DOCTORAL THESIS

THE MEMORY ASSOCIATIVE TEST OF THE DISTRICT OF SEINE-SAINT-DENIS (TMA-93) VALIDATION AS ALZHEIMER'S DISEASE DIAGNOSIS TEST

Silvia Rodrigo Herrero

Director

Emilio Franco Macías

Tutor

Miriam Echevarría Irusta

University of Sevilla, 2021

INDEX

ABBREVIATIONS

AA: Alzheimer's Association

Aβ42: Amyloid-beta 42

AD: Alzheimer’s disease

AD8: Eight-item interview to differentiate aging and dementia

ADL: Activities of Daily Living

APA: American Psychiatric Association

AUC: Area Under the Curve

aMCI: Amnestic Mild Cognitive Impairment

CERAD: Consortium to Establish a Registry for Alzheimer's Disease

CDT: Clock Drawing Test

CSF: Cerebrospinal Fluid

CVLT: California Verbal Learning Test

DMS: Diagnostic and Statistical Manual of Mental Disorders

DMS-48: Delayed Matching-to-Sample Task 48

FCSRT: Free and Cued Selective Reminding Test

FDG: Fluosdeoxyglucose

GDS: Global Dementia Scale

GP: General Practitioner

HCs: Healthy Controls

IDDD: Interview for Deterioration in Daily Living Activities in Dementia

IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly

IQR: Interquartile Range

IWG: International Working Group

MCI: Mild Cognitive Impairment

MEC: Mini-Exam Cognoscitivo

MIS: Memory Impairment Screen

MMSE: Mini-Mental State Exam

MoCA: Montreal Cognitive Assessment

MRI: Magnetic Resonance Imaging

MTL: Medial Temporal Lobe

NFL: Light Neurophilically Protein

NIA: National Institute of Aging

NINCDS-ADRDA: National Institute of Neurological and Communicative Disordes and Stroke- Alzheimer

NP1: Neuronal Pentraxin 1

NPV: Negative Predictive Value

PET: Positron Emission Tomography

PPV: Positive Predictive Value

P-Tau: Phosphorylated Tau

RAVLT: Rey Auditive Verbal Learning Test

SMC: Subjective Memory Complaints

SPMSQ: Short Portable Mental Status Questionnaire

STARD: Standards for Diagnostic Accuracy Reporting

T@M: Memory Alteration Test

TAVEC: Verbal Learning Test Spain- Complutense

TMA-93: Memory Associative Test of the District of Seine-Saint-Denis

T-Tau: Total Tau

WHO: World Health Organization

WMS: Wechsler Memory Scale

Introduction

1. ALZHEIMER'S DISEASE. HISTORY'S OVERVIEW

In **1907 Alöis Alzheimer** characterized Alzheimer's disease [1]. He described the **symptoms** of a 51-year-old woman, Auguste Deter *(Figure 1)*:

"Her memory is seriously impaired. If objects are shown to her, she names them correctly, but almost immediately afterward, she has forgotten everything…"

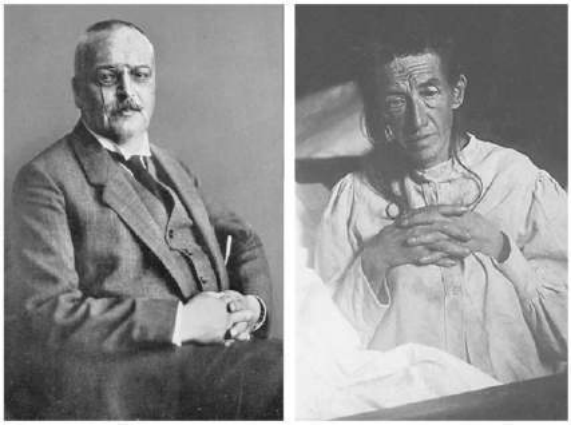

Figure 1 Photographs of Alois Alzheimer (left) and his patient Auguste Deter (right)

After Auguste Deter's death, Alzheimer examined her **brain microscopically.** He described plaques, tangles, and amyloid angiopathy, which nowadays are the signs of the disease.

During the twentieth century, the **American Psychiatric Association (APA)** first defined dementia in the ***Diagnostic and Statistical Manual of Mental Disorders (DMS)*** as a *"basic mental condition characteristically resulting from diffuse impairment of brain tissue function from whatever cause."* The main manifestations are behavioral symptoms, orientation and memory impairment, and intellectual, judgment, and affect dysfunction (APA, 1968).

During the '60s, **Beato, Tomlinson, and Roth [2]** demonstrated the **relationship** between the presence of **AD pathology** in the brain and the impairment in **cognitive tests** *(Figure 2)*.

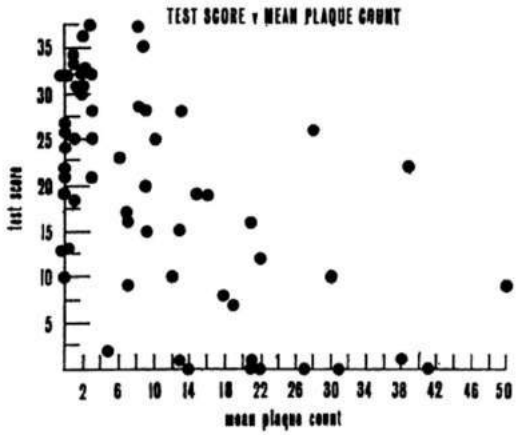

Figure 2. Mean plaque count plotted against the summary cognitive test score constructed by Blessed, Tomlinson & Roth (1968). The scatterplot resulted in a highly significant correlation coefficient of – 0.59 ($p < .001$) [2].

Edgar Miller suggested in the '**70s** that **memory** disorders were due to the inefficiency of coding and transfer information to the long-term storage systems [3,4]

In **1976, Robert Katzman** showed that presenile and senile AD were histopathologically identical [5].

By ending the twentieth century, AD became considering a major public health problem, establishing the National Research Center of American AD. In 1980, the DSM-III updated classifications for the disease, and the World Health Organization (WHO) in 1992. **Specific diagnostic criteria for AD research** was established in **1984** by the **McKhann** group [6].

2. EPIDEMIOLOGY AND CURRENT SITUATION IN OUR AREA

Alzheimer's disease is **the most frequent cause of dementia** (60-80%) and the one that causes the highest dependence in our society [7]. The current prevalence in Spain is estimated at 4-9%, higher in women, although the number of patients living with Alzheimer's dementia is expected to grow as the population is aging. In our country, the estimated number of people living with dementia in 2030 will reach almost 600,000. In **2050** we will have Spain close to **one million** people living with dementia [8-9] and almost 19 million in the European region (Figure 3) [10].

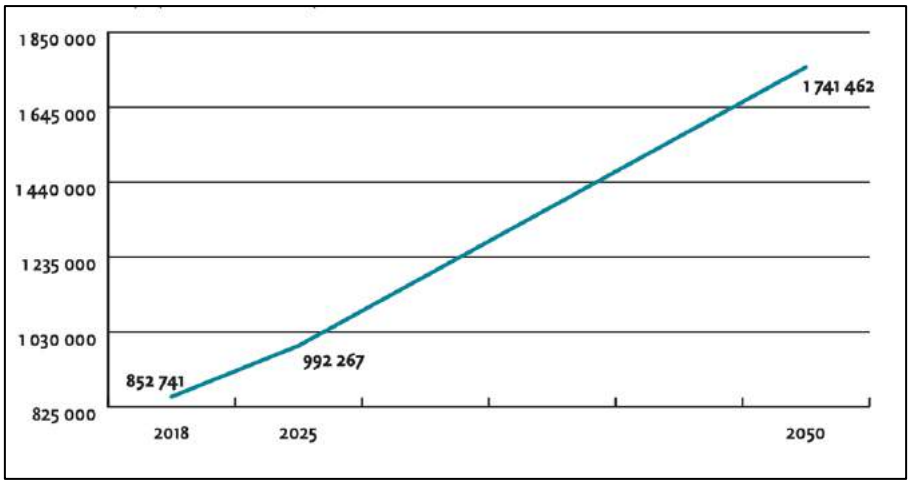

Figure 3. The number of people with dementia in Spain from 2018 to 2050. Dementia in Europe. Yearbook 2019. Estimating the prevalence of dementia in Europe [10].

AD involves an increase in morbimortality, disability, and dependence, which causes high health expenditure. The estimated cost of dementia in Spain is more than **16,000 million euros per year**, **15% of the national health expenditure** [11], mostly provided by patients' families [12], (about 87%, between 27.000 and 37.000 per year and patient) [13]. Furthermore, dementia is one of the leading causes

of institutionalization in our country [14]; about **10.5% of patients with dementia are annually institutionalized** [15]. These costs have a considerable impact on the economy and well-being of patients living with dementia and their caregivers.

Adding to the burden of care condition, the economic impact, **caregivers show a considerable increase in stress, depression, anxiety, and social isolation; and they are more likely to fall into physical illnesses, compared to their age controls** [16-18].

Facing this situation, the **WHO** published ***The Global Action Plan for 2025*** [19] in response to dementia-related challenges, to **promote early diagnosis and intervention** (which can delay the institutionalization and save associated costs [20]), and to encourage the **creation of plans and programs** that contribute to meet the needs of **caregivers**, preventing their physical and mental health, and social well-being from deteriorating.

Aligned with the WHO Global Action Plan, the Spanish Health Ministry also published in 2019 ***The National Integrated Plan for AD and other dementias*** [21], which is supposed to be implemented by 2023.

3. CLINICAL DIAGNOSIS

Diagnostic criteria for AD, postulated by **McKhann in 1984** [22], established that **episode memory decline** is usually the earliest and most prominent manifestation of AD, consistent with the higher amyloid plaques' deposition in the MTL.

