Universitat de Girona

DETERIORO COGNITIVO LEVE Y DEMENCIA TIPO ALZHEIMER EN PERSONAS CON DISCAPACIDAD INTELECTUAL: DETECCIÓN, CLASIFICACIÓN Y CARACTERIZACIÓN DE LA EVOLUCIÓN CLÍNICA

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Emili Rodríguez Hidalgo

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PROGRAMA DE DOCTORAT EN PSICOLOGIA, SALUT I QUALITAT DE VIDA

Dirigida por: Dra. Susanna Esteba Castillo

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Memoria presentada para optar al título de doctor por la Universitat de Girona

Instituciones participantes en los estudios

La Dra. Susanna Esteba Castillo, del Servei Especialitzat en Salut Mental i Discapacitat Intel·lectual de l'Institut d'Assistència Sanitària del Parc Hospitalati Martí i Julià de Girona,

DECLARO:

Que el treball titulat "Deterioro cognitivo leve y demencia tipo Alzheimer en personas con discapacidad intelectual: detección, clasificación y caracterización de la evolución clínica", que presenta Emili Rodríguez Hidalgo per a l'obtenció del títol de doctor, ha estat realitzat sota la meva direcció.

I, perquè així consti i tingui els efectes oportuns, signo aquest document

Girona, juny de 2023

La Dra. Susanna Esteba Castillo, el Dr. Javier García Alba, la Dra. Maria Buxó Pujoràs, i el Dr. Ramon Novell Alsina, com a coautors i coautores dels següents articles:

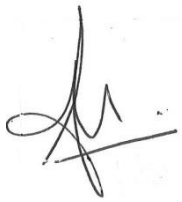
- Emili Rodríguez-Hidalgo, Javier García-Alba, Maria Buxó, Ramon Novell, Susanna Esteba-Castillo (2022). The Pictorial Screening Memory Test (P-MIS) for Adults with Moderate Intellectual Disability and Alzheimer's Disease. *International Journal of Environmental Research and Public Health, 19(17)*, 10780. https://doi.org/10.3390/ijerph191710780.
- Emili Rodríguez-Hidalgo, Javier García-Alba, Ramon Novell, Susanna Esteba-Castillo (2023). The Global Deterioration Scale for Down Syndrome Population (GDS-DS): A Rating Scale to Assess the Progression of Alzheimer's Disease. *International Journal of Environmental Research and Public Health*, *20*(6), 5096. MDPI AG. http://dx.doi.org/10.3390/ijerph20065096.

Acceptem que el Sr. Emili Rodríguez Hidalgo presenti els articles esmentats com a autor principal i com a part de la seva tesi doctoral, i que aquests articles no puguin, per tant, formar part de cap altra tesi doctoral.

I, perquè així consti i tingui els efectes oportuns, signem aquest document

Dra. Susanna Esteba Castillo

Dr. Javier García Alba



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Dont acte.

A mis padres y a mi familia

Lista de publicaciones derivadas de la tesi

Esta tesis doctoral se ha llevado a cabo mediante el formato de compendio de artículos, que se detetallan a continuación:

- **Emili Rodríguez-Hidalgo**, Javier García-Alba, Maria Buxó, Ramon Novell, Susanna Esteba-Castillo (2022). The Pictorial Screening Memory Test (P-MIS) for Adults with Moderate Intellectual Disability and Alzheimer's Disease. *International Journal of Environmental Research and Public Health, 19(17),* 10780. https://doi.org/10.3390/ijerph191710780.
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- **Emili Rodríguez-Hidalgo**, Javier García-Alba, Ramon Novell, Susanna Esteba-Castillo (2023). The Global Deterioration Scale for Down Syndrome Population (GDS-DS): A Rating Scale to Assess the Progression of Alzheimer's Disease. *International Journal of Environmental Research and Public Health*, *20*(6), 5096. MDPI AG. http://dx.doi.org/10.3390/ijerph20065096.
  Índice de calidad: [JCR IF: 4.614, Q2].

LISTA DE ABREVIATURAS

AAMR	Asociación Americana de Retraso Mental
ADNI	Alzheimer's Disease Neuroimaging Initiative
AIVD	Actividades instrumentales de la vida diaria
APOE	Apolipoproteina E
BRI-BRIEF	Behavioral Regulation Index- Behaviour Rating Inventory of Executive Function-informant's report
CAMCOG-SD	Cambridge cognitive examination for mental disorders of older people with Down's syndrome and others intellectual disabilities
CAMDEX-SD	Cambridge examination for mental disorders of older people with Down's syndrome and others intellectual disabilities
CDR	Clinical Dementia Rating
CI	Cociente Intelectual
CIE-10	Clasificación Internacional de Enfermedades, décima revisión
CIE-11	Clasificación Internacional de Enfermedades, undécima revisión
DCL	Deterioro Cognitivo Leve
DCoL	Deterioro Cognitivo Leve Conductual
DCS	Deterioro Cognitivo Subjetivo
DI	Discapacidad intelectual
DSM-IV-TR	Manual Diagnóstico y Estadístico de los Trastornos Mentales, cuarta edición revisada
DSM-V	Manual Diagnóstico y Estadístico de los Trastornos Mentales, quinta edición
EA	Enfermedad de Alzheimer
FAST	Functional Assessment Staging
FCSRT	Free and Cued Selective Reminding Test
GDS	Global Deterioration Scale
INE	Instituto Nacional de Estadística
ISTAART	International Society to Advance Alzheimer's Research and Treatment
mCRT	Modified Cued Recall Test
MIS	Memory Impairment Screen
NIA-AA	National Institute of Aging-Alzheimer's Association

OMIM	Online Mendelian Inheritance in Man
OMS	Organización Mundial de la Salud
PC	Parálisis cerebral
PET	tomografía por emisión de positrones
PET-FDG	PET de fluorodeoxyglucosa
PMIS	Picture Based Memory Impairment Screen
SD	Síndrome de Down
TB-DI	Test Barcelona para personas con discapacidad intelectual
TEA	Trastorno del espectro del autismo
TOL^{DXtm}	Tower of London-Drexel University

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ÍNDICE

Resumen/resum/abstract

1. RESUMEN/RESUM/ABSTRACT

1.1 Resumen

Introducción. La discapacidad intelectual es un trastorno del neurodesarrollo que afecta el funcionamiento intelectual y las habilidades adaptativas. El aumento de la esperanza de vida en esta población conlleva un incremento de patologías de salud mental, como la enfermedad de Alzheimer, especialmente relevante en personas con síndrome de Down. A pesar de los avances en el contexto del modelo biológico a través de biomarcadores, la exploración neuropsicológica tiene un rol primordial en el diagnóstico y la monitorización del curso progresivo de la demencia en general, harto complicado en personas con discapacidad intelectual debido al fenotipo cognitivo y conductual de cada caso. Además, a pesar de que cada vez se disponen de más instrumentos neuropsicológicos adaptados y validados en esta población, a diferencia de la población sin discapacidad intelectual, todavía se carece de un instrumento breve de cribado para la memoria, dominio fundamental en el estudio de la enfermedad de Alzheimer. Por otra parte, y también comparado con las personas sin discapacidad intelectual, tampoco existe un criterio unificado de las fases evolutivas de la enfermedad de Alzheimer en personas con síndrome de Down.

Objetivos. El objetivo de la presente tesis fue adaptar y validar dos instrumentos en personas con discapacidad intelectual. El primer instrumento fue un test de cribado para los problemas de memoria asociados a deterioro cognitivo leve y enfermedad de Alzheimer (**Estudio 1**), y el segundo una escala global de deterioro para caracterizar la evolución clínica de la enfermedad de Alzheimer en personas con síndrome de Down (**Estudio 2)**.

Metodología. El primer estudio se llevó a cabo mediante un diseño transversal. La

muestra estuvo compuesta por un total de 94 participantes de habla española y catalana con discapacidad intelectual leve y moderada (60 en el grupo control, 17 con deterioro cognitivo leve, y 17 con enfermedad de Alzheimer), reclutados del Servicio Especial de Salud Mental y Discapacidad Intelectual del Hospital Santa Caterina, de Girona. A todos ellos se les administró el PMIS-DI además de un protocolo neuropsicológico amplio. Se estudio la validez discriminante del PMIS-DI entre los participantes con deterioro cognitivo leve, enfermedad de Alzheimer y el grupo control mediante el cálculo del área bajo la curva.

El segundo estudio constó de 83 participantes (48 cognitivamente estables, 24 con deterioro cognitivo leve, y 11 con enfermedad de Alzheimer) con síndrome de Down, reclutados del Servicio Especial de Salud Mental y Discapacidad Intelectual del Hospital Santa Caterina (Girona) y de la Unidad de síndrome de Down del Hospital La Princesa (Madrid). Se propuso una escala global (GDS-SD) con seis estadios, des de ausencia de deterioro cognitivo y conductual hasta el estadio de enfermedad de Alzheimer avanzada. Dos neuropsicólogos clasificaron retrospectivamente a cada participante en cada estadio de la GDS-SD según su rendimiento en pruebas cognitivas, conductuales y de las habilidades adaptativa de la vida diaria.

Resultados. En referencia al primer estudio, se ha demostrado que es posible contar con test breve de cribado en personas con discapacidad intelectual. Un punto de corte de 4.5 en el ensayo de recuerdo inmediato arrojó una sensibilidad de 69 % y una especificidad de 80 % para detectar problemas de memoria en personas con discapacidad intelectual moderada y enfermedad de Alzheimer.

En cuanto al segundo estudio, la escala propuesta (GDS-SD) constó de seis estadios que contemplaron todo el continuo de la enfermedad de Alzheimer en personas con síndrome de Down. La fiabilidad interexaminador y el acuerdo para clasificar en cada

estadio de la GDS-SD fueron muy aceptables. Además, la puntuación total de la CAMCOG-SD y en el subtest orientación del Test Barcelona para personas con discapacidad intelectual mostraron valores decrecientes a partir del estadio 2 (deterioro cognitivo subjetivo cognitivo y/o conductual) hasta el estadio 6 (enfermedad de Alzheimer avanzada).

Conclusiones. El PMIS-DI es un test breve de cribado con buenas propiedades psicométricas para detectar problemas de memoria asociados a enfermedad de Alzheimer en personas con discapacidad intelectual moderada. Por otra parte, la escala GDS-DS puede ser un primer paso para unificar les estadios del continuo de la enfermedad de Alzheimer en personas con síndrome de Down y discapacidad intelectual leve y moderada.

1.2 Resum

Introducció. La discapacitat intel·lectual és un trastorn del neurodesenvolupament que afecta el funcionament intel·lectual i les habilitats adaptatives. L'augment de l'esperança de vida en aquesta població comporta un increment de patologies de salut mental com la demència tipus Alzheimer, especialment rellevant en persones amb síndrome de Down. Tot i els avenços en el context del model biològic amb biomarcadors, l'exploració neuropsicològica té un rol fonamental en el diagnòstic i la monitorització del curs progressiu de la demència en general, aspectes molt complicats en persones amb discapacitat intel·lectual degut al fenotipus cognitiu i conductual de cada cas. A més a més, tot i que cada vegada es disposen de més instruments neuropsicològics adaptats i validats en aquesta població, a diferència de les persones sense discapacitat intel·lectual, encara estem mancats d'un instrument breu de cribatge per a la memòria, domini fonamental en l'estudi de la malaltia d'Alzheimer. D'altra banda, i també comparat amb persones sense discapacitat intel·lectual, tampoc existeix un criteri unificat de les fases evolutives de la malaltia d'Alzheimer en persones amb síndrome de Down.

Objectius. L'objectiu de la present tesi fou adaptar i validar dos instruments en persones amb discapacitat intel·lectual. El primer instrument va ser un test de cribatge per als problemes de memòria associats al deteriorament cognitiu lleu i malaltia d'Alzheimer (**Estudi 1)**, i el segon una escala global de deteriorament per caracteritzar l'evolució clínica de la malaltia d'Alzheimer en persones amb síndrome de Down **(Estudi 2)**.

Metodologia. El primer estudi es va portar a terme mitjançant un disseny transversal. La mostra fou d'un total de 94 participants de parla espanyola i catalana amb discapacitat intel·lectual lleu i moderada (60 en el grup control, 17 amb deteriorament

cognitiu lleu, i 17 amb malaltia d'Alzheimer), reclutats del Servei Especial de Salut Mental i Discapacitat Intel·lectual de l'Hospital Santa Caterina, de Girona. A tots ells se'ls va administrar el PMIS-DI a més a més d'un protocol neuropsicològic ampli. Es va estudiar la validesa discriminant del PMIS-DI entre els participants amb deteriorament cognitiu lleu, malaltia d'Alzheimer i el grup control mitjançant el càlcul de l'àrea sota la corba.

El segon estudi va constar de 83 participants (48 cognitivament estables, 24 amb deteriorament cognitiu lleu, i 11 amb malaltia d'Alzheimer) amb síndrome de Down, reclutats del Servei Especial de Salut Mental i Discapacitat Intel·lectual de l'Hospital Santa Caterina (Girona), i de la Unitat de síndrome de Down de l'Hospital La Princesa (Madrid). Es va proposar una escala global (GDS-SD) amb sis estadis, des de l'absència de deteriorament cognitiu i conductual fins a l'estadi de malaltia d'Alzheimer avançada. Dos neuropsicòlegs classificaren retrospectivament a cada participant en cada estadi de la GDS-SD segons el seu rendiment en probes cognitives, conductuals i d'habilitats adaptatives de la vida diària.

Resultats. En referència al primer estudi, s'ha demostrat que és possible comptar amb un test breu de cribatge en persones amb discapacitat intel·lectual. Un punt de tall de 4.5 en l'assaig de record immediat va mostrar una sensibilitat de 69 % i una especificitat de 80 % per detectar problemes de memòria (AUC = 0.685; 95 % IC = 0.506 – 0.863) en persones amb discapacitat intel·lectual moderada i malaltia d'Alzheimer.

En quant al segon estudi, l'escala proposada (GDS-SD) va constar de 6 estadis que contemplaren tot el continu de la malaltia d'Alzheimer en persones amb síndrome de Down. La fiabilitat interexaminador i l'acord per classificar en cada estadi de la GDS-SD foren excel·lents. A més a més, la puntuació total de la bateria CAMCOG-SD i en el substest orientació del Test Barcelona para personas con discapacidad intelectual

mostraren valors decreixents a partir de l'estadi 2 (deteriorament cognitiu i/o conductual subjectiu) i fins al 6 (malaltia d'Alzheimer avançada).

Conclusions. El PMIS-DI és un test breu de cribatge amb bones propietats psicomètriques per detectar problemes de memòria associats a malaltia d'Alzheimer en persones amb discapacitat intel·lectual moderada. D'altra banda, l'escala GDS-SD pot ser un primer pas per unificar els estadis del continu malaltia d'Alzheimer en persones amb síndrome de Down i discapacitat intel·lectual lleu i moderada.

1.3 Abstract

Background. Intellectual disability is a neurodevelopment disorder affecting intellectual functioning and adaptive behavior. The increase of life expectancy of this population leads to an increase of mental health pathologies such as Alzheimer's diseases, especially relevant in people with Down syndrome. Despite advances in research have identifies promising biomarkers in the context of the biological model, neuropsychological examination has a fundamental role in the diagnosis and monitoring the progressive course of dementia in general, although its difficulty in people with intellectual disabilities, due to the cognitive and behavioral phenotype of each case. In addition, despite the increasing number of adapted and validated neuropsychological tools are nowadays available in this population, unlike people without intellectual disabilities, there is still a lack of a brief screening test for memory, a fundamental domain in the study of Alzheimer's disease. On the other hand and also compared to people without intellectual disabilities, there is not a unified criterion for the clinical stages of Alzheimer's disease in people with Down syndrome.

Objectives. The main objective of this thesis was to adapt and validate two instruments in people with intellectual disabilities. The first instrument was a screening test for memory problems associated with mild cognitive impairment and Alzheimer's disease (**Study 1**), and the second was a global impairment scale to characterize the clinical progression of Alzheimer's disease in people with Down syndrome (**Study 2**).

Methodology. The first study was carried out using a cross-sectional validation design. The sample consisted of a total of 94 Spanish and Catalan-speaking participants with mild and moderate intellectual disabilities (60 control group, 17 mild cognitive impairment, and 17 Alzheimer's disease), recruited from the Specialized Mental Health Intellectual Disability Unit, Institute of Health Assistance (Girona). All of them were

evaluated by neuropsychological tests including de PMIS-ID. Discriminative validity between the mild cognitive impairment, Alzheimer's disease and control group was analyzed by the area under the ROC curve.

The second study consisted of 83 participants with Down syndrome (48 cognitive stability, 24 mild cognitive impairment, 11 Alzheimer's disease) recruited from the Specialized Mental Health ID Unit, Institute of Health Assistance (Girona) and the Adult Down Syndrome Unit, La Princesa University Hospital (Madrid). A global scale (GDS-SD) with six stages was proposed, from the absence of cognitive and behavioral impairment to the stage of advanced Alzheimer's disease. Two neuropsychologists retrospectively classified the participants into each stage of the GDS-SD based on their performance on tests of cognitive, behavioral, and adaptive daily living skills.

Results. In the first study, it has been shown that it is possible to have a brief screening test in people with intellectual disabilities. A cutoff point of 4.5 on the immediate recall assay of the PMIS-ID yielded a sensitivity of 69% and a specificity of 80% for detecting memory problems (AUC = 0.685; 95 % IC = 0.506 – 0.863) in people with moderate intellectual disability and Alzheimer's disease.

In the second study, the proposed scale (GDS-SD) consisted of six stages that contemplated the entire continuo of Alzheimer's disease in people with Down syndrome. In addition, the CAMCOG-SD and orientation subtest of the Barcelona Test for Intellectual Disability total scores showed decreasing values from the stage 2 (cognitive and/or behavioral subjective cognitive impairment) to stage 6 (advanced Alzheimer's disease).

Conclusions. The PMIS-DI is a brief screening test with good psychometric properties to detect memory problems associated with Alzheimer's disease in people with moderate intellectual disability. Also, the GDS-DS scale may be a first step for unifying

the stages of the Alzheimer's disease continuum in people with Down syndrome and mild or moderate intellectual disability.

Introducción

2. INTRODUCCIÓN

2.1 Discapacidad intelectual.

2.1.1 Definición y criterios diagnósticos

La discapacidad intelectual (DI) se caracteriza por limitaciones significativas tanto en el funcionamiento intelectual como en la conducta adaptativa que se originan en el periodo de desarrollo (Schalock et al., 2021). El funcionamiento intelectual se equipara al razonamiento, resolución de problemas, planificación, pensamiento abstracto, juicio y a la capacidad de aprendizaje obtenido por la experiencia. Por su parte, la conducta adaptativa es multidimensional e incluye las *habilidades conceptuales* (lenguaje, lectura y escritura, y conceptos relacionados con el dinero, el tiempo y los números), *sociales* (habilidades interpersonales, responsabilidad social, autoestima, seguimiento de reglas y normas, resolución de problemas sociales), y *prácticas* (actividades de la vida personal, habilidades ocupacionales, manejo del dinero, seguridad, cuidado de la salud, viajes/desplazamientos, programación/rutinas y uso del teléfono).

En la quinta edición del Manual Diagnóstico y Estadístico de los Trastornos Mentales (DSM-V) (APA, 2014), la DI se engloba en la categoría de los trastornos del neurodesarrollo. Se reserva el diagnóstico de retraso global del desarrollo para los casos de menos de cinco años de edad y el de trastorno del desarrollo intelectual no especificado para los casos mayores de cinco años de edad, cuando no se puede objetivar el grado de DI con los procedimientos disponibles a causa de las características del individuo (ceguera o trastornos graves de conducta, entre otras). Asimismo, el trastorno del desarrollo intelectual es el homólogo de la DI en la undécima Clasificación Internacional de las Enfermedades (Organización Mundial de la Salud, 2022).

Atrás ha quedado el término retraso mental acuñado hasta el año 2002 en el manual de la antigua Asociación Americana de Retraso Mental (AAMR). Actualmente se aboga por un constructo de DI que tiene en cuenta la interacción entre la persona y su ambiente, y en los apoyos individualizados. El cambio de paradigma en el proceso diagnóstico de la DI otorga un papel determinante a la exploración neuropsicológica, en detrimiento del cociente intelectual (CI), indispensable en el DSM-IV-TR. De este modo, el grado de DI (leve, moderado, grave o severo) vendrá determinado por la afectación cognitiva y el nivel de soporte o apoyo que va a necesitar la persona, ya sea intermitente, limitado, extenso o generalizado según la intensidad de la afectación de las habilidades conceptuales, sociales y prácticas (Tabla 1).

Tabla 1

Características diagnósticas según el nivel de discapacidad intelectual

Niveles de DI	CI (DSM-IV-TR)	Necesidades de apoyo (DSM-V)	Tipo de intervención
Leve	50-70	Intermitente	Puntual
Moderada	35-49	Limitado	Limitada
Grave	20-34	Extenso	Regular e ilimitada
Profunda	≤ 20	Generalizado	Indefinida

Nota. DI = discapacidad intelectual, CI = cociente intelectual, DSM= Diagnostic and Statistical Manual of Mental Disorders.

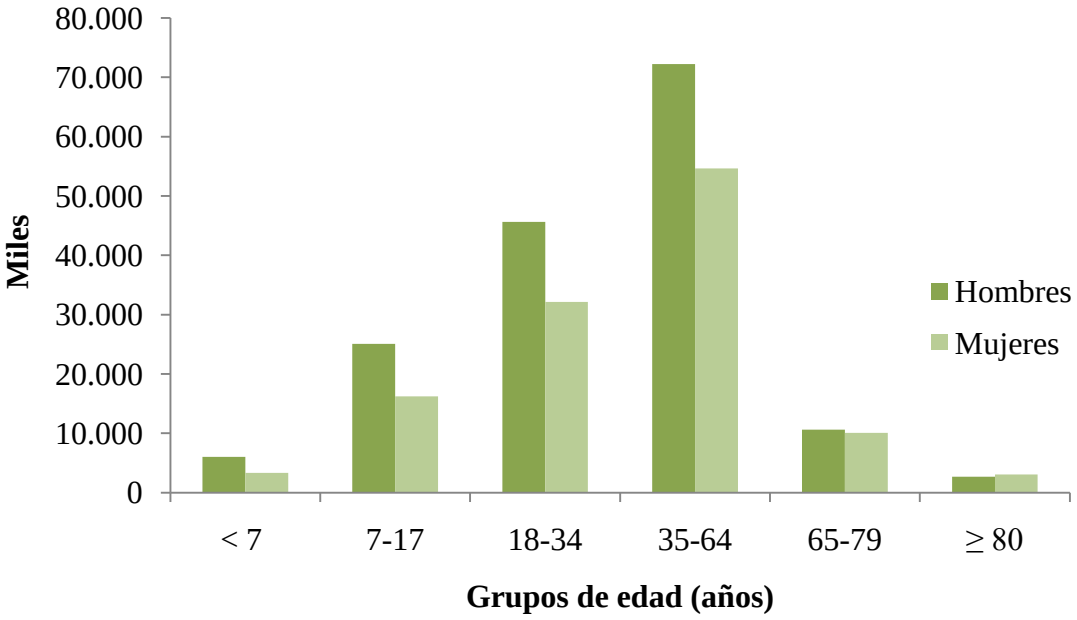
2.1.2 Epidemiología

Según el DSM-V (APA, 2014) entre el 1 y 2 % de la población mundial presenta DI. En consonancia con estos datos, a pesar de la heterogeneidad de la metodología utilizada en los diferentes estudios epidemiológicos, se estima que la incidencia y la prevalencia son similares, oscilando entre 0.05 y 1.55 % (Mckenzie et al., 2016). En

nuestro contexto, los datos de la reciente Encuesta de Discapacidad, Autonomía personal y Situaciones de dependencia (Instituto Nacional de Estadística, 2022) contabilizan en España aproximadamente 281.720 mil personas con DI, de las cuales 162.223 son hombres y 119.497 mujeres, especialmente entre los 35 y 64 años de edad (Figura1).

Figura 1

Distribución por edades de discapacidad intelectual en España



A pesar de todos los avances médicos, la DI sigue siendo un factor de riesgo de muerte prematura. Por ejemplo, en personas finesas, sólo un 20 % sobrepasaban los 60 años de edad. La diferencia de edad promedio en el momento de la muerte fue inferior en la personas con DI (22 años para los hombres y 30 años para las mujeres) comparada con la población general, además del mayor riesgo en los sujetos con DI severa o profunda (edad promedio de 44 y 43 años, respectivamente) que en sujetos con DI leve o moderada (56 y 54 años, respectivamente) (Arvio et al., 2017).

2.1.3 Etiología

El diagnóstico etiológico es importante por diversas razones. Por un lado, la etiología puede asociarse a un determinado fenotipo cognitivo, conductual y a problemas de salud que permite establecer programas de intervención y un seguimiento clínico adecuado, así como homogeneizar los grupos en investigación y facilitar el consejo genético para promover el asesoramiento previo a la concepción (Verdugo Alonso, 2011).

La etiología de la DI es multifactorial y aunque en los últimos años se ha avanzado en la evaluación genética y biomédica, la etiología a veces quedará indeterminada, como ocurre en un 25% de los casos (García-Alba et al., 2018). Además, tal como se describe en la Tabla 2, cabe considerar otros factores de riesgo sociales o conductuales asociados a la DI de causa no genética (Huang et al., 2016).

