a) the presence of any neurological diagnosis other than mild cognitive impairment or dementia, b) the

presence of a serious or unstable medical condition, c) the diagnosis of a major psychiatric disorder including schizophrenia, major depression or substance abuse, d) the presence of a global deterioration scale (GDS) score >4 [29].

Following these criteria, the subjects' sample included 78 cognitively healthy subjects. Cognitively healthy subjects had to meet the following criteria: Mini-Mental State Examination (MMSE)>24 [30], and objective cognitive performance within the normal range (1.5 SD from normative mean) in all tests on a specific test battery (see below). According to the absence or presence of abnormal CSF $A\beta_{42}$ levels ($\leq$550 pg/ml), healthy subjects were grouped into a Control group (CTR, $n = 59$) and a Preclinical AD group (Pre-AD, $n = 19$). Pre-AD subjects were classified in accordance with the guidelines proposed by the National Institute on Aging and the Alzheimer's Association (NIA-AA) for defining Pre-AD for research purposes [31]. Of these 78 subjects, 45 were GDS stage 2, defined as the presence of subjective cognitive complaints (sufficient for requiring medical assistance) in the absence of objective impairment.

The 33 subjects with CI met the following criteria: a) objective evidence of cognitive impairment on at least one test (>1.5 SD below the normative mean) from a specific test battery (see below), and b) a GDS score between 3-4. Of these, 23 presented no significant changes in instrumental activities of daily living [32] and therefore did not meet criteria for dementia. The other 10 patients were diagnosed with mild dementia on the basis of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [33]. The cognitively impaired were grouped according to the absence or presence of abnormal CSF $A\beta_{42}$ levels ($\leq$550 pg/ml) into Non-amyloid CI (NonAB-CI, $n = 12$) and Amyloid CI (AB-CI, $n = 21$).

One hundred and six informants participated in the study. Informants were close relatives or caregivers of the subjects who were familiar with the subjects' daily life activities. In the case of four CTR subjects and one AB-CI subject, no informants were available.

Procedure

Neuropsychological battery and psychological assessment

All the subjects were assessed with a 2-h comprehensive neuropsychological battery, administered on two different days by a trained neuropsychologist. The battery included the following tests to assess: MMSE, Memory Alteration Test [34], Free and Cued Selective Reminding Test (FCSRT) [35], Rey Osterrieth Complex Fig. [36, 37], Boston Naming Test (BNT) [38], Semantic Fluency (animals), Comprehension of Commands BDAE [39], ideomotor apraxia test, Digital Perception Test [40], object decision, number location and letters of the VOSP test [41], Digit Span Test [42], Trail Making Test (TMT) [43], Stroop Test [44], Digit Symbol Test [45] and phonetic fluencies [46]. All neuropsychological scores were adjusted for age and educational level. Depression and anxiety symptoms were evaluated in all subjects and informants with the Hospital Anxiety and Depression Scale (HADS) [47].

Subjective cognitive decline-questionnaire

All subjects and informants answered the validated SCD-Q [19] without previous feedback on their cognitive performance in the neuropsychological tests. The questionnaire was self-administered at home. The SCD-Q contains a form named "MyCog" (standing for my cognition) which is answered by the subject and another form named "TheirCog" (standing for their cognition) which is answered by the informant; both forms contain the same questions. The SCD-Q consists of 24 items answered in a yes/no format which assesses perceived SCD over the last two years, with items addressing changes in everyday memory, language, and executive functions tasks. Total ratings of both "MyCog" and "TheirCog" parts range from 0–24, with higher ratings indicating greater perceived cognitive change. For more details, see Rami et al. [19].

Determination of CSF biomarkers

All subjects underwent a lumbar puncture between 9 a.m. and 12 p.m. In the extraction, 10 mL of CSF was collected. The samples were centrifuged and stored in polypropylene tubes at –80°C within the first hour after extraction. CSF levels of $A\beta_{42}$, total tau (tau), and phosphorylated tau at threonine-181 (ptau) were measured by enzyme-linked immunosorbent assay kits (Innogenetics, Ghent, Belgium). In accordance with the Hospital Clinic's laboratory criteria, the following cutoff points for abnormality were considered in each CSF biomarker: a) $A\beta_{42}$ $\leq$550 pg/ml, b) tau $\geq$350 pg/ml for subjects younger than 50 years, $\geq$400 pg/ml for subjects between 50–70 years old, and $\geq$450 pg/ml for subjects older than 70 years, and c) ptau $\geq$75 pg/ml. The lumbar puncture and the administration of the SCD-Q presented a mean lag time of 1.34 (SD 1.4) years.

Statistical analysis

Statistical analyses were performed with the SPSS package for Windows (V.17.0). All statistical analysis considered a $p < 0.05$ to be significant in order to avoid type I error. Demographical, biological and psychological data means between groups were compared using Analysis of Variance (ANOVA). Cognitive test means were compared between groups using Analysis of Covariance (ANCOVA) controlling for age and years of education, and using Bonferroni adjustments for multiple comparisons. The cognitive tests selected for between-group comparisons correspond to the tests applied at both hospitals. SCD-Q ratings between groups were compared using ANCOVA, controlling for age and using the Bonferroni adjustment. Tukey *post-hoc* analyses were performed to observe the differences between the groups, and chi-squared analyses to observe the frequency of discrepancy between self and informants' SCD ratings.

In the five subjects with no available informant, only MyCog scores were used to analyze the relationship with AD biomarkers, neuropsychological performance, and psychological variables. These subjects were excluded for the crosstab analysis of MyCog and TheirCog ratings score.

Pearson Partial Correlations, controlling for age, were used to analyze the association of SCD-Q ratings with AD biomarkers, HADS, and cognitive test scores. Finally, a ROC curve analysis was performed to assess the diagnostic capacity of SCD-Q for preclinical AD in cognitively healthy subjects.

RESULTS

Demographic, biological, psychological, and cognitive data: Comparison between groups

There were no significant differences between groups in age, years of education, or gender distribution (see Table 1). With regard to AD biomarkers, CSF $A\beta_{42}$ was significantly lower in the Pre-AD and A-CI groups. CSF tau and ptau were significantly higher in the A-CI group. The groups did not differ significantly in terms of subjects' or informants' levels of anxiety and depression (see Table 1). Regarding the cognitive data, only the AB-CI had a significantly lower MMSE score than the rest of the groups (see Table 1). The neuropsychological characterization of each group, and between-group comparisons, can be seen in Table 2. CTR and Pre-AD groups did not differ significantly in any of the cognitive tests administered. NonAB-CI scored significantly better on the FCSRT and on the TMT-A and TMT-B tests than the AB-CI group.

Of the five subjects with no available informant, one was AB-CI while the other four were CTRs. Their mean age was 64.6 (range 57–73), with a mean of 11 years of education (range 8–15), and a mean MMSE score of 28.2 (range 27–29).

SCD-Q in the cognitively healthy

SCD-Q mean ratings between CTR and Pre-AD

There were no significant differences between CTR and Pre-AD groups on total "MyCog" scores (F = 1.49;

Table 1
Demographical, biological, psychological and cognitive data between groups

	Cognitively Healthy		Cognitively Impaired		F	*Post-Hoc*
	CTR ($n = 59$)	Pre-AD ($n = 19$)	NonAB-CI ($n = 12$)	AB-CI ($n = 21$)		
Age	64.8 (7.6)	69.0 (8.5)	63.4 (9.6)	69.8 (7.5)	3.3*	*n.s.*
Education	11.8 (4.5)	10.8 (4.1)	13.5 (4.1)	11.9 (5.0)	0.9	*n.s.*
Gender (%f)[a]	67.8	78.9	41.7	61.9		
CSF$A\beta_{42}$	801.4 (181.3)	394.1 (111.9)	793.1 (157.7)	390.2 (91.9)	58.9*	*Pre-AD<CTR, NonAB-CI AB-CI<CTR, NonAB-CI*
CSFtau	281.4 (195.9)	264.5 (144.3)	344.0 (248.9)	567.2 (280.8)	9.9*	*AB-CI>CTR, Pre-AD, NonAB-CI*
CSFptau	58.6 (27.9)	53.7 (24.9)	55.4 (20.9)	88.2 (34.6)	7.0*	*AB-CI>CTR, Pre-AD, NonAB-CI*
HADS-A	5.6 (3.3)	7.0 (3.4)	8.2 (4.3)	5.9 (4.5)	1.8	*n.s.*
HADS-D	3.7 (3.2)	4.0 (3.9)	5.6 (4.7)	3.8 (5.1)	0.8	*n.s.*
I-HADS-A	6.5 (.7)	7.0 (1.1)	6.2 (1.7)	6.4 (1.1)	0.0	*n.s.*
I-HADS-D	3.7 (.7)	4.4 (1.1)	3.7 (1.6)	3.9 (1.0)	0.1	*n.s.*
MMSE	28.6 (1.3)	28.1 (1.3)	27.8 (1.2)	24.2 (2.8)	27.7*	*AB-CI<CTR, Pre-AD, NonAB-CI*

Data are presented as means (SD). ANOVA and *Post-Hoc* Tukey results are shown. CSF $A\beta_{42,}$ levels of Amyloid-β in the cerebrospinal fluid (pg/ml). CSFtau, levels of total tau protein in cerebrospinal fluid (pg/ml), CSFptau, levels of phosphorylated tau in cerebrospinal fluid (pg/ml). HADS-A: Subjects' scores on hospital anxiety and depression scale anxiety items. HADS-D: subjects' scores on hospital anxiety and depression scale depression items. I-HADS-A, informants' scores on hospital anxiety and depression scale anxiety items. I-HADS-D, informants' scores on hospital anxiety and depression scale depression items. MMSE, mini mental state. *Mean difference is significant at $p < 0.05$. [a]Chi-squared analysis are not significant for gender distribution between groups with $p > 0.05$.

Table 2
Neuropsychological data between groups

	Cognitively Healthy		Cognitively Impaired		F	*Post-Hoc*[a]
	CTR ($n=59$)	Pre-AD ($n=19$)	NonAB-CI ($n=12$)	AB-CI ($n=21$)		
FCSRT_FR	28.3	25.9	16.2	9.0	48.9*	*CTR, Pre-AD>AB-CI, NonAB-CI*
FCSRT_TR	44.3	40.0	32.6	23.2	41.9*	*CTR, Pre-AD>AB-CI, NonAB-CI NonAB-CI>AB-CI*
FCSRT_DFR	10.7	10.1	6.7	1.5	41.7*	*CTR, Pre-AD>AB-CI, NonAB-CI NonAB-CI>AB-CI*
FCSRT_DTR	15.2	14.4	11.1	4.9	45.5*	*CTR, Pre-AD>AB-CI, NonAB-CI NonAB-CI>AB-CI*
SEM.FLU	20.9	20.3	16.8	12.7	8.9*	*CTR>AB-CI, NonAB-CI Pre-AD>AB-CI*
BNT	53.9	51.8	51.8	49.5	4.9*	CTR>AB-CI
TMT-A	43.4	47.4	50.8	77.3	8.9*	*CTR, Pre-AD, NonAB-CI<AB-CI*
TMT-B	117.6	148.8	125.5	504.2	30.3*	*CTR, Pre-AD, NonAB-CI<AB-CI*
DIG.FOW	5.4	5.3	5.1	5.0	0.9	*n.s.*
DIG.BACK	4.6	4.8	4.0	3.1	8.4*	*CTR, Pre-AD>AB-CI*

Data are presented as means. ANCOVA controlling for age and education. FCSRT: free and cued selective reminding test (fr: free recall, tr: total recall, dfr: delayed free recall, dtr: delayed total recall); SEM.FLU: semantic fluency, animals in one minute; BNT: Boston Naming Test (max.60); TMT-A: trail making test part A, units in seconds; TMT-B: trail making test part B, units in seconds; DIG.FOW: span digit forward; DIG.BACK: span digit backwards. *Mean difference is significant at $p<0.05$. [a]Bonferroni adjustment applied.

Table 3
MyCog scores between groups

	Cognitively Healthy		Cognitively Impaired		F	*Post-Hoc*[a]
	CTR ($n=59$)	Pre-AD ($n=19$)	NonAB-CI ($n=12$)	AB-CI ($n=21$)		
Total *MyCog*	7.6 (6.5)	10.1 (6.6)	14.1 (7.2)	10.6 (7.0)	3.7*	*NonAB-CI>CTR*
MyCog mem.	3.5 (3.5)	4.4 (3.3)	6.6 (4.2)	4.9 (3.3)	2.9*	*NonAB-CI>CTR*
MyCog lang.	2.2 (1.8)	3.0 (1.9)	3.5 (1.6)	2.8 (1.8)	2.4	*n.s.*
MyCog exec.	1.7 (1.9)	2.7 (2.2)	4.0 (2.3)	2.9 (2.4)	4.8*	*NonAB-CI>CTR.*

Data are presented as means (SD). ANCOVA and *Post-Hoc* Tukey results are shown. Total "*MyCog*", total rating in "*MyCog*" (0–24); "*MyCog*" memory, total rating in "MyCog" memory items (0–11); "*MyCog*" language, total rating in "*MyCog*" language items (0–6); "*MyCog*" executive, total rating in "*MyCog*" executive functions items (0–7). Data corresponds to mean (SD). *Mean difference is significant at $p<0.05$. [a]Bonferroni adjustment applied.

$p=0.23$), with mean scores of 7.59 (CI: 5.97–9.37) in the CTR group and 10.05 (CI: 6.78–12.86) in the Pre-AD group (see Table 3). This analysis showed an observed power of 0.25. Pre-AD scored had significantly higher total "TheirCog" scores than the CTR group ($F=6.75$; $p=0.01$), with a mean of 7.63 (CI: 5.06–9.75) in the Pre-AD compared to a mean of 3.76 (CI: 2.49–5.06) in the CTR (see Table 3). The observed power of the latter analysis was 0.73 and the partial eta squared was 0.09. Regarding the cognitive domains of "TheirCog", the mean differences in language and executive functions items reached significance ($F=3.99$; $p=0.04$, and $F=24.5$; $p=0.00$, respectively) (see Table 4).

Discrepancies of self-reports and informants' reports of SCD between groups

Following the cutoff points established by Rami et al. [19], self-reported SCD was considered when the total "MyCog" score was ≥7 points, and informants' reported SCD was considered when the total "TheirCog" score was ≥7 points. Two possible discrepancies were considered: the first when the total "MyCog" score was ≥7 points while total "TheirCog" score was below 7 points (in other words, when self-reported SCD was not confirmed by the informants); and the second when the total "TheirCog" score was ≥7 points and total "MyCog" score was below 7 points (that is, when informants reported a SCD but the self-reports did not).

The frequency of discrepancy differed significantly between the CTR and Pre-AD groups ($\chi^2=11.36$; $p=0.04$). In the CTR group, 55 subjects scored above the cutoff point for SCD in total "MyCog"; of these, 16 informants confirmed the SCD by providing scores above the cutoff point in the total "TheirCog" (29.1%). At the same time, four subjects did not present scores above the cutoff point for SCD in total "MyCog"; in

Table 4
TheirCog scores between groups

	Cognitively Health		Cognitively Impaired		F	*Post-Hoc*
	CTR ($n=55$)	Pre-AD ($n=19$)	NonAB-CI ($n=12$)	AB-CI ($n=20$)		
Total *TheirCog*	3.8 (4.9)	7.6 (5.4)	15.3 (7.3)	13.4 (6.2)	22.9*	*Pre-AD>CTR* *NonAB-CI>CTR,Pre-AD* *AB-CI>CTR, Pre-AD*
TheirCog mem.	1.8 (2.6)	3.3 (2.4)	7.3 (3.5)	7.1 (3.1)	23.5*	*NonAB-CI>CTR, Pre-AD* *AB-CI>CTR, Pre-AD*
TheirCog lang.	0.9 (1.5)	2.1 (1.9)	3.3 (2.4)	3.0 (1.7)	9.3*	*NonAB-CI>CTR* *AB-CI>CTR*
TheirCog exec.	0.9 (1.5)	2.3 (1.9)	4.8 (1.9)	3.6 (2.5)	19.4*	*Pre-AD>CTR* *NonAB-CI>CTR, Pre-AD* *AB-CI>CTR*

Data are presented as means (SD). ANCOVA and *Post-Hoc* Tukey results are shown. Total "*TheirCog*", total mean rating in "*TheirCog*" (0–24); "*TheirCog*" memory, total rating in "*TheirCog*" memory items (0–11); "*TheirCog*" language, total rating in "*TheirCog*" language items (0–6); "*TheirCog*" executive, total rating in "*TheirCog*" executive functions items (0–7). *Mean difference is significant at $p<0.05$. [a]Bonferroni adjustment applied.

these cases, none of the informants provided scores above the cutoff point in total "TheirCog", thus supporting the absence of SCD. In the Pre-AD group, 16 subjects had scores above the cutoff point for SCD in total "MyCog"; in these cases, 8 informants confirmed the SCD by scoring above the cutoff point for SCD in total "TheirCog" (50%). Meanwhile, three Pre-AD subjects did not score above the cutoff point in total "MyCog"; in these cases, all three informants scored above the cutoff point for total "TheirCog".

ROC curve of SCD for Pre-AD diagnosis

The area under the ROC curve for Pre-AD of the "MyCog" part of the SCD-Q was 0.64 ($p=0.71$). For the "TheirCog" part of the SCD-Q, the area under the curve for Pre-AD was 0.75 ($p=0.00$). A cutoff value of 4 points in total "TheirCog" showed a sensitivity of 83.3% and a specificity of 64.3% for discriminating Pre-AD in cognitively healthy subjects.

SCD-Q correlations with neuropsychological tests

In the cognitively healthy, "MyCog" only showed a significant correlation with the MMSE score ($r=-0.33$; $p=0.00$). "TheirCog" total ratings correlated significantly with MMSE scores ($r=-0.30$; $p=0.01$), and BNT score ($r=-0.25$; $p=0.04$). The "TheirCog" language item ratings also correlated significantly with BNT ($r=-0.25$; $p=0.04$). In the Pre-AD group, "TheirCog" total ratings correlated significantly with semantic fluency ($r=-0.50$; $p=0.04$), BNT ($r=-0.65$; $p=0.01$), TMT-A ($r=0.78$; $p=0.00$), and TMT-B ($r=0.61$; $p=0.03$). "TheirCog" language ratings correlated with BNT ($r=-0.62$; $p=0.02$), and "TheirCog" executive ratings correlated with TMT-A ($r=0.70$; $p=0.00$) and TMT-B ($r=0.61$; $p=0.03$) (see Fig. 1).

SCD-Q correlation with CSF biomarkers

Analyzing the correlations between SCD-Q scores and CSF biomarker levels, we found no significant correlations with either total "MyCog" scores ($A\beta_{42}$ $r=-0.98$ & $p=0.39$; tau $r=0.06$ & $p=0.59$; ptau $r=0.05$ & $p=0.69$) or total "TheirCog" scores ($A\beta_{42}$ $r=-0.13$ & $p=0.28$; tau $r=0.3$ & $p=0.78$; ptau $r=0.12$ & $p=0.34$).

SCD-Q in the cognitively impaired

The mean scores for total "MyCog" were 14.08 (CI: 9.47–18.36) in the NonAB-CI group and 10.55 (CI: 7.27–14.04) in the AB-CI group. The difference between the two means did not reach statistical significance ($F=1.33$; $p=0.26$) (see Table 3). Likewise, the NonAB-CI group scored higher in each cognitive domain of "MyCog" but the differences lacked statistical significance. With regard to the total "TheirCog" scores, the NonAB-CI group mean score was 15.33 (CI: 11.33–19.72), and the AB-CI group mean score was 13.42 (CI: 10.49–16.87). The difference between the two means did not reach statistical significance ($F=0.80$; $p=0.38$) (see Table 4). The NonAB-CI group scored higher in each cognitive domain of "TheirCog" but the differences lacked statistical significance.