AD patients show **difficulties in encoding and store new information effectively**, which constitutes the most prominent neuropsychological symptom of typical AD [23-24]. Bushcke described that coding with semantic cues is less effective in facilitating the information's recovery in patients with early-stages of AD than in healthy older people [25]. This **lack of improvement with semantic cues** can also distinguish AD from subcortical dementias, which also course with troubles in coding, but with a greater recovery improvement using semantic cues than typical AD [26-27].

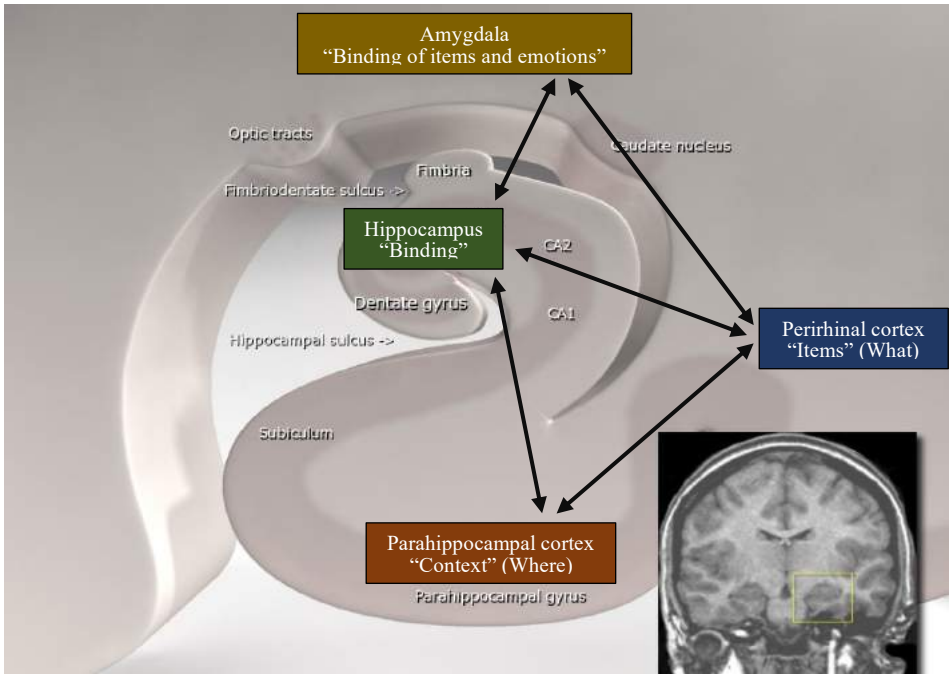

Figure 4. Binding standard model of episodic memories. The perirhinal cortex receives projections from the ventral "*What*" stream and seems to play a role in identifying and processing items and objects. The parahippocampal cortex receives projections from the dorsal "*Where*" stream and seems to play a role in processing contextual information such as the ongoing spatial and temporal context. The hippocampus receives information from both the perirhinal and parahippocampal cortex and binds the item and context information to form episodic memories.

Loss of **binding** (ability to form associations) is another early sign of **hippocampal dysfunction** (Figure 4), so it could facilitate an early diagnosis of AD. Associative Learning tasks have been proposed as useful neuropsychological tools to detect memory changes in the disease's early stages [28-29].

Since Tau and Amyloid deposits extend beyond the MTL to adjacent temporal, parietal, and frontal association cortices, high-order cognitive domains are affected. Domains usually first affected are language and executive function. **Language** changes, frequently mild but early, include the empty speech of content, anomie, and decreased verbal fluency. [30-31]. Patients complain about difficulties in divided thinking and solving problems (**dysexecutive** concerns) [33-34]. Visuospatial and praxis deficits are uncommon in the initial stages. However, both dysexecutive and visuospatial deficits could be the central concerns in the Posterior Alzheimer's variant, which appears under 65 years old [35-36].

Behavioral disturbances may be the initial manifestations of AD, sometimes appearing even years before memory decline. The most frequent ones **are apathy, depression, and irritability** [37-39]. **Psychiatric symptoms** are less common but may also appear as the disease progresses [40].

AD is considered **atypical** when the initial or predominant symptoms are different from the episodic memory deficit [41].

At the beginning of the disease, patients are usually unaware of their difficulties related to the metacognition's involvement, generally named **anosognosia** [42-43].

Independence in activities of daily living (ADL) is gradually affected in AD. First, ADL impaired are instrumental and complex activities, such as interpersonal and social functioning, being the self-maintenance the last involved [44].

3.1 Mild Cognitive Impairment

The most frequently applied concept referring to a state between healthy aging and dementia is Mild Cognitive Impairment (MCI). It refers to a **transitional state between "normality" and dementia,** including individuals with a higher risk situation to develop dementia, especially AD. Although MCI is a widely accepted term, the clinical separation between this MCI and established dementia is uncertain [45-46].

Neuropsychological examination in MCI patients involves deficits in any cognitive domain, compared with expected results by age and educational level, while the patient continues functionally independent [47-48]. However, MCI is not always due to AD. It can be secondary to other causes of dementia or non-neurodegenerative diseases. It is classified as amnesic/non-amnesic and single/multidomain [49]. Amnestic MCI (aMCI) with multidomain involvement is the most likely that evolves into an established AD.

Saykin *et al.* [50] demonstrated that both patients with MCI and those who present cognitive complaints without evident alteration in neuropsychological tests (Subjective Memory Complaints) present a regional **loss of density in the gray matter.** This pattern suggests a **continuum between *"normal aging"* and MCI**. It also leaves the door wide open to the early diagnosis of cognitive decline these densities' measurement seems more sensitive than volumetric loss or cognitive changes.

For the definitive diagnosis of an MCI due to AD (**prodromal AD**) is mandatory the analysis of **pathophysiological biomarkers** of the disease (see section 4) because,

although the aMCI is characteristic of AD, in our environment, only **62%** of these patients have positive CSF biomarkers for AD [49].

3.2 Diagnosis criteria

Until 2007, the most used diagnostic criteria were those of the **NINCDS-ADRDA** group, which established that AD could only be definitively diagnosed **retrospectively,** after the **post-mortem** confirmation [22].

With the advances in image techniques and the introduction of biomarkers, the International Working Group (**IWG**) developed in 2007 new criteria [51], revised again in 2014 (Table 1) [52]. Those criteria combine the **episodic memory** decline with the positivity of **biomarkers** and support preclinical and prodromal AD diagnosis.

By 2011, the National Institute of Aging, together with the Alzheimer's Association (**NIA-AA**), published a new update, including the indication of the use of the different biomarkers available (Table 2) [53].

After these updates, **Jack *et al.* (2018)** published a new conceptual framework for the investigation of AD [54], in which the disease is defined strictly biologically, based on the biomarker profile, without taking into account the patient's phenotype or the clinical stage (Table 3). The great novelty of this design is its basis in the **A / T / N classification**, being (A) cerebral amyloidosis, (T) Tau pathology, and (N) Neurodegeneration. According to this classification, all patients with **cerebral amyloidosis**, regardless of the presence or not of Tau or Neurodegeneration, will be classified within the **"Alzheimer's disease continuum."** Although this last update is not yet part of the usual clinical practice, it is the one that currently prevails in the investigation's field [54].

IWG-2 for typical AD (A+B)	IWG-2 for ATYPICAL AD (A+B)
A. Specific Clinical phenotype	**A. Specific Clinical phenotype (one)**
• Early and significant **episodic memory impairment** (isolated or associated with other cognitive or behavioral changes, suggestive of MCI or dementia) that includes: ○ Gradual and progressive change in memory function reported by patient or informant over more than 6 months. ○ Objective evidence of an amnestic syndrome of the hippocampal type, *based on significantly impaired performance on an episodic memory test with established specificity for AD, such as cued recall with control of encoding test.	• **Posterior variant** ○ Occipitotemporal variant ▪ Early, predominant, and progressive impairment of visuoperceptive functions or ▪ Visual misidentification of objects, symbols, words, or faces. ○ Biparietal variant**:** defined by the presence of early, predominant, and progressive difficulty with visuospatial function, Gerstmann syndrome, Balint syndrome, limb apraxia, or neglect. • **Logopenic variant:** early, predominant, and preogressive impairment of single word retrieval and repetition of sentences, in the context of spared semantic, syntactic, and motor speech abilities. • **Frontal variant:** early, predominant, and progressive behavioural changes: primary apathy, dishinibition, or predominant executive. • **Down's syndrome variant:** early behavioural changes and executive dysfunction in people with Down's syndrome
B. In-vivo evidence of Alzheimer's pathology (one of the following)	**B. In-vivo evidence of Alzheimer's pathology (one of the following)**
• Decreased AB_{1-42} together with increased T-tau of P-tau in CSF • Increased tracer retention on amyloid PET. • AD autosomal dominant mutation present (PSEN1, PSEN2 or APP)	• Decreased AB_{1-42} together with increased T-tau of P-tau in CSF • Increased tracer retention on amyloid PET. • AD autosomal dominant mutation present (PSEN1, PSEN2 or APP)
Exclusion criteria for typical AD	**Exclusion criteria for typical AD**
History • Sudden onset • Early occurrence of: gait disturbances, seizures, major and prevalent behavioral changes *Clinical features* • Focal neurological features • Early extrapyramidal signs • Early hallucinations • Cognitive fluctuations *Other medical conditions severe enough to account for memory and related symptoms* • Non-AD dementia • Major depression • Cerebrovascular disease • Toxic, inflammatory, and metabolic disorders • MRI FLAIR or T2 signal changes in the MTL, consistent with infectious or vascular insults.	*History* • Sudden onset • Early and prevalent episodic memory disorders *Other medical conditions severe enough to account for related symptoms* • Major depression • Cerebrovascular disease • Toxic, inflammatory, or metabolic disorders.

Table 1. Diagnostic criteria for AD. International Working Group Adapted from Dubois et al. 2014. Lancet Neurol [52] AD: Alzheimer's disease.