A grandes ragos, la etiología se podría dividir en tres condiciones generales:

1. **Prenatales**. Explican un 52% de los casos de DI y se pueden dar por lo siguiente:
   - **Defectos genéticos**. Son alteraciones que afectan a un solo gen (monogénicas), como por ejemplo la DI ligada al cromosoma X o anomalías cromosómicas, como el síndrome de Down
   - **Defectos en el desarrollo del sistema nervioso central**. Provocan DI por alteraciones en la neurogénesis y/o mielinizacíón. Son características las anencefalia, espina bífida o la hidrocefalia.
   - **Factores gestacionales.** El consumo de tóxicos o determinados medicamentos puede provocar daño en el cerebro en la etapa gestacional.
2. **Perinatales**. Es el periodo comprendido entre la semana 22 de gestación hasta la semana 4 de vida neonatal. Explican un 15% de los casos de DI y el feto puede resultar dañado por trastornos intrauterinos, relacionados con el parto (prematuridad,

encefalopatía hipóxico-isquémica), alteraciones metabólicas y epilepsia neonatal. entre otras.

3. **Postnatales.** Se consideran a partir de la semana 4 de vida y explican un 8% de los casos de DI por infecciones cerebrales, traumatismos craneoencefálicos, trastornos desmielinizantes, trastornos neurodegenerativos, convulsiones, malnutrición, privación ambiental.

Tabla 2

Factores de riesgo de la discapacidad intelectual

Fase	Biomédicos	Sociales	Conductuales	Educativos
Prenatal	Genéticos Metabólicos Desarrollo SNC Enfermedad materna Edad parental	Pobreza Malnutrición Violencia doméstica	Factores gestacionales (consumo parental de tóxicos)	Inmadurez parental
Perinatal	Prematuridad Lesiones nacimiento Trastornos neonatales Metabólicas	Falta de cuidados parentales	Rechazo de los padres Abandono	Falta de derivación a servicios
Postnatal	Traumatismo craneoencefálico Malnutrición Meningoencefalitis Epilepsia	Pobre interacción No estimulación Pobreza familiar	Maltrato Violencia Deprivación Trastornos	Deficiencias crianza Diagnóstico tardío

Nota. Adaptado de García-Alba, J., Esteba-Castillo, S., & Viñas-Jornet, M. (2018). *Neuropsicología del trastorno del desarrollo intelectual con y sin origen genético*. Sintesis; y de Verdugo Alonso, M. Á. (2011). *Discapacidad intelectual: definición, clasificación y sistemas de apoyo* (11ª ed.). Alianza.

Aunque muchos síndromes se manifiestan con diferentes grados de gravedad, se están haciendo esfuerzos para recopilar la máxima información para asociar un determinado genotipo con un fenotípico específico. Cabe destacar que La Society for the Study of Behavioural Phenotypes (SSBP) *(https://ssbp.org.uk)* recoge algunos de los fenotipos más conocidos en la actualidad y está en constante revisión. También disponemos de un trabajo exhaustivo sobre las particularidades cognitivas en sujetos con DI de base genética (García-Alba et al., 2018). Esta información puede ser útil para la familia y los profesionales del ámbito escolar, así como para diferenciar el proceso de envejecimiento patológico del fisiológico en el contexto clínico. En este sentido se puede establecer un espectro del deterioro cognitivo en los adultos mayores, a partir del deterioro cognitivo asociado el envejecimiento, siguiendo por el deterioro cognitivo subjetivo (DCS), el deterioro cognitivo leve (DCL) y la demencia (Jongsiriyanyong & Limpawattana, 2018) (Figura 2).

Figura 2

Espectro clínico del proceso de deterioro cognitivo

2.1.4 Envejecimiento en personas con DI

La esperanza de vida en las personas con DI ha aumentado considerablemente en las últimas décadas (Dieckmann et al., 2015). Incluso las personas con DI y necesidad de soporte extenso y generalizado pueden sobrevivir hasta los 50 años de edad gracias a la mejoras en cuanto a la prevención e intervención (Rousseau et al., 2019). Este aumento

de la esperanza de vida tiene como consecuencia un incremento de problemas de salud mental, como la demencia. A excepción de las personas con síndrome de Down, se afirma que los sujetos con DI envejecen antes que las personas sin DI (Tse et al., 2018), pero este envejecimiento prematuro es consecuencia de que el aumento de la esperanza de vida no se ha visto correspondido con una adecuada oferta de servicios residenciales y de programas de promoción de la salud, además del poco acceso a los servicios sanitarios y de la baja calidad de la atención sanitaria y social recibida (Novell et al., 2008). Como se comprueba, existe un vacío en políticas y educación que promuevan un envejecimiento saludable a nivel físico, cognitivo y social, nutritivo y de evitación de los factores de riesgo para los sujetos con DI y los familiares o cuidadores (Reppermund & Trollor, 2016).

El envejecimiento en personas con DI es complejo y heterogéneo. Se asocia con un declive de la funcionalidad, un aumento de la dependencia de los otros, de situaciones de soledad y de inseguridad que pueden conllevar efectos negativos en su la salud y bienestar (Lougheed, 2019). Condiciones clínicas como la obesidad, osteoporosis, cataratas, enfermedades cardiovasculares, y los problemas psiquiátricos son más frecuentes en la personas con DI que en la personas sin DI (de Leeuw et al., 2022). Además, con el envejecimiento, los adultos con DI sufren deterioro cognitivo adicional debido a la afectación basal en las esferas cognitiva, sensorial y de pensamiento (Janicki et al., 2022). Los menores rendimientos cognitivos y funcionales vienen determinados por la propia DI, el nivel curricular, y por el uso de instrumentos no validados en esta población (Tena-Bernal et al., 2021). En este sentido, es bien conocido el alto riesgo de padecer enfermedad de Alzheimer (EA) en las personas con SD, pero el envejecimiento en personas con DI no filiada es bastante heterogéneo a nivel cognitivo (García-Alba et al., 2018). En general, la capacidad de lenguaje, la habilidad motora y la socialización

decrecen con la edad (Rousseau et al., 2019), pero esta complejidad requiere de más estudios en esta etapa del ciclo vital.

Como ya se ha comentado, el periodo de envejecimiento se caracteriza por problemas físicos, cognitivos, sociales y enfermedades que hayan podido acontecer durante el ciclo vital, incidiendo en que las personas presenten diferente vulnerabilidad al deterioro cognitivo. En este sentido, el *síndrome de fragilidad* es un estado clínico de vulnerabilidad que resulta del declive en la reserva y función de las habilidades que permiten afrontar el día a día, que conlleva a un mayor riesgo de caídas, discapacidad, hospitalización y mortalidad (Fried et al., 2001). En este contexto, se ha acuñado la *fragilidad cognitiva* para aquellos casos de adultos mayores con evidencia de deterioro físico y cognitivo sin un diagnóstico de demencia (Kelaiditi et al., 2013) que está asociado a mayor riesgo de padecer DCL y EA, u otro tipo de demencia (Buchman et al., 2013; Panza et al., 2015). En personas con DI, el índice de fragilidad predice el declive en la movilidad y aumenta la discapacidad, polifarmacia y la intensidad del cuidado (Schoufour et al., 2017).

2.1.5 Deterioro cognitivo subjetivo en personas con DI

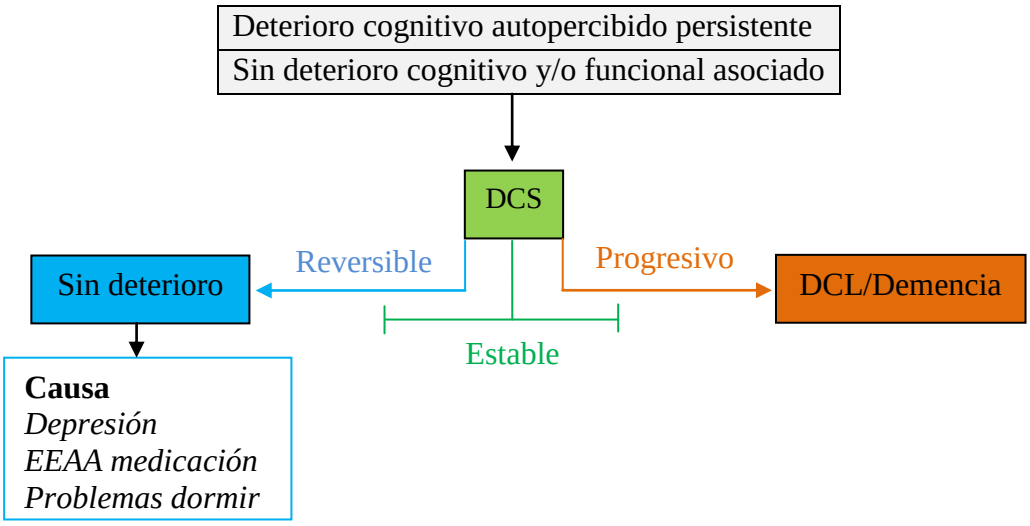
Bajo el término de deterioro cognitivo subjetivo (DCS) se engloban los casos de sujetos con la percepción de deterioro cognitivo comparado con un estado previo de normalidad, y con rendimientos normales en las pruebas de cribado o neuropsicológicas, así como en las funcionales (Jessen et al., 2020). Actualmente no es una entidad que se haya incluido en los manuales diagnósticos, pero cada vez está recibiendo más atención por ser un factor de riesgo para desarrollar demencia, ya sea tipo Alzheimer (Ben-Ami et al., 2023), o no Alzheimer (Slot et al., 2019). Así, además de la caracterización del DCS mediante biomarcadores (Eliassen et al., 2017), se están desarrollando datos normativos de instrumentos neuropsicológicos utilizados en nuestro

contexto que se están mostrando sensibles en la detección de problemas de memoria asociado al DCS (Brugulat-Serrat et al., 2021).

Aunque el DCS puede presentar diversas trayectorias (Figura 3), se ha propuesto considerar el DCS como el último estadio de la fase preclínica de la EA (Sperling et al., 2011), que se caracteriza por un incremento de los mecanismos cognitivos compensatorios y un deterioro cognitivo sutil asociado a la acumulación de patología beta amiloidea (Sánchez-Benavides et al., 2021).

Figura 3

Delimitación del deterioro cognitivo subjetivo (DCS) y trayectorias



Nota. Se observan tres posibles trayectorias del DCS): (1) la reversibilidad a un estado sin deterioro, que podría haber estado causado por causas tratables, como la depresión, efectos adversos del tratamiento farmacológico (EEAA), insomnio; (2) mantenerse estable; (3) progresar a deterioro cognitivo leve (DCL) y demencia. Adaptado de Jessen et al., 2020. Prediction of dementia of Alzheimer type by different types of subjective cognitive decline. *Alzheimer's and Dementia*, *16*(12), 1745–1749. https://doi.org/10.1002/alz.12163

De esta manera, características como el deterioro cognitivo focalizado en la memoria, con inicio en los últimos cinco años, la edad de inicio mayor de 60 años, la intensidad

de la preocupación asociada y sentimientos de menor rendimiento que las otras personas, incrementan el riesgo de progresión a DCL en los sujetos con DCS (Jessen et al., 2014).

El DCS en personas con DI no se ha considerado tan profundamente como en la población sin DI. Posiblemente se hayan obviado las posibles quejas de los sujetos con DI por sus características fenotípicas. Quizá sería conveniente considerar las quejas subjetivas de los familiares y cuidadores y equipararlas al DCS de la población general. Considerando que el DCS puede ser una condición que asocia a mayor riesgo de padecer DCL y EA, se hace imprescindible incorporar el DCS en el continuo de EA en sujetos con DI, y especialmente en personas con SD.

2.1.6 Deterioro cognitivo leve en personas con DI

El DCL o trastorno neurocognitivo menor según el DSM-V se considera como un estado intermedio entre el envejecimiento normal y la demencia (Petersen et al., 2018). Se ha descrito detalladamente en la población general y equivale al estadio 3 de la escala de deterioro global (GDS por sus siglas en inglés) (Reisberg et al., 1982). Las causas del DCL pueden ser neurodegenerativas, vasculares, metabólicas, traumáticas, psiquiátricas u otras (Winblad et al., 2004).

Disponemos de dos propuestas de criterios diagnósticos (Tabla 3). Por una parte, los de la Alzheimer's Disease Neuroimaging Initiative (ADNI) contemplan quejas cognitivas por parte del propio sujeto o informador, deterioro cognitivo objetivo (puntuaciones en los test entre -1.5 y -2 desviaciones estándar) y sin ninguna o mínima repercusión en la funcionalidad diaria (Petersen et al., 2014). Por otra parte, los criterios neuropsicológicos básicamente pretenden equilibrar la sensibilidad (definiendo deterioro en rendimientos por debajo de -1 desviación estándar) y la fiabilidad (deterioro en dos test por dominio cognitivo) e introducen valores de las actividades

instrumentales de la vida diaria (Bondi et al., 2014).

Tabla 3

Comparación simplificada de los criterios diagnósticos del DCL

	Criterios	
	ADNI	Neuropsicológicos
Test administrados por dominio cognitivo	Un test	Dos test
Cuantificación del deterioro cognitivo	-1.5 y -2 DE	-1 DE
Afectación AIVD	Subjetividad	Datos objetivos (escalas)

Nota. AIVD = actividades instrumentales de la vida diaria, ADNI = Alzheimer's Disease Neuroimaging Initiative, DE = desviación estándar.

Tanto los criterio de la ADNI como los neuropsicológicos han mostrado similar fiabilidad en cuanto a las tasas de reversión del DCL (Overton et al., 2023). A tenor de si existe alteración de la memoria o no, podemos hablar de DCL amnésico o no amnésico; y dependiendo de las funciones cognitivas alteradas, de DCL monodominio (afectación de una función específica) o DCL multidominio. Las personas con diagnóstico de DCL pueden mantenerse estables, retornar a un estado normal (entre 14.4 % - 55.6 % de los casos) o progresar a demencia (Petersen et al., 2018), de forma similar a lo descrito en el DCS. El DCL amnésico es que el que presenta mayor riesgo de conversión a EA (Ortega et al., 2019; Tangalos & Petersen, 2018).

A diferencia de la población general, no existe un consenso en cuanto a los criterios diagnósticos para el DCL en personas con DI (Janicki et al., 2022). Se han asumido los criterios diagnósticos propuestos para la población general, pero éstos no son fiables en personas con DI. Por una parte, se necesitarían datos normativos de los instrumentos neuropsicológicos en sujetos con DI y sin deterioro cognitivo según cada etiología de

DI para poder determinar cuantitativamente el nivel de declive cognitivo. Por otra parte, la funcionalidad diaria en los sujetos con DI está, en la mayoría de los casos, acotada a rutinas y bien establecidas, lo que las hace resistentes a un posible declive. De este modo, determinar que para que exista un DCL en personas con DI debe haber afectación de las actividades diarias avanzadas puede ser un hándicap para la detección precoz (Krinsky-McHale & Silverman, 2013). En general, hay que tener en cuenta que en los casos con DI leve el deterioro cognitivo suele detectarse con cierta facilidad, pero en los casos con DI moderada y severa hay que considerar el cambio de conducta como posible signo de alerta (García-Alba et al., 2018).

2.1.7 Deterioro conductual leve en personas con DI

Las alteraciones psiquiátricas o conductuales son habituales en personas con DCL (Van der Mussele et al., 2013) y pueden conllevar afectación de la funcionalidad e incrementar el riesgo de progresión de DCL a demencia (Peters et al., 2012).

La International Society to Advance Alzheimer's Research and Treatment (ISTAART) ha delimitado unos criterios diagnósticos para la investigación del deterioro conductual leve (DCoL), que se resumen en la Tabla 4.

Debe existir un cambio de conducta y personalidad en la edad adulta, que no se explique mejor por un trastorno psiquiátrico, y que persista más allá de 6 meses (Ismail et al., 2016). La incorporación del DCoL como posible entidad diagnóstica en sujetos sin demencia mejora la especificidad del diagnóstico del DCL (McGirr et al., 2022).

Aunque el DCoL no está los suficientemente desarrollado en personas con DI, el diagnóstico de demencia es habitual en los sujetos con DI que presentan alteración de conducta, indistintamente del nivel de DI (Axmon et al., 2017). Este hallazgo sugiere que en sujetos con DI se debería tener en cuenta el DCoL como factor de riesgo de demencia.

Tabla 4

Resumen de los criterios diagnósticos para el DCoL

1. Cambio en la conducta o personalidad observado por el paciente, informador o clínico, que se inicia en la edad adulta (≥ 50 años), y persiste por lo menos intermitentemente durante ≥ 6 meses.
2. Las conductas son suficientemente severas para producir una afectación mínima en al menos una de las siguientes áreas: relaciones interpersonales, rendimiento en el trabajo.
3. Aunque otras condiciones comórbidas pueden estar presentes, el cambio de conducta o personalidad no se atribuye a un trastorno psiquiátrico.
4. No se cumplen los criterios de demencia. El DCL puede coocurrir con el diagnóstico de deterioro conductual leve.

Nota. DCoL = deterioro conductual leve.

2.1.8 Demencia en personas con DI

La demencia o trastorno neurocognitivo mayor según el DSM-V (APA, 2014) se corresponde con el estadio 4 y posteriores de la escala de deterioro global (GDS) (Reisberg et al., 1982) en población general. No estaba claro que las personas con DI tuvieran más riesgo de desarrollar demencia que la población general (Silverman et al., 2013), pero hoy sabemos que el riesgo es similar, aunque puede ser mayor y presentarse en edades más precoces en algunos síndromes genéticos como el SD, síndrome de Prader-Willi y síndrome de Williams, además de aquellos sujetos con epilepsia u otras condiciones patológicas (Janicky et al., 2022).

Se ha asumido que los criterios diagnósticos para la demencia en población general tienen cierta validez para personas con DI. Resumiendo los criterios diagnósticos del DSM-V (APA, 2014) y de la CIE-11 (OMS, 2022), la demencia se caracteriza por un deterioro progresivo en múltiple aspectos cognitivos y en las habilidades adaptativas. Pero se sigue optando por considerar el diagnóstico emitido por expertos en demencia y

DI como *"gold standard",* como se ha comentado en el apartado del DCL. De esta manera, la ausencia de criterios diagnóstico universales hace que la prevalencia oscile a tenor de los criterios diagnósticos utilizados (Tse et al., 2018).

Los signos de demencia son tan comunes en sujetos menores de 40 años como en aquellos con más 70 años de edad. Ante la sospecha de demencia, se debe descartar problemas como deficiencia de vitamina B12, cistitis y disfunción tiroidea mediante analíticas. Además, durante la evaluación hay que considerar las posibilidad de depresión, apnea del sueño u otros trastornos del sueño, así como la medicación concomitante que pueden estar afectando la memoria (Arvio et al., 2021).

Dejando de lado la relación entre la EA y el SD, que se detallará en otro apartado, la etiología de la DI puede asociarse a ciertos síntomas de demencia. Así, sujetos con síndrome de Williams son más propensos a desarrollar demencia vascular a causa del trastorno metabólico que presentan (Sauna-aho et al., 2019), y los sujetos con síndrome de X frágil no parecen ser propensos a desarrollar problemas de memoria (Sauna-aho et al., 2020).

Por una parte, los casos de sujetos con trastorno del espectro del autismo (TEA) menores de 65 años de edad presentan mayor riesgo de mostrar signos de demencia que la población general, pero en menor número que los sujetos con TEA y DI (Vivanti et al., 2021). A pesar de este hecho, no parece existir una clara correlación de la demencia con la edad, que se puede explicar por la heterogeneidad clínica y etiológica de dicho trastorno, así como la intervención farmacológica crónica que reciben (Arvio et al., 2021). Pocos son los estudios en esta población, pero de momento no existe una conclusión evidente del riesgo de demencia en personas con TEA o si éste es un factor protector, debido a que los estudios se han llevado a cabo con muestras pequeñas o no han considerado la coocurrencia con otros factores médicos y psiquiátricos (Janicki et

al., 2022).

Por otra parte, la parálisis cerebral (PC) por sí misma no predispone al desarrollo de demencia, excepto en los casos con otras comorbididades como la DI, aunque se necesitan más estudios en este sentido (Smith et al., 2021).

A tenor de estos datos, para emitir el diagnóstico de demencia en personas con DI, se debe tener en cuenta el fenotipo cognitivo y conductual sobretodo en las afecciones genéticas. En los casos en los que la etiología de la DI se desconoce, es recomendable realizar seguimientos periódicos para poder discernir si hay un proceso de deterioro. Este hecho hace que en muchas ocasiones la demora en el diagnóstico perjudica la implantación de medidas farmacológicas y no farmacológicas adecuadas en el momento óptimo. Por eso es indispensable contar con instrumentos que permitan diagnosticar con validez y fiabilidad en cualquier momento de la evolución de la enfermedad.

Lo que va a decantar la emisión del diagnóstico de demencia es el criterio de funcionalidad en la vida diaria. Mientras que en el DCL ésta funcionalidad se puede considerar poco o nada afectada, en la demencia es un criterio indispensable que haya una pérdida de esta funcionalidad, tanto en las habilidades avanzadas como en las básicas.

Además, el diagnóstico de demencia en personas con DI severa o profunda es un reto. En esta población, se han descrito síntomas que se asocian con demencia, como a nivel cognitivo (pérdida de memoria, alteración del lenguaje), com conductual (apatía, agresividad, irritabilidad, alteración de la conducta alimentaria, así como perdida de las habilidades sociales, incontinencia, epilepsia de inicio tardío y alteración de la marcha (Wissing et al., 2022).

En los artículos revisados para este apartado se ha apreciado una falta de unificación en la definición de la demencia. Se utiliza indistintamente el término demencia y EA,

provocando todavía más confusión de entidades ya harto complicadas de detectar en personas con DI. En cambio, sí que se ha establecido una asociación entre EA y SD, como se detalla en los siguientes apartados.

2.2 Síndrome de Down

El síndrome de Down es la aneuploidía cromosómica más común asociada a niveles de DI que oscilan entre leves y moderados. El SD está causado por la triplicación (trisomía) de todo o determinadas porciones críticas del cromosoma 21 y afecta a 1 de cada 1000 nacimientos, aumentando el riesgo con la edad materna (*https://www.yourgenome.org/facts/what-is-downs-syndrome/*). Se estima que la prevalencia en Europa es de 6.7 por cada 100.000 individuos (de Graaf et al., 2021).

2.2.1 Características clínicas

Aparte de la DI, se reconocen unos rasgos típicos que se asocian con diversas comorbilidades con una amplia variación fenotípica. Así, un 50% de las personas con SD nacen con problemas cardíacos (Diamandopoulos & Green, 2018) y éstos pueden incidir en el desarrollo cerebral, aunque los problemas en el nacimiento que requieren cirugía no se asocian con mayor alteración de la funcionalidad en estos individuos (Rosser et al., 2018). La leucemia linfoblástica tiene una incidencia 40 veces mayor que en la personas sin SD (Chisholm, 2018). Además un 12% nacen con malformaciones gastrointestinales congénitas, y otras condiciones médicas como dificultades visuales, enfermedad periodontal, obesidad, apnea obstructiva (Asim et al., 2015).

El tratamiento exitoso de las condiciones modificables como los defectos congénitos del corazón, han hecho que la esperanza de vida aumente en las últimas décadas, aunque todavía se encuentra una diferencia de 20 años cuando se compara con la población

general, a causa de la alta prevalencia de la enfermedad de Alzheimer y los escasos tratamientos disponibles (Iulita et al., 2022).

Además, las personas con SD presentan unas características clínicas y biológicas que son compatibles con una alteración inmunológica causada por un envejecimiento precoz y acelerado (Gensous et al., 2020; Xu et al., 2022). Los rasgos físicos más destacables son fisuras palpebrales inclinadas hacia arriba, *epicantus*, cuello ancho, cara redonda, nariz pequeña y línea palpebral única. Se asocia a apnea obstructiva y problemas visuales y auditivos. En líneas generales, el fenotipo cognitivo se caracteriza por mejores rendimientos en las tareas visoespaciales que en las verbales o auditivas. Muestran mejor lenguaje receptivo que expresivo y mejor memoria espacial que verbal y en la esfera conductual, suelen mostrarse como personas agradables y sociables (Asim et al., 2015).

A pesar de estas generalidades, para entender mejor el genotipo y el fenotipo emergente, no se debe encasillar a las personas con SD como un grupo homogéneo, debiéndose considerar las diferencias individuales (Karmiloff-Smith et al., 2016) que parecen responder a la variación genética y epigenética de cada persona (García-Alba et al., 2018). En cuanto a las variaciones genéticas, existen tres tipos de SD según la alteración cromosómica:

- **Trisomía 21.** El cromosoma 21 está triplicado y representa aproximadamente un 88% de los casos.
- **SD por translocación (trisomía parcial).** Una parte o un cromosoma 21 entero está ligado a un cromosoma distinto del 21 correspondiente. Ocurre en un 4% de los casos.
- **SD por mosaicismo.** En estos casos el cromosoma 21 está triplicado pero otras poseen los dos cromosomas 21 habituales lo que hace que la afectación sea leve.

Corresponde entre un 1.3 y un 5% de los casos, pero se cree que es más habitual de lo establecido.

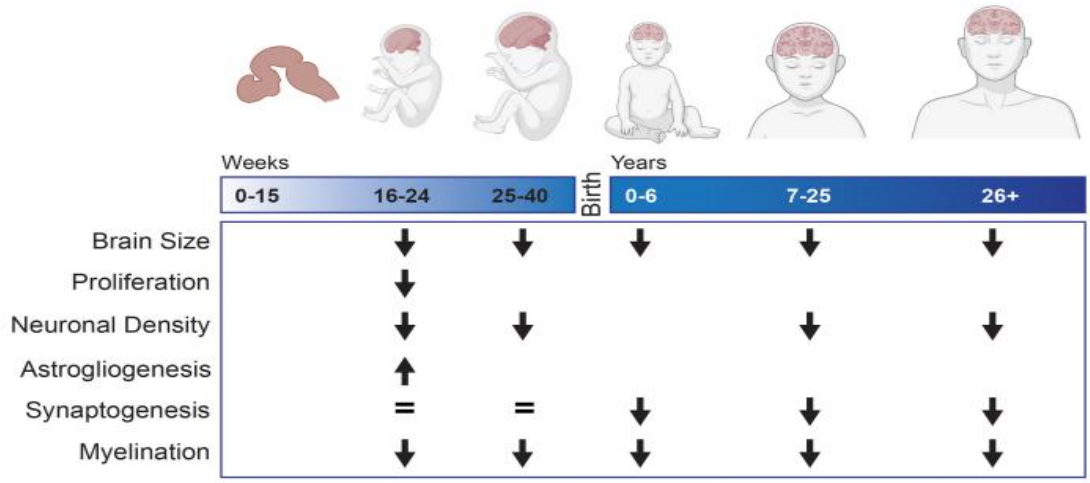
Además de la copia extra de todo o parte del cromosoma 21, las diferencias en las variaciones en el número de copias (CNVs), los polimorfismos de nucleótido simples (SNPs) y las mutaciones de *novo* observadas en la población neurotípica también se deben considerar en personas con SD.