With regard to the frequency of discrepancy between self- and informant reports of SCD, the groups did not present significant differences ($\chi^2=2.75$; $p=0.25$). In

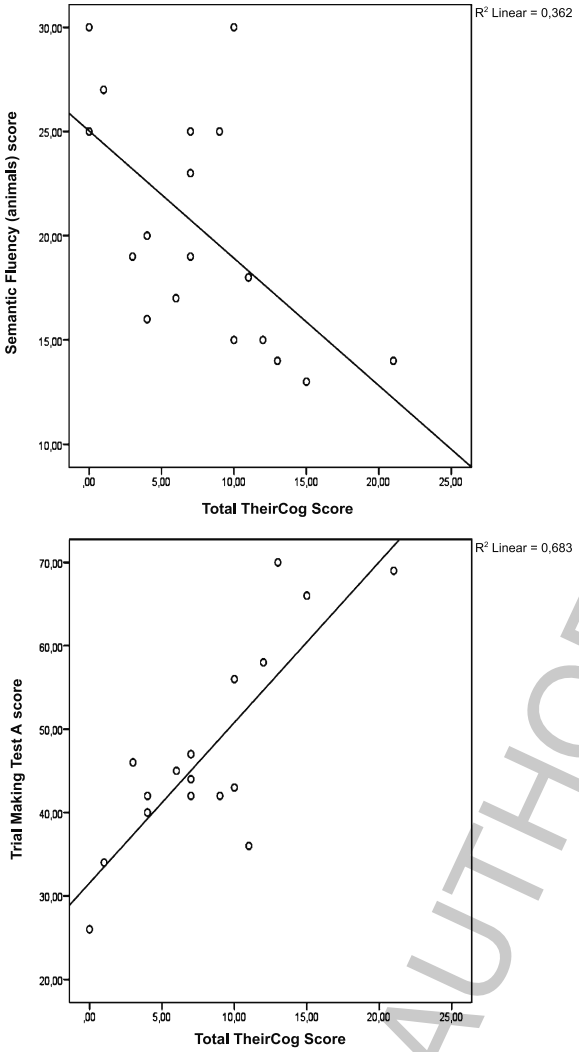

Fig. 1. Scatter plots of correlations between total "TheirCog" and language or executive cognitive tests in the Pre-AD. a) "TheirCog" total score and Semantic Fluency test correlation ($r = -0.50$; $p = 0.04$). b) "TheirCog" total score and Trail making test form A correlation ($r = 0.79$; $p = 0.00$). c) "TheirCog" total score and Trail making test form B correlation ($r = 0.78$; $p = 0.00$).

the NonAB-CI group, 10 subjects had total "MyCog" scores above the cutoff point. In these cases, the total "TheirCog" scores of nine (90%) of the informants supported the presence of SCD, being above the SCD cutoff point. Two subjects scored below the cutoff point for SCD in total "MyCog". In these cases, the total "TheirCog" scores of both their informants (100%) were above the cutoff point for SCD. In the AB-CI group, 11 subjects had total "MyCog" scores above the cutoff point for SCD. In these cases, the total "TheirCog" scores of eight (73%) of their informants were above the SCD cutoff point and thus supported the presence of SCD. Nine subjects had total "MyCog" scores below the SCD cutoff point. Seven (78%) of their informants had total "TheirCog" scores above the cutoff point for SCD.

Finally, analyzing the correlations of CSF biomarkers and SCD-Q scores, we found a significant correlation between total "MyCog" score and levels of tau ($r = -0.44$; $p = 0.02$) and ptau ($r = -0.38$; $p = 0.04$). Total "MyCog" scores did not correlate significantly with $A\beta_{42}$ ($r = 0.17$; $p = 0.35$). "TheirCog" scores did not correlate significantly with either biomarker ($A\beta_{42}$ $r = 0.15$ & $p = 0.94$; tau $r = 0.14$ & $p = 0.48$; ptau $r = 0.18$ & $p = 0.32$).

SCD-Q comparison between the cognitively healthy and the cognitively impaired

When comparing cognitively healthy and cognitively impaired groups, we found significant differences between total "MyCog" scores in NonAB-CI and CTR groups ($F = 5.13$; $p = 0.01$). As regards the cognitive domains of "MyCog", the NonAB-CI group scored significantly higher in the memory items and the executive items than the CTR group (see Table 3). The AB-CI group did not show significant differences in their mean "MyCog" scores with respect to any of the cognitively healthy groups, and at the same time the Pre-AD group did not differ significantly from either of the cognitively impaired groups (see Table 3). Both cognitively impaired groups scored significantly higher on total and on "TheirCog" memory and executive items than both cognitively healthy groups (see Table 4).

SCD-Q association with AD biomarkers and psychological variables in the whole sample

"MyCog" ratings did not show a significant correlation with any of the AD biomarkers studied. On the other hand, total "TheirCog" scores correlated significantly with each of the AD biomarkers studied (see Table 5). Regarding the cognitive domains of "TheirCog", CSF $A\beta_{42}$ levels were inversely correlated with the memory item ratings ($r = -0.25$; $p = 0.01$); CSF tau levels were directly correlated with memory item ratings ($r = 0.37$; $p = 0.00$) and executive item ratings ($r = 0.23$; $p = 0.03$) and CSF ptau levels were directly correlated with memory item ratings ($r = 0.36$; $p = 0.00$) and executive item ratings ($r = 0.26$; $p = 0.01$). With regard to the psychological variables, levels of anxiety and depression in subjects

Table 5
Correlations between SCD-Q ratings and AD biomarkers

	CSFAβ_{42}	CSFtau	CSFptau
Total MyCog	–0.09	–0.01	–0.05
MyCog mem.	–0.09	–0.09	0.03
MyCog lang.	–0.09	–0.13	–0.16
MyCog exec.	–0.06	–0.01	–0.04
Total TheirCog	–0.21*	0.28*	0.28*
TheirCog mem.	–0.25*	0.37*	0.36*
TheirCog lang.	–0.18	0.17	0.17
TheirCog exec.	–0.12	0.23*	0.26*

Pearson partial correlations controlling for age were performed. CSFA$\beta_{1\text{-}42}$, levels of Amyloid-β protein in cerebrospinal fluid in pg/ml. CSFtau, levels of total protein tau in cerebrospinal fluid in pg/ml. CSFptau, levels of "MyCog", phosphorylated tau in cerebrospinal fluid in pg/ml. Total "MyCog", total rating in "MyCog" (0–24) memory, total rating in "MyCog" memory items (0–11); "MyCog" language, total rating in "MyCog"language items (0–6); "MyCog" executive, total rating in "MyCog" executive function items (0–7). Total "TheirCog", total rating in "TheirCog" (0–24); "TheirCog" memory, total rating in "TheirCog" memory items (0–11); "TheirCog" language, total rating in "TheirCog" language items (0–6); "TheirCog"executive, total rating in "TheirCog" executive function items (0–7). *The coefficient of correlation is significant at $p < 0.05$.

correlated significantly with total "MyCog" ratings ($r = 0.31$; $p = 0.01$ and $r = 0.37$; $p = 0.00$ respectively). "TheirCog" scores did not correlate significantly with anxiety levels ($r = 0.16$; $p = 0.18$). However, depression levels of informants did show a significant correlation ($r = 0.24$; $p = 0.047$). Nonetheless, the correlation between CSF biomarkers and total "TheirCog" remained significant after controlling for HADS depressive scores in informants ($r = –0.25$; $p = 0.03$ for CSF Aβ_{42}, $r = 0.47$; $p = 0.00$ for CSF tau, and $r = 0.38$, $p = 0.00$ for CSF ptau).

DISCUSSION

The present study is the first to study the relationship between self- and informant-ratings of cognitive decline, quantified by a validated questionnaire designed using the SCD-I conceptual framework in a sample classified in accordance with their CSF AD biomarker profile. It attempts to respond to the recommendation made by the SCD-I to identify specific features of SCD that increase the likelihood of the presence of preclinical AD [3].

In this study we found that the informants' perception of their relative's cognitive decline (quantified by the "TheirCog" part of the SCD-Q) was able to discriminate the Pre-AD subjects from CTR, showing significantly higher scores in the Pre-AD group. Self-reports of SCD (quantified by "MyCog"), in contrast, did not differ significantly between the two groups. With regard to the cognitively impaired, although the NonAB-CI group scored higher than the AB-CI group in both "MyCog" and "TheirCog", the differences between the groups did not reach statistical significance. At the same time, in the whole sample CSF AD biomarkers were significantly associated with "TheirCog" scores, but not with "MyCog" scores. Finally, "TheirCog" scores were found to have a higher correlation with objective cognitive tests than "MyCog" scores, while "MyCog" scores appeared to be more strongly related to psychological variables.

The finding that "TheirCog" scores differed significantly between CTR and Pre-AD groups is consistent with previous studies which have stressed the importance of informants' reports for detecting very early AD-related decline. For example, Rabin and colleagues [6] found that the informants' reports of SCD were significantly associated with the risk of developing AD in community elderly. Carr & Gray [7] also found that informant-reported memory complaints at baseline predicted future onset of AD in cognitively healthy subjects. Even though our study was not longitudinal, our results support these findings since informants' reports of SCD were significantly higher in healthy subjects at risk of AD due to CSF Aβ_{42} abnormality, and supports the SCD-I's definition of informants' reports as a plus feature of pre-AD [3]. Indeed, our results show that only informants' reports of SCD may be useful in the diagnosis of Pre-AD, while self-reports seemed less specific to the disease.

Although Pre-AD informants reported more decline in all cognitive domains of the SCD-Q than CTR informants, only language and executive items reached statistical significance. These results were surprising, since most studies report that episodic memory decline is the most salient feature in preclinical AD [48, 49]. We stress that daily activities described in the SCD-Q involve multiple cognitive domains; for example, four of the six language items of the SCD-Q involve tasks of remembering names, in which language skills overlap with episodic memory functions. In addition, some executive items require memory functioning for their performance (e.g., planning and usage of electronic devices). In this regard, prospective neuropsychological studies indicate that tasks in which memory is combined with executive control and language tasks are an excellent indicator of future progression to AD [50]. In relation to the executive functions, some authors have found that changes may occur earlier than is commonly thought [51] and that subjective executive complaints may be early related to the AD pathological

processes [16, 52, 53]. In any case, these results highlight the importance of including multiple cognitive domains in the SCD questionnaires [3, 54].

As regards CSF AD biomarkers, although studies reporting the relation between AD biomarkers and informants' ratings of SCD are scarce, the few studies performed to date seem to point in the same direction. For example, in a sample constituted by cognitively normal and impaired subjects, Rueda and colleagues [21] found that informants' ratings of SCD correlated significantly with CSF levels of $A\beta_{42}$ and ptau, and at the same time correlated with a smaller hippocampal volume. Similarly, Okonkwo and colleagues [22] found that CSF $A\beta_{42}$, tau, and ptau levels correlated with informants' reports of functional decline in cognitively normal elderly and in a CI group. However, we found one study which did not record significant differences in the informants' reports of decline between low and high $A\beta_{42}$ healthy groups [23]. That study quantified informant-rated decline through the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE-S) [55] that compares subjects' current performance with their performance 10 years previously. This long time of comparison leads to confusion since changes may be due only to the aging process [3, 19], and the IQCODE-S includes items referring to functions which commonly become more difficult with increasing age.

In contrast to informants' ratings of SCD, "MyCog" ratings did not show any significant correlation with CSF AD biomarkers; nor did they differ significantly between the CTR and the Pre-AD groups. In our sample, total "MyCog" ratings in CTR and Pre-AD groups were higher than their respective "TheirCog" mean ratings. In this context, it is possible that the loss of significant differences between the two groups in the "MyCog" ratings is related to an underestimation of their cognitive performance in the CTR group rather than an unawareness of decline in the Pre-AD group. Indeed, the discrepancies between subjects' and informants' reports were significantly higher in the CTR group than the Pre-AD group. This finding is consistent with previous reports that non-demented elderly may complain excessively about their cognitive functions, without correlating their complaints with objective measures or longitudinal decline [7, 56]. The underestimation of performance in our CTR group seems to be due, in part, to the psychological symptoms of the subjects [17, 18]. We found that "MyCog" ratings correlated more with anxiety and depressive symptoms in respondents than "TheirCog" ratings; these findings confirm results from other studies suggesting that informants' reports are more accurate than self-reports for identifying objective cognitive difficulties, not only in AD patients but in non-demented elderly as well [6, 7, 16, 20, 57].

In our sample, objective cognitive measures were unable to discriminate between CTR and Pre-AD groups. It has been shown to be very difficult to detect the subtle cognitive changes of Pre-AD with standardized cognitive testing due to the requirement of high test sensitivity and robustness against within-subject performance variability [3, 57]. It is also possible that standard neuropsychological tests are not sensitive enough to detect the subtle cognitive changes in preclinical AD because these tests were designed to detect clinical impairment [57]. As Jessen [4] reports, the validity of standard tests for detecting cognitive impairment decreased with reduced levels of impairment. Thus, informants' reports contribute by giving a longitudinal overview of cognitive functioning; this may prove to be very informative in Pre-AD in which the detection of impairment in cross-sectional cognitive tests is still challenging [3]. Our findings support the potential discriminative power of informants' ratings of cognitive changes for detecting preclinical AD, in the absence of sensitive cross-sectional neuropsychological assessments. At the same time, "TheirCog" correlated significantly with objective measures of global cognitive functioning, language, and executive functions in the Pre-AD group. This result is in accordance with the proposed conceptual framework of the SCD-I, which emphasizes the need to assess cognitive declines rather than to restrict the analysis to memory impairments alone [3].

Finally, we did not find significant differences in "MyCog" ratings between NonAB-CI and AB-CI. This result was unexpected and is at odds with those reported in a recent study of the Alzheimer's Disease Neuroimaging Initiative (ADNI) [28] in which underestimation of cognitive problems was associated with abnormal levels of CSF $A\beta_{42}$ in subjects with cognitive impairment. Specifically, those authors found that, when comparing self-ratings, the cognitively impaired group with normal CSF $A\beta_{42}$ levels over-estimated their cognitive problems while their peers with abnormal levels of CSF $A\beta_{42}$ under-estimated their cognitive problems and presented anosognosia. Although we found higher scores in "MyCog" in the NonAB-CI group than in the AB-CI group, the difference between the means did not reach statistical significance. We also observed that NonAB-CI scored significantly higher than CTR in "MyCog" while there were no significant differences between the AB-CI and CTR groups.

It is important to bear in mind that the sample available was relatively small, which may have limited the power of the analysis. More studies with larger samples are needed to elucidate the relationship between CSF $A\beta_{42}$ and anosognosia in CI.

As we have just suggested, a limitation of the present study was the relatively small sample. Apart from decreasing the study's statistical power, this might also explain the absence of significant correlations between "TheirCog" scores and CSF biomarkers when the sample was restricted only to the cognitively healthy or CI groups. Furthermore, the mean time lapse between the lumbar puncture and the SCD-Q administration was 1.3 years (SD 1.4). As a result, CSF levels of AD biomarkers may have changed slightly by the time of the SCD-Q administration; however, studies have found that the annual variety of CSF biomarkers is relatively small, ranging from 0.5–6 pg/ml/year in CSF $A\beta_{42}$, 1.7–3.5 pg/ml/year in CSF tau and 1.5–5.1 pg/ml/year for CSF ptau [57–60]. Considering the size of these changes, only subjects with a CSF $A\beta_{42}$ value between 650–550 would have been at risk of presenting abnormal levels. In our sample, only 16 out of 111 subjects had CSF$A\beta_{42}$ levels between 650–550, and of these, ten received the lumbar puncture during the same year as SCD-Q administration. Finally, future longitudinal studies would help to elucidate the relationship between self-reported and informant-reported SCD and cognitive decline due to AD.

The SCD-Q questionnaire is an innovative tool for quantifying SCD simultaneously in subjects and informants and rigorously follows the criteria proposed by the SCD-I. Although the SCD-I criteria did not specify the need to grade the degree of complaints, this practice might be useful for refining the characterization of SCD and may help to overcome the lack of specificity of SCD due to its high prevalence among older adults [2].

In conclusion, we found that informants' ratings of cognitive decline were able to differentiate Pre-AD subjects from CTRs to a significant degree. Informants' ratings also correlated significantly with CSF AD biomarkers in the whole sample of cognitively unimpaired and impaired subjects. Our findings suggest that the SCD-Q may be a useful predictor of $A\beta_{42}$ abnormality in cognitively healthy subjects.

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Trabajo 3

Subtle visuomotor difficulties in preclinical Alzheimer's disease

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Subtle visuomotor difficulties in preclinical Alzheimer's disease

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Background. Individuals with preclinical Alzheimer's disease (Pre-AD) present non-impaired cognition, as measured by standard neuropsychological tests. However, detecting subtle difficulties in cognitive functions may be necessary for an early diagnosis and intervention.

Objectives. A new computer-based visuomotor coordination task (VMC) was developed to investigate the possible presence of early visuomotor difficulties in Pre-AD individuals. Associations between VMC task performance and AD biomarkers were studied. The influence of ApoE status on participants' performance was addressed, as well as the relationship between performance and subjective cognitive decline (SCD).

Methods. Sixty-six cognitively normal (CN) elders (19 Pre-AD and 47 control participants [CTR]) and 15 patients with AD performed the VMC task, which consisted in executing visually guided goal-directed movements that required the coordination of the visual and motor systems. All participants underwent ApoE analysis and lumbar puncture. CN participants also completed an extensive standard neuropsychological battery.

Results. Despite presenting normal cognition in standard tests, Pre-AD participants exhibited higher response times (RTs) to complete the VMC task than CTR ($p < .01$). Besides, patients with AD showed higher RTs than CTR ($p < .001$) and Pre-AD ($p < .05$), and more errors than CTR ($p < .005$). RTs in ApoE4 carriers were higher than that observed in ApoE4 noncarriers ($p < .01$). In CN individuals, RTs were related to amyloid β-protein 42 (AB42) biomarker ($p < .01$) and informant-rated SCD ($p < .01$).

Conclusions. The VMC task is able to discriminate Pre-AD from CTR individuals. Moreover, VMC results are associated with AB42 levels in CN individuals, suggesting that visuomotor dysfunction may be a sensitive marker of Pre-AD.

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An early identification of individuals at risk for Alzheimer's disease (AD) is crucial for developing strategies for an adequate therapeutic prevention. According to recent recommendations (Sperling *et al.*, 2011), the preclinical stages of AD (Pre-AD) can be identified in cognitively normal (CN) individuals when the underlying AD pathophysiological processes are observed in the absence of apparent clinical symptoms. The biomarker model by Jack *et al.* (2010) postulates that biomarkers related to brain amyloidosis, such as the reduction of amyloid β-protein 42 (AB42) levels in cerebrospinal fluid (CSF) as well as increased amyloid tracer retention on positron emission tomography, could be the first pathophysiological anomalies to appear in Pre-AD individuals, long before the appearance of neuronal injury. The preclinical phase of the disease lasts for years and usually remains undetected prior to significant cognitive impairment (Jack *et al.*, 2012).