Diagnostic category	Biomarker Probability of AD etiology	Aβ (PET or CSF)	Neuronal injury (CSFtau,FDG-PET,MRI)
PROBABLE AD dementia			
• Clinical criteria	Uninformative	Unavailable, conflicting, or indeterminate	Unavailable, conflicting, indeterminate
• 3 levels of evidence of AD pathophysiological process	Intermediate	Unavailable or indeterminate	Positive
	Intermediate	Positive	Unavailable or indeterminate
	High	Positive	Positive
Possible AD (atypical presentation)			
• Based on clinical criteria	Uninformative	Unavailable, conflicting, or indeterminate	Unavailable, conflicting, indeterminate
• With evidence of AD pathophysiological process	High but does not rule out second etiology	Positive	Positive
• Dementia-unlikely due to AD	Lowest	Negative	Negative

Table 2. AD criteria. National Institute on Aging/Alzheimer's Association, 2011. Adapted from McKhann et al. [53]. AD (Alzheimer's disease, Aβ Amyloid-beta, PET: positron emission tomography. CSF: Cerebrospinal fluid. FDG: ^{18}fluorodeoxyglucose. MRI: magnetic resonance imaging.

		Cog. Unimpaired	MCI	Dementia
Biomarker Profile	A- T- (N)-	Normal AD biomarkers. Cognitively unimpaired	Normal AD biomarkers with MCI	Normal AD biomarkers with dementia
	A+ T- (N)-	Preclinical Alzh pathologic change	Alzh pathologic change with MCI	Alzh pathologic change with dementia
	A+ T+ (N)- **A+ T+ (N)+**	Preclinical AD	MCI due to AD (Prodromal AD)	AD with dementia
	A+ T- **(N)+**	Alzh and concomitant suspected Non-Alzh pathologic change, cognitively unimpaired	Alzh and concomitant suspected Non-Alzh pathologic change with MCI	Alzh and concomitant suspected Non-Alzh pathologic change with dementia
	A- **T+** (N)- A- T- **(N)+** A- **T+ (N)+**	Non-Alzh pathologic change,cognitively unimpaired	Non-Alzh pathologic change with MCI	Non-Alzh pathologic change with dementia

Table 3. Cognitive syndrome combined with AD biomarkers. Adapted from **Jack et al. (2018)** [54]. Cog: Cognitive. MCI: Mild Cognitive Impairment. AD: Alzheimer's disease. Alzh: Alzheimer

4. IMAGE BIOMARKERS

Biomarkers allow **in vivo studies of structural and molecular changes related to AD pathophysiologic process,** increasing the diagnosis accuracy. Its inclusion in the diagnosis criteria [52-53] has led to an expansion in its use in routine clinical practice [49].

Biomarkers may be classified as pathophysiological and topographic. **Pathophysiological** ones allow the etiological substrate's identification, while **topographic** ones are not specific but better define the disease's severity and progression. [55].

4.1 Pathophysiological image biomarkers

4.1.1 Amyloid PET

Amyloid-beta tracers **cross the blood-brain barrier and bind to amyloid plaques with high affinity** (specifically insoluble fibrillary forms of Amyloid-beta 40 and 42), so they accurately mark the burden of cerebral fibrillar amyloid [56].

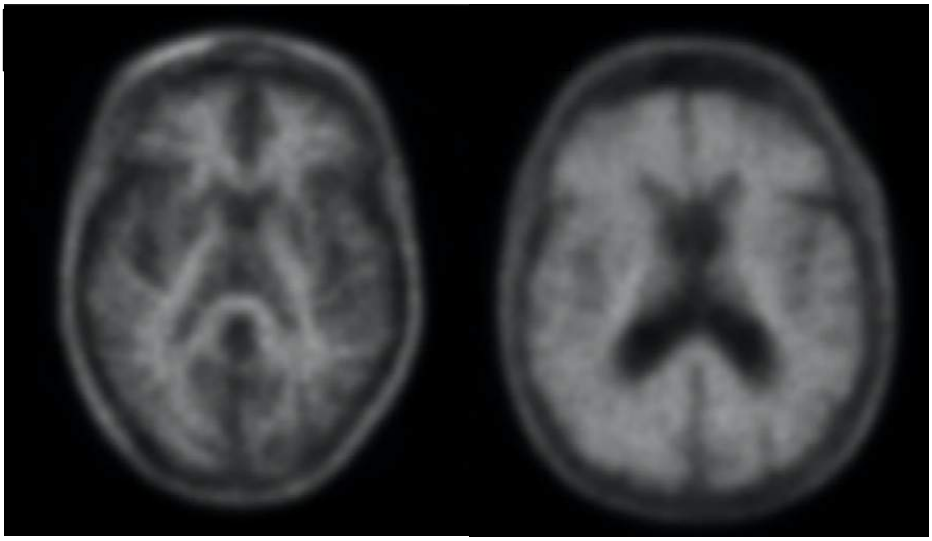

Figure 5 A) Negative 11F-Florbetaben Amyloid-PET. B) Positive 11F-Florbetaben Amyloid-PET

Amyloid-PET leads diagnostic utility to exclude the disease, with a **high Negative Predictive Value** [49]. PET scans performed during life have up to a **98% sensitivity** and 80% to 95% specificity for detecting neuritic amyloid plaques at autopsy [57].

Additionally, **patients with MCI and positive Amyloid-PET are significantly more likely to convert to established AD during the next three-year follow-up**, than those with MCI without Amyloid retention [58]. However, there are no significant differences in Amyloid retention as the patients' clinic declines. Amyloid retention reaches a plateau when patients manifest clinical symptoms, suggesting that the deposition precedes the onset of cognitive decline [59].

With the extended use of Amyloid-PET, the **Spanish Neurological Society** published **indications for Amyloid-PET** as a diagnostic tool in our country [49], which mainly includes a progressive cognitive deficit of uncertain etiology, atypical or mixed presentation, or early-onset dementia (under 65 years old).

4.1.2 Tau PET

Whole-brain tau PET could be a suitable biomarker for identifying AD-related ***in vivo*** **regional distribution of tau** (Figure 6) [60].

Ossenkoppele *et al. (2016)* suggested that **tau pathology**, against amyloid theory, **could cause clinical manifestations in AD** [61]. Furthermore, the correlation between tau and neuroinflammation has been demonstrated even without significant amyloid pathology, suggesting an Aβ-independent process [62-63].

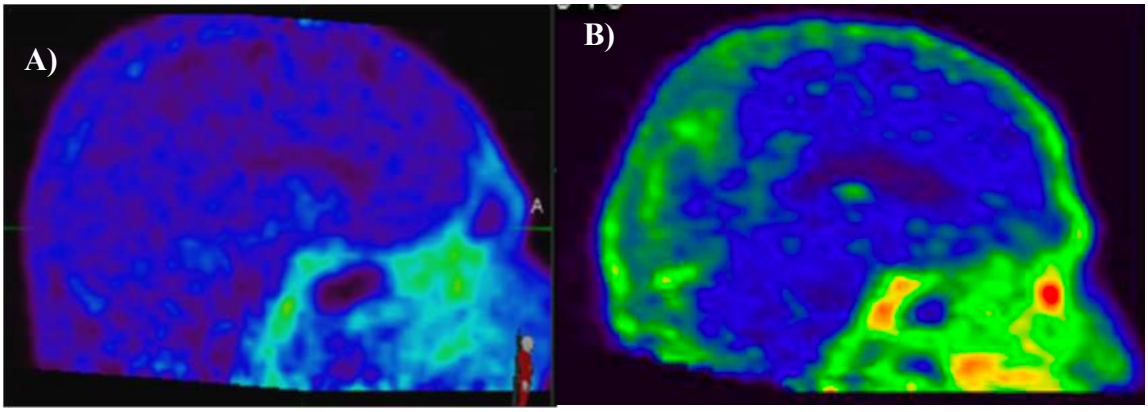

Figure 6 A) Normal ^{18}F-AV-1451 PET study illustrating a tau-PET scan from an elderly cognitively normal subject. B) Abnormal ^{18}F-AV-1451 PET study illustrating a tau-PET scan images of a patient with mil Alzheimer's disease.

4.2 Topographic image biomarkers

Topographic biomarkers are not specific but **provide a good representation of the disease's severity and progression** [55].

4.2.1 Magnetic Resonance Imaging (MRI)

MRI classically played a key role in excluding other causes of dementia, such as vascular or neoplastic etiologies. However, thanks to technological advances and improved image quality, it is currently also employed to rate the hippocampal atrophy. In **typical AD**, MRI shows **MTL, hippocampus, and entorhinal cortex atrophy** [64].

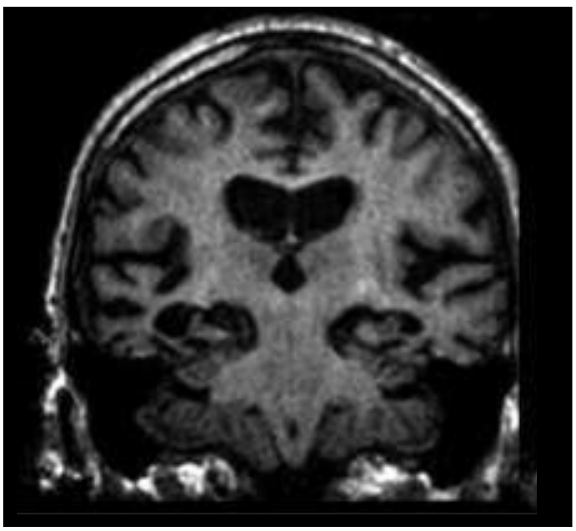

Figure 7. T1-weighted MRI image showing AD typical atrophy: medial temporal and frontotemporal cortical. Coronal view.

4.2.2 ^{18}FDG-PET

The decrease in fluorodeoxyglucose tracer (18FDG) uptake indicates **hypometabolism related to neuronal injury and synaptic dysfunction** regarding AD pathology [65].