2.2.2 Alteraciones del sistema nervioso central

El SD está caracterizado por cambios neuropatológicos que ocurren en la etapa fetal y neonatal que conducen a alteraciones en el desarrollo cerebral (Figura 4).

Figura 4

Cambios en el desarrollo neurológico en personas con síndomre de Down



Nota. Cambios observados en muestras de tejido o resonancia magnética de individuos con síndrome de Down en comparación con el desarrollo típico. Los espacios en blanco indican que no existen datos para ese período de tiempo de desarrollo. Extraído de Klein, J. A., & Haydar, T. F. (2022). Neurodevelopment in Down syndrome: Concordance in humans and models. *Frontiers in Cellular Neuroscience*, *16*(July), 1–17. https://doi.org/10.3389/fncel.2022.941855

Por una parte, se observan alteraciones en la morfogénesis. En este sentido, el tamaño del cerebro es normal entre las semanas 20 y 24 de gestación, pero las diferencias individuales emergen a partir de esta fecha, especialmente a partir del segundo trimestre de gestación, justo en la fase crítica para los procesos de maduración, formación de sinapsis y arborización dendrítica (Klein & Haydar, 2022). Muestran un reducción general del volumen cerebral, incluyendo la sustancia cerebral gris y blanca, además del cerebelo (McCann et al., 2021; Rachidi & Lopes, 2011), del hipocampo y de las áreas fronto-occipitales (Anderson et al., 2013).

Por otra parte, también se producen alteraciones en la formación de los tejidos (histogénesis), incluyendo disgenesia cortical, retraso en la mielinización, baja densidad neuronal y plasticidad anormal (Rachidi and Lopes, 2011). Ya des de la semana 24 de gestación la proliferación celular está disminuida, la formación y arborización dendrítica se estancan y se manifiestan en el nacimiento con menor arborización y sinapsis, contribuyendo a una menor conectividad cerebral (Utagawa et al., 2022). Destacar que se han generado varios modelos murinos para estudiar las correlaciones genotipo/fenotipo y en particular las alteraciones neurobiológicas en el cerebro de las personas con SD, hallándose que la acumulación de amiloide podría empezar ya durante la gestación (Zhao & Haddad, 2022).

2.2.3 Fenotipo cognitivo

En general, el SD se asocia a un fenotipo cognitivo característico, afectándose funciones cognitivas como la atención, funciones ejecutivas y memoria, en parte causado por el daño cortical. Siguiendo los datos aportados por García-Alba et al. (2018), la memoria inmediata está alterada, igual que la memoria visual a largo plazo. En cambio, la capacidad de memoria implícita es similar a la de las personas sin DI. Por su parte, la memoria visoespacial es mejor que la memoria verbal, igual que el procesamiento

global, que también es mejor que el procesamiento local.

En cuanto a memoria episódica, hay que recordar que el volumen del hipocampo es más pequeño en personas con SD. Pero cuando hay una afectación en esta estructura en un trabajo concertado con estructuras prefrontales, la memoria se altera, ya sea por alteración en la codificación o en la recuperación.

Las funciones ejecutivas suelen estar alteradas, especialmente la planificación y la capacidad de atención. Así, la disfunción ejecutiva se suele asociar a aquellos casos que presentan apnea obstructiva del sueño, igual que el CI verbal, que suele ser inferior a los casos con SD sin apnea del sueño. Así pues, el fenotipo cognitivo se caracteriza por un punto fuerte en las habilidades no verbales, mientras que la capacidad de lenguaje es un punto débil, con relación al lenguaje expresivo, sintaxis, articulación, procesamiento fonológico y memoria de trabajo verbal (Grieco et al., 2015).

Como se ha descrito, se pueden establecer unas características generales en cuanto al fenotipo cognitivo y conductual en personas con SD, pero especialmente importante es conocerlas en la etapa adulta por el alto riesgo de desarrollar DCL y EA de esta población, permitiendo diferenciarlas del envejecimiento fisiológico.

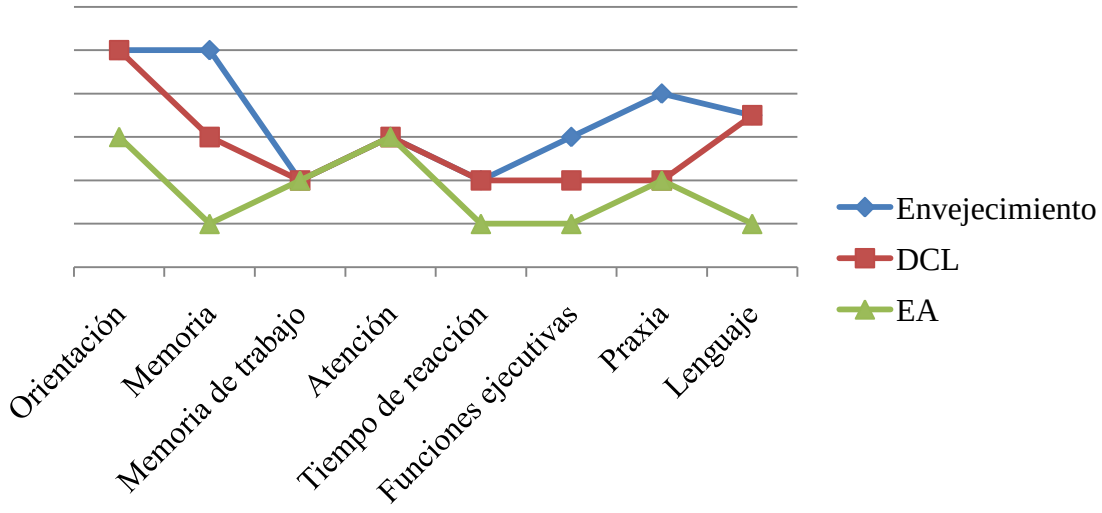
2.2.4 Envejecimiento en personas con SD

El SD se considera un síndrome progeroide ya que el envejecimiento es rápido y presenta características típicas de la población geriátrica. El envejecimiento se caracteriza por un deterioro en general, pero con un curso más lento que en los casos con EA. De este modo, la inteligencia fluida decae a partir de los 40 años de edad. Además, las habilidades motoras, de socialización y la funcionalidad diaria decaen, pero se mantienen las habilidades comunicativas y de lenguaje, éstas ya alteradas *per se* (Tsao et al., 2015). Un descenso significativo en el rendimiento en pruebas de orientación, memoria, tiempos de reacción, funciones ejecutivas y atención se suelen

asociar a DCL y EA (Figura 5).

Figura 5

Resumen de las características cognitivas de las personas con SD envejecidas, con DCL y EA.



A nivel social, suelen conservar su empleo, requieren menos cuidados y no presentan problemas de conducta comparados con los casos de demencia o con problemas psiquiátricos asociados (Esbensen et al., 2016). Teniendo en cuenta estos datos, a nivel de exploración neuropsicológica las áreas de memoria, funciones ejecutivas y orientación se deben evaluar necesariamente en las personas con SD y sospecha de deterioro cognitivo.

2.2.5 Deterioro cognitivo leve en personas con SD

Como ya se ha comentado anteriormente, el diagnóstico de DCL en población general está bastante documentado (Petersen et al., 2014), mientras que son muchas menos las publicaciones en personas con SD.

Hay que hacer hincapié en que para el diagnóstico de DCL la afectación cognitiva no debe comprometer o sólo mínimamente el desempeño de los sujetos en la funcionalidad avanzada de la vida diaria. En este sentido, en las últimas décadas se ha intentado sistematizar y caracterizar a nivel clínico esta entidad. A grandes rasgos, se ven afectados dominios cognitivos como la memoria de trabajo (Krinsky-McHale & Silverman, 2013; Oliver et al., 1998), el lenguaje receptivo (Pulsifer et al., 2020), la capacidad de aprendizaje y la organización espacial (Devenny et al., 2002), así como las funciones ejecutivas, personalidad y conducta (Ball et al., 2008).

Pero después de diversos esfuerzos, gracias al trabajo de Esteba-Castillo et al. 2022, actualmente contamos con una propuesta de criterios diagnósticos neuropsicológicos para personas con SD a partir de los 39 años de edad (Tabla 5).

Tabla 5

Propuesta de criterios diagnósticos para el DCL en personas con SD

Criterios	Test propuesto
Cambios conductuales (≤ 32 puntos)	BRI-BRIEF (Gioia et al., 2000)
Sin cambios en las habilidades adaptativas	CAMDEX-DS sección informador (Esteba-castillo et al., 2013)
Leve disfunción ejecutiva	TOLDXtm (García-Alba et al., 2017)
Empeoramiento en abstracción verbal (seguimientos)	TB-DI (Esteba-Castillo et al., 2017)
Perfil amnésico en test de memoria verbal diferida	TB-DI (Esteba-Castillo et al., 2017)

Nota. DCL = deterioro cognitivo leve, DS = Down yndrome, BRI-BRIEF = behavioral regulation index- behaviour rating inventory of executive function-informant's report, CAMDEX-DS = Cambridge examination for mental disorders of older people with Down's syndrome and other intellectual disabilities, TOLDXtm = tower of London-Drexel University, TB-DI = test Barcelona para personas con discapacidad intelectual.

Contar con esta información proporciona puntos de corte y una delimitación del DCL en personas con SD que permitirá avances en el proceso diagnóstico y para la homogeneización de grupos en los ensayos clínicos.

2.2.6 Deterioro cognitivo-conductual en personas con SD

En las etapas tempranas de la EA en personas con SD se ha reportado, además de un síndrome disejecutivo, la presencia de cambios conductuales o de personalidad, que puede ser un signo de alarma (Lautarescu et al., 2017; Sabbagh & Edgin, 2015). En este sentido, los resultados en la escala Behavioral and Psychological Symptoms of Dementia in Down syndrome (BPSD-DS II) han mostrado que síntomas relacionados con ansiedad, depresión, sueño, irritabilidad, y apatía, pueden ser cambios precoces que anuncien EA en sujetos con SD (Dekker et al., 2021). Este hallazgo, junto con lo ya comentado en el apartado de DCL en DI, van a favor de la importancia de incorporar el DCoL descrito en la población general (Ismail et al., 2016) en la exploración rutinaria de personas con SD. De esta manera, se contemplarían los casos con un posible inicio de EA conductual y amnésico, como se describirá a continuación.

2.2.7 Enfermedad de Alzheimer en personas con SD

La EA es la causa más frecuente de demencia en la población general. Se define por la presencia de placas amiloideas y ovillos neurofibrilares, que pueden ser detectados en estudios post-mortem o mediante biomarcadores (Jack et al., 2018). La presentación típica (EA esporádica) se caracteriza por un declive lentamente progresivo de memoria episódica, alteraciones en el lenguaje, pérdida del sentido de la orientación y dificultades para la planificación de tareas o la resolución de problemas. Junto a estos problemas cognitivos, se suelen dar cambios en la personalidad y en el comportamiento, de manera que la funcionalidad diaria de la persona se ve afectada progresivamente.

Pero la presentación en personas jóvenes (antes de los 65 años) se puede dar de forma atípica, presentando un fenotipo no amnésico, con predominio de afectación visual, lenguaje, funciones ejecutivas, conducta o motora (Graff-Radford et al., 2021).

En personas con SD, la triplicación de la proteína precursora de amiloide (PPA) que se codifica en el cromosoma 21 provoca una acumulación progresiva de beta amiloide con el consiguiente riesgo de padecer EA (Doran et al., 2017). Esta acumulación se produce entre dos o tres décadas antes del inicio de las síntomas clínicos, determinando un largo curso preclínico (Theofilas et al., 2015). Otros genes también están implicados en la EA y también condiciona diferencias individuales. Así el gen APOE codificado en el cromosoma 19 posee variantes comunes: el alelo ε_2 se considera protector, el ε_3 es el más habitual y es neutral con relación a la EA, y el alelo ε_4 proporciona mayor riesgo de padecer EA, especialmente en los portadores de dos alelos. De esta manera, las variantes de APOE modulan la edad de inicio de la EA en SD (Karmiloff-Smith et al., 2016). Consecuentemente, todos los adultos con SD muestran cambios neuropatológicos relacionados en EA alrededor de los 50 años de edad (Cipriani et al., 2018), aunque no todos acabarán desarrollando demencia.

La prevalencia del diagnóstico de EA en adultos con SD se ha estimado que es de 9.4% para las edades entre 40 y 49 años, aumentando al 54.5% entre los 60 y 69 años (Prasher et al., 2015), y hasta el 90 % alrededor de los 70 años de edad (McCarron et al., 2017).

La edad de inicio de la EA en personas con SD muestra una variabilidad de 25 años con una tasa de mortalidad alta que explica una diferencia de más de 20 años en la expectativa de vida comparado con la población general (Iulita et al., 2022).

Es clásico el debate entre las formas de inicio de la EA en personas con SD. Por un lado, los primeros síntomas son secundarios a alteraciones de las funciones ejecutivas afectando la conducta (Janicki et al., 2017), mientras que por otro lado la forma de

inicio se da en la disfunción de la memoria (Blok et al., 2017; Ramírez-Toraño et al., 2021). También hay que considerar que los cambios en la conducta se dan cuando los problemas de memoria ya están establecidos, habiendo pasado desapercibidos para los propios sujetos y las personas de su contexto cercano (García-Alba et al., 2018).

1.1.1.1. *Criterios diagnósticos*

Actualmente no existe un consenso para el diagnóstico de demencia en personas con DI. Básicamente, el diagnóstico de demencia en personas con DI se basa en los datos obtenidos de pruebas cognitivas directas, baterías neuropsicológicas y la información de cuestionarios (Elliott-King et al., 2016). Si el diagnósticos de demencia en personas con DI es un reto, el diagnóstico de EA en personas con SD no es una excepción. Como se ha comentado en el apartado de demencia en la DI, el diagnóstico de EA es clínico y es más inclusivo y fiable cuando lo emite un clínico experimentado, pues se considera mejor la sintomatología típica de estas personas (Sheehan et al., 2015). De hecho, se considera el "gold standard" en la mayoría de las publicaciones en personas con DI. Además, la sensibilidad aumenta cuando se objetiva deterioro mediantes exploraciones sucesivas, al discernir las manifestaciones típicas del envejecimiento o de la EA. En este sentido, la Alzheimer's Association (*https://www.alz.org/)* recomienda que las personas con SD se sometan a valoraciones cognitivas a partir de los 35 años de edad. Por eso se hace imprescindible disponer de pruebas neuropsicológicas suficientemente sensibles para el diagnóstico y monitorización en cualquier punto del continuo de la EA.

Marcadores cognitivos

El seguimiento evolutivo del deterioro cognitivo puede retardar el diagnóstico y el inicio del tratamiento farmacológico y no farmacológico. Por este motivo, se han dedicado esfuerzos para establecer marcadores cognitivos mediante diferentes puntos de

corte concretos para detectar la EA a partir de test neuropsicológicos (Tabla 6).

Tabla 6

Propuesta de marcadores cognitivos para detectar EA

	Esteba-Castillo et al. (2013)	Benejam et al. (2020)
CAMCOG-DS		
DI leve	< 68 (80%, 81%)	< 80 (75%, 87.8%)
DI moderada	< 52 (85%, 81%)	< 56 (84%, 84.3%)
mCRT		
DI leve		< 29 (100%, 100%)
DI moderada		< 28 (92.3%, 94.4%)

Nota.Valores de los puntos de corte (sensibilidad, especificidad). CAMCOG-DS = Cambridge cognitive examination for older adults with Down's syndrome and other intellectual disabilities— versión española, DI = discapacidad intelectual, mCRT = modified cued reminding test.

Sin proporcionar datos significativos pero sí a considerar en la exploración diagnóstica, también se ha demostrado que el rendimiento decrece significativamente entre la fase de DCL y EA en dominios cognitivos del TB-DI (Esteba-Castillo et al., 2017), como la orientación, fluencia verbal semántica y formal, recuerdo diferido de historias y discriminación visual, así como en la puntuación total de la CAMCOG-DS (Esteba-castillo et al., 2013), y en el subtest pensamiento abstracto de la misma batería (Benejam et al., 2020; Esteba-Castillo et al., 2022; Firth et al., 2018; García-Alba et al., 2019; Pulsifer et al., 2020).

Marcadores biológicos

En un intento de aumentar la sensibilidad diagnóstica, se ha propuesto una visión biológica de la EA mediante marcadores biológicos en población sin DI (Jack et al.,

2018). Un biomarcador es un parámetro que puede cuantificarse o medirse de forma objetiva y que proporciona información sobre los procesos biológicos tanto normales como patológicos que ocurren en el organismo. Así, la EA se correspondería al continuo resultante de la combinación de la positividad o negatividad de amiloidosis cerebral (A), patología tau (T) y neurodegeneración (N) (Tabla 7).

Tabla 7

Categorías y perfiles de biomarcadores

Perfiles AT(N)	Categoría de biomarcadores
A-T-(N)-	Biomarcadores normales para enfermedad de Alzheimer
A+T-(N)-	Cambios patológicos de enfermedad de Alzheimer
A+T+(N)-	Enfermedad de Alzheimer
A+T+(N)+	Enfermedad de Alzheimer
A+T-(N)+	Enfermedad de Alzheimer y cambios patológicos concomitantes no Alzheimer
A-T+(N)-	No cambios patológicos de enfermedad de Alzheimer
A-T-(N)+	No cambios patológicos de enfermedad de Alzheimer
A-T+(N)+	No cambios patológicos de enfermedad de Alzheimer

Nota. A = amiloidosis, T = patología tau. N = neurodegeneración. Adaptado de Jack et al. (2018). NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer's and Dementia, 14(4), 535–562. https://doi.org/10.1016/j.jalz.2018.02.018

Atendiendo a la definición biológica con biomarcadores, las personas con SD están en riesgo muy alto de desarrollar EA (Dubois et al., 2021). Por una parte, los cambios en los biomarcadores de la EA ocurren en un orden y una temporalidad similares a los descritos en la EA autosómica dominante, haciendo que se considere el SD como una

forma genéticamente determinada de la EA (Fortea et al., 2020). Por otra parte, la acumulacion patológica de proteina tau hallada mediante la tomografía por emisión de positrones (PET) se detecta en la fase prodrómica de la EA en personas con SD y se correlaciona negativamente con un adelgazamiento en regiones cerebrales temporoparietales y frontales (Padilla et al., 2022). Este hecho es similar a lo hallado en las formas tardías y autosómicas de la EA en población general, y predice los problemas cognitivos con mayor sensibilidad que la acumulación de amiloide (Rafii, 2019), especialmente en memoria episódica (Hartley et al., 2022).

A pesar del gran avance para el diagnóstico de la EA con la introducción de los biomarcadores, se hace indispensable la visión clínica, en la que la neuropsicología juega un papel fundamental (Dubois et al., 2021).

1.1.1.2. *Tratamiento*

No existe un tratamiento farmacológico idóneo para la EA en personas con SD. La administración de suplementos antioxidantes, memantina, vitamina E, e insulina intranasal no han sido lo eficaces que se esperaba, y únicamente el donepezilo ha provocado alguna mejora. En este sentido sería importante focalizar esfuerzos en la detección precoz para poder implementar tanto medidas farmacológicas como no farmacológicas (de Oliveira & de Paula Faria, 2022). Las esperanzas están depositadas en el ensayo clínico en fase II con una vacuna activa contra el amiloide para la prevención de la EA en personas con SD (https://www.acimmune.com/pipeline/clinical-trials/), en el que participará el grupo del Hospital de Sant Pau, de Barcelona.

2.3 Exploración neuropsicológica en el deterioro cognitivo leve y demencia en personas con DI

La exploración neuropsicológica es útil en el diagnóstico de los síndromes neuroconductuales focales, de la demencia y de las alteraciones cognitivas que no

alcanzan el grado de demencia. La evaluación neuropsicológica requiere una aproximación multidimensional que se realiza en etapas sucesivas, dirigidas hacia el reconocimiento detallado de los trastornos. Así, en una primera etapa básica se aplican instrumentos de cribado, para posteriormente determinar el uso en la siguiente fase de una selección de test (etapa específica) o de baterías neuropsicológicas (etapa general). Finalmente, en la etapa idiográfica, se seleccionan los instrumentos pertinentes o se crean pruebas para estudiar un caso específico (Lezak et al., 2012; Peña-Casanova, 1991). Para completar la exploración, es recomendable realizar una entrevista clínica o la administración de cuestionarios que detallarán la información de los aspectos conductuales o afectivos y de la funcionalidad en la vida diaria. Finalmente, es de una gran utilidad clínica el uso de escalas para determinar el estadio de deterioro.

Como ya se ha comentado, en sujetos con DI, hay que tener en cuenta el fenotipo cognitivo y conductual para poder determinar la presencia de un cuadro de deterioro mediante exploraciones longitudinales. De esta manera, contar con exploraciones sucesivas neuropsicológicas y funcionales en estas personas se hace indispensable (Tse et al., 2018). Además, las características propias del sujeto como el nivel de DI, la ausencia de lenguaje, dificultades visuales o motrices, condicionarán la elección de unas determinadas pruebas para una adecuada exploración (García-Alba et al., 2018; Janicki et al., 2022).

Aunque cada vez se existen más instrumentos neuropsicológicos para detectar DCL y demencia en sujetos con DI, pocos están validados en dicha población y, comparado con la población general, la cantidad de pruebas neuropsicológicas disponibles sigue siendo escasa (McKenzie et al., 2018; Paiva et al., 2020; Zeilinger et al., 2013).

En población general es factible contar con instrumentos de cribado, test que valoran una función o baterías neuropsicológicas amplias, así como cuestionarios de conducta y

escalas globales de deterioro suficientemente sensibles para ayudar al clínico en el proceso diagnóstico y de monitorización.

Por los objetivos de la presente tesis, se hará una breve descripción de los instrumentos neuropsicológicos más utilizados en personas con DI en nuestro contexto, clasificándolos según el propósito de cribado, selección de test y baterías neuropsicológicas, así como cuestionarios para los informadores y escalas globales de deterioro (Tabla 8).

Tabla 8

Instrumentos adaptados y validados en población con DI	
Cribado	No.
Selección de test	Modified cued recall test (mCRT) (Benejam et al., 2015)
	Tower of London-Drexel University 2nd edition para personas con DI (TOL^{DXtm}-DI) (García-Alba et al., 2017)
Baterías neuropsicológicas	Cambridge cognitive examination for older adults with Down's syndrome and other intellectual disabilities- version española (CAMCOG-DS) (Esteba-castillo et al., 2013)
	Test Barcelona para personas con discapacidad intelectual (TB-DI) (Esteba-Castillo et al., 2017)
Cuestionario para informadores	The behaviour rating inventory of executive function, parents form (BRIEF-P) (Gioia et al., 2000)
	Informant interview of the Cambridge examination for older adults with Down's syndrome and other intellectual disabilities- version española (CAMDEX-DS) (Esteba-castillo et al., 2013)
Escalas globales	No.

Nota. DCL = deterioro cognitivo leve, DI = discapacidad intelectual.

2.3.1 Instrumentos de cribado cognitivo

Un instrumento breve de cribado cognitivo es una prueba de fácil y rápida administración (entre 5 y 10 minutos), efectivo con relación a su coste, y con alta especificidad para de detectar las alteraciones cognitivas indicativas de demencia (Ashford et al., 2006; Gifford & Cummings, 1999; Tsoi et al., 2015). Estos instrumentos se pueden centrar en diferentes ámbitos cognitivos, como por ejemplo, el Mini Mental State Examination (MMSE) (Folstein et al., 1975), el Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), o en un ámbito cognitivo específico como la memoria, mediante el Memory Impairment Screen (MIS) (Buschke et al., 1999). Todos estos instrumentos están adaptados y validados en población general.

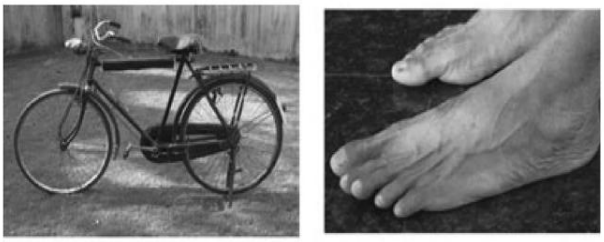
El panorama cambia radicalmente en personas con DI. La escasez o ausencia de test de cribado cognitivo en personas con DI se ha intentado paliar con el uso de test destinados a la personas sin DI con la consiguiente falta de fiabilidad por el efecto suelo, además de la necesidad de contar con un nivel de lenguaje que en muchas ocasiones los sujetos con DI no presentan. Así, el MoCA se ha propuesto como un instrumento para clasificar a los sujetos con DI según su capacidad intelectual (Edge & Ewing, 2019), pero no para detección de DCL o demencia en dicha población.

Por su parte, mediante el Severe Impairment Battery (SIB) (Saxton et al., 1990) se han comparado los perfiles cognitivos de los sujetos con EA en personas sin DI y en personas con SD, presentado similitudes, pero sin establecer datos normativos para DI (Dick et al., 2016). En población con SD de habla no española contamos con el Down Syndrome Mental Status Examination (DSMSE) (Haxby, 1989). Pero tampoco existe ningún test de cribado validado en personas con DI que valore una función tan determinante como la memoria en la demencia, como lo podemos encontrar en población general.