By definition, Pre-AD individuals present normal cognitive functions according to existing standard neuropsychological instruments until they meet criteria for mild cognitive impairment (MCI). However, new computerized tests may provide more sensitive measures than traditional tests, designed for patients who often show pronounced cognitive impairment (Rentz *et al.*, 2013). Recently-developed experimental memory tasks, for example, have shown a higher sensitivity than standard neuropsychological tests in identifying cognitive changes in CN individuals at risk of developing AD (Parra *et al.*, 2011; Rentz *et al.*, 2011). Thus, detecting any subtle cognitive difficulty using new computerized measures could be crucial in the near future to detect candidates for treatment during the preclinical stages of AD.

AD is typically associated with hippocampal damage (La Joie *et al.*, 2012). However, functional anomalies have been reported in the posterior parietal association areas at very early stages of the disease, including the Pre-AD phase (Hedden *et al.*, 2009; Mandal, Joshi, & Saharan, 2012; Rami *et al.*, 2012). The posterior parietal cortex is known to play an important role in transforming visuospatial information into goal-directed actions, and its connection with the frontal lobe underlies many visuomotor functions (Corbetta & Shulman, 2002; Culham & Valyear, 2006). While the involvement of these brain networks in AD is well documented, the possible visuomotor dysfunction caused by this functional anomaly has not yet been investigated.

Performance on classical neuropsychological tests assessing visuomotor components was found to be predictive of AD in a few recent studies (Donohue *et al.*, 2014; Ewers *et al.*, 2014; Snitz *et al.*, 2013). On the other hand, cross-sectional studies failed at finding any significant relationship between these classical measures and AD biomarkers in CN individuals (Hedden, Oh, Younger, & Patel, 2013). Considering these evidences, we believe that neuropsychological instruments for assessing visuomotor components may not be useful to capture possible subtle alterations in these functions in Pre-AD. Consequently, it is crucial to develop new computer-based measures sensitive enough to reveal fine-grained differences, for example in visuomotor performance, between Pre-AD individuals and cognitively normal elders with a normal AD biomarker profile.

Previous studies suggest that visuomotor dysfunction may be one of the first clinical symptoms to appear in patients with AD (Tippett, Sergio, & Black, 2012; Verheij *et al.*, 2012). Along the same lines, recent work has identified visuomotor impairment in high-risk AD individuals (classified on the basis of their AD family history or diagnosis of MCI), suggesting that it could be a potential marker of AD (Hawkins & Sergio, 2014). However, the previously identified AD biomarkers, such as amyloid and neuronal injury, were not considered in this previous study. Thus, it is critical to analyse the possible relationship

between these specific AD biomarkers and subtle visuomotor difficulties (as measured in computer-based tasks).

In addition to the biological markers, another important factor that may influence cognition at early stages of AD is the apolipoprotein E (ApoE) genotype. Forty to 65% of patients with AD are ApoE4 carriers, thus making it the major genetic risk factor for sporadic late-onset AD. This has been confirmed in a recent genome-wide association study (GWAS; Lambert *et al.*, 2013). The possible influence of ApoE4 in the early cognitive changes associated with AD is a relevant issue (Mormino *et al.*, 2014) and trials with asymptomatic ApoE4 carriers, and, in particular, homozygous ones, are under development.

Furthermore, the report of subjective cognitive decline (SCD), understood as the perceived experience of cognitive deterioration, has increasingly been considered as a potential predictor of AD (Jessen *et al.*, 2014). Previous studies have argued that SCD reports are associated with poorer objective cognitive performance and with AD biomarkers in a CN population (Amariglio *et al.*, 2012; Perrotin, Mormino, Madison, Hayenga, & Jagust, 2012). Thus, it may also be interesting to analyse how SCD is related to actual performance on new computer-based cognitive tasks.

The aim of the present work was to investigate the possible presence of early visuomotor difficulties in Pre-AD individuals (as compared with a group of cognitively normal elders with normal AD biomarkers profile). For this purpose, a new computer-based visuomotor coordination task (VMC) was developed. Possible associations between VMC task performance and AD biomarkers were studied. The influence of ApoE status on participants' performance in this task was addressed, as well as the relationship between VMC task performance and SCD reports.

Materials and methods

Participants

A total of 81 participants were recruited from a memory clinic. The study was approved by the hospital ethics committee, and all participants gave written informed consent prior to enrolment. Sixty-six participants with normal cognition (their scores falling within 1.5 *SD* from normative means in an extensive neuropsychological battery; see below) were recruited for this study. These cognitively normal (CN) participants were further divided into two groups: A control group (CTR) of 47 participants with a normal CSF profile (AB42 > 550 pg/ml, total tau [tau] <450 pg/ml and tau phosphorylated [p-tau] <75 pg/ml levels); a group of 19 preclinical participants (Pre-AD group) with low levels of CSF AB42 (<550 pg/ml). Four of these 19 Pre-AD individuals (21%) also presented abnormal levels of tau and/or p-tau. In addition, 15 patients were included in a third group of patients with AD. This group included participants that met NIA-AA criteria (Jack *et al.*, 2012) for AD as they had abnormal amyloid and injury markers. The presence of a major psychiatric or neurological diagnosis and/or any serious or unstable medical condition was considered as exclusion criteria.

Visuomotor coordination task

The VMC task was divided into four blocks containing 20 trials each. Participants were instructed to use their dominant hand on the first two blocks and their nondominant hand in the last two. All trials started with the participants' right/left index finger resting on a

small platform located in front of the response keyboard. A fixation point was presented at the beginning of each trial on the centre of screen for 1000 ms. Subsequently, the target represented by a green square appeared on the computer screen, randomly in one of 5 different positions (Figure 1) for 200 ms. Participants were instructed to press one of the five green keys available on the keyboard according to the on-screen target position with their index finger as fast and accurately as possible and to return to the original resting position. The position of these five keys mimicked, in a modified computer keyboard, the location of the five squares indicating the target position on the computer screen. The instructions were both given by the experimenter and displayed on the monitor.

The visual 'go' (and target position) signal consisted of one green square (120 × 120 pixels) appearing on a black background on a 19-inch computer screen (HP Compaq LA 1956X Monitor, 75 Hz). The response buttons were made of hard foam and were also green on a black background. The 'starting/resting-point' rectangle (also made of foam) was attached to the response keyboard (on its lower central part; Figure 1). DMDX presentation software (Forster & Forster, 2003), running on an Intel Core computer, was used to present the stimuli and record the participants' RTs (the response time's mean that the subject spends in responding to each stimulus). The RTs' means were calculated considering correct responses exclusively. The experimental sessions were conducted in a quiet room at the memory clinic, where participants sat down in front of the monitor at a distance of 60 cm approximately.

Cognitive, psychological, and SCD assessment

All CN participants underwent a complete 2-hr neuropsychological battery, performed by two trained neuropsychologists. Vocabulary from Wechsler Adult Intelligence Scales III (WAIS-III; Wechsler, 1997) was used as a measure of verbal intelligence. Episodic verbal memory was assessed by the Free and Cued Selective Reminding Test (FCSRT; Buschke, 1984). Semantic memory was assessed by a semantic verbal fluency

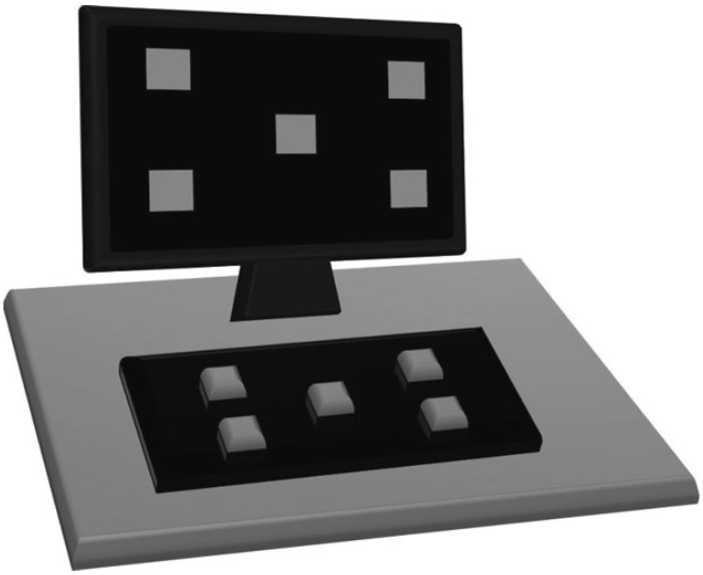

Figure 1. Schematic representation of the VMC task setting. The participants were instructed to press one of five different buttons, as previously indicated by a visual 'go' signal (that could appear in different positions) as fast and accurately as possible.

test (animals), and the Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983) was used to assess language (confrontation naming). Visual perception was assessed by means of the number location and the object decision of the Visual Object and Space Perception (VOSP; Warrington & James, 1986) battery, and by the block design test of WAIS-III. Visuomotor and executive functions were assessed by Digit Symbol Coding of WAIS-III, by Symbol Digit Modalities Test (SDMT; Smith, 1982), and by the Trail Making Test (TMT), parts A and B (Reitan & Wolfson, 1985). Inhibition of automatic response was assessed by the interference subtest of the Stroop colour–word (Golden, 1978), and finally, short-term memory was assessed by the forward and backward Digit Span from the WAIS-III. Patients with AD performed a subset of the neuropsychological battery including FCSRT, semantic fluency, number location (VOSP), TMT-A, and Digit Span. For all neuropsychological tests, normalized scalar scores for Spanish population were used (Peña-Casanova *et al.*, 1997).

The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) was used to determine the levels of anxiety and depression. The HADS is a fourteen item scale. Seven of the items relate to anxiety and seven relate to depression.

The Subjective Cognitive Decline Questionnaire (SCD-Q; Rami *et al.*, 2014) was also administrated in a subset of the sample (26 CTR, 15 Pre-AD and 11 AD participants) for the assessment of SCD. SCD-Q contains two parts: Part I (SCD-Q MyCog) is completed by the subjects themselves and indicates their self-rated cognitive decline. Part II (SCD-Q TheirCog) is completed by the informants (close relatives or caregivers of the subjects). Total ratings in both, 'MyCog' and 'TheirCog', parts range between 0 and 24, with higher ratings indicating greater perceived cognitive change.

Apolipoprotein E Analysis

Genomic DNA was extracted from peripheral blood of probands using the QIAamp DNA blood minikit (Qiagen AG, Basel, Switzerland). ApoE genotyping was performed by polymerase chain reaction amplification and HhaI restriction enzyme digestion. We classified the CN participants in two groups on the basis of the presence (carriers) or absence (noncarriers) of at least one ApoE4 allele. ApoE genotype results were not available for three participants (one for each group).

Determination of CSF biomarkers

All subjects underwent lumbar puncture in the morning (9–12 AM). CSF samples were centrifuged and stored in polypropylene tubes at −80°C. The AB42, tau, and p-tau at threonine 181 in CSF were measured by enzyme-linked immunosorbent assay (Innogenetics, Ghent, Belgium). Cut-off values of abnormality for each CSF biomarker were defined according to previous works (Antonell *et al.*, 2011; van Harten *et al.*, 2013): AB42 < 550 pg/ml, tau > 450 pg/ml, and p-tau > 75 pg/ml.

Statistical methods

Analysis of variance (ANOVA) was carried out to compare demographic/biological data means, and VMC task means in the CTR, the Pre-AD, and the AD groups using Bonferroni correction to adjust for multiple comparisons. Chi-square tests were employed to analyse categorical data. Independent sample *t*-tests were assessed to compare VMC task

performance and standard neuropsychological performance in ApoE4 carriers and noncarriers. *T*-tests were also used to compare the performance shown by the three groups (AD patients, CTR, and Pre-AD) on each of the neuropsychological tests. Pearson's correlation was employed to evaluate the relationship between VMC task measures, including RTs, errors (responding with the wrong key), and omissions (no response), and the following variables: CSF biomarkers levels, neuropsychological performance, SCD-Q and HADS scores, age, and educational level (measured in years of education). Multiple regressions were used to explore the contribution of CSF biomarkers (AB42 and tau) and the ApoE4 allele to VMC task outcome, that is how much of the variation in VMC measures can be explained by these three variables. We did not correct comparisons and correlations for age nor years of education, given that the VMC measures (RTs, errors and omissions) did not show correlations with any of them. Statistical significance was set at $p < .05$. All data were analysed using SPSS v20.0 (IBM Corp, Armonk, NY, USA).

Results

Sample characteristics

Means and standard deviations (*SD*s) for the demographic characteristics and all CSF biomarkers levels (AB42, tau, and p-tau) as well as ApoE4 allele distributions and psychological data (SCD-Q and HADS scores) are shown in Table 1. There were no statistically significant differences in terms of age and years of education between the CTR, Pre-AD, and AD groups. The AB42 levels were significantly different in the CTR group compared to both Pre-AD and AD participants ($p < .001$). The CTR and the Pre-AD groups differed significantly in tau and p-tau levels from the AD group ($p < .001$). ApoE4 distribution was significantly different in the CTR compared to both Pre-AD and AD groups ($p < .001$). Furthermore, the CTR and Pre-AD groups did not show significant differences in neuropsychological measures (see details in Table 2). Similarly, the neuropsychological performance of the CN ApoE4 carriers did not differ significantly from the CN ApoE4 noncarriers (see details in Table 3). The performance of patients with AD on neuropsychological tests was also reported in Table 2.

VMC task differences between CTR, Pre-AD, and AD

A statistically significant difference was found in RTs ($p < .001$) between the three tested groups (CTR, Pre-AD, and AD). *Post hoc* comparisons using Bonferroni test indicated that the RTs were, in average, significantly higher in Pre-AD compared to the CTR group ($p < .01$). Furthermore, RTs in the CTR ($p < .001$) and Pre-AD ($p < .05$) groups were significantly faster than RTs in the AD group. Despite the fact that possible visuomotor difficulties can be observed in RTs but not in errors or omissions, further analyses were conducted considering these variables. The ANOVA showed a significant difference for errors (responding with the wrong key) but not for omissions (no response), between the three studied groups ($p < .01$). Specifically, the number of errors was higher in the AD than in the CTR group ($p < .005$). Means and *SD*s for the CTR, Pre-AD, and AD groups are detailed in Table 4.

VMC task differences between ApoE4 carriers and noncarriers

A significant difference was found between the group of CN carriers, which included four CTR and eight Pre-AD ($M = 964.98$, $SD = 169.44$), and noncarriers, which included 42

Table 1. Demographic characteristics, cerebrospinal fluid biomarkers levels, ApoE4 status, and psychological data for CTR, Pre-AD, and AD groups

	47 CTR Mean (*SD*)	19 Pre-AD Mean (*SD*)	15 AD Mean (*SD*)	*F*-value	Effect size	*p*-Value	Comparison group	*Post hoc* *p*-value
Age (years)	65.4 (6.6)	67.4 (8.7)	68.1 (8.9)	0.938	.023	NS		
Education (years)	11.5 (4.5)	10.6 (4.2)	9.9 (4.6)	0.807	.020	NS		
AB42 (pg/ml)	799.3 (194.4)	409.1 (106.4)	360.5 (110.9)	62.006	.613	.000	CTR vs. AD	.000
							CTR vs. Pre-AD	.000
							Pre-AD vs. AD	1.000
Tau (pg/ml)	230.7 (76.4)	264.7 (146.6)	639.4 (231.5)	53.723	.582	.000	CTR vs. AD	.000
							Pre-AD vs. AD	.000
							CTR vs. Pre-AD	1.000
P-tau (pg/ml)	52.2 (13.0)	53.5 (25.1)	93.9 (27.8)	27.004	.412	.000	CTR vs. AD	.000
							Pre-AD vs. AD	.000
							CTR vs. Pre-AD	1.000
ApoE4 (%)	8.7 (4/46)	44.4 (8/18)	71.4 (10/14)	23.907*	.554	.000	CTR vs. Pre-AD	.001
							CTR vs. AD	.000
							Pre-AD vs. AD	.127
HADS-A	5.9 (3.1)	7.6 (3.8)	4.9 (3.2)	2.593	.072	.082	CTR vs. Pre-AD	.259
							CTR vs. AD	1.000
							Pre-AD vs. AD	.099
HADS-D	3.7 (2.7)	4.4 (4.2)	3.5 (5.1)	0.268	.008	.766	CTR vs. Pre-AD	1.000
							CTR vs. AD	1.000
							Pre-AD vs. AD	1.000
SCD-Q MyCog†	5.3 (7.1)	9.6 (6.5)	10.8 (6.3)	3.289	.118	.046	CTR vs. Pre-AD	.180
							CTR vs. AD	.090
							Pre-AD vs. AD	1.000
SCD-Q TheirCog†	2.0 (3.3)	7.7 (4.2)	14.5 (7.1)	26.662	.542	.000	CTR vs. Pre-AD	.001
							CTR vs. AD	.000
							Pre-AD vs. AD	.002

Notes. CTR, Control group; Pre-AD, Preclinical AD group; AD, Alzheimer's disease group; SCD-Q MyCog, self-rated Subjective Cognitive Decline Questionnaire; SCD-Q TheirCog, informant-rated Subjective Cognitive Decline Questionnaire; HADS-A, depression subscale of Hospital Anxiety and Depression Scale; HADS-D, anxiety subscale of HADS.

*Chi-square value.

†Subset of the sample including 26 CTR, 15 Pre-AD, and 11 AD.

Table 2. Means (normalized scalar scores) of standard neuropsychological tests for CTR, Pre-AD, and AD groups

	CTR 47 Mean (*SD*)	Pre-AD 19 Mean (*SD*)	AD 15 Mean (*SD*)	Comparison groups	*p* (<.05)
FCSRT: Learning	11.6 (2.5)	11.5 (2.7)	4.8 (2.7)	CTR vs. Pre-AD	NS
				Pre-AD vs. AD	.000
				CTR vs. AD	.000
FCSRT: Total learning	12.5 (2.8)	12.7 (3.5)	4.6 (3.1)	CTR vs. Pre-AD	NS
				Pre-AD vs. AD	.000
				CTR vs. AD	.000
FCSRT: Recall	11.9 (2.5)	11.6 (2.3)	2.9 (1.8)	CTR vs. Pre-AD	NS
				Pre-AD vs. AD	.000
				CTR vs. AD	.000
FCSRT: Total recall	14.0 (3.9)	12.7 (4.6)	4.7 (3.5)	CTR vs. Pre-AD	NS
				Pre-AD vs. AD	.000
				CTR vs. AD	.000
Semantic fluency	10.9 (2.7)	10.7 (2.4)	6.6 (2.7)	CTR vs. Pre-AD	NS
				Pre-AD vs. AD	.000
				CTR vs. AD	.000
VOSP: Number location	13.6 (4.2)	12.9 (4.8)	7.6 (4.4)	CTR vs. Pre-AD	NS
				Pre-AD vs. AD	.007
				CTR vs. AD	.000
TMT-part A	10.5 (2.9)	10.1 (1.6)	8.0 (1.6)	CTR vs. Pre-AD	NS
				Pre-AD vs. AD	.001
				CTR vs. AD	.008
Digit (WAIS-III): Direct	9.9 (1.5)	11.2 (2.7)	9.6 (2.3)	CTR vs. Pre-AD	NS
				Pre-AD vs. AD	NS
				CTR vs. AD	NS
Digit (WAIS-III): Inverse	12.0 (2.0)	11.8 (2.8)	9.0 (2.8)	CTR vs. Pre-AD	NS
				Pre-AD vs. AD	.018
				CTR vs. AD	.001
Vocabulary (WAIS-III)*	13.3 (3.5)	12.3 (2.4)	–	CTR vs. Pre-AD	NS
Block design test (WAIS-III)*	12.6 (2.3)	11.7 (2.7)	–	CTR vs. Pre-AD	NS
VOSP: Object decision*	11.1 (2.7)	10.7 (1.8)	–	CTR vs. Pre-AD	NS
Boston Naming Test*	11.4 (2.2)	11.2 (2.6)	–	CTR vs. Pre-AD	NS
TMT-part B*	9.7 (2.6)	8.5 (2.0)	–	CTR vs. Pre-AD	NS
Stroop word*	10.8 (2.2)	10.1 (1.9)	–	CTR vs. Pre-AD	NS
Stroop colour*	10.5 (2.5)	9.9 (3.0)	–	CTR vs. Pre-AD	NS
Stroop colour–word*	11.0 (2.6)	10.3 (2.3)	–	CTR vs. Pre-AD	NS
Digit Symbol (WAIS-III)*	12.9 (2.5)	12.2 (2.2)	–	CTR vs. Pre-AD	NS
Symbol Digit Modalities Test*	10.6 (2.0)	10.3 (2.7)	–	CTR vs. Pre-AD	NS

Notes. FCSRT, Free and Cued Selective Reminding Test; CTR, Control group; VOSP, Visual Object and Space Perception battery; WAIS, Wechsler Adult Intelligence Scale; TMT, Trail Making Test.
*Neuropsychological tests administered to CTR and Pre-AD, but not to AD group.