Apart from the severity rate based on posterior cingular and temporoparietal hypometabolism, 18FDG-PET seems to have an outstanding accuracy in discriminating between Alzheimer's dementia and controls. Hence, **a normal 18FDG-PET almost excludes a neurodegenerative disease being the patient's cognitive symptoms cause** [66-67].

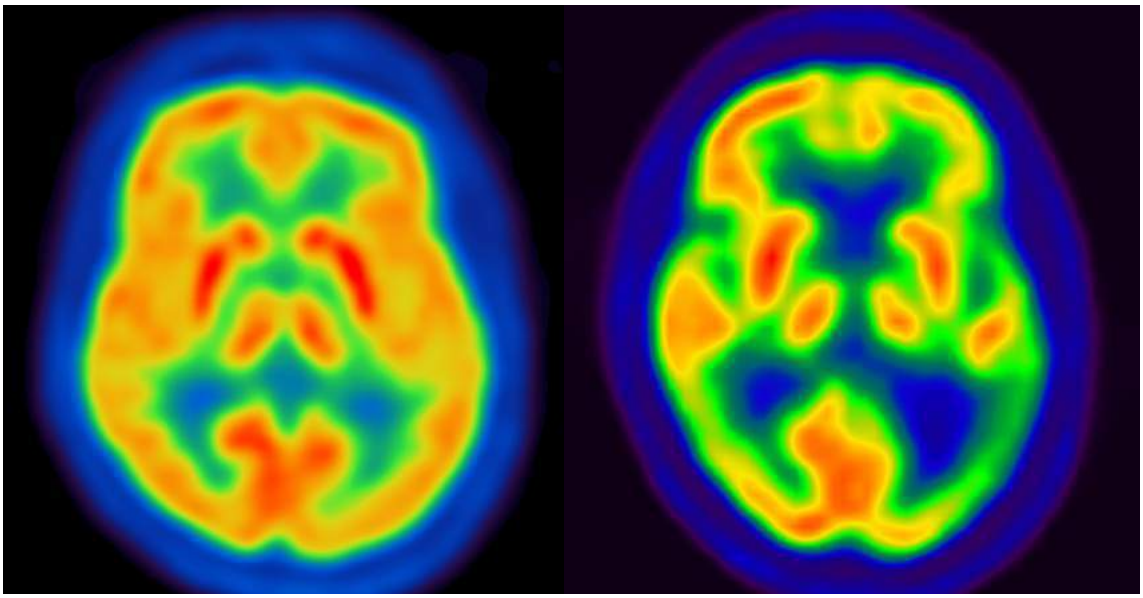

Figure 8. A) Normal ^{18}FDG-PET metabolism in healthy control. B) Characteristic ^{18}FDG-PET hypometabolism in AD pathology.

5. BIOMARKERS IN BIOLOGICAL LIQUIDS

Fluid biomarkers are promising tools for clinical staging and personalized patient monitoring, and for establishing a proper treatment [68]. They have the advantage of being easy to implement in clinical trials and allow the analysis of various biomarkers in the same sample [69].

5.1 Cerebrospinal Fluid biomarkers

CSF amyloid-beta 42 (Aβ42), total tau (t-tau), and phosphorylated tau (p-tau), are the most widely recognized as CSF pathophysiological biomarkers [70-71]. Likewise, they are the most accepted inclusion criteria and outcome measures in clinical trials [72].

The **decrease in Aβ42** CSF levels is **inversely correlated** with the **amyloid load on brain plaques** [73]. Aβ42 remains relatively stable over time in patients with AD dementia, so it only has a limited utility for progression monitoring [74].

Aβ40 is the predominant amyloid peptide in the brain, CSF, and plasma but does not appear to be as pathogenic as Aβ42 [75]. However, the Aβ42/Aβ40 ratio seems to be a better predictor than CSF Aβ42 alone; comparable to the T-tau/Aβ42 and P-tau/Aβ42 ratios [76].

CSF T-tau and P-tau levels have demonstrated a high validity to **differentiate AD from healthy controls** and other causes of dementia [77] and predict disease **progression** [78]. In combination with Aβ42, both **T-tau/Aβ42 and P-tau/Aβ42 ratios outperform AD diagnosis utility** [79].

Apart from the etiological markers, it has been recently described the usefulness of other associated processes' biomarkers, such as neurodegeneration, synaptic dysfunction, or inflammation [80-81]. **Neurodegeneration** biomarkers include **Light Neurophilically Protein (LNP)** [81-82] and **YKL-40**, which also measures **glial activation** [83]. Regarding synaptic dysfunction, we can mention **Neurogranin Synaptic Protein, NPTX2, or SNAP25** [81, 84]. Some studies also describe the benefit in measuring the concentration's increase of **chemokines**, as **CCL23** [85].

5.2 Plasma biomarkers

Since blood is more accessible than CSF, biomarkers measurement for AD diagnosis is preferable in this fluid. However, while there is a free exchange of molecules between the brain and CSF, only a small fraction of the Central Nervous System's proteins enters the bloodstream, and they are easily degraded or metabolized [81].

Recent immunoassay studies suggest that **Aβ may be a useful plasma biomarker**, despite previous contradictory studies [71]. Aβ42 and Aβ42/Aβ40 plasma ratio are correlated with high Aβ deposition levels in CSF and brain PET, and the **Aβ42/Aβ40** ratio is associated with the **risk of progression to clinical AD** in individuals with subjective memory complaints [86].

Ultrasensitive immunoassay techniques have also demonstrated **increased Tau-plasma levels in AD** compared to healthy controls. However, these differences, although significant, are low to be considered diagnostically useful [81]. Alternatively, T-tau or P-tau measurement in exosome preparations could improve its performance as a blood biomarker [87].

Other plasma biomarker candidates, still under-investigation, are axonal **Light Neurofilament Protein,** which reports neurodegeneration [88], **phosphatidylcholines** [89], **cardiolipins** [90], **neuronal pentraxin 1 (NP1)** [91], and **RNA levels** [92].

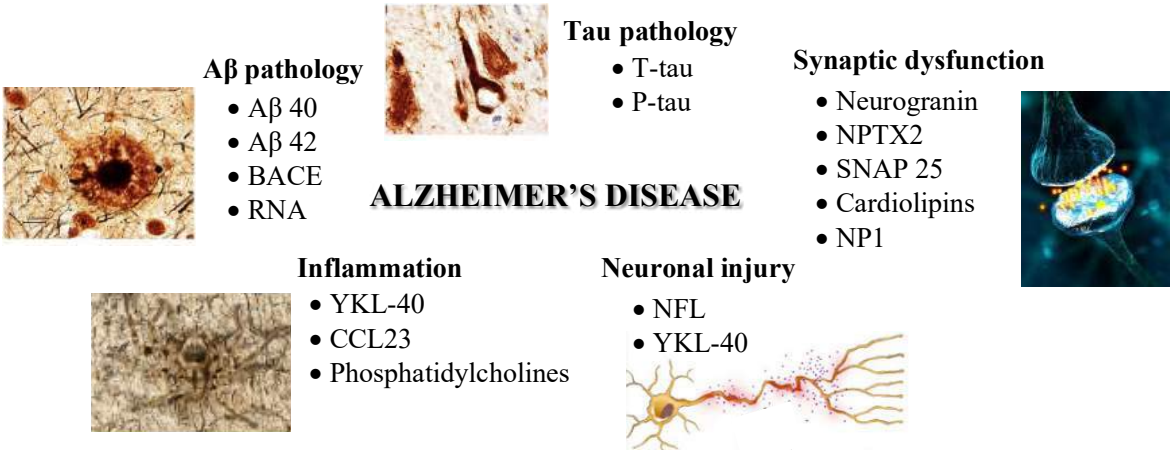

Figure 9. Diagram with main biomarkers for AD diagnosis

6. MEMORY EVALUATION IN OUR AREA

Accumulation of amyloid plaques and neurofibrillary tangles in AD begins at least a decade before the first cognitive symptoms [68]. For this reason, **early recognition and diagnosis are essential in order to plan care for our patients,** including treatments, non-pharmacological interventions, or participation in clinical trials.

For the neuropsychological evaluation of a patient with cognitive complaints, it is recommended to conduct an extended battery that tests all domains, not just the memory [93]. Additionally, before providing a definitive clinical diagnosis, it would be recommended its discussion by a multidisciplinary team. However, this idyllic situation is not the reality we face in our country.

Most clinical practice guidelines recommend that the first step in achieving an early diagnosis of AD rests with **General Practitioners, who play a critical role in early recognition of their patients' cognitive decline** [94]. In Spain, General Practitioners (GPs) only have 6 minutes per patient to perform a global evaluation. Due to this overloaded situation, Spanish doctors need to adapt to the circumstances of time constraints and spaced reviews, with the use of screening and short memory tests [95]. After the diagnostic's orientation in primary care centers, the situation does not change in the specialized outpatient clinics of Neurology or Geriatrics, where doctors only have half an hour in the best situation to perform the medical record, clinical and neuropsychological exam, and to achieve a definitive diagnosis and expected prognosis.

We also have to keep in mind that different memory tests are not interchangeable because they measure different items, such as free recall, categorical coding and recall,

and simple recognition tests [96]. It is essential to select effective, short, and easy-applicable so that we can test the memory in the limited time we have.

In addition to this time-challenge situation, we cannot ignore the **low educational level we have in Spain.** According to the latest available data up to the time of writing this work, 5.8% of the over 65 years old subgroup of people cannot read or write. Although the situation has significantly improved in recent years, 59% of the population over 65 years of age in our country had not completed primary studies [97]. This data is also assumed to be even worse in Andalusia, where, according to Unesco (www.ine.es/dyngs/INEbase/es/categoria.htm?c=Estadistica_P&cid=1254735971047), 2.16% of the Andalusian population (all age ranges) are illiterates.