La memoria es uno de los dominios habitualmente explorados en la evaluación neuropsicológica en el deterioro cognitivo leve y demencia, especialmente en la EA. Algunos test de cribado tienen una gran sensibilidad para detectar problemas de memoria en la población general. Por ejemplo, Buschke et al. (1999) desarrollaron el MIS, un test breve de cuatro ítems basado en el aprendizaje controlado y recuerdo facilitado con excelente poder para detectar individuos con alto riesgo de padecer demencia. Siguiendo el mismo paradigma, se han realizado diferentes versiones, como el MIS-S, con palabras para personas de habla española (Böhm et al., 2005), o el Picture Based Memory Impairment Screen (PMIS) (Verghese et al., 2012), una versión pictórica para personas con bajo nivel educativo de habla inglesa (Figura 6).

Figura 6

Ejemplos de las imágenes del PMIS



Nota. Extraído de Verghese et al. (2012). *Picture-Based Memory Impairment Screnn for Dementia. Journal of the American Geriatrics Society, 60(11), 2116–2120. https://doi.org/10.1158/0008-5472.CAN-10-4002.BONE*

Comparado con la población general y atendiendo a estos datos, es evidente la falta de un test de cribado para la detección de problemas de memoria validado en personas con DI en nuestro contexto.

2.3.2 Selección de test

En esta segunda fase de la exploración neuropsicológica es habitual en la práctica clínica diaria, después de la administración de los test de cribado cognitivo, la elección de instrumentos que evalúan una función o la administración de baterías neuropsicológicas amplias.

En población general podemos hallar una elevada cantidad de test que exploran algún ámbito cognitivo específico (Lezak et al., 2012; Spreen & Strauss, 1998), incluso en personas de habla española con demencia avanzada (Salmerón Ríos et al., 2020). En personas con DI de habla española contamos con algunos instrumentos que exploran un dominio específico concreto, que se detallan a continuación.

- ***Tower of London-Drexel University 2nd Edition para personas con DI (TOL^{DXtm} - DI)***

El TOL^{DXtm} -DI (García-Alba et al., 2017) es una modificación a partir del test original TOL^{DXtm} (Culbertson & Zillmer, 2001) para población general. Explora funciones ejecutivas como la planificación, verificación y establecimiento de alternativas en la resolución de problemas. El test se compone de dos piezas de madera, uno para el examinador y otro para el examinado. Cada pieza de madera contiene tres ejes verticales de distinta medida, en los que hay que colocar tres bolas de diferente color (roja, verde y amarilla). Los ítems a resolver son 10 y los movimientos máximos para la resolución de cada uno es de 20, con un tiempo límite de 120 segundos. La versión infantil contempla de 3 a 7 movimientos y la versión de adultos de 4 a 7 para resolver los ítems. Proporciona información sobre los movimientos (correctos y totales) el tiempo (latencia, resolución y total) y las violaciones (tipo I y tipo II, y recuerdo de las instrucciones).

En su adaptación y normalización para personas con SD y niveles de DI leve o moderada, se simplificaron la complejidad de las ejecuciones y se contempló una nueva variable denominada *Hit*, que fueron los ítems resueltos independientemente de los movimientos efectuados. En general, las propiedades psicométricas fueron satisfactorias para todas las variables. Especificamente, fueron fiables para la diferenciación entre sujetos con DI leve y moderada, así como una alta asociación con otras medidas de funciones ejecutivas. Las variables de movimientos correctos y movimientos totales mostraron alta consistencia interna. Se proporcionaron datos normativos para todas las variables, pero la variable de movimientos correctos fue la más aconsejable para determinar el grado de éxito en la ejecución.

– ***Modified cued recall test***

Los test amplios de memoria con ensayos diferidos y de reconocimiento son útiles para detectar cambios (Sano et al., 2011). Específicamente, tanto el Free and Cued Selective Reminding Test (FCSRT) (Buschke, 1984) para población general, como el Cued Recall Test (CRT) (Devenny et al., 2002) para personas con SD, utilizan las técnicas del aprendizaje controlado y selectivamente facilitado optimizando el proceso de codificación (Tulving & Thomson, 1973), especialmente alterado en los estadios iniciales de la EA. Actualmente contamos con los resultados preliminares de una versión pictórica del FCSRT para población general de habla española con DCL y EA (Rodrigo-Herrero et al., 2019), así como para personas con SD (Krinsky-McHale et al., 2022). En este sentido, en nuestro contexto, disponemos del Modified Cued Recall Test (mCRT) (Benejam et al., 2015) para personas con SD y nivel de DI leve y moderada de habla española. Consta de doce dibujos en blanco y negro que se presentan en tres láminas de cuatro estímulos cada una. Cada estímulo representa una categoría semántica

diferente. La administración transcurre mediante un ensayo de aprendizaje, en la que el sujeto debe denominar y señalar el dibujo que pertenece a una categoría semántica que pregunta el examinador. Se retiran los estímulos y se le pide al sujeto que recuerde los estímulos que acaba de denominar. Se sigue la misma mecánica para las otras láminas. La fase de examen consiste en tres ensayos de recuerdo libre y facilitado. Se insta al sujeto a recordar los 12 dibujos denominados, y si no recuerda alguno, se le facilita la clave semántica idéntica a la proporcionada en la fase de aprendizaje. De esta manera se generan tres puntuaciones: recuerdo libre, facilitado y total (recuerdo libre + facilitado). La puntuación máxima es 36. Se ha mostrado sensible en la detección de la fase prodrómicas y de EA (Benejam et al., 2020).

Pero la exploración con estos test en personas con DI se hace lenta y complicada, por eso se necesitan desarrollar test válidos para el cribado de la memoria que puedan ser utilizados en primaria y en servicios de neurología especializados en esta población.

2.3.3 Baterías neuropsicológicas

Las baterías neuropsicológicas avalúan varios dominios cognitivos. El tiempo de aplicación suele ser largo, pero son las más recomendadas para el diagnóstico de demencia en personas con DI (Elliott-King et al., 2016). En personas con DI en nuestro contexto existen dos baterías adaptadas y validadas.

- ***Cambridge examination for mental disorders of older people with Down's syndrome and other intellectual disabilities (CAMDEX-DS)***

La CAMDEX-DS (Ball et al., 2006) ha sido adaptada y validada en personas de habla española con DI (Esteba-Castillo et al., 2013). Este instrumento consta de cuatro apartados:

- *Entrevista CAMDEX-SD*. Se administra al informador o familiar sin la presencia del paciente. Proporciona información recopilada en cuatro áreas básicas: funcionamiento de la persona, deterioro cognitivo y funcional, salud mental y salud física.
- *Cambridge cognitive examination for older adults with Down's syndrome* (CAMCOG-SD). Es la parte cognitiva administrada al paciente y se recogen datos mediante una entrevista clínica, exploración neuropsicológica y observaciones durante la exploración
- *Guía para el diagnóstico clínico.* Permite establecer el diagnóstico diferencial mediante un diagrama de flujo y una lista de comprobación de los criterios diagnósticos según el CAMDEX-SD, la Clasificación Internacional de Enfermedades (CIE-10), décima revisión, y el Manual diagnóstico y estadístico de los trastornos mentales, cuarta edición (DSM-IV).
- *Recomendaciones para la intervención en personas con deterioro cognitivo.* En este apartado se proporcionan pautas generales para desarrollar una correcta intervención en los casos con deterioro cognitivo.

La CAMDEX-SD muestra una buena fiabilidad test-retest (kappa = 0.92 ($p < 0.01$) y una alta concordancia interjueces (kappa = 0.91 ($p < 0.001$). La concordancia entre los criterios diagnósticos del CAMDEX-SD y del DSM-IV (kappa = 0.95 ($p < 0.001$), y de la CIE-10 (kappa = 0.97 ($p < 0.001$) fue elevada. La fiabilidad interna fue también bastante satisfactoria (α de Chronbach = 0.93). Para la personas con DI leve, un punto de corte de 68 en el CAMCOG-SD arrojó una sensibilidad del 80% y una especificidad del 81% en el diagnóstico de deterioro cognitivo. Por su parte, para personas con DI moderada, una puntuación total de 52 mostró una sensibilidad del 85% y una especificidad del 81%). El CAMCOG-SD se ha mostrado como un instrumento sensible

para monitorizar la progresión de EA en sujetos con SD (Paiva et al., 2020; Videla, et al., 2022) y las puntuaciones han mostrado una correlación con los niveles de neurofilamento de cadena ligera (NfL) en plasma y en los niveles de AB1-42, t-tau, p-tau y NfL, tanto en la fase prodrómica como en la fase de demencia (Fortea et al., 2021).

– ***Test Barcelona para personas con discapacidad intelectual***

El Test Barcelona para personas con discapacidad intelectual (TB-DI) (Esteba-Castillo et al., 2017) es una batería de diagnóstico clínico neuropsicológico para personas con DI leve y moderada desarrollada a partir del Programa Integrado de Exploración Neuropsicológica-Test Barcelona (Peña-Casanova, 1991). Consta de siete subtest repartidos en ocho dominios cognitivos: orientación, memoria, memoria de trabajo, lenguaje, praxia, memoria, funciones ejecutivas y visuconstrucción. Su tiempo de aplicación es de dos horas y media. Proporciona datos normativos para DI leve y moderada según la edad y la competencia curricular, permitiendo la selección de subtest para la exploración de diferentes dominios cognitivos, lo que disminuye considerablemente el tiempo de aplicación. La consistencia interna de los subtest es aceptable (α = 0.70 -0.93), con una alta fiabilidad test-retest (α = 0.91) y un acuerdo entre examinadores de 0.95. Aunque no es una batería destinada para el diagnóstico de DCL o demencia, permite detectar cambios que pueden estar asociados al proceso de deterioro. En este sentido, los subtest de orientación temporal, memoria demorada historias y discriminación visual se han mostrado sensibles para detectar cambios que sugieren una transición de la fase de DCL a EA en sujetos con SD (García-Alba et al., 2019).

2.3.4 Cuestionarios de informadores

Las escalas o cuestionarios aplicados a los informadores se usan frecuentemente en el cribado de la demencia en personas con DI (Zeilinger et al., 2022). En nuestro contexto los instrumentos más relevantes se presentan a continuación.

- ***Behavior Rating Inventory of Executive Function, parents' form (BRIEF-P)***

El BRIEF-P (Gioia et al., 2000) es un cuestionario administrado a los padres, cuidadores o tutores que evalúa la función ejecutiva o la autoregulación del sujeto explorado en el entorno. Proporciona dos índices, el Behavior Regulation Index (BRI), que se compone de las escalas relacionada con la inhibición, cambio y control emocional, y el Metacognitive Index (MI), que se calcula a partir de las escalas de iniciar, memoria de trabajo, planificación y monitorización.

Aunque no está adaptado ni validado en personas con DI, destaca su aportación al estudio del DCL en sujetos con SD. En este sentido, se ha podido establecer que una puntuación menor de 32 en el BRI permite clasificar a los sujetos con DCL (Esteba-Castillo et al., 2022).

- ***The informant interview of the Cambridge examination for older adults with Down's syndrome and other intellectual disabilities – version española (CAMDEX-DS)***

Como se ha comentado en el apartado de baterías neuropsicológicas, la parte de la entrevista clínica de la CAMDEX-SD, versión española (Esteba-castillo et al., 2013) se aplica a los familiares o informadores y permite recoger información del deterioro en base al mejor nivel de funcionamiento del sujeto, teniendo en cuenta los aspectos cognitivos, mentales, físicos y de funcionalidad diaria.

2.3.5 Escalas clínicas evolutivas de la gravedad del deterioro cognitivo

En la práctica clínica se hace imprescindible cuantificar la evolución del cuadro de deterioro y establecer el estado del proceso. Aunque no exista una escala válida en todos los casos debido a la diversidad etiológica, clínica y evolutiva de las demencias, la Clinical Dementia Rating (CDR) (Hughes et al., 1982) y la Global Deterioration Scale (GDS) (Reisberg et al., 1982) son las más utilizadas debido a que conjugan aspectos cognitivos y funcionales.

– ***Clinical Dementia Rating (CDR)***

La CDR diferencia cinco estados de la enfermedad desde la normalidad (CDR = 0) hasta la demencia grave (CDR = 3). Los estadios se concretan mediante seis áreas: memoria, orientación, juicio y capacidad de resolución de problemas, actividades sociales, actividades domésticas y aficiones, cuidado y aseo personales. La afectación de la memoria es la condición *sine qua non* que determinará el estadio general. La CDR no se ha mostrado eficaz en el diagnóstico de DCL por sí sola (Woolf et al., 2016).

Su correcta aplicación requiere de unos 30-40 minutos, pues consta de una entrevista clínica estructurada con el informador y con el paciente. Además, no considera áreas de conducta ni de lenguaje, omitiendo así dos síntomas importantes en el continuo de demencia (Mioshi et al., 2017). Ha sido adaptada para personas con SD (Lessov-Schlaggar et al., 2019), basándose en la información de cuestionarios y entrevistas con los familiares, cuidadores o tutores.

– ***Escala global de deterioro (GDS)***

Por su parte, la GDS permite graduar la evolución del proceso de demencia, especialmente diseñada para la EA (Tabla 9).

La GDS se complementa con la escala Functional Assessment Staging (FAST)

(Reisberg, 1988), que consta de siete fases que detallan el deterioro funcional.

Ambas escalas constan de siete estadios, pero a partir de la fase 6 de la escala FAST se subdivide en estadios que van des de la normalidad (GDS 1) hasta la demencia avanzada (GDS 7).

Su tiempo de aplicación es bastante menor que la aplicación de la CDR, y la fase se determina a partir de pruebas cognitivas, la entrevista con los familiares y la observación clínica. La GDS se correlaciona con los rendimientos de las exploraciones neuropsicológicas y de neuroimagen, así como con la progresión del envejecimiento cerebral normal a las etapas de DCL y EA (Reisberg et al., 1988). Se han propuesto unas determinadas puntuaciones orientativas del Mini Examen Cognoscitivo (MEC) (Lobo et al., 1979) para cada estadio de la GDS (Tabla 9).

Tabla 9

Estadios de la GDS y equivalencias con la puntuación del MEC

Estadio	Déficit cognitivo	Fase clínica	MEC
GDS 1	Inexistente	Sin deterioro subjetivo ni objetivo	30-35
GDS 2	Muy leve	Deterioro cognitivo subjetivo	25-30
GDS 3	Leve	Deterioro Cognitivo Leve	20-27
GDS 4	Moderado	Demencia leve	16-23
GDS 5	Moderadamente grave	Demencia moderada	10-19
GDS 6	Grave	Demencia moderadamente grave	0-12
GDS 7	Muy grave	Demencia grave	0, impracticable

Nota. MEC = Mini Examen Cognoscitivo, GDS = Global Deterioration Scale.

En nuestro contexto, es la escala propuesta para determinar el inicio y la interrupción de la intervención farmacológica, siguiendo las directrices del Pla d'Atenció Sanitària a les Persones amb Deteriorament Cognitiu Lleu i Demencia a Catalunya (PLADEMCAT) (Bullich et al., 2022), y de la Societat Catalana de Neurologia (SCN) (Bello López et

al., 2015). Dado que la GDS es específica para contemplar el curso de deterioro de la EA, cobra especial relevancia disponer de la GDS adaptada y validada en sujetos con SD por su alto riesgo para la EA.

Objetivos e hipótesis

3. OBJETIVOS E HIPÓTESIS

El objetivo general de la presente tesis fue adaptar y validar dos instrumentos para su aplicación en personas de habla española y catalana con discapacidad intelectual leve y moderada: uno para detección rápida de problemas de memoria asociados al deterioro cognitivo y EA, y otro para la caracterización de las fases clínicas de la EA en personas con SD.

A partir de este objetivo general se desprenden los siguientes objetivos específicos:

1. Adaptar el Picture-Based Memory Impairment Screen (PMIS) (Verghese et al., 2012) en personas con DI **(Estudio 1).**
2. Proporcionar datos normativos y de validez discriminativa del nuevo instrumento (PMIS-DI) para la detección de problemas de memoria asociados al DCL y EA en personas con DI (**Estudio 1).**
3. Adaptar la Global Deterioration Scale (GDS) (Reisberg et al., 1982) en personas con SD (GDS-SD) **(Estudio 2).**
4. Anclar el rendimiento en los test neuropsicológicos y de conducta aplicados a los participantes a cada estadio de la GDS-SD (**Estudio 2).**

Se plantearon las siguientes hipótesis:

- Es factible utilizar un test breve de cribado para detectar los problemas de memoria asociados al deterioro cognitivo leve y enfermedad de Alzheimer en personas con discapacidad intelectual **(Estudio 1).**
- Se podrán proporcionar datos normativos diferentes para personas con discapacidad intelectual leve y moderada con deterioro cognitivo leve y enfermedad de Alzheimer **(Estudio 1).**
- Es posible adaptar una escala global de deterioro para el continuo de la

enfermedad de Alzheimer para personas con síndrome de Down **(Estudio 2).**

- Los instrumentos neuropsicológicos y de conducta aplicados mostrarán un descenso progresivo a través de los estadios de la GDS-SD **(Estudio 2).**

Publicaciones

4. PUBLICACIONES

Estudio número 1

The Pictorial Screening Memory Test (P-MIS) for Adults with Moderate Intellectual Disability and Alzheimer's Disease

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The Pictorial Screening Memory Test (P-MIS) for Adults with Moderate Intellectual Disability and Alzheimer's Disease

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Abstract: In this study, we examined normative data and diagnostic accuracy of a pictorial screening test to detect memory impairment for mild cognitive impairment (MCI) and Alzheimer's disease (AD) in Spanish-speaking adults with intellectual disability (ID). A total of 94 volunteers with ID (60 controls, 17 MCI, and 17 AD), were evaluated by neuropsychological tests including the PMIS-ID in a cross-sectional validation study. Discriminative validity between the MCI, AD, and control group was analyzed by the area under the ROC curve. A cut-off score of 4.5 on the immediate recall trial had a sensitivity of 69% and a specificity of 80% to detect memory impairment (AUC = 0.685; 95% CI = 0.506–0.863) in the AD group. The PMIS-ID is a useful screening test to rule out a diagnosis of memory decline in people with moderate level of ID and AD, and it shows good psychometric properties.

Keywords: screening; memory; mild cognitive impairment; Alzheimer's disease; dementia intellectual disability

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1. Introduction

Intellectual disability (ID) is a neurodevelopment disorder affecting intellectual functioning and adaptive behavior [1]. Globally, the prevalence of ID varies between 0.05 and 1.55% [2]. The underlying health conditions and the increased life expectancy of this population makes them more vulnerable to developing mild cognitive impairment (MCI) and dementia [3,4]. Although the epidemiological data of MCI and dementia in people with ID without Down's syndrome (DS) has not been accurately set, recently, in Japanese people, the prevalence data for MCI hovers around 3% from the age of 45 onwards, and from 0.8% to 13.9% in those aged between 45 and 74 years old for dementia [5].

There is increasing evidence of a link between neurodevelopment disorders as ID and dementia [6]. Specifically, Alzheimer disease (AD) is the most common syndrome of dementia in DS [7], with incidence rates from 75% to 100% in those aged 60 and older [8]. Beyond DS, people with autism spectrum disorder (ASD) with ID are also at high risk for developing early onset AD (EOAD) [9], and ASD behaviors may be present in geriatric people with MCI and AD without ID [10]. Cerebral palsy (CP) by itself increases the risk of EOAD and related dementias [11], having an accelerated aging that predisposes patients to MCI and AD [12]. Based on these facts, certain ID conditions increase the risk of suffering AD. Therefore, early detection of MCI and AD in people with ID is required to implement appropriate interventions on the optimal therapeutic window.

It is well-known that identifying MCI or AD in people with ID poses a challenge to clinicians. Strengths and weaknesses of the cognitive and behavioral phenotype of each etiology must be taken into account when considering changes that may herald MCI

or dementia in aging [13]. Therefore, some studies try to cognitively characterize the stages of MCI and AD in ID population. In people with mild or moderate levels of ID and unspecified etiology, decline in orientation questions and depressive symptoms [14] or decline in memory measured by a paired-learning task [15] have been found. By the Dementia Questionnaire for Mentally Retarded People [16], memory and orientation were altered [17]. Furthermore, cognitive decline is similar between people with ID and the general population with AD [18], exhibiting difficulties in learning and visuoverbal memory, semantic verbal fluency, and attention/executive functions, measured with the Fuld Object-Memory Evaluation [19], the Controlled Oral Word Association Test [20], and the Color Trail Test [21], respectively. In people with moderate and severe levels of ID, significantly lower scores were found in autobiographical memory and orientation in people with AD compared to healthy people [22]. In this same work, performance on a modified Objective Memory Test was lower in the group with AD, but only in the immediate recognition trial and in both immediate and delayed memory subtests of a Picture Recognition Test, a visuoverbal learning and memory test developed for the purpose of their work, that has proven able to detect memory troubles in people with moderate and severe levels of ID and DS [23]. Despite the different etiologies studied, memory decline arises as a common factor associated with MCI or AD.

As AD is the most common form of dementia and it is especially linked with DS, the majority of studies focused on this population have used cognitive measures. In this sense, a recent study of functional brain connectivity in people with DS [24] showed that low scores on the Cambridge Cognitive Examination for Older Adults with Down's Syndrome (CAMCOG-DS) Spanish version [25] and decreased performance in verbal and visual memory appear to be key indicators of MCI and AD. Also, a slight impairment in delayed verbal and visual memory could be considered as a potential cognitive marker of MCI, with an increase in memory deficit in AD stage [26,27]. However, more important is the proposal model for MCI diagnosis in which decline or change in the Behaviour Regulaltion Index (BRI) from the Behaviour Rating Inventory of Executive Function-Informant's Report (BRIEF) [28], and in the delayed verbal and visual memory domains from the Barcelona Test for Intellectual Disability (TB-DI) [29] are good predictors for MCI diagnosis [30]. Upon collecting these data, it is evident that memory declines across the AD continuum. Hence, there is a need to develop sensitive and screening test for daily clinical practice to detect memory changes associated with MCI or AD in this population.

Memory tests including a delayed recall trial are useful to detect longitudinal changes [31], as are recognition trials that improve the sensibility to detect retrieval alterations [32]. The word-based Free and Cued Selective Reminding Test (FCSRT) [33] for the general population and the pictorial Cued Recall Test (CRT) [34] for people with DS are tests with controlled learning techniques to optimize the coding processes [35] that are specially altered in the early stage of AD. It is well-known that scores of word and pictorial versions are not equivalent [36,37], although it is suggested that poor results in the free recall essay are associated with a reduction of the hippocampal volume in both tests [38]. As of today, a few screening tests are available that yield robust data with high accuracy in detecting memory deficits in the general population. For instance, the Memory Impairment Screen (MIS) [39] is a brief tool of four items that controls learning and cued recall, providing excellent properties to detect individuals at higher risk to develop AD. Different MIS-based versions are currently available, such as the Picture-Based Memory Impairment Screen (PMIS) [40], with four pictorial stimuli for English people with low levels of education. A Spanish pictorial memory test is also available that reports preliminary results for the general population with amnesic MCI and AD [41], as well as for people with DS [42]. When compared to the general population, there is no picture memory screening test available for Spanish people with ID. Furthermore, the administration of the available tests is hard to acquire for people with ID and time is short for routine appointments. Clearly, there is a need to develop valid memory screening tests suitable for primary care and specialized services in this population.

In light of these facts, the main aims of the current study were (a) to adapt the PMIS [40] for people with ID, (b) to provide normative data, and (c) to assess its feasibility as a screening tool for memory decline to discriminate healthy ID subjects from those with amnestic impairment typical of MCI or AD.

2. Materials and Methods

2.1. Participants

We undertook a prospective single-center cross-validation study with a convenience sample from December 2017 to December 2018. A total of 116 subjects recruited from the Specialized Service in Mental Health Unit for Adults with ID (SESM-DI, Parc Hospitalari Martí i Julià, Girona, Spain) were identified. All the participants were 18 years old or older, with a mild or moderate level of ID according to DSM-5 criteria (5th ed.; DSM-5) and with no drug treatment that could had significant effects on cognition. Those showing psychiatric or neurological conditions that could cause a dementia-like presentation or cognitive decline (depression, clinical hypo/hyperthyroidism, uncontrolled B9/B12 vitamin deficiency, seizures, delirium) and uncorrected auditory or visual sensory impairment that would make a neuropsychological assessment impossible were excluded. Of the subjects selected, 12 did not agree to participate in the study, 4 were excluded due to an absence of expressive language, and 6 more were excluded due to non-stable medical conditions at the moment of the assessment. The final sample consisted of 94 adults with ID (mean age = 47.33 ± 5.18 years; males = 57.4%, females = 42.6%) due to different etiology (54 Down's syndrome, 4 tuberous sclerosis, 4 fragile X syndrome, 2 cerebral palsy, and 30 unknown). The baseline level of at least one year of all participants was available through annual follow-up in our service, in which most of the cognitive and functional tests that are part of the present study are routinely administered. The sample was divided into three groups: CN group (subjects without symptoms of MCI or AD), MCI group (subjects fulfilling criteria for MCI diagnosis), and AD group (subjects with AD diagnosis). The diagnosis of MCI or AD was based on expert multidisciplinary clinical judgment according to recent publications [27,30,43–46]. The diagnosis of MCI was made when participants presented a single or multiple cognitive decline(s) without significant functional loss. On the other hand, the diagnosis of AD was made in participants with memory decline and another cognitive impairment as aphasia, apraxia, agnosia, or disexecutive syndrome, and loss of functionality. In both conditions, changes from previous level of performance had to be supported by information obtained from a close caregiver [27,43,45].