CTR and 10 Pre-AD, (M = 855.37, SD = 109.84) in RTs, $t(62) = -2.79$, $p = .007$, two-tailed, Cohen's $d = .76$) but not in errors or omissions. When comparing carriers and noncarriers within the Pre-AD group, no significant differences were found on any measure of the VMC task.

Table 3. Means (normalized scalar scores) of standard neuropsychological tests for CN ApoE4 carriers and noncarriers

	CN ApoE4 noncarriers 52 Mean (*SD*)	CN ApoE4 carriers 12 Mean (*SD*)	*p* (<.05)
Vocabulary (WAIS-III)	13.0 (2.9)	12.8 (3.9)	NS
Block design test (WAIS-III)	12.5 (2.3)	12.0 (3.1)	NS
FCSRT: Learning	11.5 (2.4)	11.4 (3.2)	NS
FCSRT: Total learning	12.7 (3.1)	11.4 (2.3)	NS
FCSRT: Recall	11.9 (2.5)	11.5 (2.3)	NS
FCSRT: Total recall	13.7 (3.9)	12.9 (5.3)	NS
Boston Naming Test	11.6 (2.3)	10.6 (2.4)	NS
Semantic fluency (animals)	10.8 (2.3)	10.7 (3.9)	NS
VOSP: Number location	13.5 (4.2)	13.7 (5.2)	NS
VOSP: Object decision	10.6 (2.1)	12.0 (3.6)	NS
TMT-part A	10.5 (2.6)	10.2 (2.5)	NS
TMT-part B	9.6 (2.3)	8.9 (3.3)	NS
Stroop word	10.6 (2.1)	11.0 (2.0)	NS
Stroop colour	10.4 (2.7)	10.1 (2.7)	NS
Stroop colour–word	11.0 (2.3)	10.5 (3.5)	NS
Digit Symbol (WAIS-III)	13.1 (2.3)	11.7 (2.5)	NS
Symbol Digit Modalities Test	10.7 (2.1)	9.5 (2.7)	NS
Digit (WAIS-III): Direct	10.4 (1.9)	10.7 (2.9)	NS
Digit (WAIS-III): Inverse	12.2 (2.3)	11.0 (2.2)	NS

Notes. CN ApoE4 noncarriers, cognitively normal individuals not carrying the ApoE4 allele; CN ApoE4 carriers, cognitively normal individuals carrying the ApoE4 allele; FCSRT, Free and Cued Selective Reminding Test; VOSP, Visual Object and Space Perception battery; WAIS, Wechsler Adult Intelligence Scale; TMT, Trail Making Test.

Correlations between VMC task and CSF biomarkers (and demographic data)

Considering the whole sample (i.e., including data from the CTR, the Pre-AD, and the AD groups), significant correlations were found between the RTs and CSF biomarkers ($p < .001$ for all biomarkers). Furthermore, when considering CN participants (CTR and Pre-AD), RTs correlated with CSF AB42 levels ($p < .01$; Figure 2), but not with tau or p-tau levels. Neither age nor years of education correlated with VMC measures in any of the tested groups, with the exception of a significant association found between RTs and years of education in AD group ($p < .05$). Correlation coefficients of RTs with CSF biomarkers and demographic data are summarized in the Table 5. Analyses conducted for errors and omissions yielded a significant association exclusively between errors and p-tau levels ($r = .246$, $p < .031$).

Correlations between VMC task and cognitive/psychological measures

Correlation coefficients between RTs and psychological measures are summarized in the Table 5. Significant positive correlations were found between RTs and informant-rated SCD measured by the SCD-Q TheirCog, when considering the whole sample ($p < .001$) and also when restricting the analysis to CN ($p < .01$) and Pre-AD individuals ($p < .05$). Moreover, RTs correlated with self-rated SCD measured by SCD-Q MyCog in the whole sample ($p < .05$), but not with anxiety nor depression levels measured by HADS in any of

Table 4. Mean of visuomotor coordination (VMC) task measures (RTs, errors, and omissions) for CTR, Pre-AD, and AD groups (ANOVA and Bonferroni *post hoc* test)

	CTR 47 Mean (*SD*)	Pre-AD 19 Mean (*SD*)	AD 15 Mean (*SD*)	*F*-value	Effect size	*p*-Value	Comparison groups	*Post zhoc* *p*-value
Errors	0.5 (0.7)	0.8 (1.3)	2.8 (5.3)	5.457	.127	.006	CTR vs. Pre-AD	1.000
							Pre-AD vs. AD	.056
							CTR vs. AD	.005
RTs (ms)	844.7 (100.5)	961.8 (154.1)	1077.4 (201.6)	17.872	.314	.000	CTR vs. Pre-AD	.007
							Pre-AD vs. AD	.050
							CTR vs. AD	.000
Omissions	2.9 (4.1)	3.8 (4.9)	3.4 (3.2)	0.315	.008	NS		

Notes. RTs, the response time's mean spent in responding to each stimulus; Errors, responding with the wrong key; Omissions, no response.

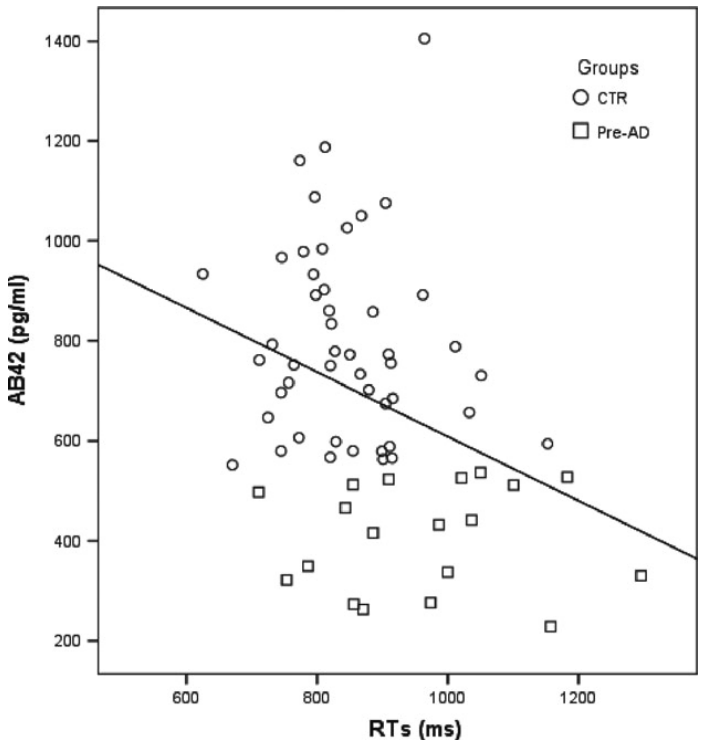

Figure 2. Scatter plot shows cerebrospinal fluid (CSF) AB42 levels and response times (RTs) of visuomotor coordination (VMC) task in CTR and Pre-AD groups.

Table 5. Pearson correlations of response times (RTs) with cerebrospinal fluid biomarkers levels, demographic characteristics, and psychological measures

	Whole sample (n = 81)		CN (n = 66)		CTR (n = 47)		Pre-AD (n = 19)		AD (n = 15)	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
AB42 (pg/ml)	−.428	.000	−.333	.006	−.088	.555	.019	.939	.079	.781
Tau (pg/ml)	.470	.000	.161	.199	.009	.954	.189	.439	.211	.451
P-tau (pg/ml)	.393	.000	.071	.576	−.021	.891	.131	.594	.219	.434
Age (years)	.105	.349	.222	.073	.153	.303	.235	.334	−.324	.239
Education (years)	.011	.922	−.089	.475	.016	.918	−.188	.441	.548	.034
HADS-A	−.051	.675	.131	.326	−.106	.508	.239	.356	−.292	.358
HADS-D	−.043	.722	.116	.386	−.167	.296	.368	.146	−.303	.338
SCD-Q MyCog*	.299	.031	.251	.113	.060	.772	.299	.280	.162	.634
SCD-Q TheirCog*	.465	.001	.406	.010	−.152	.478	.600	.018	.197	.619

Notes. Whole sample: CTR, Pre-AD and AD groups; CN, Cognitively normal participants; CTR, Control group, Pre-AD, Preclinical Alzheimer disease group; AD, Alzheimer's disease group; SCD-Q MyCog, self-rated Subjective Cognitive Decline Questionnaire; SCD-Q TheirCog, informant-rated Subjective Cognitive Decline Questionnaire; HADS-A, depression subscale of Hospital Anxiety and Depression Scale; HADS-D, anxiety subscale of Hospital Anxiety and Depression Scale.
*Subset of the sample including 26 CTR, 15 Pre-AD, and 11 AD individuals.

the groups studied. Errors in VMC task also correlated with SCD-Q TheirCog ratings in the whole sample ($r = .395$, $p < .007$). Regarding the cognitive performance on the neuropsychological battery, RTs correlated with the following tests in CN participants: The SDMT and the TMT-part B (both $p < .005$) and TMT-part A and Digit Symbol Coding (both $p < .05$; see Table S1). When analyses were conducted for errors and omissions, only deleted recall subtest of FCSRT showed a significant association with errors ($r = -.263$, $p < .035$).

Predictors of VMC task performance

Standard multiple regression analysis was used to assess the ability of CSF biomarkers and the presence ApoE4 allele in predicting RTs in the VMC task. Because of collinearity among tau and p-tau biomarkers, we decided to include p-tau in the analysis, based on previous literature indicating that p-tau is more sensitive and specific for AD (Koopman *et al.*, 2009). When examining the whole sample, all variables, including p-tau levels ($\beta = .268$, $p = .010$), AB42 levels ($\beta = -.277$, $p = .011$), and the ApoE4 allele ($\beta = .236$, $p = .032$), made a unique contribution to the model. When restricting the analysis to CN participants, the variables making a significant contribution to the prediction of RTs were AB42 levels ($\beta = -.279$, $p = .028$) and the presence of ApoE4 allele ($\beta = .255$, $p = .042$), but not p-tau levels. When conducting regression analysis separately for errors and omissions, the contributions of each of the independent variables studied were not significant.

Discussion

The new computerized VMC task employed in the present study discriminated Pre-AD from control participants, suggesting the presence of early visuomotor difficulties in Pre-AD individuals. RTs of the VMC task were negatively correlated to CSF AB42 levels in CN individuals, and significantly higher in Pre-AD than in control group, even though these two groups did not present any difference in performance measured by standard tests. This pattern of results allows us to conclude that the new computerized VMC task is able to identify subtle cognitive difficulties in visuomotor coordination that cannot be detected otherwise. Moreover, CN subjects carrying the ApoE4 allele showed higher RTs than those without it in the VMC task. Besides, RTs positively correlated with informant-rated SCD, but not with self-rated SCD.

Cognitive performance has generally been considered inherently normal in the Pre-AD stage (Dubois *et al.*, 2014). However, new efforts have been devoted to design new tests that can measure subtle cognitive difficulties at this stage (Rentz *et al.*, 2013). In this context, computerized timed tests may offer additional benefits when measuring performance in Pre-AD individuals. Accordingly, performance in our VMC task was similar in the Pre-AD and CTR participants when measuring accuracy (as determined by the number of errors). Crucially, instead, these groups showed differences in their RTs. These results suggest that, while accuracy seems to be useful in detecting differences in patients with AD, RTs as obtained in speeded tasks may be more suitable for identifying less obvious differences between Pre-AD and CTR individuals.

Although AD is typically associated with impairments in memory and other aspects of cognition, it has been suggested that visuomotor function is equally impaired in patients with AD (de Boer, Mattace-Raso, van der Steen, & Pel, 2014). Crucially, a subtle deterioration in visuomotor control has been observed, not only in patients with fully

developed AD, but also at earlier stages (Tippett *et al.*, 2012; Verheij *et al.*, 2012). However, the exploration of visuomotor functioning in nondemented individuals is still scarce. Hawkins and Sergio (2014) proposed that visuomotor alterations are already present before the onset of dementia in individuals with increased risk of developing AD (participants with a family history or MCI were considered a unique AD risk group). However, the AD pathophysiological processes (including AB deposition) were not studied in this previous research. The present study went one step further and examined the possible relationship between visuomotor functioning and specific AD biomarkers in people with normal cognition as evaluated by several cognitive tests.

Higher RTs were associated with decreased CSF AB42 levels in CN individuals, but not with tau levels. Furthermore, when analysing the influence of ApoE4 allele on the results observed in the VMC task, we found that CN ApoE4 carriers presented higher RTs than noncarriers, despite the fact that neuropsychological tests did not show any difference between them. In accordance, previous studies found that computerized measures of cognitive domains other than memory may be associated with the presence of ApoE4 allele (Espeseth *et al.*, 2006; Reinvang, Winjevoll, Rootwelt, & Espeseth, 2010). Moreover, multiple regression analyses confirmed that ApoE4 allele and AB42 levels were both predictors of RTs in CN participants.

Our findings suggest that visuomotor dysfunction occurs at a very early stage of the disease and may be associated with AB42 deposition, the neuropathological hallmark of AD, and with ApoE4 allele, the major known genetic risk factor for sporadic AD (Lambert *et al.*, 2013). However, further research is still needed to elucidate the relative impact of AB42 biomarker and ApoE4 allele on visuomotor performance in CN individuals.

As previously mentioned, standard cognitive measures of visuomotor components may present some limitations at detecting subtle difficulties in Pre-AD individuals. Based on our present results, performance on the VMC task was found to be associated with these standard measures, specifically to TMT, SDMT, and Digit Symbol Coding (see Results section). However, the performance on these tests was similar in the CTR and Pre-AD groups, and its relationship with AD biomarkers was not significant. In that respect, the relation between standard tests that assess visuomotor abilities and AD biomarkers still remains unclear (Hedden *et al.*, 2013). One possible explanation for the lack of agreement in previous literature could be that standard tests of visuomotor abilities assess a broader range of cognitive domains, including executive functioning. In contrast, the VMC task introduced here was designed to tackle visuomotor coordination while reducing as much as possible engagement of other cognitive abilities. We suggest that applying adequate measures of specific functions may be crucial to find AB42-related dysfunctions in Pre-AD individuals.

Another possible advantage of the VMC task is its independence of compensatory mechanisms, such as educational level or cognitive reserve, considered a major confounder of the relationship between the cognitive performance and the AD pathophysiological processes (Rentz *et al.*, 2010; Stern, 2009). Thus, while cognitive reserve is mostly associated with higher order executive functioning (Tucker & Stern, 2011), it may have less impact on visuomotor coordination functions.

Our examination of possible links between SCD and the VMC task indicated that only informant-rated SCD, but not self-reported SCD, is associated with response slowness in the VMC task in CN participants. This finding is not surprising given that cognitive complaints are often related not only to memory problems, but also to other difficulties in everyday functioning (Amariglio *et al.*, 2012; van Norden *et al.*, 2008) which often involve visuomotor coordination abilities. Accordingly, a previous study described

significant associations between informant-rated SCD and standard neuropsychological measures of visuomotor components in CN individuals (Rami *et al.*, 2014). On the other hand, the nonsignificant correlation found between the VMC measure and the self-reported SCD-Q suggests that Pre-AD individuals might have some degree of unawareness of their subtle difficulties. This evidence is in line with previous literature on AD and anosognosia (Mograbi & Morris, 2014). Our results are also consistent with previous literature showing that informant reports can be more reliable predictors than self-reports of subjects' cognitive performance, not only when referring to cognitively impaired individuals but also to individuals showing normal cognition as measured with standardized tests (Rabin *et al.*, 2012; Rami *et al.*, 2014; Slavin *et al.*, 2010). Interestingly, the international Subjective Cognitive Decline Initiative (SCD-I) work group recently proposed the confirmation of SCD by others as an important feature for an increased risk of AD (Jessen *et al.*, 2014).

Although the ability of the VMC task to correctly identify Pre-AD individuals is promising, neuroimaging studies would be needed to fully uncover the pathophysiological mechanisms underlying the visuomotor coordination anomalies observed in the Pre-AD individuals. In this context, it should be noted that the VMC task has also a marked spatial attentional component, as participants have to attend to the location of the target on the computer screen and move their attentional focus towards the appropriate button of the keyboard. As confirmed in several imaging studies (Corbetta & Shulman, 2002; Culham & Valyear, 2006), the posterior parietal cortex is crucial in spatial attention and in integrating attention and motor systems. Interestingly, functional changes in the posterior parietal regions have been described in Pre-AD individuals (Hedden *et al.*, 2009; Rami *et al.*, 2012). Hence, it may be of particular importance to corroborate the possible association between the visuomotor anomalies, at a behavioural level, and the functional alterations found in parietal regions in early stages of AD.

A limitation of the current study could be the small sample size for the Pre-AD group, which could possibly limit our power to identify differences between ApoE4 carriers and noncarriers within the Pre-AD group. Furthermore, the cross-sectional nature of this study precludes the possibility of testing the usefulness of the VMC task at predicting the subsequent cognitive decline in later stages of the disease. Moreover, although in the present study the VMC difficulties were found in otherwise asymptomatic individuals, we cannot rule out the possibility that subtle dysfunctions in domains other than visuomotor coordination could be observed, in these target individuals, with the use of more sensitive methods.

Overall, our results indicate that the VMC task is a sensitive tool for an early detection of subtle cognitive difficulties in Pre-AD stage and is related to AB42 levels in CN individuals. Moreover, the presence of ApoE4 allele and informant-rated SCD, considered both potential predictors of AD, seems to be related to these visuomotor anomalies. Further research is required to evaluate visuomotor function as a sensitive marker for detecting the early effects of AB42 deposition and ApoE4 status. In conclusion, the knowledge derived from the present work can be used to develop new highly specific computer-based measures to detect subtle dysfunctions in Pre-AD individuals and model future preclinical trials.

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Supporting Information

The following supporting information may be found in the online edition of the article:

Table S1. Correlations between response time (RTs) of visuomotor coordination (VMC) task and standard neuropsychological tests.

Trabajo 4

Evidence of motor deficits in preclinical Alzheimer's disease

En revisión

Mollica MA, Navarra J, Fernández-Prieto I, Valech N, Olives J, Tort A, Lleó A, Martínez-Lage L, Molinuevo JL, Rami L.