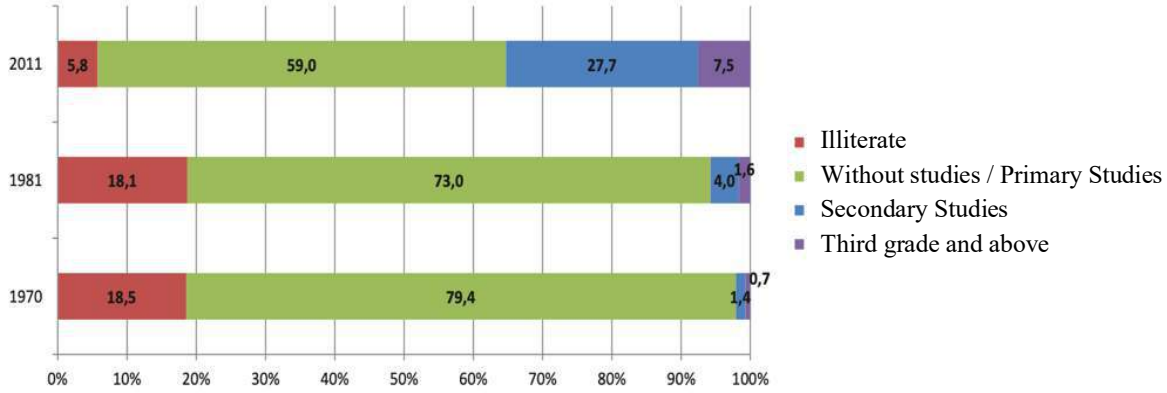

Figure 10. Spanish educational level's evolution in people aged 65 and over, from 1970 to 2011, according to data from the Population Censuses of the National Institute of Statistics (Data published in 2019) [97]

This low educational level situation turns difficult the neuropsychological exploration of our elders, who, even knowing how to read and write, will hardly perform tasks such as remembering word lists or doing serial subtractions.

Furthermore, we should also consider **"relative illiteracy"**: literate people in their native languages but unable to read or write in the host country language. This phenomenon is increasing due to rises in emigration and tourism, and we either cannot use verbal-based tests in this situation [98].

6.1 Screening tests

Screening tests are simple tasks designed to be quickly administered by non-specialized personnel to assess one or more cognitive domains. General Practitioners routinely apply them for **testing cognitive decline, assessing treatment responses, and monitoring evolution.** Their results sometimes also serve as **criteria for access to studies, treatments, and disability benefits** [95-96].

When administering neuropsychological tests, especially if they are screening ones, we must keep in mind that results may be influenced by conditions such as gender, age, hearing or visual deficits, or the patient's educational level, among others [95, 99-100].

Validated screening questionnaries or tests in our country are the Informant Questionnaire on Cognitive Decline in the Elderly (**IQCODE**) [101], Eight-item interview to differentiate aging and dementia (**AD8**) [102] Mini-Mental State Exam (**MMSE**) [103], **Mini-Cog** [104], Mini-Exam Cognoscitivo (**MEC**) [105], the Memory Impairment Screen (**MIS)** [106], the **Clock Drawing Tetst** [107] **Seven Minute test** [108], **Eurotest** [109], Short Portable Mental Status Questionnaire (**SPMSQ**) [110], **Phototest** [111] or Memory Alteration Test (**T@M**) [112].

There is a wide range of available screening tests, but there is no perfect one. Doctors must know and manage several ones, to choose the perfect one for each patient

and time, depending on the care circumstances, patient's characteristics, evaluator's experience, and the validation and normative studies' data in our country [99].

Therefore, a careful evaluation of the available instruments is necessary to establish reproducibility and understand the differences in population and score that can lead to significant variation in test performance [113].

Below we present a brief description of each of the screening tests mentioned above, including their psychometric properties and validation and regulatory studies available today in our country.

6.1.1 Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [101]

IQCODE questionnaire was designed to **assess memory** (single-domain) **through a self-administered questionnaire by a family member or caregiver** to detect mild dementia in the patient [101]. It is also sensible to identify subjects likely to develop dementia in the future, although it lacks specificity for this purpose [114].

Like the rest of the informant-based questionnaires, this test provides a complementary and advantageous approach for evaluating patients with difficulty collaborating due to illness, low educational level, or sensory deficits [115].

One of its significant advantages is that, unlike other screening tests, such as the MMSE, **IQCODE is not contaminated by sociodemographic variables such as age, educational level, or patient's premorbid capacity** [116]. However, the informant's mental health, burden, and the relationship's quality between the informant and the patient [115].

The original version consists of 26 items, rated on average, assessing the patient's cognitive changes in the last ten years. It has excellent psychometric properties, with a **Sensitivity of 80%, Specificity of 82%,** and Internal consistency measured with **Cronbach's alpha of 0.96** [101]. The author of the questionnaire published in 1994 a short version in English [117], with 16 items, with a correlation of $r = 0.98$ with the original version, and comparable validity.

The **Spanish version** (S-IQCODE), known as the *"Informant's Test or Test del Informador (TIN),"* also has an abbreviated form (SS-IQCODE) [116]. The short version maintains the diagnostic characteristics, with an **Sensitivity of 86%, Specificity. of 92%, Positive Predictive Value (PPV) of 54%, Negative Predictive Value (NPV) of 98%, and internal consistency measured with Cronbach's alpha of 0.95,** being more efficient by reducing 30% the administration time.

In conclusion, **IQCODE is an excellent detection option for cognitive decline detection, especially for patients with low educational levels, different spoken language from the country of residence, or monitoring patients with prior cognitive control** [115].

6.1.2 The AD8: "Eight-item interview to differentiate aging and dementia" [102]

The AD8 was developed as a brief instrument to help discriminate between signs of normal aging and mild dementia [102]. It was originally validated as an informant-based interview completed by a person who knows the patient well. The AD8 contains 8 items that test for memory, orientation, judgment, and function. It is short, simple, and

quick to administer (~ 3 minutes). Cutoff points are normal cognition 0-1; impairment in cognition 2 or greater.

A Spanish version of AD8 has been validated in our country. The questionnaire showed high diagnostic accuracy to discriminate between patients with cognitive impairment and healthy controls (AUC 0.90; CI 95%, 0.86-0.93). The best cutoff was 3/4 (Sens. 93%; Spec. 81%) [118].

6.1.3 Mini-Mental State Exam (MMSE) [103]

The Mini-mental State Examination (MMSE) was **designed by Folstein in 1975** [103] **as an instrument for a brief mental state assessment.** Widely disseminated, it is the most frequently cited cognitive test on Medline and the one with the largest language versions. It is the most adapted test for standardized cognitive evaluation in clinical settings, having data for screening, staging, and treatment monitoring [119].

MMSE is a brief test structured in eleven questions, able to administer within 5-10 minutes. It attempts to **examine various cognitive functions: orientation, immediate and deferred memory, concentration, language, and visuospatial function** [103]. The total score must be adjusted to the demographic characteristics of the individual and study population.

The test's Sensitivity to the dementia patients' diagnosis is 77.0%, and the Specificity 91.2%. However, the precision in identifying of MCI versus healthy controls is lower, with a Sensitivity of 63.4%, and a Specificity of 65.4%. **Its properties also change depending on the cut-off point** selected: for 23/24, the Sensitivity is 85%, and

the Specificity 90%, while for a 24/25 cut-off point, Sensitivity is 87%, and Specificity is 82% [119-120].

The MMSE presents a **good agreement between General Practitioners and neuropsychologists in specialized memory units**. Although the scores obtained by the GPs are generally lower (15.8 vs. 17.4 for specialized units; $p < 0.01$), the *Kappa* index of the agreement is 0.86 [121].

In Spain, we have several validations and normative studies for the different versions. For its original one, according to *Blesa et al.* (2001) [122], Cronbach's alpha coefficient was 0.94. For an estimated cut-off point in MCI patients of 24/25 Sensitivity is 87.32%, and Specificity 89.19%.

The **psychometric test properties vary depending on the population prevalence and the selected cut-off point** [119-120]. This statement has also been demonstrated in Spain where, for a general Primary Care population, the recommended cut-off point for dementia patients is 22/23 [123], while for specialized memory clinics ("hyper selected" patients), it is preferable 24/25 [124] or 26/27 [125] as optimal cut points.

We can conclude that **MMSE meets the psychometric requirements of reliability and reproducibility for distinguishing patients with cognitive impairment from healthy controls**. However, it is only modestly accurate, turning it more **suitable for its use in the Primary Care setting**, needed to combine it with other neuropsychological tests for purposes such as differentiation between MCI and AD.

6.1.4 Mini-Cog [104]

The Mini-Cog is a **short and easy cognitive test, consisting of a three-element verbal memory task and a simplified assessment of the Clock Drawing Test**. It was developed as a brief test to discriminate people with dementia from healthy elders in a typical heterogeneous population of a Primary Care setting. According to its authors, it is also free of educational and cultural biases [104].

The standard scoring system involves assigning 0 to 3 points on the word retrieval task for correct retrieval of 0, 1, 2, or 3 words, respectively. The rating of the clock drawing part is as "normal" or "abnormal" (0 vs. 2 points).

The Mini-Cog has been validated in Spain [126]. The test showed high diagnostic accuracy for discriminating between patients with cognitive impairment against healthy controls (AUC ± Sensitivity: 0.88 ± 0.01). The instrument was less useful for screening individuals with low education levels (AUC ± Sensitivity: 0.74 ± 0,05). A cut-off point of 2/3 in the Mini-Cog achieved a Sensitivity of 0.90 and a Specificity of 0.71 [104].