The CN group included 60 subjects (47.47 ± 5.78 years; males = 65%, females = 25%) and was used to obtain normative data of the PMIS-ID. Both the MCI group, composed of 17 subjects (45.76 ± 4.22 years; male = 47.05%, females = 52.95%), and the AD group, composed of 17 subjects (48.41 ± 3.34 years; males = 41.18%, females = 58.52%), were used to gain the diagnostic accuracy properties of the PMIS-ID.

2.2. Instuments

Each participant underwent a comprehensive clinical and neuropsychological assessment. A neuropsychologist administered a large cognitive evaluation and informed-based measures during three different sessions.

2.2.1. To Detect ID Level

- Kaufman Brief Intelligence Test manual, second edition (K-BIT-2) [47];
- Vineland Adaptive Behaviour Scales-Second Edition (Vineland II) [48];

2.2.2. Neuropsychological Assessment with Cognitive Tools Adapted and Validated for ID Spanish-Speaking Population

- Barcelona Test for people with Intellectual Disability (TB-DI) [29]. This neuropsychological test battery consists of different subtests related to eight cognitive domains (language, working memory, orientation, praxis, attention, executive function, visuo-

construction, and memory). For this study, orientation and verbal learning were used (internal consistency of $\alpha = 0.87$ and $\alpha = 0.73$, respectively);

- CAMCOG-DS Spanish version [25]. This is the cognitive assessment module of the CAMDEX-DS Spanish version. It covers different cognitive domains mainly memory. For this study, memory subtests were used (new learning, remote, recent and memory total score).
- Picture Memory Impairment Screen for people with Intellectual Disability (PMIS-ID). It was applied at the beginning of the cognitive exam to mitigate the possible interferences with the rest of the tests.

2.2.3. Parents Interview

- Cambridge Examination for Mental Disorders of Older People with Down's syndrome and Others with Intellectual Disabilities (CAMDEX-DS) Spanish version [25]. It consists of a structured informant-based interview, cognitive evaluation, diagnostic criteria guide, and recommendations for the interventions. The Spanish version presents an internal consistency of $\alpha = 0.93$, considering performance on the memory subtest of the cognitive form and the memory section of the informant interview.

2.2.4. Picture Memory Impairment Screen for People with Intellectual Disability (PMIS-ID)

The PMIS-ID consists of four-color photographs semantically unrelated in each quadrant of a DIN-A4 sheet. It includes four distinct parts: Identification (I), Learning (L), Immediate Recall (IR), and Delayed Recall (DR).

In the I and L parts, a sheet with four different categories of photographs (*horse*, *ludo*, *sofa*, *cherry*) is presented to the subject who has to name each one. Afterwards the subject has to identify them according to a cue (category) provided by the examiner (*animal*, *board game*, *fruit*, *furniture*). If the subject does not recognize or identify a photograph, the administration is ruled out. If items are correctly identified, the sheet is removed and the subject is told that they will be asked to repeat the words in a short time. Exploration must go on with another non visuoverbal task.

After three minutes, in the IR part, the participant is asked to recall the name of the four photographs (Immediate Free Recall, IFR). If any of the four items is missed, the examiner provides a category cue [Immediate Cued Recall (ICR)]. In case of failure, the target stimulus and two more distracters of an equal semantic category are orally provided (*cherry*, *pear*, *kiwi*; *goose game*, *cards*, *ludo*; *table*, *sofa*, *chair*; *horse*, *cow*, *tiger*) and the subject has to detect the right stimulus [Immediate Recognition (IRC)]. Correct stimulus has to be provided again if failure persisted. Finally, after twenty minutes, the DR part is administered, with the same tasks as in the IR part: Delayed Free Recall (DFR), Delayed Cued Recall (DCR) and a Delayed Recognition Recall (DRC).

The scores are calculated as two points for each correct response in FR, one point for each one in CR task, and 0.5 point in the RC. Immediate Total Recall (ITR) and Delayed Total Recall (DTR) are calculated separately (FR scores + CR scores + RC scores) of the FR, the CR and the RC parts. Total PMIS-ID (TPMIS-ID) score (0–16) is the sum of ITR and DTR, both ranging from 0 to 8.

- PMIS-ID adaptation

The PMIS test [40] was adapted by: (1) introducing different items and categories suitable for people with mild and moderate ID; (2) translating the instructions with easiest vocabulary; (3) introducing Delayed Recall (DR) and Recognition (RC) tasks both for the Immediate Recall (IR) and Delayed Recall (DR) trials; and (4) by implementing a new scoring system. The numbers of items were consistent with the original version. An iterative procedure in line with practices recommended by Muñiz, Elosua, and Hambleton (2013) was followed, considering the particularity of this memory visuoverbal test. A pool of 12 color photographs belonging to four different semantic categories according to Spanish typicality norms were extracted [49,50]. To provide the sufficient complexity and avoid the ceiling effect, six stimuli corresponded to the first third while the other six to the second

third of the total responses by category. The photographs were shown to 30 volunteers with mild and moderate ID (men age 43.8 ± 3.55; males = 55%; females = 45%) who were not enrolled in the validation study. Then, stimuli were reduced to the four most recognized and the remaining ones were introduced as distracters for the recognition task. Two native-English specialized psychologists in ID translated the test instructions. The two versions were discussed by the research team. An independent English linguist completed the back-translation of the document. Finally, a neurologist and a speech therapist reviewed the process and agreed to a pre-final version. The pre-final version was rounded off to implement further modifications during a pilot test in the same sample for the stimuli selection phase. During test administration, the examiner controlled the execution time and also checked the comprehension of the instructions, asking the volunteer to repeat and to explain them with their own words. The PMIS-ID was applied again in a convenience subsample of 20 participants within four weeks to assess test–retest reliability and in another 20 participants by two different examiners (SEC, ERH) to assess inter-rater reliability.

2.3. Data Analysis

The working database includes entries from February to December 2018. A descriptive analysis was applied to the entire group sample to describe the demographic variables (age and sex), the ID level, and performance on the cognitive protocol (TB-DI memory and orientation, CAMCOG-DS memory subtest). Due to the small sample size in some subgroups, a nonparametric statistical analysis was conducted. Means comparisons were made by independent samples t-test or ANOVA for qualitative data, and χ^2-test for category data. These data were presented as median and interquartile range (IQR) and were compared by Kruskal–Wallis test with Bonferroni adjustment. Multiple linear regression analysis was used to verify the possible influence of sociodemographic variables (age, sex) and the level of ID (mild, moderate) on the PMIS-ID immediate total score, delayed total score, and total score. Reliability was estimated by the test–retest and inter-rater methods and by calculating Pearson and intraclass correlation coefficients, respectively. For the MCI and AD groups, a descriptive analysis was applied for the sociodemographic variables (age, sex, and ID level). Construct validity of the PMIS-ID was verified using the coefficient corrected kappa statistic between the PMIS-ID total score and MCI and AD groups. Spearman's rho was run to evaluate convergent validity between the PMIS-ID total score and the memory subtest performance of the TB-DI and the CAMCOG-DS. Normative data was presented in line of the assumption of the MCI or AD prevalence (%) for the different PMIS-ID cut-scores (PPV and NPV). Receiver operating characteristic curve (ROC) and the Youden index were used to determine the optimal cut-off point of the PMIS-ID (immediate, delayed, and total scores) as a screening memory test for MCI or AD. The areas under the curve (AUC) were compared between the different trials [51].

All statistical analyses were conducted using the software program G-Stat (version 2.0) and the statistical software program SPSS (version 27.0; SPSS Inc., Chicago, IL, USA). Bilateral significance levels were set at a p-value of less than 0.05.

3. Results

3.1. Demographics

Results in Table 1 shows that the CN group was similar to the MCI and AD groups in mean age ($p = 0.315$), level of ID ($p = 0.159$), and sex distribution ($p = 0.136$).

Table 1. Demographic characteristics and cognitive performance by group.

	Control	MCI	AD
n	**60**	**17**	**17**
Age	47.47 ± 5.78 (40–60)	45.76 ± 4.22 (42–55)	48.41 ± 3.34 (43–54)

Table 1. *Cont.*

	Control	MCI	AD
n	**60**	**17**	**17**
SEX			
Male	39 (65%)	8 (47.06%)	7 (41.18%)
Female	21 (35%)	9 (52.94%)	10 (58.82%)
ID LEVEL			
Mild	32 (46.67%)	10 (58.82%)	5 (29.41%)
Moderate	28 (53.33%)	7 (41.18%)	12 (70.59%)
TB-DI			
Verbal learning	26.7 (20–33.5)	24.4 (16–31)	17.6 (9–24) ***
Delayed free recall	4.7 (2.5–7)	3.6 (0–6)	1.6 (0–3) ***
False positives	3.5 (0–6.5)	6.1 (1–12) *	8.5 (4–12) ***
Delayed word recognition	10.2 (10–12)	11.4 (12–12)	10.6 (10–12)
CAMCOG-DS			
New learning	13.5 (11–16)	11.5 (8–15)	8.8 (7–11) ***
Remote	2.7 (2–4)	2.6 (2–4)	1.5 (0–2) ***
Recent	2.6 (2–4)	1.9 (1–3)	0.9 (0–2) ***
Memory total	18.8 (15–23)	16.1 (11–21)	11.2 (9–15) ***

Values are given by means and range; sex in percentages for each group. ID, intellectual disability; TB-DI, Barcelona Test for People with Intellectual Disability; CAMCOG-DS, Cambridge Examination for Mental Disorders of Older People with Down's Syndrome and Others with Intellectual Disability (brief neuropsychological battery); MCI, mild cognitive impairment; AD, Alzheimer's disease. * $p < 0.05$, *** $p < 0.001$, using Kruskal–Wallis with Bonferroni correction or χ^2-test for category data between MCI and AD groups compared with the control group.

3.2. Between-Group Comparison of Cognitive Performance

Compared to the CN group, the scores were significantly lower for the AD group on verbal learning, delayed free recall subtest, and false positive scores of the TB-DI and on new learning, remote, recent, and memory total score subtest of the CAMCOG-DS. Performance on the subscales of both tests was similar between the MCI and CN groups (Table 1).

In people with mild ID, the performance of the CN and MCI groups was similar on the entire subtest. Between the CN group and AD group, significant differences were shown in performance on verbal leaning, delayed free recall, and false positives of the TB-DI. No significant differences were observed on the subtests of the CAMCOG-DS (Table 2).

Table 2. Cognitive scores by group for mild intellectual disability sample.

	CN	MCI	AD
n	**32**	**10**	**5**
TB-DI			
Verbal learning	31.2 (26–36)	26 (17–33)	20 (17–24) **
Delayed free recall	5.9 (4–8)	3.8 (0–7)	1.8 (1–3) **
False positives	2.2 (0–3)	4.2 (1–9)	6.8 (3–12) *
Delayed word recognition	10.5 (10–12)	10.9 (9–12)	11.2 (10–12)
CAMCOG-DS			
New learning	14.2 (12–16)	12.6 (9–15)	11.8 (10–11)
Remote	2.9 (2–4)	2.9 (2–4)	2.2 (2–3)
Recent	2.9 (2–4)	2.2 (1–4)	1.4 (0–2)
Memory total	19.9 (17–23)	17.7 (13–21)	15.4 (11–19)

Values are given by means and range. TB-DI, Barcelona Test for People with Intellectual Disability; CAMCOG-DS, Cambridge Examination for Mental Disorders of Older People with Down's Syndrome and Others with Intellectual Disability (brief neuropsychological battery); CN, control group; MCI, mild cognitive impairment; AD, Alzheimer's disease. * $p < 0.05$, ** $p < 0.01$, using Kruskal–Wallis with Bonferroni correction between MCI and AD groups compared with the control group.

In people with moderate ID, no significant differences were observed between the CN group and the MCI group on all the subtests. Significant differences were observed on the false positives score, and no significant differences but moderate decline were observed on verbal learning and delayed free recall subtests of the TB-DI. Significant differences were observed on new learning, remote, recent, and memory total score of the CAMCOG-DS (Table 3).

Table 3. Cognitive scores by group for moderate intellectual disability sample.

	CN	MCI	AD
n	**28**	**7**	**12**
TB-DI			
Verbal learning	21.5 (17–26)	22.1 (15–24)	16.6 (4.5–24)
Delayed free recall	3.3 (1–4)	3.4 (0–6)	1.6 (0–2)
False positives	4.9 (0–10)	9.3 (6–12)	8.9 (3–12) **
Delayed word recognition	9.9 (7.5–12)	12 (12–12)	10.4 (10–12)
CAMCOG-DS			
New learning	12.8 (11–15)	10 (5–13)	7.6 (4.5–11) ***
Remote	2.6 (2–4)	2.3 (2–3)	1.3 (0–2) **
Recent	2.3 (0.5–4)	1.6 (0–2)	0.7 (0–2) **
Memory total	17.5 (15–21)	13.9 (9–18)	9.5 (5.5–13) ***

Values are given by means and range. TB-DI, Barcelona Test for People with Intellectual Disability; CAMCOG-DS, Cambridge Examination for Mental Disorders of Older People with Down's Syndrome and Others with Intellectual Disability (brief neuropsychological battery); CN, control group; MCI, mild cognitive impairment; AD, Alzheimer's disease. ** $p < 0.01$, *** $p < 0.001$, using Kruskal–Wallis with Bonferroni correction between MCI and AD groups compared with the control group.

3.3. Between-Group Comparison of PMIS-ID Performance

The AD group performance differs from the CN group on free recall and total scores from both immediate and delayed part, as well as on the total PMIS-ID score, whereas the performance of the MCI and CN groups was similar on all the trials (Table 4). Analyses according the ID level show that these differences were valid for adults with a moderate level of ID, but not for those with mild ID (Table 5).

Table 4. PMIS-ID descriptive scores by group.

	CN	MCI	AD
n	**60**	**17**	**17**
Immediate			
Free recall	4 (3–4)	3 (2–4)	2 (0–4) **[a]
Cued recall	0 (0–1)	0 (0–1)	0 (0–1)
Recognition	0 (0–0)	0 (0–0)	0 (0–1)
Total	8 (7–8)	7 (6–8)	6 (2.5–8) **[a]
Delayed			
Free recall	4 (3–4)	3 (0–4) *[b]	0 (0–3) ***[a]
Cued recall	0 (0–1)	0 (0–1)	1 (0–2)
Recognition	0 (0–0)	0 (0–1)	0 (0–1)
Total	7.5 (6.5–8)	7 (2.5–8)	3.5 (1–6.5) ***[a]
Total PMIS-ID	15 (11.8–16)	13 (9.5–16)	10.5 (4–13) **[a]

Median (first quartile–third quartile) for each variable is summarized. PMIS-ID, Picture Memory Impairment Screen for People with Intellectual Disability; CN, control group; MCI, mild cognitive impairment; AD, Alzheimer's disease; [a] Between CN and AD group. [b] Between MCI and AD group. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ using Kruskal–Wallis with Bonferroni correction between MCI and AD groups compared with the control group.

Table 5. PMIS-ID descriptive scores by group and level of intellectual disability.

	Mild ID			Moderate ID		
	CN	**MCI**	**AD**	**CN**	**MCI**	**AD**
n	**32**	**10**	**5**	**28**	**7**	**12**
Immediate						
Free recall	4 (3–4)	4 (2–4)	2 (1–4)	4 (3–4)	3 (0–4)	1.8 (0–3.5)
Cued recall	0 (0–1)	0 (0–1)	1 (0–2)	0 (0–1)	0 (0–1)	0 (0–1)
Recognition	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–1)	0 (0–1)
Total	8 (7–8)	8 (6–8)	6 (3.5–8)	8 (7–8)	6.5 (0.5–8)	5.2 (1.3–7.5) *ab
Delayed						
Free recall	4 (3–4)	4 (2–4)	2 (1–4)	3 (2–4)	0 (0–3)	0 (0–2.5) **a
Cued recall	0 (0–1)	0 (0–1)	1 (0–1)	0 (0–1)	1 (0–2)	0.5 (0–2)
Recognition	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–1.5)	0.3 (0–1)
Total	8 (7–8)	8 (6–8)	5 (3–8)	7 (3.5–8)	2.5 (1–7)	0.3 (0–6.3) **a
Total PMIS-ID	16 (14–16)	15.5 (12–16)	11 (6.5–16)	14 (11–16)	10 (1–13.5)	10.5 (1.3–12.3) **a

Median (first quartile–third quartile) for each variable is summarized. PMIS-ID, Picture Memory Impairment Screen for People with Intellectual Disability; ID, intellectual disability; CN, control group; MCI, mild cognitive impairment; AD, Alzheimer's disease. [a] Between CN and AD group. [b] Between MCI and AD group. * $p < 0.05$, ** $p < 0.01$, using Kruskal–Wallis with Bonferroni correction between MCI and AD groups compared with the control group.

3.4. Analysis of Control Group

To study the demographics and level of ID impact on the PMIS-ID scores, a multiple linear regression analysis for the PMIS-ID immediate total score ($r2adj = 0.032$; $F = 1.006$; $p = 0.397$), delayed total score ($r2adj = 0.515$; $F = 1.102$; $p = 0.356$), and total score ($r2adj = 1.357$; $F = 1.271$; $p = 0.293$) was performed for the CN group. Neither the level of ID (immediate: $t = -1.523$, $p = 0.133$, $B = -0.615$; delayed: $t = -1.419$, $p = 0.161$, $B = -0.895$; total: $t = -1.509$, $p = 0.069$, $B = -1.509$) nor the age (immediate: $t = -1.078$, $p = 0.286$, $B = 0.0.38$; delayed: $t = -0.689$, $p = 0.494$, $B = -0.037$; total: $t = -0.001$, $p = 0.999$, $B = -0.001$) nor sex (immediate: $t = -0.602$, $p = 0.549$, $B = -0.615$; delayed: $t = -0.350$, $p = 0.7274$, $B = -0.222$; total: $t = -0.568$, $p = 0.572$, $B = -0.466$) were significantly related to the PMIS-ID total scores. Hence, no adjustment of the PMIS-ID total scores was required.

3.5. Reliability

The Pearson's correlation coefficient for the total PMIS-ID score was 0.90 ($p < 0.0001$), a very strong test–retest association. The inter-examiner agreement was found to be good, with a mean intra-class correlation coefficient (ICC) of 0.96 ($p < 0.0001$).

3.6. Validity

3.6.1. Convergent Validity

The correlations patterns between the PMIS-ID total score for the whole sample and by level of ID and the TB-DI and CAMCOG-DS subtest are displayed in Table 6.

Considering the total sample, the overall correlations were significant. For the mild ID sample, the total score of the PMIS-ID was low but positive in correlation with the verbal learning and delayed free recall subtest of the TB-DI and with the new learning ant total memory score of the CAMCOG-DS. In the moderate sample, satisfactory positive correlations were found between verbal learning and delayed free recall subtest of the TB-DI, and new learning, recent, and total memory score subtest of the CAMCOG-DS. Low negative correlation was found between false positives score of the TB-DI and total PMIS-ID total score. Weak positive and negative correlations were found for the other subtest of both sample and the PMIS-ID total score.

Table 6. Convergent validity values by groups.

	PMIS-ID Total Score		
	Total	**Mild ID**	**Moderate ID**
TB-DI			
Verbal learning	0.622 **	0.409 **	0.665 **
Delayed free recall	0.549 **	0.381 **	0.558 **
False positives	−0.459 **	−0.216	−0.522 **
Delayed word recognition	−0.215 *	−0.138	−0.289 *
CAMCOG-DS			
New learning	0.688 **	0.519 **	0.763 **
Remote	0.395 **	0.182	0.398 *
Recent	0.454 **	0.186	0.560 **
Total memory	0.679 **	0.481 **	0.743 **

TB-DI, Barcelona Test for People with Intellectual Disability; CAMCOG-DS, Cambridge Cognitive Examination Adapted for Individuals with Down Syndrome; PMIS-ID, Picture Memory Impairment Screen for People with Intellectual Disability; ID, intellectual disability. * $p < 0.05$, ** $p < 0.01$ (two-tailed test), using Spearman's correlation coefficient.

3.6.2. Discriminative Validity

Three ROC curves for each total PMIS-ID trial with enough discriminatory power between CN and AD groups with moderate ID were plotted (Figure 1) and comparisons between AUCs were calculated (Table S1 of the Online Supplement). The AUCs to discriminate between CN and AD groups had good diagnostic utility. For immediate total recall (ITR), the AUCs were 0.685 (CI 95%: 0.506–0.863) and 0.757 (CI 95%: 0.612–0.903) for the total delayed recall (TDR) and 0.749 (CI 95%: 0.597–0.901) for the TPMIS-ID. Paired comparison of the AUCs of the three totals scores were not statistically significant ($z = -0.842$, $z = -1.021$, $z = 0.229$). Hence, immediate total recall (ITR) was the best and most time-efficient trial for our purpose.

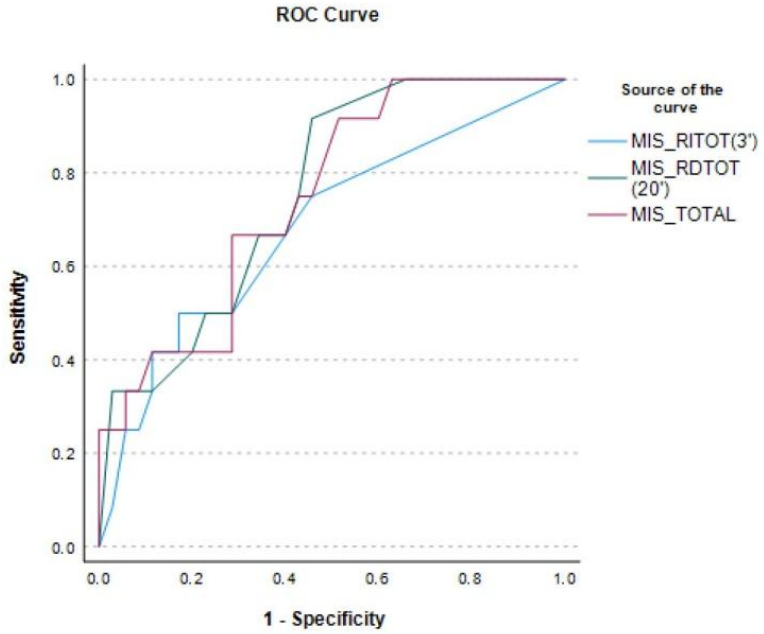

Figure 1. Receiver operating characteristics (ROC) of the PMIS-ID as a screening memory tool for AD in people with a moderate level of ID.

3.7. Normative Data

The values of sensitivity, specificity, positive likelihood ratio (+ LR), negative likelihood ratio (−LR), and the Youden indexes for various cuts-off scores of the PMIS-ID for the AD group with mild and moderate level of ID were calculated. For the group with moderate level of ID, the delayed and total recall trials normative data are presented in Tables S2 and S3 of the Online Supplement, and for the immediate recall (IR) in Table 7. Data for the sample with mild ID and AD is presented in Tables S4–S6 of the Online Supplement. Considering that the base rate in the moderate ID sample was 25.5%, for the immediate total recall (ITR), a cut-off score of ≤4.5 provided a moderate sensitivity (69%) and a high level of specificity (80%).

Table 7. Normative data of the PMIS-ID immediate total score for different cut-off points for AD in moderate level of ID sample.

Cut-Off Points	S	Sp	*J*	PPV [a]	NPV [a]
0	0.00	1.00	0.00	0.64	1.00
0.5	0.31	1.00	0.31	0.67	1.00
1	0.50	1.00	0.50	0.71	1.00
1.5	0.50	1.00	0.50	0.72	1.00
2	0.50	0.86	0.36	0.72	0.94
2.5	0.50	0.96	0.46	0.74	0.94
3	0.56	0.96	0.52	0.76	0.94
3.5	0.56	0.90	0.46	0.74	0.84
4	0.62	0.90	0.52	0.76	0.84
4.5	0.69	0.86	0.55	0.76	0.80
5.5	0.69	0.83	0.52	0.75	0.76
6.5	0.75	0.79	0.54	0.74	0.73
7.5	0.87	0.62	0.49	0.78	0.59
8	1	0.00	0.00	1.00	0.36

MIS-ID, Picture Memory Impairment Screen for People with Intellectual Disability; S, sensitivity; Sp, specificity; *J*, Youden's J statistic; PPV, positive predictive values; NPV, negative predictive values. [a] 25.5% is the prevalence of AD in the sample.

4. Discussion

This is the first validation study of a pictorial screening memory test for people with ID, providing normative data and assessing its diagnostic utility to detect memory decline. The PMIS-ID demonstrates good discriminant validity for distinguishing between people with moderate ID and AD from healthy population with ID, and exhibits good convergence validity and reliability.

Our results show that it is possible to detect memory impairment with the PMIS-ID in people with moderate ID in a quick and simple way. It is easy to administer, brief (no more than five minutes), and cost-effective. Also, it shows good convergent validity with memory subtest of the TB-DI and CAMCOG-DS. Considering that the verbal memory subtest of the TB-DI presents good internal consistency [29] and the CAMCOG-DS is recommended for follow-up studies [52], this proves that the PMIS-ID measures memory processes. Furthermore, AUC is acceptable (above 0.7) and the discriminant validity for the proposed cut-off score of the PMIS-ID (4.5) shows good specificity (86%) and appropriate sensitivity (69%). Values of specificity are in line with the majority of the MIS-based screening tests in the general population that yield specificities values higher than 80%: the MIS [39], MIS-S [53], MIS-E [54], MIS-D [55], and PMIS [40]. The PMIS-ID also identifies healthy subjects correctly as the aforementioned screening tests. Consequently, the PMIS-ID is an excellent screening memory test for use in daily clinical specialized services for people with moderate ID.