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Evidence of motor deficits in preclinical Alzheimer's disease

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AUTHOR CONTRIBUTIONS

Maria A Mollica contributed to the study design, statistical analysis, data interpretation, and drafting of the manuscript. Jordi Navarra contributed to the study design, conceptualization of the study, and drafting of the manuscript. Irune Fernández-Prieto contributed to the conceptualization of the study and statistical analyses. Natalia Valech contributed to the data interpretation and drafting of the manuscript. Jaume Olives contributed to the statistical analysis and data interpretation. Adrià Tort contributed to the statistical analysis and data interpretation. Alberto Lleó contributed to the interpretation of data and revision of the manuscript for content, Pablo Martínez-Lage contributed to the interpretation of data and revision of the manuscript for content, José L Molinuevo contributed to the study design, data interpretation, and revision of the manuscript for content. Lorena Rami contributed to the study design, conceptualization of the study, drafting of the manuscript, and revision of the manuscript for content.

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AUTHOR DISCLOSURES

Maria A Mollica, MS reports no disclosures; Jordi Navarra, PhD reports no disclosures; Irune Fernández-Prieto, MS reports no disclosures; Natalia Valech, MS reports no disclosures, Jaume Olives, MS reports no disclosures; Adrià Tort, MS reports no disclosures; Alberto Lleó MD, PhD reports no disclosures, Pablo Martínez-Lage, MD, PhD reports no disclosures, José L Molinuevo MD, PhD, reports no disclosures and Lorena Rami PhD reports no disclosures.

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ABSTRACT

Objective:

To investigate the presence of subtle motor deficits in cognitively normal (CN) individuals with preclinical Alzheimer's disease (pre-AD) and the possible relationship between motor performance and cerebrospinal fluid (CSF) amyloid-beta levels.

Methods: 72 right-handed individuals were recruited for the present cross-sectional study. The 57 CN participants were divided into two groups: 20 Pre-AD participants with abnormal levels of CSF amyloid-beta and 37 controls (CTR) with a normal CSF profile. A third group of 15 AD patients was also included. A computerized version of the Finger Tapping Task (FTT) was designed to measure tapping speed and within-person motor variability (i.e., inconsistency of motor performance). Participants underwent apolipoprotein E (ApoE) genotyping and lumbar puncture for the CSF analysis. CN participants were administered a neuropsychological test battery, and cardiovascular risk factor and physical activity assessment.

Results: The pre-AD group had normal scores on traditional neuropsychological measures but lower tapping speed and higher tapping variability than the CTR group. The pre-AD group also showed faster tapping rate than the AD group, but similar tapping variability. Both speed and variability correlated with CSF amyloid-beta levels. The present results were independent of several potential variables that might influence motor functioning, such as demographic variables, Apoe4 status, and cognitive status.

Conclusions: The present findings suggest that subtle motor difficulties assessed using a new computerized task occur at the pre-AD stage, and may be related to CSF levels of the amyloid-beta biomarker.

INTRODUCTION

By definition, in the preclinical stage of Alzheimer's disease (pre-AD) individuals present normal cognition according to existing standard tests until they meet criteria for mild cognitive impairment (MCI)[1]. However, new computerized measures may be more suitable than traditional tests for the detection of subtle difficulties at this early stage of the disease[2]. Research in recent years has reported that motor dysfunction may be a sensitive marker of pre-AD[3-4]. Although previous literature has mainly focused on analyzing motor speed[5-7], a few recent studies have suggested that variability (i.e., the inconsistency of performance) might also be a relevant marker of early AD[8-9]. However, new accurate tests of motor function, especially using quantitative measures of speed and variability, are still needed to fully capture these subtle difficulties at the preclinical stages of AD.

In the present study, a new version of the Finger Tapping Task (FTT)[10] was developed to explore two indicators of motor function (speed and within-person variability)[11] in pre-AD individuals, a control group of CNs with normal AD biomarker profile, and a group of AD patients, and also to assess their relationship with levels of AD biomarkers. We hypothesized that the FTT would prove to be a useful test able to detect the presence of subtle motor deficits in pre-AD individuals. The pre-AD group would exhibit lower speed and greater variability than controls and similar response patterns to those of the AD group. We also expected to find an association between tapping performance and the levels of AD biomarkers.

METHODS

Standard protocol approvals, registrations, and patient consents

The Hospital Clinic's ethics committee approved the study and all participants provided written informed consent prior to enrollment.

Participants

72 right-handed participants, recruited from the Alzheimer's Disease and Other Cognitive Disorders Unit of the Hospital Clinic (Spain), from the Memory Unit of the Hospital de la Santa Creu i Sant Pau in Barcelona (Spain) and from the CITA Alzheimer Foundation in San Sebastián (Spain), completed the study between April 2013 and July 2016). The following exclusion criteria were applied: significant psychiatric and medical conditions, joint problems, parkinsonian signs, essential tremor, suspected non-amyloid pathologies (SNAPs), severe cerebral atrophy or white matter hyperintensities. The sample consisted of 57 cognitively normal (CN) individuals and 15 patients with AD dementia. The 57 CNs were further divided into two groups according to their CSF amyloid-beta 42 protein (Aß42) levels: a control group (CTR) defined as CNs with normal CSF Aß42 levels (n=37) and a group of pre-AD defined as CNs with abnormal CSF Aß42 levels (n=20). The 15 AD patients met the NIA-AA criteria[12] for dementia highly likely to be due to AD in view of the abnormal amyloid and degeneration markers. See details about the selection of participants, inclusion/exclusion criteria and missing data in Appendices e-1 and e-2.

Finger Tapping Task Design and Procedure

E-Prime 2.0 (Psychology Software Tools Inc., Pittsburgh, PA) was used to create a modified computerized version of the standard (and manually-administered) FTT[10]. Details about the current protocol are provided in Appendix e-3.

The measures of interest were the tapping rate (i.e., the total number of taps) and within-person motor variability, which was obtained after calculating the coefficient of variation (CoV)[11]. CoV is the standard measure of within-person variability and is computed by dividing the individual's SDs by his/her mean (SD/mean). Higher CoV indicated more inconsistent

performance across trials. The participants' performance in FTT varies in terms of velocity and variability but there are no errors.

Functional, cognitive, and risk and protective factors for cardiovascular disease variables

Before performing the FTT, all CNs underwent a 1-hour neuropsychological battery assessing memory, language, visual perception, and visuomotor and executive functions. The battery is described in detail in Appendix e-4. Furthermore, as cardiovascular risk factors may have a significant effect on motor functioning, the clinical histories of CN participants were reviewed to record information on the presence or absence of hypertension, diabetes, and hyperlipidemia, and on smoking history. Body mass index (BMI) was calculated from height and weight measurements. Frequency of involvement in physical activities was assessed by responses to questions from a leisure activities questionnaire[13].

Apolipoprotein E and CSF biomarker analyses

Participants underwent apolipoprotein E (ApoE) genotyping and a lumbar puncture for the CSF analysis. Appendix e-5 presents a detailed description of the methodology used.

Statistical methods

As the distribution of tapping variability was positively skewed, we applied a logarithmic (log10)[14] transformation in order to obtain normality so as to be able to use parametric analyses (e.g., regression models) (see box plots with speed and variability for each group in Figure e-1). Analyses of variance (ANOVA), Fisher's exact tests, and T-Tests were carried out to compare demographic and clinical data, and CSF levels of biomarkers in the CTR, pre-AD, and AD groups. Since Group x Hand interactions were not significant all the analyses of tapping performance included data from both hands. Analyses with FTT and cognitive measures were performed controlling for the effects of the demographic variables (age, gender and educational level). Analyses of covariance (ANCOVA) were performed to compare

cognitive performance in the CTR and the pre-AD groups, and tapping speed and variability performances across the three groups. Repeated measures ANCOVA were run to address the possible 'fatigue effects' between the first and the last block for both rate and variability (results are detailed in Appendix e-8). A logistic regression model including both tapping speed and variability as dependent variables and the group factor (CTR vs. pre-AD group) as the independent variable was also performed. ROC curves were used to compare the diagnostic accuracy of the FTT measures in discriminating between pre-AD and AD group from controls.

Correlations were employed to evaluate the relationship between FTT performance and cognitive test battery (see results in Appendix e-7 and Table e-2). Correlations between FTT measures and cardiovascular risk factors were also assessed. Multiple regression analyses were performed with either variability or speed as the outcomes, and including AD biomarkers as independent variables. A series of models examined amyloid-beta, tau, and p-tau alone (models 1-3 models), in combination (model 4), and in interaction with each other (models 5-6). Statistical significance was set at $p<.05$. See Supplementary Material for details on statistical methods (Appendix e-6).

RESULTS

Demographic and clinical characteristics

There were no differences in terms of age, years of education, gender, and cardiovascular risk factors between groups (see table 1). The percentage of ApoEε4 carriers are given in table 1. Performances in FTT were not correlated with any of the cardiovascular risk factors studied (p value range .200—.543 for rate, p value range .202—.906 for variability).

Neuropsychological differences between CTR and pre-AD groups

The CTR and the pre-AD groups did not show differences on any of the neuropsychological measures assessing episodic verbal memory, semantic memory, language, visuoperceptual functions, visuomotor and executive functions, and inhibition of automatic responses (see Table e-1).

Group comparisons in tapping performance

The pre-AD group showed lower speed and greater variability than the CTR group, and higher speed than the AD group (see Table 2). The pre-AD and AD groups did not differ in terms of variability. At the same time, the AD group showed lower speed and greater variability than the CTR group. Logistic regression model including both tapping speed and variability showed that tapping variability made a unique contribution to the prediction of amyloid abnormality (CTR vs pre-AD), over and above the effect of tapping rate ($p<.037$). ROC curves of tapping rate and variability yielded an AUC (Area Under the Curve) of .654 ($p=.057$) and .731 ($p<.005$), respectively. ROC curves for discriminating the AD group from CTR yielded an AUC of .875 and .836 (both $p<.001$), for rate and variability, respectively.

Relationship between CSF AD biomarkers and tapping performance

As expected, the CSF levels of AD biomarkers were different between groups (see Table 1). Multiple regression analyses with variability or speed as the outcomes revealed moderate associations with amyloid-beta levels, after ruling out potential confounding effects such as age, gender, education, ApoE status, time interval between FTT and lumbar puncture, and GDS (model 1) (see Table 3). The associations between amyloid-beta levels and tapping measures remained significant after the tau biomarker was included in the model (model 4). In contrast, the contributions of tau or p-tau levels on tapping performance were not significant (models 2 and 3). However, when cognitive status was not included in the model as a covariate, motor speed was related to tau (beta=-.353, $p<.001$) and p-tau (beta=-.274,

p<.016) levels. The interaction terms between tau and amyloid biomarkers were added in the final models (models 5 and 6), showing that the contribution of the explained variance was significant for tapping variability (see figure e-2).

DISCUSSION

In the present study, the pre-AD group showed both lower tapping speed and greater tapping variability (i.e., more inconsistent performance) than controls in a newly-developed version of the Finger Tapping Task. Moderate associations were found between CSF beta-amyloid levels in tapping speed and, above all, in variability. These associations were corrected for age, gender, education, Apoe4 status and participants' cognitive status. Taken together, this pattern of results suggests that motor dysfunction may be associated with AD pathology and may emerge during the pre-AD stage.

Considering that the neuropsychological test batteries suffer from insufficient variability in healthy controls, several authors suggested that the detection of subtle deficits should be based on the application of newly-developed experimental tests[2]. In this line of research, the results from this study emphasize the importance of applying adequate measures of specific brain functions to finding early AD-related dysfunctions in healthy adults. Our newly developed computer-based tapping task is suitable for studying subtle anomalies in an otherwise asymptomatic population (as measured by means of traditional neuropsychological tests). In this regard, the tapping task proved to be easy enough to be understood, brief enough not to generate fatigue, and easy to administer independently of educational level, which is known to be a main confounder of the relationship between AD-related changes and cognitive performance. The computerized tapping task also provided precision and accuracy in the assessment of different indicators of motor function, such as

frequency of motor responses in very brief time intervals (i.e., motor speed) and intraindividual variability between consecutive taps.

The present results are in line with recent studies suggesting that motor dysfunction may be a sensitive marker of pre-AD [3-4]. Previous reports showed that motor speed declines in CN individuals before cognitive deterioration and conversion to AD dementia[5-6]. An association between gait speed and regional brain amyloid in CN and mildly impaired individuals has been observed[7]. Interestingly, this relationship was independent of participants' cognitive status. However, measures of neural degeneration were not available in this study. The current study pushes this line of research further and shows that motor speed in a manual tapping task is associated with CSF amyloid levels. In contrast, tau levels did not correlate with tapping performance. In this regard, we want to highlight that motor speed was also related to tau in our sample, under the condition in which the effects of the cognitive status were not ruled out. This result suggests that tau levels may affect motor function, and also that its effects are mediated by the cognitive/clinical status of the participants.

No less important, in our sample of CN participants, controls, and pre-AD group did not differ in terms of tau levels. While the control group only included individuals with normal levels of both, tau and amyloid biomarkers (SNAP condition was considered an exclusion criterion), mostly of the preclinical participants had normal tau levels, with only 3 out of 20 having tau levels slightly above the normal limits. Therefore, according to NIA-AA criteria[12] which proposed 3 different preclinical stages, most of the pre-AD individuals of the present study were at stage 1. So we believe that the insufficient inter-subject variability in tau values within the CN participants made it difficult to find correlations between tau and our motor measures.

A tentative interpretation of our findings might be that motor dysfunctions are related to an initial amyloidosis, which is, according to the 'amyloid cascade hypothesis', the earliest

biomarker at the asymptomatic stage of AD[15]. In this context, the FTT may be a sensitive tool for identifying subtle motor deficits that occur early in the development of AD. However, further studies in larger samples at different stages of AD are needed to clarify the extent to which tapping performance is related to amyloid and/or tau levels.

While the correlations between tau or p-tau levels alone with tapping variability were not significant, the association of amyloid with tapping varies with level of tau. Specifically we found that the associations between amyloid and variability were stronger for higher levels of tau (see Figure e-2). However, for the cases in which tau protein reached pathological levels (i.e., in late preclinical AD stages or in clinically diagnosed AD), the association seemed to lose its significance. This may be because, according to the cascade model of AD pathogenesis, amyloid biomarker reaches a plateau at early stages along the axis of AD development, once tau levels have become abnormal. Therefore, the present findings lend further support to the idea that motor variability is especially sensitive to the AD-related changes that occur at the earliest stages of the pre-AD.

To our knowledge, very few studies have investigated motor variability in AD. These previous studies suggested that motor variability might also be a relevant marker of early AD[8-9]. For instance, Verghese et al. (2008)[9] reported that individuals with mild AD presented greater variability when walking than did healthy adults. Our results are even more consistent with a study suggesting that a group with mild AD exhibited greater variability during the execution of tapping movements than a group of older healthy adults[16]. Unfortunately, AD biomarker analyses were not available in that study. In line with these previous works, we also report an increase in tapping variability in our AD group. In this line, our results clearly show the potential role of this less studied motor measure in distinguishing the pre-AD group from controls.

When comparing the role of rate versus variability in determining the classification of controls and pre-AD individuals, tapping variability was found to be the only variable that made a unique contribution to the prediction of amyloid abnormality, independently of tapping rate. In line with our results, a previous study found that intraindividual variability during a psychomotor task, predicted the classification of MCI versus healthy elders, beyond the effects of speed[17]. When comparing the diagnostic accuracy of the FTT measures, both aspects of motor performances have an important role in AD discrimination at different stages of the disease. However, variability showed, again, to be more accurate than rate at the earliest AD stage. These results provide strong support for the use of this less common measure to detect preclinical motor deficits.

Motor variability is an inherent feature of motor performance[18]. The increased variability of voluntary movements in older adults has been linked with altered activation of the involved muscles, likely because of structural and neural changes that occur with aging[19]. If motor variability is sensitive to the neural changes of normal aging, it may further increase as a result of neuropathological processes. Therefore, in light of the present findings, motor variability might be a sensitive indicator of preclinical neural changes. Although our findings are promising, further research is needed to confirm our preliminary results.

The mechanisms by which AD pathology (amyloid deposition and neurofibrillary tangles) leads to the motor dysfunctions observed in the pre-AD stage still remain unknown. However, neuropathological studies suggest that AD pathology may be present in many cortical areas including regions that subserve motor functions, such as the primary and supplementary motor cortex, striatum, and substantia nigra[20-21]. This is so not only in AD patients[22] but in CNs as well[23], suggesting that perhaps the presence of AD pathology in cortical motor areas contributes to motor dysfunction.

It is worth mentioning that tapping performance is not merely automated motor activity[24]. Indeed, the internal generation of movement requires executive components such as initiation and sustained attention in order to execute an action and maintain it to achieve the task goals. Consistent with these assumptions, our analyses of correlations between tapping performance and the traditional cognitive tests revealed that the former was especially associated with tests assessing attention and executive functions, such as TMT, Digit Symbol, and Stroop tests.

The present study has some limitations. Small sample size may limit the generalisability and diminish the validity of the conclusions drawn from this study. We are also aware that cardiovascular risk factors might have affected the present finding of motor dysfunction in the pre-AD group[25]. However, it is important to highlight that the groups tested in the present study did not differ in terms of cardiovascular risk factor status, and performance in FTT (as assessed by means of both rate and variability) was not associated with any of these factors. Since we focused on tapping performance, additional motor measures may be necessary to characterize our groups' motor status. Furthermore, considering the cross-sectional nature of our study, our findings preclude the possibility of determining whether amyloid-related motor difficulties are also associated with subsequent cognitive impairment due to AD. Moreover, although motor dysfunctions were found in otherwise asymptomatic individuals (as measured in a traditional neuropsychological exploration), these results do not imply that subtle dysfunctions cannot be found in domains other than motor control when they are appropriately tested (perhaps with the use of more sensitive methods).

Overall, the present results suggest the newly developed version of FTT may be a useful test able to detect subtle motor deficits in pre-AD individuals. Both speed and variability were related to CSF amyloid levels. Interestingly, tapping variability turned out to be a better

predictor of amyloid levels than tapping speed, thus providing strong support for the use of this less common measure for detecting preclinical motor deficits. Therefore, our findings suggest that an accurate assessment of motor functions may be crucial for characterizing individuals at the pre-AD stage and for modeling future preclinical trials with disease-modifying therapies.

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Table 1

Demographic and clinical characteristics.