6.1.5 Cognitive Mini-Exam (MEC) [105]

Lobo's MEC is a Spanish adapted and validated version of the MMSE [105]. It is a dementia screening test, also useful in their evolutionary monitoring. There are two versions, 30 (MEC-30) and 35 (MEC-35) points. The items are grouped into five sections in both versions that examine orientation, fixation memory, concentration and calculation, delayed recall, language, and construction. The 35-point version adds a 3-point digit item in the "concentration and calculation" section and another 2-point abstraction item in the "language and construction" section. It is more advisable to use the 30-points version. The cut-off point for dementia is usually set at 24 points.

According to *Lobo et al.* (1980) [105], this is a useful screening test to discriminate between patients with cognitive decline from healthy controls, with test-retest reliability of 0.87.

6.1.6 Memory Impairment Screen (MIS) [106]

Memory Impairment Screen (MIS) is a **short and easy-to-administer detection test, which through four words** (or drawings in its version for illiterates), evaluates **free and cued reminding.** It uses controlled learning to specify attention, induce specific semantic processing, and modify the coding specification to improve cognitive decline detection [106].

Although its psychometric data varies depending on the cut-off point, they are excellent, with a Sensitivity between 85-90% and Specificity between 90-98%. As it is a memory-based test, its performance is better for AD or mixed dementia than vascular dementia [106].

MIS also has excellent discriminatory data for MCI and AD for its **Spanish versions**, similar to the English version. However, in our country, most of the authors' chosen cut-off point is 4, granting a Sensitivity over 90% and Specificity over 80%. It also has an adequate interobserver (0.85) and test-retest (0.81) Specificity [127-129].

A recent study further demonstrates that **MIS Sensitivity is better for non-English speakers and less educated people, minimizing cultural bias in ethnically diverse populations** [130]. Together with its excellent diagnostic utility values and its brevity

and ease of administration, those properties make MIS a r**easonable alternative to other screening methods.**

6.1.7 Clock Drawing Test (CDT) [107]

The Clock Drawing Test (CDT) is a **short and easy to administer screening test**. Introduced at the beginning of the 20th century as an apraxia sign for detecting parietal lesions [107], soon after, it also became used as early detection of cognitive decline. The CDT is **one of the most widely used** brief cognitive tests. However, it has significant disadvantages. In addition to having a discrete diagnostic utility, it does not explicitly explore episodic memory, is not adapted for low-educated patients, and is not provided by a unified correction method [131].

There **are more than fifteen validated variants**. Some of them comprise the drawing on a **blank sheet**, from a **previous circle**, or combining the **spontaneous drawing with a copy** [132-136]. Each one of these variants has its scoring system [137].

CDT is a short and easy to administer screening test, with **excellent internal consistency and reliability among evaluators.** However, due to the high number of different scoring systems, its accuracy is still debated. These problems could be solved when **combining the CDT with the MMSE**, both variants **improving its diagnostic utility** [138]. We also have **validation and normative values for CDT in Spain**, although they give similar results to other countries [139].

Concluding, **CDT can reliably and accurately differentiate patients with dementia from healthy controls,** providing crucial clinical information. However, its

diagnostic utility is discrete in differentiating MCI from Healthy Controls. This limited utility, adding to the fact that it is not suitable for illiterate patients, and does not include any specific memory examination, turns it into a second option as a screening test for a memory outpatient clinic [131].

6.1.8 Seven Minutes Screen [108]

The 7 Minute Screen Test (7MS) was designed by Solomon et al. (1998) [108] as a **screening instrument for dementia,** especially for the Primary Care setting. Its main contribution is the **inclusion in a single instrument of several tests that had previously demonstrated excellent diagnostic performance** [108].

The 7MS includes four subtests that examine specific affected areas early affected in AD (temporal orientation, episodic memory, visuospatial and visuoconstructive capacity, and semantic memory).

In its Spanish version [140], the tests included are the Benton Temporal Orientation Test, a version of Buschke's Free and Cued Selective Reminding Test (FCSRT), the CDT, and a category fluency test. **The Benton Temporal Orientation Test** includes five temporal orientation questions and evaluates the error and the deviation degree from the correct answer. The **FCSRT** variation of the one proposed by *Buschke et al*. examines episodic memory (free and facilitated recall) after conducting the semantic processing of 16 drawings. By establishing guided learning with a semantic cue, it minimizes the interference due to distraction or anxiety. The Spanish adaptation of the original FCSRT employs drawings rather than words, allowing testing on low-educated patients. The **Clock Drawing Test** assesses visuospatial and visuoconstructive skills through a

simplified version. Finally, semantic memory is explored using a **category fluency test** (animals in 1 minute).

According to the original study [108], the test is **highly sensitive (92%) and specific (96%)** on diagnosing dementia**,** in addition to specifying excellent test-retest reliability (0.91). This **high ability to discriminate between AD patients and healthy controls** has been confirmed internationally [141] and in its Spanish version [140, 142]. However, it seems that gender, age, and educational level have a higher impact on results than described initially.

7MS is an excellent instrument for dementia diagnostic screening. However, despite being short, it is needed a mean of 12.4 minutes (between 8 and 22) for its complete administration [143], so it is not suitable for a short memory outpatient consult.

6.1.9 Eurotest [109]

The Eurotest is an instrument designed in Spain, **based on the money knowledge and management,** adapted from the Money Test. It is **easy to administer, useful, and applicable to illiterate and low-educated patients** [109].

Among its psychometric properties, it stands out with a 93% Sensitivity and 87% Specificity on differentiating dementia from Healthy Controls, similar values to MMSE and 7MS, but with less administration time needed. The Eurotest ecological validity is guaranteed by the day-to-day nature of the tasks and materials, and the proper construct validity is guaranteed by the significant correlation between the Eurotest score and the Global Dementia Scale [144].

Therefore, the Eurotest is a **rapid, easy, and useful screening test for dementia in routine clinical practice. It is not influenced by sociodemographic variables such as educational level, which is advantageous over other available screening tests** [145-146].

6.1.10 Short Portable Mental Status Questionnaire (SPMSQ) [110]

The Short Portable Mental Status Pfeiffer (SPMSQ) was **developed in 1975 to differentiate organic and functional disorders** [110]. Through ten questions and a serial math subtraction, briefly **evaluate short and long-term memory, orientation, information on daily events, and executive function.** Its main advantage is its easy administration since it does not require any specific tool for its completion, and it applies to low-educated patients. The scoring encompasses four categories: 0-2 (cognitively intact), 3-4 (medium damaged), 5-7 (moderately disabled), and 8-10 (severely disabled) [147].

It is a **sensitive and specific screening test for moderate to severe dementia** in the community and in-hospital patients. However, its diagnostic utility for the MCI diagnosis is limited [148-149].

For its **Spanish adaptation**, results on differentiating dementia from Healthy Controls are similar to the original version, with an AUC of 0.892 and at outstanding reliability, interobserver (k = 0.734) and intraobserver (k = 0.925) [150]. The most recommendable cut-off point in our setting is three mistakes, the same recommended by *Pfeiffer et al.* [110], or 4 in the case of illiterates. [150].

SPMSQ is a relatively sensitive screening test for dementia both in the community and in pluripathological inpatients. It is easy to administer, even in illiterate or elders. However, its **diagnostic utility for MCI is limited**, so this evaluation must be completed with other neuropsychological tests or batteries.

6.1.11 Phototest [111]

The Phototest, developed in Spain, is a **brief and easy-to-administer instrument feasible for illiterates. It evaluates visual recognition and denomination, verbal fluency, and memory,** evaluating the cue efficiency [111].

A **complete diagnostic validation** of this test has been carried out, including phases I [111], II [151], and III [152], in addition to a normative study [153]. Phototest shows **good test-retest and interobserver reliability**, and cutoff scores of 26/27 and 28/29 points give adequate discriminatory validity for dementia and cognitive decline, respectively [154].

Phototest seems to be **more precise and less expensive than MMSE**. It has **similar diagnostic effectiveness to MIS,** being also applicable to illiterate patients [154].

Phototest is a brief and easy-to-administer screening test with good diagnostic accuracy for dementia and cognitive decline. **It is influenced by age, gender, and educational level, but it is suitable for illiterates.** Those properties make it **feasible for the primary care setting and general neurology outpatient clinic**.

6.1.12 Memory Alteration Test (M@T) [112]

M@T is another screening test developed in Spain, brief, easy-to-administer, and score. It covers **tasks evaluating temporal orientation and episodic and semantic memories** [112]. It provides useful and **valid discrimination between** patients with Subjective Memory Complaints **(SMC) and aMCI, SMC and mild AD, and between aMCI and mild AD** [155-156].

M@T constitutes a short and reliable screening test that could be applicable by GPs in primary care clinics. However, it has not normative values, and it should not be used singly to define dementia, as it only evaluates memory and temporal orientation, not valid to detect atypical AD or other dementias.

6.2 Specific memory tests

In our country, there is no standardization in the use of memory tests. Some of the most widely used are word lists, logical memory tests, or those evaluating the semantic cue's efficiency. The choice usually depends on the available time and suspected disease.

6.2.1 Verbal memory tests by word lists

Some of the most used in our environment are: ***"The California Verbal Learning Test" [157], "The Rey Auditive Verbal Learning Test" [158], "Word-List memory subtest of the CERAD" [159]***, and de Spanish ***"Verbal Learning Test Spain-Complutense (TAVEC)" [160].***

The **California Verbal Learning Test (CVLT)** is one of the most commonly used tests to assess older adults' verbal episodic memory. It evaluates the free and cued

recovery through word lists, serial position effects, intrusions, interference, and recognition [161]. The CVLT has been a useful tool to diagnose memory disorders in healthy aging, MCI, and AD. Both its original form and the alternative CVLT-II have shown good test-retest reliability [162].

We do not have a normative study of this test in Spain, although we validate subjects with subjective memory complaints and aMCI [163].

The **Rey Auditive Verbal Learning Test (RAVLT)** [158] assesses episodic memory through verbal learning from a list of 15 words, presented up to five times. An immediate subject's evocation follows each presentation. Finally, a sixth free recall is requested after a non-mnestic interference task. It is an easy test to administer, although its administration time is long, about 15 minutes.