Data gained from the immediate total recall (ITR) part of the PMIS-ID in isolation well enable detection of memory impairment in adults with moderate ID and AD. The inclusion of a delayed recall is tautological, opposite to the improvement described in the general

population with MCI [53], but closer to the use of pictorial memory test based in learning trials without delayed recall in people with low educational level [41] and in people with ID [42]. Our results reveal that when performance is scarce in the immediate recall, it is also in the delayed recall. Moreover, in our sample, people with lower performance in free recall do not gain with the inclusion of a cued recall in the immediate or in the delayed recall. These results are aligned with those described for the MIS-S [54] and cued recall test [42]. Also, learning of relational material depends on the functionality of the hippocampus [55] and free recall trials of the FCSRT picture versions could be considered as an indicator of hippocampus structural integrity [38]. Furthermore, longitudinal memory score variation is specifically associated with volume change in the hippocampus [45,56]. For these reasons, it can be concluded that the PMIS-ID is a noninvasive tool to detect memory impairment due to hippocampus dysfunction in people with moderate ID and AD.

In our study, significant memory decline is the predominant symptom in people with moderate level of ID and AD. Memory decline has been described in MCI and AD in the general population and those with ID [57]. Especially, in people with DS, a slight memory impairment is usually found in MCI, with a significant decline in AD [24,26,27,30,58]. Possibly, memory processes in people with moderate level of ID are not semantic-dependent, and other strategies should be considered because deep processing is beyond their capability [59]. Other promising alternatives could involve developing a test under the associative learning paradigm (binding) that depends on the integrity of the medial temporal lobe structures, as in the general population with hopeful results for AD [60], MCI [41], and in adults with mild and moderate ID [61].

Although stimuli selection in our work was accurate, the scores on the PMIS-ID have a low ceiling effect. Despite the apparent easiness of the four proposed pictorial stimuli, the PMIS-ID measures the same function as a standard memory test. High concordance was obtained between the PMIS-ID total score and memory subtests of the CAMCOG-DS [25] and the TB-DI [29], especially for people with a moderate level of ID. For instance, the satisfactory concordance in our study for the verbal learning subtest of the TB-DI ($r = 0.62$, $p < 0.001$) has also been described between the MIS-E [62] and the analogue subtest of the original version of the TB-DI, the Barcelona Test [63] ($r = 0.78$; $p < 0.001$) in the general population. In this sense, it is important to consider that assessing memory in people with ID is a complex task for clinicians. In clinical practice, pictorial tests seem to be better accepted due to an increased feeling ability to solve the task. In return, the ceiling effect in pictorial tests has already been considered in the general population because the selected drawings are excessively simple and with little ecological validity [64]. This is consistent with the enhancement of performance with pictorial memory test in older adults [37] and in a Spanish population with amnesic MCI [41] and with AD [36] compared with word memory test. Our results confirm the classical dual-coding information theory [65] that postulates superiority in picture processing against words. In this context, increasing the number of stimuli could reduce the ceiling effect, improving its diagnostic capacity for adults with mild ID.

Our results show a slight decrease of the performance on the PMIS-ID for MCI compared with the CN group, both for mild and moderate level of ID groups. Medians are similar in both groups for each trial, but values of the first and third quartile are wider again in each trial, especially for the moderate ID group. This fits with the discrete accuracy to detect MCI compared with the satisfactory data for AD in people with ID. Until recently, few studies had shed light on how to detect preclinical or prodromal stages of AD. Thus, in the recent proposed diagnostic criteria for MCI in DS [30], three variables from a comprehensive neuropsychological examination have proven sensitive enough for this fact: the BRI of the BRIEF and the abstraction and delay memory subtest from the TB-DI. Also, the PAL first-trial memory is one of the most sensitive variables to detecting changes between the preclinical and prodromal phases of AD in people with DS [7]. Furthermore, it is feasible to diagnose AD with neuropsychological tools such as the CAMCOG-DS or the modified Cued Recall Test (mCRT) [34]. In this sense, a decline of performance on both tests

was evident in the continuum of AD, but performance on the mCRT was not discriminative for people with DS in the prodromal stage of AD. Analyzing these results, one can deduce that the most tangible changes occur when AD is established, but not in the prodromal phases. Possibly, the course of AD is different in comparison to the general population, in which MCI can be considered a slowly progressive transitional phase in cases of conversion to AD; sensitive neuropsychological instruments are available to detect these changes. Based on results in subjects with ID, changes between the preclinical and prodromal phase would be minimal and undetectable with current neuropsychological instruments, and are only sensitive when performance declines abruptly. From this data, it can be hypothesized that memory deficits with more or less intensity are part of the phenotype of almost all people with ID, and this implies that falls in memory are more difficult to detect than in the general population, in which the margins of scores are greater. This also might suggest that the course of the disease may not be slowly progressive and early detection is essential to initiate proper intervention. Therefore, neuropsychological tools with normative data for all ID ranges are needed to reduce misdiagnosis and to interpret cognitive profiles better in normal and pathological ageing.

Overall, our clinical experience reveals that in the general population, the diagnostic of MCI or DA poses a challenge in those with high educational level, just as learning disorders can be masked in exceptional children. In this sense, intelligence, education, and occupational level influence the onset and course of deterioration due to the reserve cognitive assumption [66]. This is also evident in people with ID in which the presentation and natural history of AD varies according to the level of ID [46]. Furthermore, declines in CAMCOG-DS scores are more evident in people with moderate ID [56], and adults with Klinefelter syndrome with higher values in intelligence tests performed better in working memory and executive functions [67]. Thus, the impact of the level of intelligence on neuropsychological tool performance seems contrasted. That is why sufficiently reliable neuropsychological tools should be available for different ranges of intellectual capacity and the level of cognitive reserve must be regarded.

There are some limitations that need to be considered when interpreting our findings; some caution is required.

First, even if the sample is acceptable for a preliminary study, participants were classified by level of ID, decreasing the size of the MCI and AD groups and limiting statistical and discriminatory power. Therefore, future research should be carried out with a representative sample, calculating power estimation before the onset of the study.

Second, alternatives forms are desirable to use in clinical practice and research in neuropsychology. In our study, the PMIS-ID stimuli were chosen according to the data in the general population, which could contribute to the ceiling effect of the scores. To avoid this bias and to expand its use for people with mild ID, we recommend carrying out studies to provide norms for word prototipicity and picture familiarity, according to appropriate cultural context, for people with ID.

Third, the predictive capacity of the PMIS-ID cannot be evaluated reliably because it is a cross-sectional study. Also, we have not considered the stage or severity degree of AD. Our objective was to develop a rapid measure of memory decline associated with MCI or AD to be applied in daily primary care, but it is well-known that follow-up of cognitive decline is required in people with ID to confirm a diagnosis of MCI or AD. Therefore, we recommend carrying out longitudinal studies with various time points and adapting current staging scales in the general population for people with ID.

5. Conclusions

Limitations notwithstanding, the PMIS-ID is a valid memory screening test for people with a moderate level of ID for use in primary health care centers and in clinical specialized services. The findings in the current pilot study suggest that the PMIS-ID does not provide a comprehensive memory assessment but may be useful as a first step in the diagnostic

process to help clinicians in healthcare settings to determine the need to carry out a broader diagnostic evaluation.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijerph191710780/s1, Table S1: Paired comparisons of the areas under the curve of the PMIS-ID trials diagnostic accuracy; Table S2: Normative data of the PMIS-ID delayed total score for different cut-off points for AD in moderate level of ID sample; Table S3: Normative data of the PMIS-ID total score for different cut-off points for AD in moderate level of ID sample; Table S4: Normative data of the PMIS-ID immediate total score for different cut-off points for AD in mild level of ID sample; Table S5: Normative data of the PMIS-ID delayed total score for different cut-off points for AD in mild level of ID sample; Table S6: Normative data of the PMIS-ID total score for different cut-off points for AD in mild level of ID sample.

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Supplementary material

Comparisons of the area under the curve of PMIS-ID total scores for MCI and AD in people with moderate level of ID.

Table S1. Paired comparisons of the areas under the curve of the PMIS-ID trials diagnostic accuracy.

Paired results	z	Bilateral signification	AUC difference	SE difference	CI 95 % (asymptotic) Lower limit	Upper limit
MCI						
TIR - TPMISID	0.38	0.970	0.04	0.474	-0.181	0.188
AD						
TIR – TDR	-0.842	0.400	-0.073	0.398	-0.242	0.096
TIR – TPMISID	-1.021	0.307	-0.064	0.398	-0.188	0.059
TDR -TPMISID	0. 229	0.819	-0.008	0.376	-0. 063	0.080

MCI, Mild Cognitive Impairment; TIR, Total immediate recall, TPMISID, Total picture memory impairment screen for people with intellectual disability; AD: Alzheimer's disease; TDR, Total delayed recall; AUC, Area under the curve; SE, Standard error; CI, confidence interval,

Normative data of the PMIS-ID delayed and total recall for people with AD and moderate level of ID.

Table S2. Normative data of the PMIS-ID delayed total score for different cut-off points for AD in moderate level of ID sample.

Cut-off points	S	Sp	*J*	PPV[a]	NPV[a]
0	0.00	1.00	0.00	0.64	1.00
0.5	0.12	0.96	0.08	0.70	0.94
1.5	0.18	0.93	0.11	0.71	0.89
2	0.31	0.86	0.17	0.71	0.80
2.5	0.37	0.86	0.23	0.76	0.80
3	0.37	0.79	0.16	0.74	0.73
4.5	0.50	0.72	0.22	0.78	0.67
5	0.50	0.69	0.19	0.77	0.64
6	0.62	0.65	0.27	0.79	0.62
6.5	0.66	0.62	0.28	0.86	0.59
7.5	0.75	0.37	0.12	0.85	0.47
8	1.00	0.00	0.00	1.00	0.36

PMIS-ID, Picture Memory Impairment Screen for people with Intellectual Disability; S, Sensitivity; Sp, Specificity; *J*, Youden's J statistic; PPV, Positive predictive values; NPV, Negative predictive values.

[a]25.5 % is the prevalence of AD in the sample.

Normative data of the PMIS-ID immediate, delayed and total recall for people with AD and mild level of ID.

Table S4. Normative data of the PMIS-ID immediate total score for different cut-off points for AD in mild level of ID sample.

Cut-off points	S	Sp	*J*	PPV[a]	NPV[a]
<2	0.00	1.00	0.00	0.00	0.14
3	0.70	0.80	0.50	0.92	0.25
3.5	0.84	0.60	0.44	0.93	0.38
4.5	0.87	0.60	0.47	0.93	0.43
5	0.90	0.60	0.50	0.90	0.40
5.5	0.94	0.60	0.54	0.91	0.50
6	0.97	0.40	0.37	0.91	0.67
6.5	1.00	0.40	0.40	0.91	1.00
7.5	1.00	0.40	0.40	0.89	1.00
8	1.00	0.00	0.00	0.86	1.00

PMIS-ID, Picture Memory Impairment Screen for people with Intellectual Disability; S, Sensitivity; Sp, Specificity; *J*, Youden's J statistic; PPV, Positive predictive values; NPV, Negative predictive values.
[a]25.5 % is the prevalence of AD in the sample.

Table S5. Normative data of the PMIS-ID delayed total score for different cut-off points for AD in mild level of ID sample.

Cut-off points	**S**	**Sp**	***J***	**PPV[a]**	**NPV[a]**
0	0.00	1.00	0.00	0.00	0.14
0.5	0.62	1.00	0.62	0.86	0.20
2	0.84	0.80	0.84	0.90	0.38
3.5	0.90	0.60	0.50	0.90	0.50
4.5	0.90	0.60	0.50	0.93	0.40
5.5	0.94	0.40	0.50	0.94	0.50
6.5	0.94	0.40	0.34	0.97	0.50
7.5	0.94	0.40	0.34	1.00	0.50
8	1.00	0.00	0.00	1.00	1.00

PMIS-ID, Picture Memory Impairment Screen for people with Intellectual Disability; S, Sensitivity; Sp, Specificity; *J*, Youden's J statistic; PPV, Positive predictive values; NPV, Negative predictive values.
[a]25.5 % is the prevalence of AD in the sample.

Table S6. Normative data of the PMIS-ID total score for different cut-off points for AD in mild level of ID sample.

Cut-off points	S	Sp	*J*	PPV[a]	NPV[a]
<4	0.00	1.00	0.00	0.00	0.14
5	0.55	0.80	0.35	0.89	0.18
7	0.68	0.60	0.84	0.91	0.23
9.5	0.80	0.60	0.40	0.93	0.33
11	0.84	0.40	0.24	0.93	0.38
12	0.88	0.40	0.28	0.93	0.43
12.5	0.90	0.40	0.30	0.93	0.50
13.5	0.90	0.40	0.30	0.90	0.40
14.5	1.00	0.40	0.40	0.91	1.00
15.5	1.00	0.40	0.40	0.89	1.00
16	1.00	0.00	0.00	0.86	1.00

PMIS-ID, Picture Memory Impairment Screen for people with Intellectual Disability; S, Sensitivity; Sp, Specificity; *J*, Youden's J statistic; PPV, Positive predictive values; NPV, Negative predictive values.

[a]25.5 % is the prevalence of AD in the sample.

Estudio número 2

The Global Deterioration Scale for Down Syndrome Population (GDS-DS): A Rating Scale to Assess the Progression of Alzheimer's Disease

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The Global Deterioration Scale for Down Syndrome Population (GDS-DS): A Rating Scale to Assess the Progression of Alzheimer's Disease

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Abstract: The aim of this study is to adapt and validate the global deterioration scale (GDS) for the systematic tracking of Alzheimer's disease (AD) progression in a population with Down syndrome (DS). A retrospective dual-center cohort study was conducted with 83 participants with DS (46.65 ± 5.08 years) who formed the primary diagnosis (PD) group: cognitive stability (n = 48), mild cognitive impairment (n = 24), and Alzheimer's disease (n = 11). The proposed scale for adults with DS (GDS-DS) comprises six stages, from cognitive and/or behavioral stability to advanced AD. Two neuropsychologists placed the participants of the PD group in each stage of the GDS-DS according to cognitive, behavioral and daily living skills data. Inter-rater reliability in staging with the GDS-DS was excellent (ICC = 0.86; CI: 0.80–0.93), and the agreement with the diagnosis categories of the PD group ranged from substantial to excellent with κ values of 0.82 (95% CI: 0.73–0.92) and 0.85 (95% CI: 0.72, 0.99). Performance with regard to the CAMCOG-DS total score and orientation subtest of the Barcelona test for intellectual disability showed a slight progressive decline across all the GDS-DS stages. The GDS-DS scale is a sensitive tool for staging the progression of AD in the DS population, with special relevance in daily clinical practice.

Keywords: global deterioration scale; rating scale; cognitive decline; cognitive testing; Alzheimer's disease; dementia; down syndrome; intellectual disability

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1. Introduction

Life expectancy in people with Down syndrome (DS) has increased considerably, to up to sixty years on average [1], evidencing an accelerated aging phenotype [2]. The risk of developing Alzheimer's disease in people with DS (AD-DS) is greatly elevated due to the gene overexpression produced by the chromosome 21 trisomy, in which amyloid precursor protein and other gene modulations involve an accumulation of extracellular amyloid beta and neurofibrillary tangles [3,4]. AD neuropathology is present in more than 60% of people with DS by the age of 40 to 50 years [5]. Therefore, people with DS are considered at absolute risk of developing AD [6] and become a genetic paradigm for translational research with regard to the general population [7]. Despite these conceptual advances, AD-DS is usually diagnosed around the age of 50 years [8,9], later than expected [10], and these individuals are usually excluded from the clinical trials of typically developing individuals with AD [11].

Some major stages of the natural course of AD-DS have been suggested. Diagnostic categories in some studies are as follows: asymptomatic, cognitively stable, preclinical, prodromal AD, AD dementia, and uncertain [12–14]. Recently, under the biological definition and diagnosis relying on biomarkers, five stages have been proposed for AD-DS [15]:

cognitively stable (CS), preclinical AD, mild cognitive impairment (MCI), prodromal AD and dementia. Bearing these data in mind, it seems self-evident that there is a lack of consensus on the proposed stages to capture the entire clinical continuum of AD-DS which, on the contrary, are based primarily on biological criteria. Furthermore, recent studies in the general population suggest different initial stages on the dementia continuum. In this sense, a subjective cognitive decline (SCD) stage has been proposed as a risk condition announcing possible dementia [16,17], but it must be supported by objective cognitive impairment to be considered part of the AD continuum [18]. Additionally, mild behavioral impairment (MBI) [19,20] has been proposed as a prodromal neuropsychiatric stage of emergent dementia. Due to the high risk of developing AD in subjects with DS, and considering that AD-DS pharmacological interventions are not efficient enough [21,22], it is necessary to arrange a grading scale that captures the whole clinical spectrum of the AD-DS with the inclusion of these recently proposed diagnostic categories to detect early therapeutic windows.

Although the biological perspective research framework has meant a forward leap in the prediction of MCI and AD, cognitive markers continue to be essential. There are several cases in daily clinical practice in which neuroimaging and biomarker findings suggest a certain diagnosis but without being supported by a neuropsychological examination, as in cases of biomarker positivity for AD without associated or progressive cognitive impairment [18]. Because biomarkers may fail in the diagnosis of AD, a neuropsychological examination can provide crucial cognitive information in the diagnostic and follow-up processes of the ID population [23]. In this sense, the aspects that should be explored in any longitudinal assessment for the entire continuum of AD-DS are dysexecutive cognitive or behavioral features, episodic memory, orientation, and general global cognitive decline [24–27].

The high prevalence of MCI and AD in individuals with DS has resulted in much research concerning the detection of both diagnoses. In a recent paper, the diagnostic criteria to delimit MCI in people with DS (MCI-DS) have been proposed [28], a stage that can be considered as prodromal of AD [29]. These authors showed that scores in the behavior rating inventory of the executive function parent form (BRIEF-P) [30] combined with scores on abstract thinking and verbal memory are useful values for detecting MCI-DS. Furthermore, the memory, language, and communication sections of the National Task Group-Early Detection Screen for Dementia (NTG-EDSD) seem to be sensitive to MCI-DS [31]. The Cambridge Cognitive Examination for Older Adults with Down's syndrome—Spanish version (CAMCOG-DS) [32], with different cut-offs points, has been provided to detect prodromal AD or MCI and AD in people with DS and mild or moderate ID [13,32]. Furthermore, visuospatial-paired associate memory, hand–eye coordination, and semantic verbal fluency may be relatively sensitive events in the prodromal stage of AD-DS [10]. Finally, the performance of episodic memory using a modified cued recall test discriminates between individuals with preclinical, prodromal, and clinically manifest AD, albeit of mild degree [33]. Compared with the aforementioned major phases, the later stages of the AD-DS spectrum have not received special attention nor an international official definition.

The progression of the disease in the clinical setting is assessed through cognitive, behavioral, psychiatric, and clinical tests. Additionally, rating scales provide a common language to diagnose, monitor, and evaluate therapeutic interventions. A good rating scale would be practical and properly validated in the target population, embracing different domains beyond cognition, and be sensitive to change in all stages to measure therapeutic effects [34], both pharmacological and non-pharmacological. In the general population, there are two reference scales for grading dementia. One of them is the clinical dementia rating scale (CDR) [35], a semi-structured interview with a patient and a close caregiver, covering six domains (memory, orientation, judgment and problem solving, work in the community, performance at home and in hobbies, and personal care). The results are distributed on a five-point scale from cognitive normality to severe dementia. Interestingly,

an adaptation of the CDR, the CDR for frontotemporal lobar degeneration (CDR-FTDL) [36], was developed with the inclusion of language and behavior domains not contemplated in the original CDR, and has been shown to be sensitive in distinguishing disease progression between FTLD and AD in the general population [37]. Additionally, a modified CDR for adults with DS based on questionnaires and patient/caregiver interviews is available [38], capturing the progressive deterioration of AD in this population.

The second grading dementia scale is the global deterioration scale (GDS [39], which determines the degree of functional loss based on the severity of the cognitive impairment. It consists of descriptions of the clinically differentiated stages of the AD continuum, from stage 1 (normal) to 7 (severe AD). Subsequently, the functional assessment staging (FAST) [40] provides the GDS with a division of phases 6 and 7, involving the progressive inability to maintain basic activities of daily living. The GDS is easier to apply than the CDR as it correlates with neuropathological, functional, global, and cognitive changes in the progression of MCI to AD [41] and with the hippocampal volume [42]. Furthermore, in our context, the GDS is the instrument of choice that determines the introduction and withdrawal of pharmacological and non-pharmacological treatment in patients with AD [43,44]. Therefore, it would be desirable to arrange a global deterioration rating scale which contemplates the amnesic [45,46] and the behavioral [47,48] forms of onset classically described in AD-DS. Consequently, such a scale would improve both the response to health needs according to the time point of disease progression and provide researchers in this field with a common language in our context.

The main objective of the present study is to examine the feasibility of an adapted GDS for its use in people with DS on the continuum of AD. We expect to find that the stages proposed for GDS-DS are anchored to the performance of cognitive and behavioral instruments that are well established in people with DS and a mild or moderate level of ID.

2. Materials and Methods

2.1. Study Design and Description of the Sample

This is a retrospective, dual-center cohort study of Caucasian adults with DS. A total of 87 participants were identified from the Servicio Especializado en Salud Mental y Discapacidad Intelectual (Specialized Mental Health ID Unit, Institute of Health Assistance, Girona) and the Unidad de Adultos con Síndrome de Down (Adult Down Syndrome Unit, La Princesa University Hospital, Madrid, Spain).

A neurological, psychiatric, and laboratory examination was applied to all the participants. The neurological examination consisted of taking the participant's history (e.g., previous central nervous system alterations, relevant drug treatment, substance abuse, sleep disorders) and a physical examination. Psychiatric data were collected using the psychiatric assessment schedule for adults with a developmental disability (PAS-ADD) [49]. Blood samples were obtained in order to detect hypothyroidism, vitamin B12 deficiency, and anemia.

The inclusion and exclusion criteria of the study are displayed in Table 1. Going into detail, the age cut-off was chosen based on previous studies which reported that being above 39 years of age represents a high risk of developing cognitive decline from a previous level of efficiency in people with DS [50]. The level of ID was determined according to the DSM-5 criteria [51]. All participants were required to have a reliable informant available to report on the present and past adaptive skills and behavior of the participants.

Those with sensory impairments that prevented the completion of the research protocol, those with a history of alterations of the central nervous system (e.g., brain tumors, head injury, stroke), those with uncontrolled sleep disorders (e.g., obstructive sleep apnoea), and individuals suffering from substance abuse were excluded. Patients were also excluded if they had untreated anemia, vitamin B12 deficiency, or uncontrolled hypothyroidism because of their potential risks of influencing behavior.

Table 1. Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
≥39 years old	Severe sensory impairments
Both sexes	No reliable informant
Mild or moderate intellectual disability	Untreated anemia
DS confirmed karyotype	Vitamin B12 deficiency
	Uncontrolled hypothyroidism
	Behavior disorder (comorbid, affecting normal functioning)
	Uncontrolled sleep disorders
	Substance abuse
	Previous central nervous system alterations
	Relevant drug treatment

It should be noted that cases of conduct disorder, depression, and anxiety were not automatically ruled out. Those cases caused by a stressful event in the past six months, were excluded but those (un)treated cases related to normal daily functioning were not, according to clinical judgment.

Finally, participants exposed to a high anticholinergic burden through polypharmacy from psychotropics, gastrointestinal and cardiovascular medications were excluded if the treatment was considered ineffective, according to clinical judgment.

Our study was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The study protocol was approved by the Clinical Research Ethical Committee of the Parc Hospitalari Santa Caterina (Girona). Written informed consent was obtained from parents and written and pictorial assent were additionally obtained.

2.2. *Clinical Assessment*

The protocol consisted of a cognitive test and behavioral and daily living skills questionnaires that have been shown to be most sensitive to cognitive impairment in Spanish-speaking subjects with DS.

2.2.1. Cognitive Assessment

The protocol with the following test was applied to all the participants:

- The level of ID was based on the results from the Kaufman brief intelligence test, second edition (KBIT-II) [52] and Vineland adaptive behavior scales–second Edition (Vineland II) [53].
- The *KBIT-II* is a test designed for the measurement of verbal and non-verbal intelligence. It consists of two sub-tests that assess crystallized intelligence and fluid intelligence and allow the establishment of the level of ID.
- The *Vineland II* scale measures adaptive behaviors, including communication, daily living skills, socialization, and motor skills.
- General cognitive abilities were assessed using the following scales: the Cambridge cognitive examination for older adults with Down's syndrome and other intellectual disabilities—Spanish version (CAMCOG-DS) [32], and the Barcelona test for intellectual disability (BT-ID) [54].
- The CAMCOG-DS comprises seven cognitive domains (orientation, language, memory, attention, praxis, abstract thinking, and perception). The maximum score is 109 points. The psychometrical properties are good: test–retest reliability = 0.92, ICC = 0.91, internal consistency = 0.70 − 0.93, and κ values of 0.95 and 0.97 versus DSM-IV [51] and ICD-10 [55] criteria, respectively. It is a reliable tool for the assessment of cognitive impairment in people with ID with and without DS with mild and moderate levels of ID.

- The *BT-ID* consists of *67* subtests grouped into eight cognitive domains (language, working memory, orientation, praxis, attention, executive function, visuoconstruction, and memory). It shows good psychometric properties: test–retest reliability = 0.91, ICC = 0.95, internal consistency = 0.70 − 0.93. It provides normative data for five groups based on intellectual disability level, age, and curricular competence.
- Planning and problem solving were assessed with the Tower of London—Drexel University: 2nd edition ID version [56]. Its psychometric properties are reliable for differentiation between subjects with mild and moderate ID, and are associated with other measures of executive functions. Additionally, it demonstrated sufficient evidence of reliability and validity in adults with Down syndrome.