	CTR (N=37) Mean (SD)	pre-AD (N=20) Mean (SD)	AD (N=15) Mean (SD)	F	Effect size	p[a]	Post-hoc comparisons	p[a]
Age (years)	64.6 (6.4)	66.5 (7.7)	67.35 (8.5)	.836	.024	NS		
Education (years)	11.7 (4.2)	11.2(4.3)	10.8 (5.1)	.238	.007	NS		
% females	64.8 (24/37)	70.0 (14/20)	60.0 (9/15)	.445	.073	NS		
Aß42(pg/ml)	822.9(177.7)	442.8(103.9)	368.6 (109.2)	60.801	*.672	.001	CTR vs pre-AD CTR vs AD pre-AD vs AD	.001 .001 .146
tau(pg/ml)	232.1 (76.0)	232.7 (115.9)	624.1 (217.1)	55.984	*.619	.001	CTR vs pre-AD CTR vs AD pre-AD vs AD	.988 .001 .001
p-tau(pg/ml)	52.6 (12.7)	47.8 (20.2)	94.3 (26.4)	33.411	*.492	.001	CTR vs pre-AD	.350

							CTR vs AD	.001
							pre-AD vs AD	.001
							CTR vs pre-AD	.016
% ApoEε4	10.8 (4/37)	40.0 (8/20)	57.1 (8/14)	12.751	*.423	.001	CTR vs AD	.001
							pre-AD vs AD	.487
% smoking history	17.1 (6/35)	10.0 (2/20)			.097	.696		
% hypertension	28.6 (10/35)	50.0 (10/20)			.214	.149		
% hyperlipidemia	20.0 (7/35)	20.0 (4/20)			.000	1.000		
% diabetes	8.6 (3/35)	10.0 (2/20)			.024	1.000		
BMI	24.7 (SD 3.6)	26.3 (SD 5.7)			-	.315		
Physical activity	53.2 (SD 16.8)	46.2 (SD 13.9)			-	.185		

CTR: Cognitively normal individuals with normal amyloid-beta levels; pre-AD: Cognitively normal individuals with abnormal amyloid-beta levels

AD: Alzheimer disease group; [a] analysis of variance and T-test for continuous variables; Fisher's test value for categorical variables; CTR=

Cognitively normal individuals with normal levels of CSF Aß42; pre-AD= Cognitively normal individuals with abnormal amyloid-beta levels; AD: Alzheimer disease group. *statistically significant (p<.05).

Table 2

Motor performance in the Finger Tapping Task and group comparisons.

FTT measures	CTR (N=37) Mean (SD)	pre-AD (N=20) Mean (SD)	AD (N=15) Mean (SD)	F	Effect size	p[a]	Post-hoc comparisons	p[a]
Tapping speed	344.37 (36.6)	320.70(32.3)	283.53 (35.1)	19.379	*.370	.001	CTR vs pre-AD	.022
							CTR vs AD	.001
							pre-AD vs AD	.001
Tapping variability[b]	-.75 (.21)	-.57(.19)	-.46(.19)	11.405	*.257	.001	CTR vs pre-AD	.003
							CTR vs AD	.001
							pre-AD vs AD	.126

CTR: Cognitively normal individuals with normal amyloid-beta levels; pre-AD: Cognitively normal individuals with abnormal amyloid-beta levels; AD: Alzheimer disease group; Tapping speed: total number of taps; Tapping variability: coefficient of variation (SD/mean, CoV) of the time interval between taps; [a] analyses of covariance (controlling for gender, age, and educational level); [b] Log10 scaled. *Statistically significant (p<.05). Analyses were repeated including Apoe4 as a covariate and these showed similar outcomes (CTR vs pre-AD: p=.04 for speed and p=.005 for variability; pre-AD vs AD: p<.001 for speed and p=.087 for variability; CTR vs AD: both p<.001).

Table 3

Multiple regression analyses with variability or speed as the outcomes and CSF AD biomarkers as the independent variables.

Regression Models	AD biomarkers	Tapping rate		Tapping variability[a]	
		BETA (CI 95%)	p	BETA (CI 95%)	p
Model 1	Aß42	*.277 (.009-0.082)	**.016**	*-.549 (-.001-.000)	**.001**
Model 2	tau	-.143 (-.087-.028)	.312	.061 (.000-.000)	.726
Model 3	p-tau	-.071 (-.537-302)	.578	-.080 (-.004-.002)	.613
Model 4	Aß42	*.292 (.011-.085)	**.012**	*-.550 (-.001-.000)	**.000**
	p-tau	-.118 (-.601-.212)	.304	-.007(-.003-.003)	.958
Model 5	Aß42xtau (interaction)	.064 (.000-.000)	.541	*-.275 (.000-.000)	**.033**
Model 6	Aß42xp-tau (interaction)	.133 (.000-001)	.187	*-.360 (.000-.000)	**.003**

Beta: standardized coefficient; CI: Confidence interval; [a]Log10 scaled; *Associations that remained significant (p <0.05) after including the potential confounding effects (age, gender, education, APOE status, time interval between administration of FTT, and Lumbar puncture and GDS).

Appendix e-1: Selection of participants, inclusion and exclusion criteria

The following exclusion criteria were applied: i) significant psychiatric symptoms, ii) serious or unstable medical conditions, iii) hand arthritis or arthrosis, iv) parkinsonian signs, v) essential tremor, vi) suspected non-amyloid pathologies (SNAPs), vii) severe cerebral atrophy or pathological white matter hyperintensities (WMH), and viii) any previous neurological disease (with the exception of AD in the dementia group).

A total of 86 individuals participated in this study. Seventy were classified as cognitively normal, scoring within the normal range according to a standard neuropsychological battery, and 15 were cognitively impaired. From the cognitively normal sample, 14 individuals were excluded for the following reasons (leaving a total of 72 participants for the final analyses): six controls were classified as SNAP; one pre-AD individual had pathological white matter hyperintensities (according to the Fazekas scale); 1 pre-AD presented a parkinsonian sign; 1 pre-AD and 2 controls presented osteoarthritis; and 1 pre-AD and 1 control presented essential tremor. One pre-AD, scoring below 1.5 SD on the TMT-B test, was also excluded (initially this test was not used to classify subjects as cognitively normal or not).

The sample consisted of 57 cognitively normal (CN) individuals and 15 patients with AD dementia. Normal cognition was defined as a score falling within the normal range (1.5 standard deviations (SDs) from normative means) in every test of an exhaustive neuropsychological battery (see below). The 57 CNs were further divided into two groups according to their CSF amyloid-beta 42 protein (Aß42) levels: a control group (CTR) defined as CNs with normal CSF Aß42 levels (n=37) and a pre-AD group defined as CNs with abnormal CSF Aß42 levels. The 15 AD patients met the NIA-AA criteria for dementia highly likely to be due to AD in view of the abnormal amyloid and degeneration

markers. Participants' clinical global status was evaluated with the Global Deterioration Scale (GDS) (Reisberg et al., 1982). Twenty-eight CN participants were stage 1 (16 CTR and 12 pre-AD) and 29 stage 2 (21 CTR and 8 pre-AD). Six AD patients were stage GDS 3, and nine stage 4. AD patients with a GDS>4 (i.e., with moderate or severe dementia) were not recruited, so as to ensure that the task would be correctly understood by all participants.

References e-1

Reisberg, B, Ferris, SH, de Leon, MJ, and Crook, T (1982). The global deterioration scale for assessment of primary degenerative dementia. American Journal of Psychiatry, 139:1136-1139.

Appendix e-2: Missing data

From the cognitively normal subsample (37 controls and 20 pre-AD), data concerning vascular risk factors were available for 55 participants (35 controls and 20 pre-AD). Physical activity questionnaire scores were available for 47 subjects (34 controls and 13 pre-AD) and BMI for 36 (18 controls and 18 pre-AD) CN individuals. We could not address cognitive or cardiovascular evaluations for the AD group. ApoE genotype was not available for 1 AD patient.

Appendix e-3: The experimental protocol

Participants were instructed to tap repeatedly and as fast as they could on the computer keyboard's spacebar with their index finger while looking at a fixation point, until a STOP sign appeared on the screen. Instructions were given verbally by the experimenter and also displayed on the monitor. The participants sat in front of the monitor at a distance of approximately 60cm, with the palms of their hands facing downwards and their fingers extended on a table. The test included six different blocks of 10s each (three

right-hand blocks and three left-hand blocks, in alternating order). Participants were asked to begin tapping with their right index finger and were allowed to rest for 30s between each 10s block. As soon as they began tapping, the software registered the number of taps and the time between consecutive taps. The FTT task was administered using an Intel Core computer connected to a 19-inch LCD monitor (HP Compaq LA 1956X Monitor, 75 Hz) in a quiet room. The experimental session, including instructions, lasted approximately 10 minutes. The FTT is an experimental test based on the original FTT test that is included in the Halstead–Reitan Neuropsychological Test Battery. In the original test the participant was first asked to tap with his or her dominant index finger for five consecutive 10-second trials. The same procedure was followed with the nondominant index finger. In our adaptation, participants performed three non-consecutive 10-second trials with each index finger, with 30sec. pauses between trials. The right- and left-finger blocks were alternated. Furthermore, a key from a computer keyboard was used for tapping, instead of the traditional lever mounted with a counter, thus allowing us to obtain an accurate index of intraindividual variability.

Appendix e-4: Neuropsychological assessment

The Free and Cued Selective Reminding Test (FCSRT) (Buschke, 1984) and the semantic fluency test (animals) were administered to assess episodic verbal memory and semantic memory, respectively. The Boston Naming Test (BNT) (Kaplan et al. 1983) was used to evaluate language by means of confrontation naming. Visuoperceptual function was assessed by means of the Number Location subtest of the Visual Object and Space Perception (VOSP) battery (Warrington & James 1986). Visuomotor and executive functions were assessed using the Trail Making Test (TMT), parts A and B (Reitan &

Wolfson 1993). The inhibition of automatic responses was assessed with the Stroop Color and Word test (Golden 1978).

References e-2

Buschke, H. Cued recall in amnesia. Journal of Clinical and Experimental Neuropsychology 1984;6:433-440.

Kaplan E, Goodglass H, Weintraub S. The Boston naming test. Philadelphia: 2nd ed. Lea & Febiger;1983.

Warrington EK, James M. Visual object recognition in patients with right-hemisphere lesions: axes or features? Perception 1986;15:355-66.

Retain RM, Wolfson D. The Halstead-Reitan Neuropsychological Test Battery: theory and clinical interpretation. Tucson, AZ: Neuropsychology Press;1985.

Golden C. Stroop color and word test. Illinois: Stoelting Company; 1978.

Appendix e-5: Apolipoprotein E and CSF biomarker analyses

Genomic DNA was extracted from peripheral blood of probands using the QIAamp DNA blood minikit (Qiagen AG, Basel, Switzerland). Apolipoprotein E genotyping was performed by polymerase chain reaction amplification and HhaI restriction enzyme digestion. All participants were classified on the basis of the presence (carriers) or absence (non-carriers) of at least one ApoEε4 allele. Apoe4 genotyping was not available for one AD participant. Participants underwent a lumbar puncture in the morning (9–12 AM). CSF samples were centrifuged and stored in polypropylene tubes at -80°C. The CSF levels of Aß42, tau and p-tau at threonine 181 were measured using enzyme-linked immunosorbent assay (Fujirebio-Europe, Ghent, Belgium). Cut-off abnormality values for each CSF biomarker were defined based on previous studies (Mollica et al. 2015, Alcolea et al. 2015): Aß42≤ 550 pg/ml, tau≥ 450pg/ml and p-tau≥ 75 pg/ml. There was a

mean time lag of 2.2 (SD 1.5) years between the lumbar puncture and the administration of the FTT. Despite this time lag, all the participants included in the pre-AD group still presented normal scores on a traditional neuropsychological assessment at the time of administration of the FTT.

References e-3

Mollica MA, Navarra J, Fernández-Prieto I, et al. Subtle visuomotor difficulties in preclinical Alzheimer's disease. J Neuropsychol Epub 2015 Jul 14.

Alcolea D, Martínez-Lage P, Sánchez-Juan P, et al. Amyloid precursor protein metabolism and inflammation markers in preclinical Alzheimer disease. Neurology 2015;85:626-633.

Appendix e-6: Supplement to the Methods

As the distribution of tapping variability was positively skewed, we applied a logarithmic (log10) transformation in order to obtain normality and thus be able to use parametric analyses (e.g., regression models) (see box plots with speed and variability (log10 scaled) for each of the three groups in Figure e-1). Analyses of variance (ANOVA) and Fisher's exact tests were carried out to compare demographic/biological data and ApoEε4 status (presence or absence of at least one ApoEε4 allele) in the CTR, pre-AD and AD groups. Differences between CTR and pre-AD groups were tested using Fisher's test for cardiovascular risk factor status (i.e., presence/absence of hypertension, hyperlipidemia, and diabetes, and smoking history), and t-tests for the levels of physical activity and BMI. Since Group x Hand interactions were not significant all the analyses of tapping performance included data from both hands. To compare cognitive performance in the CTR and pre-AD groups, analyses of covariance (ANCOVA) were performed controlling for the effects of the demographic variables (age, gender, and educational level).

Tapping speed and variability were examined using analysis of covariance to compare performance across the three groups, adjusting for possible effects of age, gender, and education. A subgroup analysis was also conducted including Apoe4 status as covariate. A logistic regression model including both tapping speed and variability as dependent variables and the group factor (CTR vs. pre-AD group) as the independent variable was used compare the role of rate versus variability in determining the classification of CTR and pre-AD individuals. Pearson correlations were employed to evaluate the relationship between FTT performance and cardiovascular risk factors, or cognitive test battery. ROC curves were used to compare the diagnostic accuracy of the FTT measures in discriminating between pre-AD or AD group and controls.

Multiple regression analyses were performed with either variability or speed as the outcomes, and including CSF AD biomarkers as independent variables. A series of models examined amyloid-beta, tau, and p-tau alone (models 1-3 models), in combination (model 4) and in interaction with each other (models 5-6) to determine which ones had a greater effect on our measures of motor performance. In the regression model in which amyloid and tau were examined together, only p-tau (shown in the literature to be more sensitive and specific for AD) (Koopman et al. 2009) was included in the analyses; this was done to avoid collinearity among tau and p-tau biomarkers. Several covariates (age, gender, education, ApoE status, time interval between administration of FTT, and lumbar puncture (LP), and participants' cognitive status (as measured by the GDS)) were included in each of the models so as to show clearly the relationship between CSF AD biomarkers and motor performance, after controlling for the aforementioned covariates.

We assessed repeated measure analyses of the first and last block for both rate and variability in the sample of cognitively healthy individuals (CTR and pre-AD groups) and the whole sample of unimpaired and impaired participants in order to find possible 'fatigue effects'. Results are detailed in Appendix e-7. Statistical significance was set at p<.05.

References e-4

Koopman K, Le Bastard N, Martin JJ, Nagels G, De Deyn PP, Engelborghs S. Improved discrimination of autopsy-confirmed Alzheimer's disease (AD) from non-AD dementias using CSF P-tau181P. Neurochemistry International 2009;55:214-218.

Appendix e-7: Relationship between tapping performance and cognition, and between tapping measures

Lower tapping speed was associated with greater tapping variability both in the whole sample (r=-.432; p<.001) and the CN sample (r=-.368; p<.005).

Considering the group of CN participants as a whole, both tapping rate speed and variability correlated with TMT-A, TMT-B, and Stroop Color-Word. Tapping speed also showed a weak association with BNT. Subgroup correlation analyses were also performed separately for CTR and pre-AD groups. Demographic variables were used as the covariates in these analyses. The results of these analyses are detailed in Table e-2.

Appendix e- 8: Relationship between FTT blocks

We assessed repeated measure analyses of the first and last block (since group x hand interactions were not significant analyses included data from both hands) for both rate and variability in the CN sample (controls and pre-AD groups) and the whole sample of unimpaired and impaired participants. The results showed no differences between the first and last blocks in each of these conditions (in CN sample, F=.177, p=.676 for rate;

F=.011, p=.917 for variability; in the whole sample, F=.329, p=.568 for rate; F=.074, p=.786 for variability). These results may appear to be in contrast with previous studies (Teo et al., 2012; Rodrigues et al., 2009) showing that frequency of tapping decreases after a few seconds. However, we think that the discrepancy between our findings and those of previous studies is probably due to differences in the task characteristics. In our version of FTT, indeed, participants were allowed to rest for 30s between each 10s block. In contrast, in the other studies the tapping protocol did not include rest periods between blocks, or else the trial periods lasted for longer intervals (e.g, 20s). Therefore, we argue that our version of FTT reduces the possible effects of fatigue.

References e-5

Teo WP, Rodrigues JP, Mastaglia FL, Thickbroom GW (2012). Post-exercise depression in corticomotor excitability after dynamic movement: a general property of fatiguing and non-fatiguing exercise. Exp Brain Res. 216(1):41-9.

Rodrigues JP, Mastaglia FL, Thickbroom GW (2009) Rapid slowing of maximal finger movement rate: fatigue of central motor control? Exp Brain Res. 196:557–563.

Table e-1

Means of standard neuropsychological tests for CTR and pre-AD groups.

Neuropsychological assessment	CTR (N=37)		pre-AD (N=20)			
	Mean	SD	Mean	SD	F	p[a]
FCSRT: Free recall	29.86	5.39	27.35	5.67	2.112	.152
FCSRT: Total recall	45.00	2.47	44.40	3.18	.328	.569
FCSRT: Delayed free recall	11.43	2.27	10.50	2.30	2.088	.154
FCSRT: Delayed total recall	15.37	0.79	14.90	1.11	3.123	.083
BNT	57.54	2.15	56.80	1.70	1.204	.277
Semantic fluency	22.43	5.36	22.35	5.55	.055	.815
TMT-part A	36.29	12.40	41.05	12.93	.884	.351
TMT-part B	98.16	49.08	105.90	35.32	.014	.907
VOSP: Number location	9.21	.94	8.95	1.09	.859	.358
Stroop color-word	40.14	12.04	35.05	6.70	1.685	.201

FCSRT: Free and cued selective reminding test; VOSP: Visual Object and Space Perception battery; WAIS: Wechsler Adult Intelligence Scale; TMT: Trail Making Test, BNT: Boston Naming Test; CTR: Cognitively normal individuals with normal amyloid-beta levels; pre-AD: Cognitively normal individuals with abnormal amyloid-beta levels; [a] analyses of covariance (controlling for gender, age, and educational level.

Table e-2

Correlations* between Finger Tapping Task measures and neuropsychological tests.

	CN sample (N=57)		CTR (N=37)		pre-AD (N=20)	
Neuropsychological tests	**speed**	**variability[a]**	**speed**	**variability[a]**	**speed**	**variability[a]**
FCSRT: Free recall	.002	-.121	-.267	.063	.031	-.168
FCSRT: Total recall	-.032	-.001	-.011	.005	-.131	.007
FCSRT: Delayed free recall	.003	-.167	-.192	-.015	.118	-.240
FCSRT: Delayed total recall	.253	-.143	.178	.045	.259	-.382
BNT	*.271	-.165	.171	-.119	.109	.001
Semantic fluency	.050	-.120	-.097	-.051	.106	-.233
VOSP: Number location	.082	-.109	.089	-.142	-.033	.063
TMT-A	*-.403	*.297	-.223	*.398	-.419	.044
TMT-B	*-.424	.267	-.338	*.377	*-.462	-.020
Stroop word-color	*.355	*-.466	*.265	*-.451	.518	-.418

CN: Cognitively Normal; CTR: Cognitively normal individuals with normal amyloid-beta levels; pre-AD: Cognitively normal individuals wi

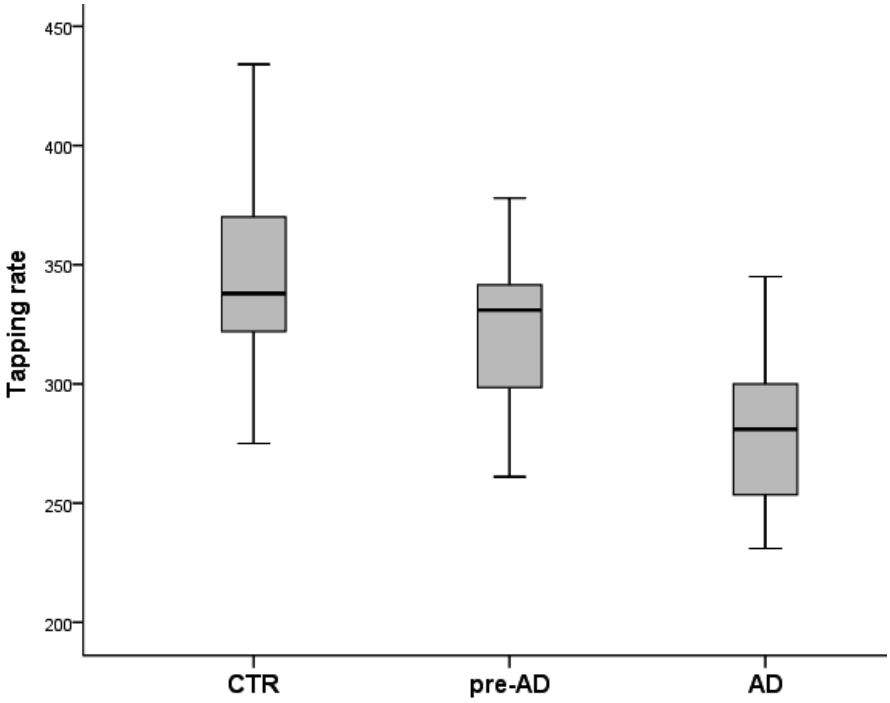
abnormal amyloid-beta levels; FCSRT: Free and Cued Selective Reminding Test, VOSP: Visual Object and Space Perception battery,

WAIS: Wechsler Adult Intelligence Scale, TMT: Trail Making Test, BNT: Boston Naming Test; [a]Log10 scaled; *statistically significant

(p<.05, 2-tailed); *Partial correlation coefficients, controlling for gender, age, and educational level.