In Spain, we also do not have a RAVLT normative study. However, we do have a prospective validation in patients with Subjective Memory Complaints, where RAVLT seems to help to identify those patients with Subjective Memory Complaints with high risk to progress to AD dementia-type, and also differentiate them from the preclinical AD phase, mild cognitive impairment, and healthy aging [164].

A RAVLT reduced version has traditionally been more used, including 10 items in the list of words to remember. This version is part of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) by Morris et al. 1989 [159]: **The Word-List memory subtest of the CERAD.**

This subtest has three trials. It starts with the task of reading words, followed by a free recall. Although it does not include the semantic cue's efficiency or the binding, it is

a quick and straightforward administration test, which has been useful to differentiate AD dementia patients from healthy controls [159, 165].

Despite being one of the most widely used verbal memory tests in our country, we also did not have a normative or validation study for this subtest.

The **Verbal Learning Test Spain-Complutense (TAVEC)** [160] is a modified version of the test of the fifteen words of André Rey 1958 [158]. The distinctive TAVEC's feature is the incorporation of a neurocognitive memory model for data interpretation.

It evaluates episodic verbal memory and learning ability. It consists of 3 learning lists of 16 words, read several times by the examiner: a learning list (list A), an interference list (list B), and a third recognition list. Lists A and B consist of two semantic categories, each (shared categories). TAVEC provides information on the subject's learning curve, primacy, and recency effects, learning stability, learning strategies, susceptibility to interference, delayed memory, the benefit of semantic keys, perseverations, and intrusions [160].

From all the tests previously named as word list verbal learning, TAVEC is the only one for which we have normative and validation studies in our country [160].

6.2.2. Logical memory tests

Assessment of free recall and recognition through short stories is another effective way of detecting initial episodic memory impairment [166].

The Wechsler Memory Scale (WMS) [167] has long been used in clinical assessment all over the world since 1987. Parts or variants of this test are included in most neuropsychological batteries for cognitive evaluation. The complete battery consists of fifteen tests on its last edition (WAIS-IV): **Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed.** A Total Intelligence Quotient can be obtained from the top ten test scores, a good measure of general intellectual functioning. The time required to apply the 10 main tests of the WAIS-IV is approximately 80-90 minutes; the time varies between 100 and 115 minutes for the full-scale application [168].

The WMS allows the rater to obtain five Indices: Auditory Memory Index, Visual Memory Index, Immediate Memory Index, Delayed Memory Index, and Visual Working Memory Index.

One of the traditionally most used subtests in our environment was the "Logical Memory Subtest", which evaluates immediate recall. The task consists of the free recall of the higher possible ideas from two stories previously read by the evaluator. After a 20-30 minutes interval, the evaluator asks the evaluated person to remember the two stories and answer the stories' questions (recognition) [168].

In 2008, the Psychological Corporation published the fourth version of the scale (Wechsler Memory Scale- Fourth Edition) and, in 2013, the Spanish adaptation of the fourth edition, the Wechsler-IV memory scale [169-170].

Another logical memory test that is also widely used in Spain is the **Barcelona logical memory subtest**, part of the Barcelona Test [171-172]. The Barcelona Test was the first neuropsychological examination instrument developed in our country to assess

cognitive status. It includes a broad number of cognitive functions, such as language, orientation, attention-concentration, reading, writing, praxis, visual recognition, memory, and abstraction, with a total of 106 subtests in 42 sections. One of the historically most used subtests is the **Logical Memory subtest.** It tests immediate and delayed free recall of two short stories and recognition items through yes/no answer questions.

This test, developed in our country, has normative data, both for its original version [172] and its abbreviated one [173].

6.2.3 Memory evaluation based on semantic categories and cued recall. Free and Cued Selective Reminding Test (FCSRT) [174]

The **FCSRT** is a measure of memory under conditions that **control attention and cognitive processing to obtain an assessment of memory without confusion for normal age-related cognition changes.** Its performance has been associated with preclinical and early dementia in several longitudinal epidemiological studies [175].

The test begins with a **coding phase,** in which the participants must examine 16 easily recognizable pictures, represented in groups of 4, in 4 different cards. The patient is asked to **point and name each item after its semantic clue.** Immediate recovery is initially evaluated with clues after each of the cards. Subsequently, three recall trials are examined, freely, and provided with clues. Its original version also includes a delayed recall [175].

The unique FCSRT‘s feature is its **emphasis on coding specificity during learning and recall.** Through this coding, attention, cognitive processing, and effective strategies are ensured [176]. **Coding specificity is a technique that produces efficient**

learning and memory in normal subjects. This task is particularly sensitive in the early stages of AD [177].

A significant advantage of the FCSRT is that it **allows the distinction between registration** (ensuring that all items have been registered), **storage** (by providing the semantic cues), **and retrieval** (by different recall phases) [178].

There are different versions of the FCSRT. They vary in the number of memorized items, the use of words or pictures as stimuli, and the method of administering the test. The most widespread version is the 16-item verbal version (Figure 9) [179]. The FCSRT + IR (Immediate Recall) version includes only the three immediate recall trials, suppressing the delayed recall phase and reducing its administration time.

Poor free recall performance on FCSRT shows to predict future dementia, up to 5 years before, with a Sensitivity of 85% [180]. However, despite having good Sensitivity and Specificity, in many cases, it is not possible to administer it in a regular neurology consultation in our public health system because it takes about 15 minutes to administer [181].

We have both FCSRT normative and validation studies as part of the Neuronorma project [177].

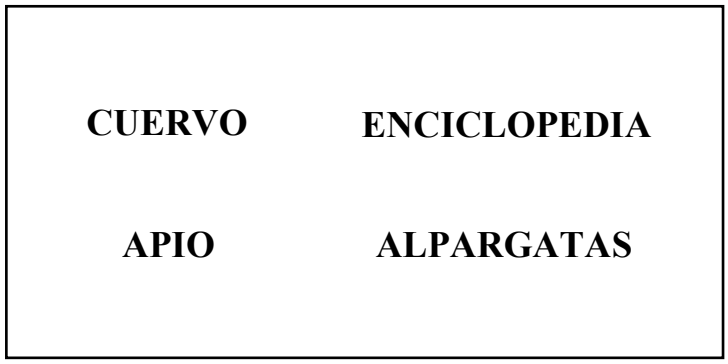

Figure 9a. Word-Sheet of the Free and Cued Selective Reminding Test. Spanish Validated Version. Adapted from Peña-Casanova et al. (2009) Arc Clin Neuropsychology [177].

CATEGORÍA	ÍTEM	Ensayo 1		Ensayo 2		Ensayo 3		Recuerdo diferido	
		L	F	L	F	L	F	L	F
Ave	Cuervo								
Mat. Lectura	Enciclopedia								
Verdura	Apio								
Calzado	Alpargatas								
Reptil	Caimán								
Material de Construcción	Mármol								
P. Preciosa	Turquesa								
Edificio	Piso								
Mueble	Escritorio								
Vehículo	Autocar								
Herramienta	Hoz								
Inst. Musical	Armónica								
Utensilio de cocina	Colador								
Deporte	Gimnasia								
Planta	Jazmín								
Tipo de Barco	Pesquero								
Recuerdo Libre Total									
Recuerdo Facilitado Total									
RECUERDO TOTAL									

Figure 9b. Score-Sheet of the Free and Cued Selective Reminding Test. Spanish Validated Version. Adapted from Peña-Casanova et al. (2009) Arc Clin Neuropsychology [177]. L: Free recall. F: Cued Recall.

6.2.4. Verbal Binding tests.

The poor performance of explicit episodic memory in older adults seems to be due to the difficulty in merging attribute-units. Although elderly individuals can memorize each of the components to a reasonable degree, the **associations linking the units together are weakened in old age** [182]. This associative deficit appears mainly in name-face pairs [183] or colored objects [184] and does not depend on the recognition

test format. Questionnaires assessing binding appear to have better sensitivity than the FCSRT, especially in longitudinal studies, thus facilitating the measurement of minor memory decline and the detection of very early AD [185].

One of the most employed verbal binding tests is the **Associated Pairs subtest of the Wechsler Scale** [167]. This subtest assesses immediate recall with a list of between 10 and 14 “easy” (E.g., North/South) and “difficult” (E.g., School/Cellar) pairs of words presented orally. Assess long-term recall with semantic cues, as well as verbal recognition. As we mentioned before, we do have a Spanish adaptation of the fourth edition, the Wechsler-IV memory scale [169-170].

The most widely used associative memory test is ***The Memory Binding Test (MBT)*** [186]. It is based on the specificity of coding and the evaluation of free memory strategies and with a semantic key, through the memorization of two lists with items of the same semantic categories in both lists; this is how the two lists' interference is evaluated.

The MBT owns a reasonable validity for aMCI discrimination of healthy controls [187], and we also have a validation study in our country [188].

6.2.5 Visual Memory tests.

An advantage of tests that evaluate memory using images is that they are adequate for illiterate and low-educated patients [189].

The most used ones have been the **Copy and reproduction of the Rey Complex Figure** [187] and the **Visual Reproduction subtest of the Wechsler Scale** [167].

The task of copying the Rey figure is a widely used test in routine clinical practice. It consists of **reproducing a meaningless figure of high geometric complexity due to its richness of details.** A second phase can be performed, which assesses visual memory at 3 and 30 minutes. It usually takes about 10 minutes to administer [181]. One of its drawbacks is that it has several scoring systems, although the best known is the 36-point system developed by Osterrieth [191].

The visual reproduction subtest of the Wechsler Scale evaluates the immediate and delayed recall of simple geometric figures, presented for 10 seconds. Evaluates the copy, recognizing the drawings presented among others presented as distractions, and their memory.