2.2.2. Informants' Questionnaires

- The behavior rating inventory of executive function, parents' form (*BRIEF-P*) [30] measures executive functions or self-regulation in their everyday environments. It consists of two indexes: (1) Behavioral regulation index (BRI), composed of inhibit, shift, and emotional control scales; and (2) the metacognitive index (MI), composed of initiate, working memory, planning, organization, and monitor scales.
- The informant interview of the Cambridge examination for older adults with Down's syndrome and other intellectual disabilities—Spanish version (CAMDEX-DS) [32]. It consists of (1) a structured interview with the informant/family member to collect information to detect a decline in the individual's best level of functioning, their cognitive and functional impairment, and the mental and physical health of the participant, including depression, anxiety, paranoid symptoms, delirium, substance abuse, physical disability, hypothyroidism, cerebrovascular problems, and pharmacological treatment; (2) the CAMCOG-DS (see the cognitive test scale section in this article); (3) a guide for the clinical diagnosis of AD, capturing changes in daily adaptive skills (section A), memory (section B), other cognitive domains (section C1), personality/behavior (section C2) and confusional acute syndrome (section D); and (4) suggestions for the correct intervention in people with ID and dementia. In this study, the CAMDEX-DS was used only for clinical diagnostic purposes to avoid the risk of circularity.

The participants of the PD group were classified according to three diagnostic categories: cognitive stability, MCI and AD. The diagnosis of cognitive stability was made when participants had no cognitive impairment or decline in adaptive skills, according to the CAMDEX-DS informant section. As there is currently no internationally accepted official definition for MCI-DS [57], the diagnosis of MCI or AD was based on expert multidisciplinary clinical judgment according to recent publications, as is recommended in standard practice for DS [26,28,58–61]. In detail, a participant fulfilled the diagnosis of MCI when presented with a single or multiple cognitive decline and/or loss of functionality according to the CAMDEX-DS informant section [26]. The diagnosis of AD was obtained if participants had memory decline or another cognitive impairment, such as aphasia, apraxia, agnosia, or dysexecutive syndrome, or loss of functionality [62]. In both conditions, the information about changes from previous levels of performance must be supported by a close caregiver [26,58,60]. It should be noted that the CAMDEX-DS was used only for diagnostic purposes, whereas performance on the neuropsychological tests confirmed the diagnosis through a longitudinal clinical study [26].

2.2.3. Global Deterioration Scale for Down Syndrome (GDS-DS)

The GDS-DS began at stage 1 (cognitive and behavioral stability), in which subjects were placed if they had neither subjective complaints nor cognitive or behavioral impairments identified by the instruments of the study protocol. Stage 2 (subjective cognitive and/or behavioral impairment) included those subjects with changes in cognition, behavior or adaptive skills, as self-reported or reported by caregivers but not supported by objective data. Stage 3 (mild cognitive and/or behavioral impairment) corresponded to those cases with reports of cognitive or behavioral impairment by the patient or confirmed by a reliable

informant, supported by objective data, with no or very mild loss of adaptive skills. Stages 4 (mild Alzheimer's disease), 5 (moderate Alzheimer's disease) and 6 (advanced Alzheimer's disease) were reserved for those subjects presenting mild to severe deterioration in cognitive and behavioral domains, as reported by an informant, supported by objective data and demonstrating affected adaptive skills (Table 2).

Table 2. Stages and diagnostic criteria for each stage of the GDS-DS.

	Stages
1	Cognitive and behavioral stability All must be present I. BRIEF-P BRI index: ≥33 II. CAMCOG-DS total: ≥83 (mild ID); ≥65 (moderate ID) III. Any CAMDEX-DS diagnostic criteria (no A, B, C1 or C2)
2	Subjective cognitive and/or behavioral impairment All must be present I. BRIEF-P BRI index: ≤33 II. CAMCOG-DS total: ≥ 83 (mild ID); ≥65 (moderate ID) III. CAMDEX-DS diagnostic criteria: B or C1 or C2
3	Mild cognitive and/or behavioral impairment (I and/or II) + III must be present I. BRIEF-P BRI index: ≤32 II. CAMCOG-DS total: ≤82 − 69 (mild ID), ≤64 − 57 (moderate ID) III. CAMDEX-DS diagnostic criteria: B or C1 or C2 ≤2 supporting criteria
4	Mild Alzheimer's disease (I and/or II) + III must be present I. BRIEF-P BRI index: ≤32 II. CAMCOG-DS total: ≤68 (mild ID), ≤56 (moderate ID) III. CAMDEX-DS diagnostic criteria: A, B, C1 or C2, no D ≥2 supporting criteria
5	Moderate Alzheimer's disease (I and/or II) + III must be present I. BRIEF-P BRI index: ≤32 II. CAMCOG-DS total: ≤68 (mild ID), ≤56 (moderate ID) III. CAMDEX-DS diagnostic criteria: A, B, C or C2, no D ≥3 supporting criteria
6	Advanced Alzheimer's disease (I and/or II) + III must be present, or III and V I. BRIEF-P BRI index: ≤32 II. CAMCOG-DS total: ≤68 (mild ID), ≤56 (moderate ID) III. CAMDEX-DS diagnostic criteria: A, B, C1 or C2, no D ≥3 supporting criteria Incomplete or no administered neuropsychological examination

GDS-DS, global deterioration scale for people with Down's syndrome; BRIEF-P BRI, behavior rating inventory of executive function, parents' form behavioral regulation index; CAMCOG-DS, Cambridge cognitive examination for older adults with Down's syndrome and other intellectual disabilities; ID, intellectual disability; CAMDEX-DS, Cambridge examination for older adults with Down's syndrome and other intellectual disabilities.

- GDS-DS adaptation

The GDS-DS was constructed on the basis of the global deterioration scale (GDS) [39]. Some modifications were introduced to adapt this scale to the study population. First, the original GDS scale consists of seven stages (1–7), whereas the GDS-DS consists of six stages (1–6). Secondly, because growing evidence suggests that subjective cognitive decline [16,17] and mild behavioral impairment [19,20] could predict AD, subjective cognitive and behavioral aspects were considered. Therefore, stage 2 was labeled as subjective cognitive and/or behavioral impairment and stage 3 as mild cognitive and/or behavioral impairment.

In general, for the delimitation of the GDS-DS stages, the performance of the participants in the cognitive instruments and the information of the behavioral questionnaire and caregivers gathered from the study protocol were classified as mandatory or supporting criteria, according to the recent literature about AD and DS (Table 2).

- Mandatory criteria

The mandatory criteria were established based on those cognitive and behavioral instruments that had obtained sufficient quantitative data to differentiate MCI and AD, in addition to adaptive skills. The purpose was to establish criteria that were as inclusive as possible; thus, the following instruments and scores were considered:

1. Behavioral Regulation Index—BRIEF-P [30]. This questionnaire demonstrates that, in people with DS, a cut-off point of ≥ 55 allows the classification of stable subjects at the cognitive and behavioral levels (sensitivity = 90), while a cut-off point of <32 allows the classification of subjects with MCI (specificity = 0.90). For scores between 32 and 55, the diagnosis is more doubtful [28]. According to these data, the following cut-off points were assigned for our study: ≥ 33 would be a criterion for cognitive and behavioral stability (stage 1) and subjective cognitive and/or behavioral impairment (stage 2), and ≤ 32 would be a criterion for mild cognitive or behavioral impairment (stage 3) and mild, moderate and advanced AD (stages 4, 5 and 6, respectively).
2. Regarding the total score of the *CAMCOG-DS* [32], it has become clear that a cut-off point of the total score = 68 allows the detection of AD in subjects with DS and mild ID (sensitivity: 80%; specificity: 81%), and a cut-off point of 52 (sensitivity: 85%; specificity: 81%) in those with moderate ID [32]. Additionally, in another study of subjects with DS and mild ID, a cut-off point of 82 (sensitivity: 80%, specificity 80.5%) differentiated between asymptomatic and prodromal AD, and a cut-off point of 80 (sensitivity: 75%, specificity 87.8%) differentiated asymptomatic and dementia AD. In the same study, for those with moderate ID, a cut-off point of 64 (sensitivity: 66.7%, specificity 72.3%) differentiated between asymptomatic and prodromal AD, and a cut-off point of 56 (sensitivity: 84%, specificity 84.3%) between asymptomatic and dementia AD [13]. The data of these two previous studies were incorporated for all the stages of the GDS-DS, according to the ID level and the CAMCOG-DS total score.
3. The Guide to clinical diagnosis of the CAMDEX-DS—Spanish version [32]. The decline of daily life skills is decisive in the diagnostic process of AD, since in the MCI, these are preserved or only very mildly affected. Therefore, in our study, positive scores in sections B (memory), section C1 (other cognitive domains) or section C2 (personality/behavioral) were considered indicative of mild cognitive and/or behavioral impairment (stage 3). Furthermore, positive scores in section A (daily living skills), section B and sections C1 or C2 and negative scores in section D (acute confusional syndrome) are indicative of AD (stages 4, 5 and 6).

It should be noted that the BRIEF-P (BRI index) and the CAMCOG-DS, in addition to providing a quantitative basis for each stage of the GDS-DS, also cover the symptoms of the two most frequent forms of AD onset in the DS population, either the amnestic [45,46] or the behavioral variants [47,48].

- Supporting criteria

The supporting criteria were established based on those cognitive and behavioral instruments of the protocol study that demonstrated a decrease associated with an increase in the clinical intensity of AD-DS from the MCI-DS phase. These criteria might not be mandatory, but their presence helped determine the stage of the GDS-DS that would be assigned to each participant. The instruments considered for this purpose were:

1. BT-ID: the orientation, semantic fluency (eating and drinking), formal fluency, delay verbal memory (stories) and visual discrimination subtests.
2. CAMCOG-DS: abstract thinking subtest.

Recent studies claim that significantly lower scores on the above subtests can be indicative of MCI-DS and the early phase of AD [10,13,26,28]. Therefore, these were added as supporting criteria for AD-DS from stage 3 (mild cognitive and/or behavioral impairment) upward (stages 4, 5 and 6).

It should be emphasized that in order to identify the stages of AD (4, 5 and 6), in addition to the mandatory and supporting criteria established, the degree of deterioration (mild, 4; moderate, 5; and advanced, 6) would have to be determined by the judgment and clinical experience of specialists, who play a decisive role in this regard.

For stage 6 (advanced Alzheimer's disease), an additional criterion was established. Based on our clinical experience and other studies of populations with DS, it has been suggested that some tests cannot be administered to those with advanced stages of AD or in populations with severe intellectual disabilities [57] because they do not provide enough information due to the "floor effect" [22]. Therefore, the criterion of not being able to administer all or any cognitive tests from the screening protocol to participants would, on its own, be an indicator of advanced AD, supported by affected adaptive skills.

2.3. Procedures

Cognitive, behavioral and adaptive skills data from the PD group were used retrospectively to place each participant in a stage of the GDS-DS and thus form the GDS-DS group. Two neuropsychologist specialists in DS blinded to the diagnosis of the PD group (SEC, JGA) placed each subject into one of the six levels of the proposed GDS-DS rating scale, according to the level of ID of each participant and the mandatory and supporting criteria established (Table 1). It should be highlighted that in order to avoid circularity, the two specialists were different to those who made the diagnoses for the PD group. The degree of agreement between the examiners in placing the subjects in the stages of the GDS-DS was checked. The inter-rater reliability test was applied to the two raters' first GDS-DS classifications. Then, the classifications of the two raters was transformed into single values as follows: if they matched the GDS-DS assignment, the same value was maintained, and when the two raters did not agree on the classification using the GDS-DS, the case was discussed until a consensus was reached. Additionally, the demographic and the diagnostic categories of the PD and the GDS-DS groups were analyzed in order to observe possible similarities.

The agreement between the two raters classifying the participants using the GDS-DS compared with the PD group was analyzed. For this purpose, the stages 1 (cognitive and behavioral stability) and 2 (subjective cognitive and/or behavioral impairment) of the GDS-DS were associated with the cognitive stability diagnosis of the PD group; stage 3 (mild cognitive and/or behavioral impairment) of the GDS-DS was associated with the diagnosis of mild cognitive impairment of the PD group; and stages 4, 5 and 6 (Mild, Moderate and Advanced Alzheimer's disease) of the GDS-DS were associated with the Alzheimer's disease of the PD group. Codes associated with each category of the PD group are displayed in Table 3.

Table 3. Recode numeric values.

GDS-DS Stages	Primary Diagnosis
1. Cognitive and behavioral stability 2. Subjective cognitive and/or behavioral impairment	0. Cognitive stability
3. Mild cognitive and/or behavioral impairment	1. Mild cognitive impairment
4. Mild Alzheimer's disease 5. Moderate Alzheimer's disease 6. Advanced Alzheimer's disease	2. Alzheimer's disease

GDS-DS, global deterioration scale for people with Down's syndrome.

Finally, as the progressive deterioration of adaptive skills was an immovable criterion and an analysis with this variable could lead to a circularity problem, the authors checked for a possible association of the GDS-DS stages with a selection of the cognitive and behavioral instruments included as mandatory and supporting criteria for each stage.

2.4. Statistical Analysis

We performed all statistical analyses using the software program SPSS (version 27.0; SPSS Inc., Chicago, IL, USA). Bilateral significance levels were set at a p-value of less than 0.05. The normality of data was assessed using the Kolmogorov–Smirnov test, and subsequently, non-parametric analyses were carried out. For the GDS-DS group, demographic characteristics, level of ID, and performance on selected neuropsychological tests were analyzed by a non-parametric Kruskal–Wallis test followed by the Bonferroni correction for post hoc pairwise comparisons or Pearson's chi-square test for category data. Spearman's correlation analysis was used to determine the associations between the stages of the GDS-DS with the cognitive and behavioral data selected. A Mann–Whitney U test was performed with pairs of the GDS-DS groups because the effect size between the cognitive and behavioral performance across the GDS-DS stages was computed using the non-parametric probability of superiority estimation (PSest), interpreted as small (≥56), medium (≥0.64), and large (≥0.71) [63]. Inter-rater agreement and concordance between the stages issued by rater 1 and rater 2 with the primary diagnosis of the study were analyzed by using Cohen's weighted kappa values.

3. Results

3.1. Sample and Demographics

Of the subjects selected, four ultimately did not agree to participate in the study. The final sample formed the primary diagnosis (PD) group and consisted of 83 subjects (46.65 ± 5.08 years; male = 46 (55.4%), female = 37 (44.6%)) and was divided into three groups: (1) cognitively stable group, with 48 subjects (45.10 ± 3.83 years; male = 24 (50%), female = 24 (50%)); (2) mild cognitive impairment group, with 24 subjects (47.46 ± 5.35 years; male = 16 (66.7%), female = 8 (33.3%)); and (3) Alzheimer's disease group, with 11 subjects (51.64 ± 6.05 years; male = 6 (54.5%), female = 5 (45.6%)). Seven of the initial candidates had to be excluded because they could not undergo the neuropsychological assessment.

The demographic details of the PD group are reported in Table 4. Of the total 83 participants, about half were diagnosed as being cognitively stable, one third as having mild cognitive impairment and a smaller number as having Alzheimer's disease. The mean age of the subjects with AD was significantly higher than the stable subjects but not than the MCI group. No statistical differences were observed in the gender and level of ID across the groups.

Table 4. Demographics of the primary diagnosis sample.

	Total	Cognitive Stability	Mild Cognitive Impairment	Alzheimer's Disease	p
n	83	48	24	11	
Age	46.65 (39–63)	45.10 (39–43)	47.46 (39–61)	51.64 (43–63)	0.01 * a
Gender					0.41
Male	46 (55.4%)	24 (50%)	16 (66.7%)	6 (54.5%)	
Female	37 (44.6%)	24 (50%)	8 (33.3%)	5 (45.6%)	
ID level					0.61
Mild	49 (59.1%)	29 (60.4%)	15 (62.5%)	5 (45.6%)	
Moderate	34 (40.9%)	19 (39.6%)	9 (37.5%)	6 (54.6%)	

Age values are shown as means and range. For the sex and ID level, percentages regarding the group are shown. ID, intellectual disability. * $p < 0.05$, according to Kruskal–Wallis test with Bonferroni correction for age, or χ^2-test for gender and ID level. a, between cognitive stability and Alzheimer's disease.

Within the GDS-DS group (Table 5), 27 participants were diagnosed as having cognitive stability (stage 1) and with subjective cognitive and/or behavioral impairment (stage 2), 25 with mild cognitive and/or behavioral impairment (stage 3) and 31 participants with any degree of AD (stages 4, 5 or 6). Interestingly, comparing these two groups, a similar number of participants were classified as MCI with both methods and 20 more subjects as AD. There were more participants diagnosed as more cognitively stable in the PD group than those placed in stage 1 of GDS-DS (48 and 9, respectively). As expected, subjects diagnosed with AD in the PD group and those placed on the stage 6 of the GDS-DS (advanced Alzheimer's disease) were the oldest.

Table 5. Demographics for each stage of the global deterioration scale for people with Down's syndrome.

		GDS-DS Stages						*p*
	Total	1	2	3	4	5	6	
		Cognitive/ Behavioral Stability	Subjective Cognitive/ Behavioral Impairment	Mild Cognitive/ Behavioral Impairment	Mild Alzheimer's Disease	Moderate Alzheimer's Disease	Advanced Alzheimer's Disease	
n	83	9	18	25	10	14	7	
Age	46.65 (39–63)	46.44 (40–61)	44.72 (39–54)	45.60 (39–54)	46.60 (42–52)	47.43 (41–54)	54.14 (49–63)	0.02 * a, * b
Gender								0.15
Male	46 (55.4%)	8 (88.9%)	11(61.1%)	10(40.0%)	4(40.0%)	9 (64.3%)	4 (57.1%)	
Female	37 (44.6%)	1 (11.1%)	7 (38.9%)	15 (60.0%)	6 (60.0%)	5 (35.7%)	3 (42.9%)	
ID level								0.08
Mild	49 (59.1%)	4 (44.4%)	15 (83.3%)	17(68.0%)	4 (40.0%)	6 (42.9%)	3 (42.9%)	
Moderate	34 (40.9%)	5 (55.6%)	3 (16.7%)	8 (32.0%)	6 (60.0%)	8(57.1%)	4 (57.1%)	

Age values are shown as means and range. For the sex and ID level, percentages regarding the group are shown. ID, intellectual disability. * $p < 0.05$, according to Kruskal–Wallis test with Bonferroni correction for age, or χ^2-test for gender and intellectual disability level. a, between subjective cognitive/behavior impairment and advanced Alzheimer's disease; b, between mild cognitive/behavior impairment and advanced Alzheimer's disease.

3.2. Cognitive and Behavioral Data across the GDS-DS Stages

These analyses were conducted without the data from the stage 6 subjects, who were excluded because they could not complete the study protocol.

The analysis of the correlations revealed negative significant correlations between performance on the tests and the GDS-DS, except for the BRIEF-P and the visual discrimination BT-ID subtest. The correlations were moderate between the GDS-DS and the CAMCOG-DS Total score, orientation subtest and formal fluency, but weak with abstract thinking subtest of the CAMCOG-DS, free memory delay (stories) and semantic fluency of the BT-ID (Table 6).

Table 6. Correlations between GDS-DS stages and cognitive/behavioral assessment.

Cognitive and Behavioral Assessment	Rho
BRIEF-P	
BRI index	−0.17
CAMCOG-DS	
Total score	−0.70 **
Abstract thinking	−0.39 **
BT-ID	
Orientation	−0.78 **
Free delay memory (stories)	−0.37 **
Semantic fluency (eat/drink)	−0.38 **
Formal fluency	−0.54 **
Visual discrimination	−0.11

GDS-DS, global deterioration scale for people with Down's syndrome; BRIEF-P, behavior rating inventory of executive function parents' form; BRI, behavioral regulation index; CAMCOG-DS, Cambridge cognitive examination for older adults with Down's syndrome and other intellectual disabilities; BT-ID, Barcelona test for intellectual disability. ** $p < 0.01$, (two-tailed test), using Spearman's correlation coefficient.

The performance on the cognitive and behavioral tools across the GDS-DS stages is displayed in Table 7. Overall, the performance on the CAMCOG-DS total score and the orientation subtest (BT-ID) decreased significantly across stage 1 (cognitive and/or behavioral stability) to 5 (moderate Alzheimer's disease).

Table 7. Cognitive and behavioral performance across the GDS-DS stages.

		GDS-DS Stages					*p*
	Total	1 Cognitive/ Behavioral Stability	2 Subjective Cognitive/ Behavioral Impairment	3 Mild Cognitive/ Behavioral Impairment	4 Mild Alzheimer's Disease	5 Moderate Alzheimer's Disease	
BRIEF-P							
BRI index	40.99 (35–47)	47.00 (39–49)	40.00 (36–47)	36.00 (30–42)	40.00 (36–45)	37.00 (36–51)	
CAMCOG-DS							
Total score	72.00 (55–88)	**84.00 (76–87)**	**82.50 (76–87)**	**71.00 (60–78)**	**61.50 (50–71)**	**49.5 (44–55)**	** a, ** b, ** c, ** d, e **
Abstract thinking	2.00 (0–4.5)	4.00 (1–5)	4.50 (0–5)	2.00 (0–4)	1.00 (0–4)	0.00 (0–1)	* b
BT-ID							
Orientation	91.00 (48–109)	**103.00 (97–113)**	**109.00 (102–114)**	**91.00 (73–108)**	**46.00 (35–49)**	**28.50 (21–40)**	** a, ** b, ** c, ** d, ** e, ** f
Delay stories	2.00 (0–4)	3.00 (2–6)	**3.00 (2–5)**	3.00 (1–4)	1.50 (0–4)	**0.00 (0–2)**	* d, * e
Semantic fluency (eat/drink)	9.00 (6.5–12)	10.00 (9–12)	**10.5 (8–13)**	10.00 (8–11)	9.00 (5–13)	**6.00 (5–8)**	* d
Formal fluency	2.00 (0–4)	**3.00 (2–4)**	4.00 (2–6)	2.00 (1–4)	**0.00 (0–3)**	**0.00 (0–1)**	** b, ** c, *** d
Visual discrimination	18.00 (16–19)	18.00 (16–19)	18.00 (17–20)	18.00 (16–19)	16.00 (16–19)	18.00 (16–19)	

Values are given as median and range: GDS-DS, global deterioration scale for people with Down's syndrome; BRIEF-P, behavior rating inventory of executive function parents' form; BRI, behavioral regulation index; CAMCOG-DS, Cambridge cognitive examination for older adults with Down's syndrome and other intellectual disabilities; BT-ID, Barcelona test for intellectual disability. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, according to Kruskal–Wallis test with Bonferroni correction. a, between cognitive/behavioral stability and mild Alzheimer's disease; b, between cognitive/behavioral stability and moderate Alzheimer's disease; c, between subjective cognitive/behavioral impairment and mild Alzheimer's disease; d, between subjective cognitive/behavioral impairment and moderate Alzheimer's disease; e, between mild cognitive/behavioral impairment and moderate Alzheimer's disease; f, between mild cognitive/behavioral impairment and mild Alzheimer's disease. Significant differences in bold.

In terms of sectors, performance significantly decreased regarding:

- Delay stories (BT-ID) between stage 2 (subjective cognitive and/or behavioral impairment) and 5 (moderate Alzheimer's disease) and stages 3 (mild cognitive and/or behavioral impairment) and 5 (moderate Alzheimer's disease).
- Formal fluency (TB-ID) between stage 1 (cognitive and/or behavioral stability) and 5 (moderate Alzheimer's disease), stage 2 (subjective cognitive and/or behavioral impairment), stage 3 (mild Alzheimer's disease) and stage 4 (moderate Alzheimer's disease).
- Semantic fluency (BT-ID) between stages 2 (subjective cognitive and/or behavioral impairment) and 5 (moderate Alzheimer's disease).

Note that (i) the performance on abstract thinking, orientation, delay stories, and formal fluency subtest (BT-ID) did not decrease between stage 1 (cognitive and behavioral stability) and 2 (subjective cognitive and/or behavioral impairment); (ii) the performance on the BRI index (BRIEF-P) decreased between 1 (cognitive and behavioral stability) and 3 (mild cognitive impairment), but was heterogeneous from stage 3 (mild cognitive and/or behavioral impairment) to stage 5 (moderate Alzheimer's disease); (iii) the performance on delay stories subtest (BT-ID) did not show significant oscillations between stage 2 (subjective cognitive and/or behavioral impairment) and 3 (mild cognitive and/or behavioral impairment); and the performance on the visual discrimination subtest (BT-ID) was similar

across all the stages. These data had an impact on the posterior analysis of the effect sizes values.

The raw differences that showed a progressive decrease between performances on the selected tests across the GDS-DS stages are displayed in Table 8 and Table S1 of the online Supplementary Materials.

Table 8. Effect sizes between the GDS-DS stages.

	GDS-DS Stages							
	1–2		2–3		3–4		4–5	
	P	PS_{est}	P	PS_{est}	P	PS_{est}	P	PS_{est}
BRIEF-P								
BRI index	0.395	0.60 [a]	0.061	0.67 [b]	0.183	0.61	0.567	0.51
CAMCOG-DS								
Total score	0.938	0.51	**0.010** *	**0.80** [c]	**0.027** *	**0.69** [b]	0.088	**0.68** [b]
Abstract thinking	0.595	0.56	0.139	**0.63** [a]	0.549	0.51	0.129	0.65
BT-ID								
Orientation	0.314	0.62	**0.002** **	**0.78** [c]	**0.000** ***	**0.94** [c]	0.057	**0.71** [c]
Free delay memory (stories)	0.775	0.53	0.663	0.54	0.331	0.55	0.467	**0.56** [a]
Semantic fluency (eat/drink)	0.856	0.52	0.265	0.60	0.906	0.49	0.114	**0.63** [a]
Formal fluency	0.364	0.61	**0.011** *	**0.73** [c]	0.118	**0.66** [b]	0.716	0.44
Visual discrimination	0.733	0.54	0.367	0.58	0.363	**0.56** [a]	0.305	0.58

GDS-DS, global deterioration scale for people with Down's syndrome; BRIEF-P, behavior rating inventory of executive function parents' form; BRI, behavioral regulation index; CAMCOG-DS, Cambridge cognitive examination for older adults with Down's syndrome and other intellectual disabilities; BT-ID, Barcelona test for intellectual disability. P, *p* value; PS_{est}, probability of superiority effect size; * $p < 0.05$, ** $p < 0.01$, *** < 0.001; [a] $PS_{est} \geq 56$, [b] $PS_{est} \geq 0.64$, [c] $PS_{est} \geq 0.71$. Significant effect sizes and *p* values with progressive decrease on the performance across the stages (Table 7) in bold.