Figure e-1

Box plots with tapping speed and variability (log10 scaled) for each of the three groups.



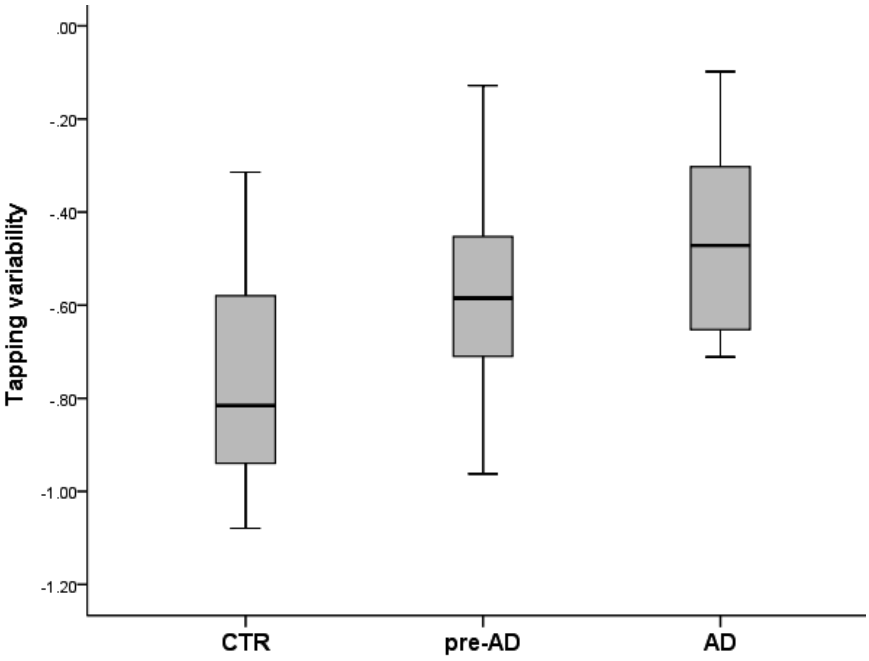
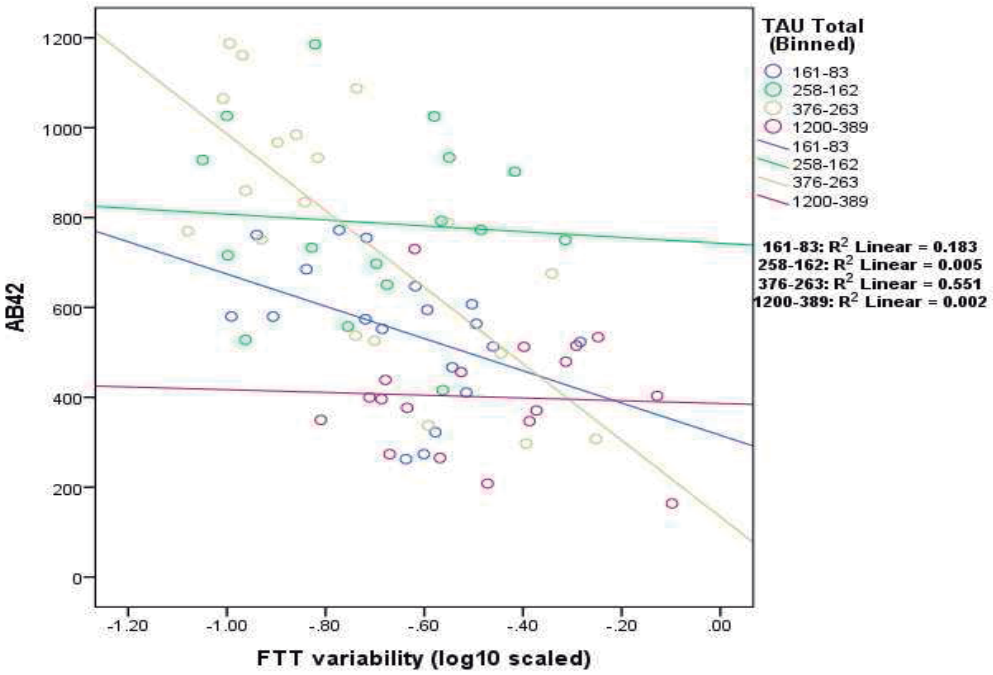
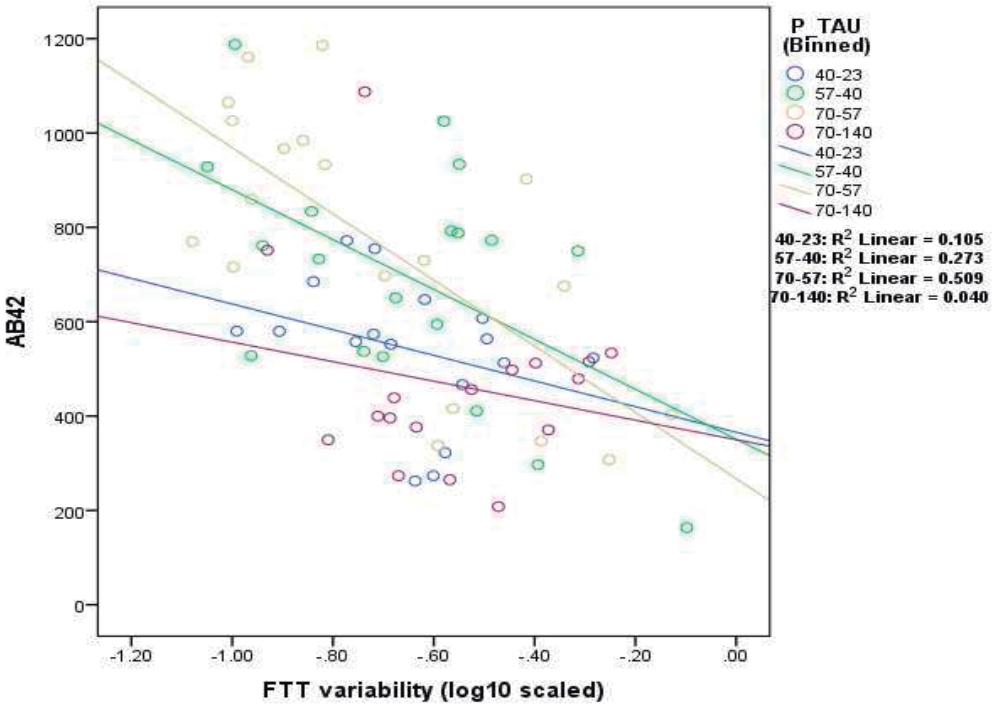


Figure e-2

Interaction between amyloid-beta and tau on tapping variability.





V. DISCUSIÓN GENERAL

En la última década, frente al fracaso de los tratamientos farmacológicos para detener el proceso patológico de la enfermedad de Alzheimer, la fase preclínica se ha convertido en un importante foco de investigación, puesto que se ha postulado que la intervención temprana puede ofrecer la mejor oportunidad de éxito terapéutico. En este contexto, el enfoque de la investigación se ha ampliado desde las fases clínicas de la enfermedad hacía fases preclínicas, donde pueden aparecer tanto una percepción subjetiva de declive como posibles disfunciones cognitivas o motoras sutiles detectables por nuevos test computarizados más sensibles que las pruebas neuropsicológicas clásicas.

En la presente tesis, que incluye 4 trabajos científicos, hemos desarrollado nuevos instrumentos para evaluar tanto el rendimiento subjetivo como el objetivo en la fase preclínica. En el grupo preclínico, el declive cognitivo subjetivo referido por el informador, evaluado a través del nuevo cuestionario, fue mayor que en el grupo control. Además, en comparación con el grupo control, el grupo preclínico mostró un peor rendimiento en las pruebas experimentales de coordinación visuomotora y control motor. Por último, el rendimiento en estas medidas experimentales se encontró asociado con los niveles de β-amiloide (el primer biomarcador afectado en el continuum de la enfermedad de Alzheimer) en la muestra de individuos cognitivamente sanos.

1. El declive cognitivo subjetivo

1.1. Cuestionario de declive cognitivo subjetivo

En los últimos años se ha sugerido que el deterioro cognitivo subjetivo podría representar una de las primeras manifestaciones sintomáticas de la enfermedad de Alzheimer. Por otro lado, su valor pronóstico sigue siendo poco claro, quizás debido a su alta prevalencia en la población mayor, a su fuerte relación con el estado de ánimo y a la alta variabilidad observada en los métodos de medición. En este contexto, el grupo internacional *Subjective Cognitive Decline Initiative* (Jessen y cols., 2014) ha propuesto unas características específicas del declive cognitivo subjetivo y más

recientemente Molinuevo y cols. (2016) han proporcionado unas recomendaciones concretas para facilitar su uso en investigación (ver apartado 4.2. de la introducción).

Teniendo en cuenta estas recomendaciones, en el trabajo 1 diseñamos y validamos el cuestionario de declive cognitivo subjetivo, una nueva herramienta que cuantifica el declive cognitivo subjetivo percibido tanto por el propio individuo como por un informador en los últimos 2 años, en participantes cognitivamente normales sin quejas y con quejas cognitivas, y en pacientes con deterioro cognitivo asociado a la enfermedad de Alzheimer. Recientemente han sido diseñados y validados nuevos cuestionarios de medición del deterioro cognitivo subjetivo (Rabin y cols., 2015), pero pocos estudios han utilizado medidas de declive cognitivo subjetivo percibido simultáneamente por el propio individuo y por un informador (Gifford y cols., 2015) o referido a un periodo de tiempo relativamente corto (por ejemplo, entre 2 y 5 años), o han estudiado la posible discrepancia entre ambas medidas (Rattanabannakit y cols., 2016).

1.2. El declive cognitivo subjetivo del individuo y del informador en el envejecimiento y en la enfermedad de Alzheimer

En los trabajos 1 y 2 el declive cognitivo subjetivo percibido por el propio individuo no fue capaz de diferenciar entre grupos según el estado cognitivo y clínico de los participantes, o según la presencia de un perfil alterado de biomarcadores de la enfermedad de Alzheimer. En concreto, en el trabajo 1, a la hora de determinar la validez discriminante del cuestionario de declive cognitivo subjetivo experimentado por el propio individuo, encontramos que los individuos sanos que acuden a una consulta en una unidad especializada por presentar quejas cognitivas subjetivas y los pacientes con deterioro cognitivo presentaban niveles similares de declive cognitivo subjetivo. De manera análoga, en el trabajo 2 el declive cognitivo subjetivo experimentado por el propio individuo no discriminó la fase preclínica de la normalidad. Por otro lado, en ambos trabajos el declive cognitivo subjetivo referido por el propio individuo se vio asociado al grado de ansiedad y depresión, pero no al rendimiento cognitivo objetivo.

Este patrón de resultados sugiere que el declive cognitivo subjetivo percibido por el propio individuo es una entidad fuertemente relacionada con el estado de ánimo y poco precisa para identificar disfunciones incipientes relacionadas con la patología de la enfermedad de Alzheimer en la fase asintomática de la misma (Buckley y cols., 2013). Estudios anteriores han encontrado poca o ninguna correlación entre las quejas autopercibidas y el rendimiento cognitivo, concluyendo que las quejas autopercibidas estarían más fuertemente asociadas con las variables psicológicas que con la función cognitiva o la presencia de deterioro objetivo (Slavin y cols., 2010).

Globalmente considerados, nuestros resultados sobre el declive cognitivo subjetivo referido por el propio individuo sugerirían que los síntomas psicológicos como la ansiedad y la depresión podrían reducir la validez de la propia percepción de deterioro cognitivo. Por lo tanto, ante la dificultad de determinar las quejas que indican enfermedad de Alzheimer subyacente frente a síntomas psicológicos, evaluaciones psicológicas más exhaustivas pueden ser recomendadas para caracterizar mejor el perfil psicológico de la población a estudio.

En contraste con el declive cognitivo subjetivo experimentado por el individuo, el declive cognitivo subjetivo referido por un informador permitió diferenciar los grupos a lo largo del continuum de la enfermedad de Alzheimer. Específicamente, en el trabajo 1 encontramos mayor declive cognitivo subjetivo referido por un informador en los pacientes con deterioro cognitivo moderado que en los pacientes con deterioro cognitivo leve, y en los grupos con deterioro cognitivo leve o moderado que en el grupo de individuos cognitivamente sanos. Además, en el trabajo 2 el declive cognitivo subjetivo referido por el informador fue capaz de discriminar los individuos preclínicos de los controles y se encontró relacionado con los niveles de biomarcadores de la enfermedad de Alzheimer.

Estos hallazgos concuerdan con estudios previos que han destacado la importancia de los informadores para la detección del deterioro cognitivo relacionado con la enfermedad de Alzheimer, y con el hecho de que los informadores son más precisos que los individuos mismos en discriminar la presencia de deterioro, no solo en las fases de demencia sino también en las fases asintomáticas de la enfermedad de Alzheimer.

Concretamente, publicaciones anteriores han encontrado que el declive cognitivo subjetivo referido por un informador, en comparación con el declive cognitivo subjetivo experimentado por el propio individuo, predecía mejor la futura aparición de síntomas de la enfermedad de Alzheimer y distinguía mejor a los sujetos con demencia de los sujetos cognitivamente sanos (Rabin y cols., 2012, Carr y cols., 2000). Estos resultados ponen de manifiesto la necesidad de obtener la opinión de los informadores con el fin de mejorar la identificación de individuos con deterioro cognitivo asociado a la enfermedad de Alzheimer, o incluso de individuos en la fase preclínica. De hecho, el declive cognitivo subjetivo reportado por el informador es reconocido como uno de los requisitos para el cumplimiento de los criterios clínicos de la enfermedad de Alzheimer (Petersen y cols., 2001) y, sobre todo, como una característica relevante de la enfermedad de Alzheimer preclínica (Jessen y cols., 2014).

Además, en el estudio 2 se analizaron las puntuaciones del declive cognitivo subjetivo en los diferentes dominios cognitivos (memoria, lenguaje y funciones ejecutivas). Encontramos que la diferencia entre el declive cognitivo subjetivo referido por un informador, de ambos grupos control y preclínico, era más pronunciado en relación a los ítems de lenguaje y de funciones ejecutivas, mientras que el declive cognitivo subjetivo referido por un informador sobre problemas de memoria no alcanzó significación estadística. Estos hallazgos pueden ser inesperados, ya que el deterioro de la memoria episódica se considera la manifestación más temprana del proceso patológico de la enfermedad de Alzheimer. Sin embargo, con un análisis más profundo, cuatro de los seis ítems de lenguaje implican tareas de recordar nombres, por lo que es probable que las habilidades lingüísticas se solapen con las funciones de la memoria episódica. Por otro lado, algunos estudios defienden que el declive cognitivo también afectaría a dominios no mnémicos, especialmente a las funciones ejecutivas, en las etapas de pre-demencia de la enfermedad de Alzheimer (Snitz y cols., 2012; Mortamais y cols., 2016).

Hasta donde sabemos, el nivel de declive cognitivo subjetivo referido por un informador acerca de las funciones ejecutivas ha sido poco explorado en estadios

precoces de la enfermedad de Alzheimer. Recientemente, el declive cognitivo subjetivo sobre funciones ejecutivas se ha evaluado en individuos con enfermedad de Alzheimer inicial, indicando que los informadores de estos percibían mayor nivel de declive cognitivo subjetivo que los del grupo de individuos sanos (Fogarty el al., 2016). Estos resultados ponen de relieve el hecho de que la evaluación de las quejas cognitivas en la enfermedad de Alzheimer debe extenderse más allá de los dominios de la memoria. Esto implica la importancia de incluir elementos de múltiples dominios al evaluar el declive cognitivo subjetivo.

En el trabajo 2, las puntuaciones del declive cognitivo subjetivo referido por un informador se asociaron con los niveles de β-amiloide, tau total y p-tau en una muestra constituida por individuos con cognición normal y con deterioro cognitivo pero no en la muestra de individuos cognitivamente sanos, considerada por separado. Esta asociación se mantuvo incluso una vez que se controló dicha relación por el efecto de los niveles de ansiedad y depresión. A pesar de que los estudios que documentan la relación entre los biomarcadores de la enfermedad de Alzheimer y el declive cognitivo subjetivo son escasos, las pocas investigaciones realizadas hasta la fecha parecen apuntar en la misma dirección. Por ejemplo, en muestras constituidas por sujetos cognitivamente sanos y con deterioro cognitivo, se ha encontrado que el declive cognitivo subjetivo referido por el informador correlacionaba con los niveles de amiloide y tau (Rueda y cols., 2014, Okonkwo y cols., 2010).

Además de analizar por separado el declive cognitivo subjetivo referido por el propio individuo y por un informador, examinamos las discrepancias de puntuaciones entre ambos. Encontramos que estas discrepancias eran mayores en el grupo control que en el grupo preclínico. En este sentido, es posible que la pérdida de diferencias significativas entre los dos grupos en el declive cognitivo subjetivo referido por el individuo no se debiera a una falta de conciencia del deterioro cognitivo en el grupo preclínico, sino más bien a una subestimación del rendimiento cognitivo en el grupo control. Estas evidencias, junto con la asociación encontrada entre el declive cognitivo subjetivo y los síntomas depresivos, pueden sugerir que las quejas cognitivas del grupo control se deben, en parte, a los niveles de ansiedad y depresión en este grupo

(Buckley y cols., 2013). Además, este patrón de resultados concuerda con estudios previos según los cuales las quejas cognitivas subjetivas son muy frecuentes en los individuos mayores sanos sin que dichas quejas se correlacionen con la cognición objetiva (Mark y Sitskoorn, 2013).