Overall, small to large effect sizes were observed between stage 2 (subjective cognitive and/or behavioral impairment) and 5 (moderate Alzheimer's disease) for the CAMCOG-DS total score and orientation subtest (BT-ID).

The effect sizes ranged from small to medium between stages 1 (cognitive and behavioral stability) and 3 (mild cognitive and/or behavioral impairment) for the BRI index (BRIEF-P). Medium to large effect sizes were observed for the formal fluency subtest (BT-ID) between stage 2 (subjective cognitive and/or behavioral impairment) and stage 4 (mild Alzheimer's disease).

The effect sizes ranged from small to medium for free delay memory and semantic fluency subtest (BT-ID) between stage 4 (mild Alzheimer's disease) and 5 (moderate Alzheimer's disease).

A small effect size was observed between stage 3 (mild cognitive and/or behavioral impairment) and 4 (mild Alzheimer's disease) on the *visual discrimination* subtest (BT-ID).

3.3. Reliability

The inter-rater reliability for staging using GDS-DS was excellent, with a mean Cohen weighted κ value of 0.86 (CI: 0.80–0.93). The agreement between the two raters classifying the PD group using the GDS-DS was excellent, as determined by specialists, with κ values of 0.82 (CI: 0.73–0.92) and 0.85 (CI: 0.77–0.94).

4. Discussion

The main goal of the present study was to devise a global rating scale for AD in people with DS based on the GDS scale [39]. The resulting GDS-DS amplifies the classical phases of the AD-DS (stability, prodromal AD and AD). Our purpose was to provide a scale that captures progressive decline in the entire AD-DS continuum. The GDS-DS meets this requirement from the cognitive stability to AD stages, especially in relation to performance on the CAMCOG-DS *total score* and *orientation* subtests of the BT-ID and dementia.

The GDS-DS ranges through six stages from cognitive and behavioral stability (stage 1) to advanced Alzheimer's disease (stage 6), contrasting with the seven stages of the global deterioration scale (GDS) [39] for the general population. In view of the results obtained in the present work, in which an overall decrease in deterioration is detected by the CAMCOG-DS total score, six stages capture the entire continuum of AD in people with DS and, in addition, they are consistent with the stages of AD proposed in research of the National Institute on Aging and the Alzheimer's Association (NIA-AA) [6].

The six stages of the GDS-DS differ from the five stages of the clinical dementia rating scale (CDR) [35] and the modified clinical dementia rating scale for people with Down syndrome questionnaire (CDR-QDS) and interview (CDR-IDS) forms [38]. These two rating scales (CDR and CDR-IDS/CQR-IDS), as opposed to our GDS-DS, do not include stage 2 (subjective cognitive and/or behavioral impairment). This can lead to misdiagnosis because subjective cognitive impairment is increasingly seen as an early symptom of dementia risk in the general population [16,17] and although it is not a sensitive aspect by itself [18], it must be considered with complementary clinical data as a different entity from MCI. In addition, behavioral aspects are also not considered in these scales, although they are important factors for detecting possible changes associated with prodromal AD in subjects with DS [47]. Furthermore, in our clinical dementia contexts, the global deterioration scale (GDS) [39] is used to monitor, design and modify appropriate pharmacological treatment in patients with AD in the general population [43,44]. Thus, the authors consider the GDS-DS a closer instrument for daily clinical practice and recommend its use for clinical trials in subjects with AD-DS.

Seven participants were placed in the stage 6 (advanced Alzheimer's disease) category of the GDS-DS in our study. The criterion to be placed in this stage was that the subject did not endure the neuropsychological examination proposed in the protocol and this was, in turn, an exclusion criterion for the PD group on which the present work is based. Some DS adults in the symptomatic stages of AD are not able to complete a neuropsychological examination [22]. The authors of the present study agree, as routine follow-up visits have encountered this setback. As a result, despite progress in terms of instruments adapted for people with ID, the neuropsychological tests used in the aforementioned studies and in daily clinical practice are not sufficiently valid to capture the deterioration in advanced stages of AD-DS nor for severe/profound intellectual disability [57,64,65]. Therefore, in terms of daily clinical practice, for people placed in stage 6 in our study, the authors recommend the use of adapted tools, such as the cognitive exploration scale for people with intellectual disability and extended support (ECDI-SE) or the modified ordinal scales of psychological development for people with intellectual disability (M-OSPD-ID). However, at the same time, this also means that using these instruments in the early stages of AD can lead to a ceiling effect on the scores. Future studies should focus on valid instruments for all phases of AD, avoiding ceiling and floor effects, regardless of the severity of symptoms.

Performance in the orientation subtest of BT-ID decreased significantly throughout the GDS-DS stages. Although not pathognomonic of AD, temporal disorientation is frequently observed in daily clinical practice in subjects with cognitive impairment. This requires semantic and episodic information activation [66] and has been linked to atrophy in the posterior hippocampus [67] and the disconnection between the posterior part of the right medial temporal gyrus and the posterior cingulate cortex [68]. The progressive loss of orientation has already been described in the transition from MCI to AD in people with DS [26]. In view of these facts, this subtest should be present in longitudinal follow-ups in individuals with ID.

Performance on executive functions (abstract thinking, free delay memory (stories), semantic and formal fluency) shows a slight decline with modest sustained effect sizes in some stages of the AD continuum. The anatomical substrate of these functions is linked with the temporoparietal, precuneus-posterior cingulate and occipital areas [24], which show a decreased volume [41,60] and loss of integrity in white matter tracts [58,69] in individuals with AD-DS. In addition, an increase in alpha band synchronization using

magnetoencephalography has been found in the functional connectivity in the AD continuum in the general and in the DS population and is associated with cognitive decline in executive function, language and working memory [62]. Additionally, MCI-DS individuals with confirmed amyloid positivity who progress to AD have shown a pattern of increased delta activity in frontal regions [70]. The clinical relevance of these findings suggests that all these cognitive functions also should be examined in longitudinal clinical follow-ups

Declines in the CAMCOG-DS total score have been shown to be related to changes in all of the stages of the GDS-DS. A decline in performance on CAMCOG-DS has been found in the entire AD-DS continuum [13,26,28,62], regardless of whether the level of ID is mild or moderate [22]. Interestingly, performance on CAMCOG-DS is linked to amyloid deposition [71], and it is recommended that longitudinal studies assess cognitive changes related to ID and dementia [72]. Therefore, CAMCOG-DS could be a suitable instrument for anchoring the GDS-DS stages of our context, in a similar way that the mini examen cognoscitivo (MEC) [73] is anchored to the global deterioration scale [39] in the general population.

The *BRI* index of BRIEF-P [30] does not change significantly across the GDS-DS stages, but it drops slightly from the cognitive/behavioral stability to mild cognitive and/or behavioral impairment, stages 1 to 3, respectively. The authors selected the *BRI* index because worse scores on this index could differentiate between healthy and MCI-DS subjects [28], and our results partially replicate this. In light of these results, the inclusion of behavioral impairment in the GDS-DS seems appropriate. In addition, in the general population, mild behavioral impairment [19] improves the specificity of MCI as an at-risk state for incident dementia [74] and has been associated with higher AD polygenic risk scores [75]. Considering that behavioral changes are able to herald AD in the DS population [47], the authors recommend the use of the *BRI* index scores to detect behavioral impairment in the DS population in the earlier stages.

The main strength of the present study is that the GDS-DS, with the inclusion of behavioral aspects, allows the capture of subjects in the initial stages of AD-DS either due to memory or behavioral difficulties, in addition to being associated with performance in cognitive and behavioral tests that have been shown to be reliable in the DS population.

Additionally, the GDS-DS could be the first step in unifying the criteria for classifying the continuum of Alzheimer's disease in people with DS. It allows a common language for communication between clinicians and researchers and could be a basic instrument for the selection of samples in clinical trials in people with DS.

Furthermore, the GDS-DS, can also be used to inform families about the stages of Alzheimer's disease, when sufficient data from future studies have been collected to construct specific clinical profiles in combination with functional assessment staging. Knowing the continuum can complement the neurological diagnosis and facilitate family members' understanding of the expected prognosis.

However, some limitations have to be acknowledged. In this study, we used cross-sectional information that relied on the longitudinal data of a three-year follow-up study. We first wanted to verify that the GDS-DS was applicable to people with DS. As this has been proven to be feasible, future studies could investigate the application of the scale in longitudinal follow-ups to minimize possible cohort effects.

Additionally, our study was based on data collected from neuropsychological tests, behavioral questionnaires and informant interviews. Today, neuroimaging or neurophysiological techniques provide rich complementary data that correlate brain changes with cognitive features in aging and AD. Thus, future studies must include the linking of neuroimaging and neurophysiological data with the stages of GDS-DS.

5. Conclusions

In summary, GDS-DS is not designed as a diagnostic tool but as a quantitative measure of disability. The insights delivered in this paper show that the proposed GDS-DS rating scale represents an important attempt at staging people with DS throughout the continuum

of AD, providing a unique method of classification that can be useful in clinical trials and in daily clinical practice. As noted in the development of the original GDS [39], the limits of each of the GDS-DS stages are not axiomatic, but they do allow graduation as a guideline that facilitates the monitoring of the AD-DS continuum.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijerph20065096/s1, Table S1: Effect sizes between groups of the GDS-DS stages.

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Supplementary material

Comparisons of the probability and effect sizes effect values by consecutives groups of the GDS-DS stages.

Table S1. Effect sizes between groups of the GDS-DS stages.

	GDS-DS stages											
	1-2			2-3			3-4			4-5		
	U	P	PS_{est}	U	P	PS_{est}	U	P	PS_{est}	U	P	PS_{est}
BRIEF- P												
BRI index	64,500	0.395	**0.60**[a]	149.00	0.061	**0.67**[b]	87.500	0.183	0.61	57.500	0.567	0.51
CAMCOG-DS												
Total score	79.500	0.938	0.51	91.500	**0.010***	**0.80**[c]	70.500	**0.027***	**0.69**[b]	38.000	0.088	**0.68**[b]
Abstract thinking	71.00	0.595	0.56	166.00	0.139	**0.63**[a]	110.000	0.549	0.51	41.000	0.129	0.65
TB-DI												
Orientation	71.00	0.314	0.62	97.000	**0.002****	**0.78**[c]	13.000	**0.000*****	**0.94**[c]	33.500	0.057	**0.71**[c]
Free delay memory (stories)	61.500	0.775	0.53	207.000	0.663	0.54	101.000	0.331	0.55	52.000	0.467	**0.56**[a]
Semantic fluency (eat/drink)	75.500	0.856	0.52	180.000	0.265	0.60	114.000	0.906	0.49	43.500	0.114	**0.63**[a]
Formal fluency	77.500	0.364	0.61	123.000	**0.011***	**0.73**[c]	76.500	0.118	**0.66**[b]	66.000	0.716	0.44
Visual discrimination	63.500	0.733	0.54	189.000	0.367	0.58	99.000	0.363	**0.56**[a]	49.000	0.305	0.58

GDS-DS, global deterioration scale for people with Down's syndrome ; BRIEF-P, behavior rating inventory of executive function parents form; BRI, behavioral regulation index; CAMCOG-DS, Cambridge cognitive examination for older adults with Down's syndrome and other intellectual disabilities; BT-DI, Barcelona test for intellectual disability; U, Mann–Whitney U test; P, *p* value; PS_{est}, probability of superiority effect size; * $p < 0.05$, ** $p < 0.01$, *** < 0.001; [a] $PS_{est} \geq 56$, [b] $PS_{est} \geq 0,64$, [c] $PS_{est} \geq 0,71$. Significant effect sizes and *P* values with progressive decrease on the performance across the stages (Table 7) in bold.

Discusión general

5. DISCUSIÓN GENERAL

El objetivo principal de la presente tesis por compendio de artículos fue adaptar y validar dos instrumentos ampliamente utilizados en el estudio del continuo Alzheimer en población general para personas con DI leve y moderada de habla española y catalana.

El primer estudio se ha centrado en un instrumento breve de cribado para detectar problemas de memoria. Los instrumentos de cribado cognitivo, tanto a nivel cuantitativo con los puntos de corte, como a nivel cualitativo a través de la semiología, permiten una primera aproximación y un establecimiento de hipótesis diagnóstica que es de gran valor clínico para guiar la exploración neuropsicológica completa. Por su base pictórica, se ha adaptado y validado el Picture-Based Memory Impairment Screen (PMIS, Verghese et al., 2012) en personas con DI leve y moderada. El instrumento resultante, el Pictorial Memory Screening Test para personas con Discapacidad Intelectual (PMIS-DI) permite detectar fiablemente los problemas de memoria en sujetos con EA y un nivel de DI moderada.

En el segundo estudio se ha podido progresar un paso en la concreción de las fases del continuo Alzheimer en personas con SD. Para cumplir este propósito, la Global Deterioration Scale (GDS) (Reisberg et al., 1982) se presumió la más adecuada, por su extendido uso en población general para el estadiaje de la EA y su amplio conocimiento en el ámbito clínico de su relación numérica con cada estadio. La Global Deterioration Scale for people with Down's síndrome (GDS-DS) resultante permite posicionar a cada sujeto en un continuo de seis fases, según el rendimiento en pruebas neuropsicológicas y la información recogida en los cuestionarios de conducta. Mediante la GDS-SD se establece un idioma transversal en el devenir clínico diario.

5.1 Instrumento breve para el cribado de los problemas de memoria en el continuo Alzheimer en personas con DI leve y moderada

Los esfuerzos de los últimos años para contar con instrumentos neuropsicológicos adaptados y validados en personas con DI de habla española están dando sus frutos. Actualmente contamos con dos baterías neuropsicológicas para ser utilizadas en esta población, como son la parte cognitiva de la Cambridge examination for mental disorders of older people with Down's syndrome and other intellectual disabilities (CAMDEX-DS) (Esteba-Castillo et al., 2013) y el Test Barcelona para personas con discapacidad intelectual (TB-DI) (Esteba-Castillo et al., 2017). Además, en referencia a selección de test que exploran un dominio cognitivo, también disponemos de un instrumento para valorar primordialmente la planificación, como el Tower of London-Drexel University 2nd Edition para personas con discapacidad intelectual (TOL^{DXtm} - DI) (García-Alba et. al., 2019), y el Modified Cued Recall Test (mCRT) (Benejam et al., 2015), para la memoria episódica.

Al iniciar la presente tesis, no se contemplaba ningún test de cribado de memoria para su uso en la primera fase de la exploración neuropsicológica en personas con DI. La memoria es uno de los dominios, por no decir el nuclear, que debe ser explorado ante la sospecha de deterioro cognitivo. En población general española, en esta área, contamos con el Memory Impairment Screen (MIS) (Böhm et al., 2005), que a pesar de su fácil y rápida administración (no más de cinco minutos) proporciona unos datos normativos robustos para detectar demencia y especialmente EA. El único inconveniente es que los estímulos son cuatro palabras que deben ser leídas y puede ser un hándicap para los sujetos con bajo nivel educativo o no escolarizados. Para paliar este hecho, el Picture-Based Memory Impairment Screen (PMIS) (Verguese et al., 2012) detecta demencia con fiabilidad mediante cuatro estímulos pictóricos, facilitando su administración para los sujetos sin escolarizar en población no española. De estos dos instrumentos, uno por

ser pictórico y el otro destinado a población española, nace la propuesta de adaptar y validar el PMIS-DI. Los resultados del primer estudio muestran que el PMIS-DI cumple con los criterios de un test breve de cribado, y detecta problemas de memoria en sujetos con DI moderada y EA.

Mediante el PMIS-DI se esperaba proporcionar datos normativos para personas con DI leve y moderada con DCL y EA. En general, la detección del DCL es un reto. En personas sin DI se han hallado unas tasas de reversión del DCL que oscilan entre un 10% y un 59% (Chung et al., 2019). Se intentaron mejorar los criterios de Petersen con criterios neuropsicológicos (Bondi et al., 2014), pero la aplicación de las dos propuestas de criterios han mostrado tasas similares de reversión, alrededor del 45% (Overton et al., 2023). Además, la progresión de los sujetos con DCL puede ser atípica, y prolongarse más de lo esperado hasta progresar a EA (Rosenbloom & Barclay, 2023). Asimismo, en personas sin DI, hasta el momento de la redacción de la presente tesis, a diferencia de la personas sin DI, no existen criterios diagnósticos aceptados internacionalmente. Por esta razón, se ha intentado caracterizar cognitivamente el DCL, y se han descrito cambios sutiles en memoria y orientación, así como un descenso en las puntuaciones totales del CAMCOG-DS (García-Alba et al., 2019, Startin et al., 2018). Los resultados del PMIS-DI siguen esta línea, con descenso de las puntuaciones entre los grupos control y DCL con DI leve y moderada, pero sin llegar a ser significativos. Se espera que la fiabilidad en el diagnóstico de DCL mejore a raíz de nuevos estudios, con muestras más amplias. En este sentido, se han aportado datos objetivos que han servido para desarrollar los criterios sobre los que pivotaron los estadios de la escala GDS-SD del segundo estudio de la presente tesis, con instrumentos como el mCRT (Benejam et al., 2015), el CAMCOG (Benejam et al., 2020; Esteba-Castillo et al., 2013) y el BRIEF-P (Esteba-Castillo et al., 2022). Hasta el momento, y teniendo en cuenta que

en estudios de seguimiento evolutivo se deben contemplar los cambios respecto al nivel basal independientemente del QI y no tanto atender a datos normativos (Videla et al., 2022), cabe sospesar la posibilidad de utilizar el PMIS-ID como instrumento de cribado para el seguimiento evolutivo.

5.2 Escala global de deterioro para el continuo de la enfermedad de Alzheimer en personas con síndrome de Down

La acumulación de Aß y ovillos neurofibrilares está presente en casi la totalidad de los sujetos con SD a partir de los 40 años de edad (Cipriani et al., 2018) . Estos cambios neuropatológicos se inician sobre los 8 años de edad (Leverenz & Raskind, 1998), e incluso puede que antes, ya entre las 8 y 12 semanas de gestación, tal como se ha mostrado con organoides cerebrales (Zhao & Haddad, 2022). Esto hace que la EA en sujetos con SD sea casi universal y sorprende la falta de un criterio unificado en cuanto a la clasificación de los sujetos en los estudios, que básicamente se distribuyen en tres: controles, DCL o fase prodrómica y EA. Por este motivo, el objetivo del segundo estudio de esta tesis fue adaptar y validar la Global Deterioration Scale (GDS, Reisberg et al., 1982) en personas con SD y nivel de DI leve y moderada.

El dividir el continuo EA en más estadios, aunque pueda percibirse contradictorio, permite contextualizar los cambios sutiles en estadios precisos y se puede prever el cambio de fase sin esperar a una caída abrupta. Además, facilita el seguimiento evolutivo que se contempla mandatorio en las personas con DI. Ante la pregunta de cómo clasificar a los sujetos, se buscó la respuesta en crear una escala de clasificación con más estadios intermedios y estudiar el comportamiento en las puntuaciones de los test administrados en cada estadio.

La escala propuesta se denominó Global Deterioration Scale para personas con SD (GDS-SD). Los seis estadios engloban todo el proceso de deterioro de la EA típica, des

de la ausencia de deterioro (estadio 1) hasta la EA avanzada (estadio 6). Aún teniendo una fase menos que la GDS, coincide con los estadios de la EA según el marco de investigación del National Institute on Aging y la Alzheimer's Association (NIA-AA) (Jack et al., 2018).

Se esperaba anclar cada estadio con puntuaciones descendentes en los instrumentos cognitivos y conductuales a través de loes estadios de la escala. Las puntuaciones totales del CAMCOG-DS han mostrado un descenso progresivo significativo a través de todos los estadios de la GDS-SD. Esta batería ya se ha mostrado sensible a los cambios en el continuo de la EA (Benejam et al., 2020; Esteba-Castillo et al., 2022; García-Alba et al., 2019; Videla et al., 2022), y el rendimiento está relacionado con la deposición de amiloide (Cole et al., 2017) y muchas son las evidencias de que la CAMCOG-SD debería ser el instrumento de elección para los seguimientos evolutivos en personas con DI (Paiva et al., 2020).

Comentar que actualmente se ha desarrollado la CAMCOG-DS 2, una revisión de la misma que se espera hacer más énfasis en las funciones ejecutivas y atención (Esteba-Catillo, comunicación personal, febrero 2023).

El Behaviour Regulation Index (BRI) del BRIEF-P (Gioia et al., 2000) se ha mostrado sensible a los cambios de conducta entre el estadio 2 (deterioro cognitivo y/o conductual subjetivo) y la fase 3 (deterioro cognitivo y/o conductual leve). Este instrumento ya se ha mostrado fiable en la detección del DCL en personas con SD (puntuación < 32) y es un criterio diagnóstico objetivo recientemente propuesto (Esteba-Castillo et al., 2022). Aunque las puntuaciones en el BRI no decaen a través de todas las fases de la GDS-DS, su inclusión en los protocolos de exploración se hace indispensable, especialmente en la detección de deterioro conductual leve.

Por su parte, las puntuaciones en el subtest *orientación* del TB-DI (Esteba-Castillo et

al., 2017) también han mostrado un descenso progresivo a través de los estadios de la GDS-DS. La *orientación* también es un dominio sensible al deterioro en personas sin DI. Aunque no es un síntoma patognomónico de la EA, la desorientación temporal es frecuentemente observada en la práctica clínica diaria con estos sujetos. Requiere de la activación de la información semántica y episódica (Devinsky & D`Esposito, 2004) y se ha relacionado con la atrofia en el hipocampo posterior (Yew et al., 2012) y la desconexión entre la parte posterior del giro temporal medial derecho y el córtex cingulado posterior (Yamashita et al., 2019). El curso progresivo de pérdida de la orientación ya se ha descrito en personas con SD sin deterioro, con DCL y EA (García-Alba et al., 2019). En vista de estos hechos, este subtest debería estar presente en los seguimientos longitudinales en personas con DI.

6. CONTRIBUCIONES DE LA PRESENTE TESIS E IMPLICACIONES

A pesar de las limitaciones, el PMIS-DI es el primer test para el cribado de los problemas de memoria en sujetos con DI moderada y EA en nuestro contexto. El PMIS-DI por sí solo no proporciona una exploración exhaustiva de la memoria, pero puede ser útil como primer eslabón del proceso diagnóstico. Además, permite a los clínicos decidir la conveniencia de llevar a cabo una exploración diagnóstica más profunda. Este instrumento podría ser útil tanto a nivel clínico diario en servicios especializados como para su uso en atención primaria.

Debemos ser capaces de detectar estos cambios sutiles en un punto determinado del continuo EA sin deber esperar controles evolutivos en que las puntuaciones en los test decaigan significativamente. Para futuras investigaciones sería adecuado estudiar cómo se comporta el PMIS-DI a través de las fases de la GDS-SD y en sujetos caracterizados con biomarcadores positivos para la EA.

Puesto que en personas con SD a partir de los 40 años aproximadamente se produce un declive cognitivo global y de la memoria, y teniendo en cuenta el trastorno de conducta como una forma de inicio de la EA, cabría considerar la posibilidad de incluir la CAMCOG-SD, el PMIS-ID, el índice BRI del BRIEF-P, y la escala GDS-SD como instrumentos recomendados para la detección y monitorización del deterioro cognitivo y conductual.

7. LIMITACIONES Y LÍNEAS FUTURAS

Los estudios que completan la presente tesis presentan algunas limitaciones que se deben considerar para futuros trabajos.

La primera limitación se debe a la naturaleza del tipo de estudio. El primer estudio del PMIS-DI un estudio transversal y el segundo de la escala GDS-SD un estudio retrospectivo, pero de carácter transversal. En futuros estudios sería interesante llevar a cabo estudios longitudinales que serían más apropiados por la idiosincrasia de los estudios planteados en esta tesis.

En segundo lugar, el primer estudio es unicéntrico y la muestra obtenida es modesta, lo que conlleva que haya que generalizar los hallazgos con cautela y en otros contextos de nuestra geografía.

En tercer lugar, hay que considerar que aunque los marcadores cognitivos y conductuales muestran cada vez más fiabilidad en personas con DI en el contexto de las demencias, viene siendo condición cada vez más indispensable relacionar los datos de la exploración neuropsicológica con técnicas de neuroimagen o neurofisiológicas, además de la inclusión de biomarcadores. En este sentido, tendría un especial interés poder relacionar el comportamiento en el CAMCOG-DS en personas con biomarcadores positivos para EA a través del continuo de la GDS-SD.

Dado que el mCRT y el PMIS-ID comparten el modelo teórico para la exploración de la memoria a través del aprendizaje facilitado, sería interesante poder estudiar la posible correlación de las puntuaciones del PMIS-DI con las del mCRT a través de los estadios de la GDS-SD.

Conclusiones

8. CONCLUSIONES

De forma general, con estos dos nuevos instrumentos, se llena un vacío existente en referencia a la primera fase de exploración neuropsicológica en sujetos con DI y en lo concreción de los estadios del continuo Alzheimer en personas con SD.

El PMIS-DI se ha mostrado como un instrumento válido, breve y fácil de administrar que permite detectar con fiabilidad los problemas de memoria asociados a la EA en personas con DI moderada.

Por su parte, la GDS-DS abarca satisfactoriamente los estadios de deterioro cognitivo del continuo EA en personas con SD y discapacidad leve y moderada, mediante datos cuantitativos a partir de la puntuación *total* de la CAMCOG-SD y, de forma complementaria, mediante el subtest *orientación* del TB-DI. Además, proporciona un método de clasificación unitario que puede ser útil en los ensayos clínicos y en la práctica clínica diaria.

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