En general, nuestros resultados corroboran la utilidad del declive cognitivo subjetivo referido por un informador como medida subjetiva sensible a disfunciones cognitivas relacionadas con la enfermedad de Alzheimer que se producen en las primeras etapas de esta enfermedad y probablemente se extienden más allá del dominio de la memoria. Esto puede llegar a ser muy informativo en la enfermedad de Alzheimer preclínica en la que, como fue mencionado en la introducción, la detección del deterioro por medio de pruebas cognitivas en estudios trasversales es una tarea difícil. La asociación entre el declive cognitivo subjetivo y los biomarcadores, observada en el trabajo 2, puede sugerir que los niveles de declive cognitivo subjetivo estarían relacionados con la acumulación de la patología de la enfermedad de Alzheimer (β-amiloide, tau total y p-tau). No obstante, dada la falta de asociación entre el declive cognitivo subjetivo y estos biomarcadores en la muestra de sujetos cognitivamente sanos, nuestros resultados no son del todo concluyentes; y estudios futuros deben dilucidar la influencia de los biomarcadores de la enfermedad de Alzheimer sobre el declive cognitivo subjetivo en las etapas asintomática de la enfermedad.

2. Medidas objetivas de coordinación visuomotora y control motor

Los estudios 3 y 4 mostraron que las nuevas pruebas computarizadas que miden la coordinación visuomotora y el control motor permitieron diferenciar el grupo control del grupo preclínico. El rendimiento en estas pruebas se asoció con los niveles de β-amiloide en la muestra de individuos cognitivamente sanos y esta relación fue independiente de factores demográficos y genéticos.

Tal como se ha mencionado anteriormente, las baterías de pruebas neuropsicológicas no presentan suficiente variabilidad en los controles sanos, por lo que son poco sensibles para detectar las dificultades cognitivas sutiles en la población sana (Collie y Maruff, 2000). Teniendo en cuenta estas limitaciones, varios autores han sugerido que

la detección de las dificultades cognitivas sutiles debe basarse en la aplicación de nuevas pruebas experimentales (Rentz y cols., 2013). En esta línea de investigación, los resultados de nuestros estudios hacen hincapié en la importancia de aplicar medidas adecuadas de funciones visuomotoras y motoras específicas, con el objetivo de encontrar disfunciones incipientes relacionadas con la enfermedad de Alzheimer en individuos sanos en riesgo de desarrollar la enfermedad.

Creemos que varias características hacen de las tareas computarizadas que hemos empleado en estos estudios medidas adecuadas para el estudio de dificultades sutiles en una población sin síntomas cognitivos (según las pruebas neuropsicológicas tradicionales). En este sentido, las tareas experimentales presentadas en esta tesis proporcionaron precisión y exactitud en la evaluación de indicadores específicos de las funciones visuomotoras y motoras (número de errores, velocidad y variabilidad intra-individual). Ambas tareas mostraron también ser bastante fáciles de entender, fueron lo suficientemente breves como para no generar fatiga y fueron sencillas de administrar. Además, el rendimiento en ambas no se vio influenciado por el nivel educativo, el cual se sabe que es el factor de confusión principal de la relación entre los cambios relacionados con la enfermedad de Alzheimer y el rendimiento cognitivo (Rentz y cols., 2010). Por lo tanto, mientras que el nivel educativo se asocia sobre todo con funciones de orden superior, puede tener menos impacto en funciones visuomotoras y motoras específicas.

2.1. Disfunciones incipientes en la coordinación visuomotora y el control motor en la fase preclínica de la enfermedad de Alzheimer: comparación entre grupos

El papel potencial de la tarea de coordinación visuomotora (trabajo 3) y de la tarea de control motor (trabajo 4) como herramientas sensibles para detectar dificultades incipientes en la fase preclínica ha sido especialmente apoyado por un rendimiento significativamente más bajo del grupo preclínico en la ejecución de ambas tareas, en comparación con el grupo control. Concretamente, el grupo preclínico presentó mayor enlentecimiento visuomotor y motor, y mayor variabilidad intra-individual motora. Por otro lado, el rendimiento en la tarea visuomotora fue similar en el grupo preclínico y en los controles en cuanto al número errores. Estos resultados señalan que el tiempo

de respuesta y la variabilidad intra-individual pueden ser parámetros más sensibles que el número de errores, para la identificación de diferencias sutiles entre individuos preclínicos y controles. Además, el rendimiento en la tarea motora no se vio asociado con los factores de riesgo vascular o la actividad física, que está descrito que podrían afectar al funcionamiento motor (Dumurgier y cols., 2010), independientemente de la patología de la enfermedad de Alzheimer subyacente.

A pesar de que está documentado que las alteraciones en la memoria episódica representan las primeras alteraciones cognitivas que aparecen a lo largo del proceso patológico que conduce a la demencia asociada a la enfermedad de Alzheimer, hay un creciente reconocimiento de que disfunciones incipientes en la coordinación visuomotora y el control motor pueden ser indicadores precoces de este proceso (Verheij y cols., 2012; Albers y cols., 2015). En cuanto a la función visuomotora, algunos estudios indican que el deterioro en funciones visuomotoras podría también aparecer en las primeras fases del continuum de la enfermedad de Alzheimer. Por ejemplo, Hawkins y Sergio (2014) han documentado de una lentitud visuomotora en el grupo de individuos cognitivamente sanos con un riesgo incrementado de desarrollar la enfermedad de Alzheimer (con antecedentes familiares de la enfermedad) en relación con los controles. Esta diferencia fue más pronunciada en las condiciones de la prueba que requería una mayor demanda cognitiva. Así, nuestros resultados sugieren que los individuos cognitivamente sanos con confirmación patológica de la enfermedad de Alzheimer (o sea, con niveles alterados de β-amiloide) se caracterizarían por una emergente lentitud visuomotora, incluso en una tarea con mínimas demandas cognitivas, como es el caso de nuestra tarea de coordinación visuomotora.

En lo que respecta a la función “puramente” motora, hasta la fecha, dicha función ha sido estudiada en pacientes que presentan demencia asociada a la enfermedad de Alzheimer, y sobre todo con métodos cualitativos y usando la velocidad de la marcha como parámetro. Sin embargo, la velocidad en *tapping* manual, otro indicador importante de la función motora, ha recibido poca atención en la investigación de la enfermedad de Alzheimer. Los pocos estudios existentes, apuntan en la misma

dirección que nuestro propio trabajo (Buracchio y cols., 2010, Camicioli y cols., 1998). Por ejemplo, como descrito en Camicioli y cols. (1998), los individuos que en años posteriores desarrollan deterioro cognitivo leve realizarían movimientos de *tapping* más enlentecidos en comparación con los controles.

Mientras que la función motora ha sido analizada con mayor frecuencia en relación con la velocidad, hay un creciente reconocimiento de que la variabilidad intra-individual de la función motora predice un futuro deterioro cognitivo y demencia (Verghese y cols., 2007). Además, se ha propuesto que los individuos con deterioro cognitivo leve presentan una mayor variabilidad mientras caminan o durante la ejecución de movimientos de *tapping* que los individuos cognitivamente sanos (Bangert y Balota, 2012; Verghese y cols., 2008). En correspondencia con estos trabajos previos, nosotros encontramos también un aumento en la variabilidad en el grupo de pacientes con deterioro cognitivo asociado a la enfermedad de Alzheimer. Sin embargo, la contribución más importante de nuestro trabajo es el hallazgo de que la variabilidad motora fue capaz de distinguir incluso el grupo preclínico del grupo control.

Cuando comparamos el papel de la velocidad y la variabilidad en el mismo análisis de regresión, encontramos que la variabilidad era la única variable que hacía una contribución independiente a la clasificación de los grupos control y preclínico. En relación con nuestros resultados, en un estudio previo (Dixon y cols., 2007) la variabilidad intra-individual durante una tarea psicomotora predijo la clasificación del grupo con deterioro cognitivo leve versus el grupo de ancianos sanos, más allá de la influencia de la velocidad. El aumento de la variabilidad motora en los adultos mayores se ha relacionado con cambios neuronales que se producen con el envejecimiento (Aoki y cols., 2003). Si la variabilidad motora es sensible a los cambios neuronales del envejecimiento normal, puede aumentar aún más como resultado de procesos neuropatológicos. Por eso, a la luz de los presentes resultados, la variabilidad motora podría ser un indicador sensible de los cambios neuronales preclínicos. Aunque nuestros resultados son prometedores, se requieren futuros estudios para confirmar estos descubrimientos preliminares.

Los resultados de los estudios 3 y 4 sugieren en su conjunto que una evaluación precisa de funciones visuomotoras y motoras específicas, mediante el uso de medidas cuantitativas de velocidad y de variabilidad intra-individual, puede ser adecuada para la detección de dificultades incipientes en un grupo de individuos que tienen un substrato neuropatológico de la enfermedad de Alzheimer, sin exhibir por ello síntomas clínicos.

2.2. Asociación entre las medidas de coordinación visuomotora y control motor y los biomarcadores de la enfermedad de Alzheimer en líquido cefalorraquídeo

Uno de los resultados más importantes de los trabajos 3 y 4 fue el hallazgo de que el rendimiento en ambas tareas se asoció con el nivel de marcadores biológicos de la enfermedad de Alzheimer. Concretamente, en el grupo de individuos cognitivamente sanos los niveles más bajos de β-amiloide en líquido cefalorraquídeo se relacionaron con un enlentecimiento en la respuesta tanto en la tarea de coordinación visuomotora como en la tarea de control motor, y con una mayor variabilidad intra-individual motora. Por otro lado, los niveles de tau total y p-tau se asociaron con el enlentecimiento visuomotor y motor, pero solo en la muestra completa constituida por los individuos cognitivamente sanos y con deterioro cognitivo. En cuanto a la influencia del ApoE4, nuestros resultados sugieren que la presencia de ApoE4 no modularía la relación entre los biomarcadores de la enfermedad de Alzheimer y las funciones visuomotoras y motoras.

El hecho de que la relación con tau no se encontrara en la muestra de individuos cognitivamente sanos tiene diferentes explicaciones potenciales. Aunque estos resultados podrían sugerir que los niveles de tau afectan las funciones visuomotoras y motoras en fases más tardías de la enfermedad, cabría destacar que el grupo control y el grupo preclínico no diferían en cuanto a los niveles de tau. Ello es debido a que, de acuerdo con los criterios NIA-AA, la fase preclínica puede definirse solo en base a niveles de proteína β-amiloide, por lo que la mayoría de los participantes preclínicos tenían niveles de las proteínas tau normales. Por consiguiente, creemos que la insuficiente variabilidad inter-individual en los valores de tau en los participantes

cognitivamente sanos hizo que sea difícil encontrar correlaciones entre tau y nuestras medidas experimentales.

Una interpretación global de los hallazgos observados de asociación entre los rendimientos en las tareas de coordinación visuomotora y control motor y los niveles de β-amiliode podría ser que el rendimiento en funciones visuomotoras y motoras específicas estaría relacionado con la agregación y posterior depósito de los monómeros de amiloide. Al mismo tiempo, estas anomalías en el rendimiento visuomotor y motor pueden aparecer incluso antes del deterioro en los dominios cognitivos, evaluados con las pruebas estándar, que a su vez estaría más estrechamente relacionado con la presencia de patología tau o degeneración neuronal (reflejadas por los niveles de p-tau y tau total, respectivamente). La realización de estudios futuros podría ayudar a aclarar en qué medida las funciones visuomotoras y motoras estarían relacionadas con los niveles de β-amiloide, tau total o p-tau en las diferentes etapas de la enfermedad de Alzheimer.

En consonancia con nuestros resultados de correlación entre los niveles de β-amiloide y la tarea motora (trabajo 4), un estudio reciente ha documentado una asociación entre la función motora, que usó como parámetro la velocidad de la marcha, y los niveles de amiloide cerebral en individuos cognitivamente sanos y con deterioro cognitivo leve (del Campo y cols., 2016). Sin embargo, los marcadores de degeneración neuronal y de patología tau no estaban disponibles en este estudio previo.

En lo que respecta al trabajo 3, los posibles vínculos entre los biomarcadores de la enfermedad de Alzheimer y las funciones específicas de coordinación visuomotora aún no se han establecido de forma concluyente. En un trabajo reciente, en una muestra de individuos cognitivamente sanos, el rendimiento en el test de coordinación visuomotora “Identification Test”, de la batería computarizada CogState, se ha encontrado asociado con los biomarcadores de degeneración neuronal (hipometabolismo cerebral), pero no con los niveles de amiloide cerebral (Mielke y cols., 2014). Creemos que la discrepancia con nuestros resultados podría deberse a las diferentes características de las pruebas empleadas. Efectivamente, aunque ambas tareas evalúen funciones perceptivas y motoras coordinadas, en el “Identification

Test", en el cual el sujeto tiene que dar una respuesta motora en función del color del estímulo visual, la característica perceptiva del objeto target es el color, mientras que en nuestro estudio es la ubicación espacial. Por esto, solamente la realización de nuevos estudios, empleando diferentes paradigmas experimentales, podría permitir determinar cuáles funciones visuomotoras específicas serían más sensibles a los biomarcadores de amiloide o de degeneración neuronal.

En cuanto a la influencia de factores genéticos sobre los resultados observados, cuando el ApoE4 (el principal factor conocido de riesgo genético para la enfermedad de Alzheimer esporádica) se incluyó como co-variable en los análisis de correlación con los biomarcadores de la enfermedad de Alzheimer, se encontró que las correlaciones se mantenían significativas en ambas tareas de coordinación visuomotora y de control motor, lo cual sugiere que la presencia del ApoE4 no modularía en nuestro estudio la relación entre los biomarcadores de la enfermedad de Alzheimer y las funciones estudiadas. En cambio, en los análisis de comparación entre grupos, hallamos un enlentecimiento general en los portadores del ApoE4 comparados con los participantes no portadores en toda la muestra de individuos cognitivamente sanos. Los presentes resultados corroboran los de estudios previos en los cuales se ha observado un mayor enlentecimiento en individuos sanos portadores del ApoE en tareas psicomotoras (Reinvang y cols., 2010).

Nuestros hallazgos, en su conjunto, sugieren que las disfunciones visuomotoras y motoras parecen producirse en fases asintomáticas de la enfermedad de Alzheimer y estarían asociadas con la acumulación de la proteína β-amiloide, y en menor medida con el genotipo ApoE4. No obstante, todavía se necesitan más investigaciones para dilucidar el efecto relativo de los biomarcadores de la enfermedad de Alzheimer y del ApoE4 en funciones cerebrales específicas con compontes motores.

2.3. Relación entre el rendimiento visuomotor y motor con la cognición

Como hemos señalado anteriormente, las pruebas experimentales presentadas en esta tesis han sido diseñadas para medir funciones motoras y visuomotoras específicas, reduciendo al mismo tiempo la posible participación de otras habilidades

cognitivas. Sin embargo, un aspecto que vale la pena tener en cuenta a la hora de interpretar nuestros resultados es que, a pesar de su relativa simplicidad, es probable que para ambas tareas sean necesarios unos recursos cognitivos mínimos y, de manera especial, atencionales.

En lo que se refiere a la prueba visuomotora, es importante destacar que, aparte de la participación de los sistemas perceptivo y motor, la tarea tiene también un marcado componente de atención espacial, puesto que los participantes tienen que atender a la ubicación del objetivo en la pantalla del ordenador y mover su foco de atención hacia el botón correspondiente del teclado. Por otro lado, la tarea de control motor es una versión computarizada y modificada de la tarea motora *tapping*. Recientemente se ha postulado que el *tapping* no es meramente una actividad motora automatizada, sino que es una actividad que requiere componentes ejecutivos tales como la iniciación y la atención sostenida, con el fin de ejecutar una acción y mantenerla para alcanzar los objetivos de la tarea (Amboni y cols., 2013). De hecho, en condiciones de "dual task" la reducción de recursos atencionales y el aumento de la carga cognitiva reducen la velocidad y aumentan la variabilidad en el *tapping* (Montero-Odasso y cols., 2009).

Tomando en cuenta esta evidencias, no debe sorprendernos que la velocidad visuomotora y motora así como la variabilidad intra-individual motora se encontraran asociadas con los tests clásicos que miden la velocidad psicomotora y las funciones atencionales y ejecutivas (específicamente las pruebas *Symbol Digit*, *Trail Making* y de interferencia de Stroop). En cambio, el rendimiento en estas pruebas clásicas fue similar en el grupo control y preclínico, de acuerdo con la idea, ya discutida anteriormente, de que las pruebas clásicas no son adecuadas para detectar dificultades incipientes en la enfermedad de Alzheimer preclínica.

3. Limitaciones y recomendaciones

Las limitaciones de cada trabajo han sido descritas detalladamente en cada uno de ellos. En términos más generales, la principal limitación asociada con las conclusiones de esta tesis es que el tamaño de la muestra del grupo preclínico es relativamente pequeño. Los estudios futuros deben determinar si estos resultados son verificables en

muestras independientes de mayor tamaño. Por otra parte, teniendo en cuenta el carácter transversal de los estudios aportados por nosotros, nuestros resultados excluyen la posibilidad de determinar si las dificultades relacionadas con la anormalidad de los niveles de β-amiloide también se asocian con el posterior deterioro cognitivo debido a la enfermedad de Alzheimer. Además, la muestra está compuesta en su totalidad por individuos de la población española. Por consiguiente, antes de que los resultados observados en esta tesis se puedan generalizar, tendrán que ser replicados en otras poblaciones.

En general, los estudios actuales sugieren que el fenotipo de la enfermedad de Alzheimer debería seguir ampliándose más allá de su caracterización tradicional como un trastorno mnésico y cognitivo. Necesita ser estudiada una gama más amplia de "comportamientos", como por ejemplo la percepción subjetiva de pérdida en funciones cognitivas no mnésicas o el rendimiento objetivo en tareas experimentales de funciones cognitivo-motoras especificas.

En este contexto, creemos que nuevas herramientas de evaluación del deterioro cognitivo subjetivo y de funciones cognitivo-motoras específicas (y quizás más cercanas y más sensibles a los precoces cambios neuronales que ocurren en la enfermedad de Alzheimer), como la velocidad y la variabilidad intra-individual, pueden ofrecer información adicional única en la identificación de individuos que presentan un substrato patológico de la enfermedad de Alzheimer, sin exhibir por ello síntomas clínicos. En conclusión, el conocimiento derivado de la presente tesis puede aportar una contribución sustancial a la comprensión de las primeras manifestaciones de la enfermedad de Alzheimer.

VI. CONCLUSIONES

1. El declive cognitivo subjetivo medido a través del informador permite distinguir entre los diferentes estadios de la enfermedad de Alzheimer (desde la fase preclínica a la fase de demencia) y los individuos con enfermedad de Alzheimer preclínica de los individuos sanos.

2. La magnitud del declive cognitivo subjetivo referido por el informador se asocia con los niveles de biomarcadores (β-amiloide, tau total y p-tau) en la muestra completa constituida por los individuos cognitivamente sanos y con deterioro cognitivo asociado a la enfermedad de Alzheimer.

3. El declive cognitivo subjetivo referido por el informador presenta una mayor asociación con el rendimiento cognitivo objetivo del individuo, mientras que el percibido por el mismo individuo tiene mayor relación con el estado emocional.

4. Las pruebas computarizadas de coordinación visuomotora y de control motor permiten diferenciar los individuos con enfermedad de Alzheimer preclínica de los individuos sanos.

5. La coordinación visuomotora y el control motor se asocian con los niveles de β-amiloide en el grupo de individuos cognitivamente sanos y con los niveles de tau total y p-tau en la muestra completa constituida por los individuos cognitivamente sanos y con deterioro cognitivo asociado a la enfermedad de Alzheimer, sin estar influidos por la presencia del ApoE4.

6. En individuos cognitivamente sanos, las medidas computarizadas de coordinación visuomotora y de control motor presentan una asociación directa con las pruebas cognitivas clásicas que miden la velocidad psicomotora y las funciones atencionales y ejecutivas.

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