We might highlight **The Delayed Matching-to-Sample Task 48 (DMS48)** [192] within the **visual recognition tests**. This type of visual recognition test is severely impaired in the **perirhinal cortex lesions**, compared to hippocampal lesions, where it is mildly affected or even intact [193], due to neurofibrillary tangles are initially deposited in the perirhinal cortex rather than in the entorhinal cortex or the hippocampal formation [194].

The DMS48 test presents 48 visual stimuli, colored drawings divided into three types of elements: abstract, paired, and unique. It consists of a coding phase and three recognition tasks of the drawings seen in the first phase, together with another distractor [192].

In addition to being suitable for illiterate or low-educated patients, it appears relatively independent of attentional processes. Although it requires 30 minutes between sets 1 and 2, the administration of each of them takes around 5 minutes [192].

The biggest drawback is that we do not have normative or validation studies in our setting, having to be guided by the references of the French [195] and Chinese [196] studies. In its French normalization, it shows a good balance between sensitivity and specificity, both for immediate recall (Sensitivity 70.6%; Specificity 79.6%) and delayed recall (Sensitivity 79.4%; Specificity 72.9%). Furthermore, it has a high negative predictive value, around 98.5% [195].

The **Free and Cued Selective Reminding Test (FCSRT),** already discussed above *(Headland 6.2.3),* also has an available **pictorial version**. It is essential to know that their verbal and pictorial versions are not equivalent. The scores are higher in the pictorial one since both in MCI and healthy adults, the information presented graphically improves coding performance [197]. **This better performance observed in memory tests that use images instead of words could be related to the "dual coding theory,"** which proposes that images are more beneficial than words because images evoke both verbal and image codes, while words only trigger an abstract verbal code [198].

Both verbal and pictorial versions demonstrate appropriate discriminant validity between Healthy controls and MCI patients, with a Sensitivity over 90% for the Free Recall (FR), over 85% for the Total Recall (TR), and a Specificity over 90 % for both FR and TR [198].

Following the line of the Memory Binding Test [186] and its relationship with hippocampal injury [188], we find a new test assessing memory by association is the

"Memory Associative Test of the District of Seine-Saint-Denis" TMA-93 [199], which **examines binding by images: drawings of familiar objects of everyday life.** By using images, this test overcomes the difficulty of testing memory in low educated individuals. In the original paper, the test demonstrated optimal diagnostic accuracy to differentiate AD patients from healthy controls in a poorly educated and culturally diverse population [199].

The TMA93 evaluates binding memory by ten semantically related pairs of daily life objects. Those pairs of objects are shown in the encoding phase (Figure 10a), while in the recall phase (Figure 10b), only one of the two items has to recall the missing one.

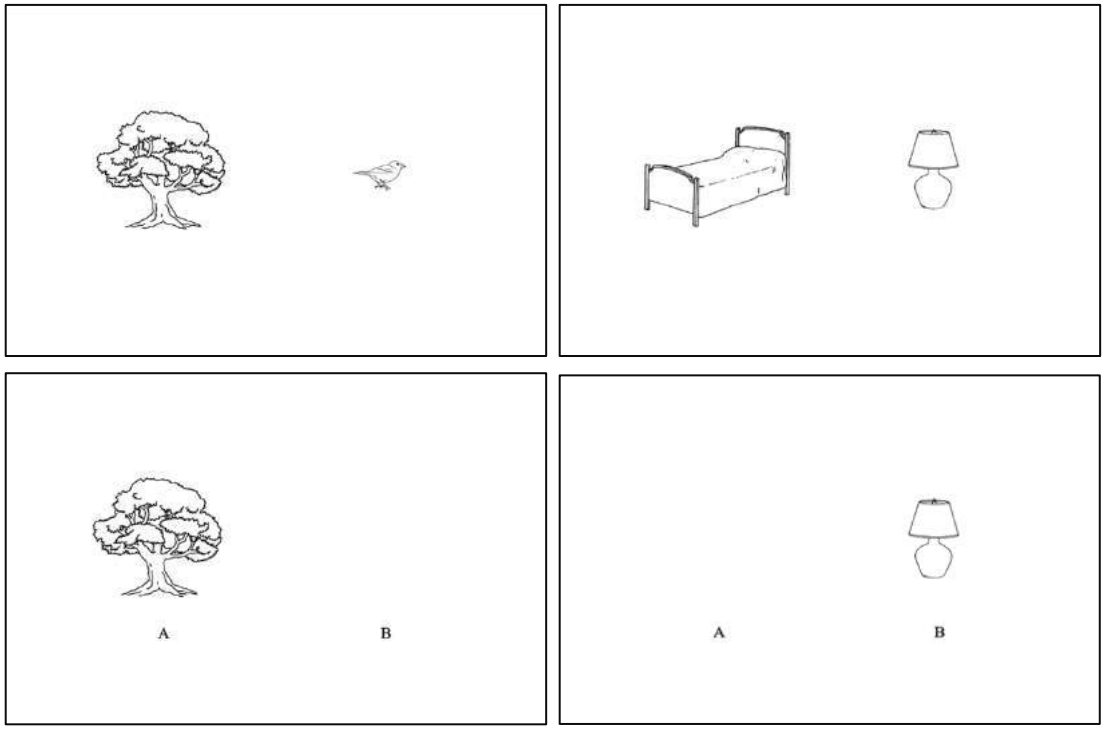

Figure10. TMA-93. Example sheets of the TMA-93. *Maillet et al, 2017.* **A)** Sheets for the coding task. **B)** Sheets for the recall task.

In its original validation study, the TMA-93 total score identified AD patients with high sensitivity (88%) and specificity (97%), with the total score strongly correlated with the FCSRT free memory and total memory scores [199].

7. DEVELOPMENT OF A DIAGNOSTIC TEST

Similar to treatments, new diagnostic methods need a rigorous evaluation process before their introduction in routine clinical practice [200].

7.1 Definition of the test

The first step is accurately defining **the test's purpose** because this will influence many of the later steps in the selection process. Considerations may include the disease or condition to be diagnosed, whether a single test or diagnostic algorithm is required, and whether the test should or could provide a qualitative or quantitative result. It is also crucial to **correctly define its potential final user** (for example, specialized neurologist or neuropsychologist, or a primary care worker). It will also be vital to determine its clinical use for detection (sensitive test) or for diagnostic confirmation (a very high specificity will be the choice) [201-202].

After selecting the test that we are preparing to develop, we must review other similar tests available for that same condition.

7.2 Validation studies

After selecting our objective test, the first is to perform a **preliminary validation (I)** [200], a cross-sectional or case-control study with a convenience sample. This preliminary validation aims **to confirm differences in results between patients and Healthy Controls (HCs)**. The belonging to patients or HCs group must be determined by a gold-standard applied before the test to validate.

The formed groups must be different concerning the diagnosis and not regarding other variables (age, gender, educational level). The new test's diagnostic accuracy is analyzed using ROC curves and estimated by the area under the curve, using the gold standard as a reference criterion. The diagnostic accuracy (or diagnostic utility) is considered Good if the area under the curve is higher than 0.80 and optimal if the area under the curve is higher than 0.90. The ideal cut-off is calculated by using the Youden index, which optimizes sensitivity and specificity.

Phase II consists of a cross-sectional design, but the sample includes a **broader representation of the process to be diagnosed,** with doubtful cases and different process stages, in the same proportion as it appears in the test conditions is theoretically going to be applied.

The critical characteristic of **phase III** is that the test to be validated is administered **before the gold-standard**, constituting a cohort. This design allows for evaluating the predictive-diagnostic capacity of the test.

When conducting discriminative validation studies, it is necessary to follow the **Standards for Diagnostic Accuracy Reporting (STARD),** updated in 2015 [204-206], which guide how to improve the quality of reports, in order to avoid failures in study design, data collection, or test interpretation, among others. The STARD Statement lists 30 essential recommendations to include in any validation study to minimize biases and improve the results' generalizability and applicability [207].

Assessments should be performed in the target population in which the test will be used, as this will provide clinical precision data that is appropriate for the prevalence of the disease locally and for other context-specific factors that could influence the precision, like common comorbidities.

7.3 Reliability studies

Reliability studies include two concepts: the **tool's internal consistency** and the evaluation of the **measurement's precision:** the result does not change according to the observer (inter-observer reliability), and the result is reproducible in repeated studies (test-retest reliability).

Internal consistency analyzes whether the different parts of the test measure the evaluated construct homogeneously, without low correlation or redundant items. It is estimated mainly by Cronbach's alpha: a greater value than 0.70 is considered acceptable, optimal between 0.90 and 0.95, but redundant if higher than 0.95.

Interobserver variability studies test the agreement between two or more raters on test scores. Ideally, they include healthy and cases with less or greater severity.

Test-retest variability studies are essential to assess precision, mainly if the measure will test longitudinal evaluations. There are typically included Healthy Controls. The period between first and second evaluations, conducted by the same rater, should take between 2 and 4 months. If the interval is shorter than two months, it could appear a "practical effect": if longer than four, we could find a potential diagnostic status change.

The interobserver and test-retest reliability studies' statistic of choice is the Intraclass Correlation Coefficient for continuous variables.

7.4 Normative studies

Normative studies are carried out on a **healthy reference population**, **with a broad representation,** to assess how sociodemographic variables (age, gender, educational level) influence the test score [208].

The effect of sociodemographic variables on the test score is analyzed statistically. Depending on the result variables distribution, regressions or an approximation based on percentile references are followed to establish tables that allow knowing which scores correspond to 1.5 SD or 5th - 10th percentiles according to strata of combinations of sociodemographic variables. They will be the threshold that determines the pathological score cutoff.

7.5 Applicability studies

After evaluating the precision, diagnostic evaluation studies should demonstrate the beneficial effects and potential harm derived from its implementation, the **real utility, through studies of effect and applicability** [209]. This validation phase needs a **random assignment** to determine whether participants take the index test or not, and the results are evaluated in terms of health, quality of life, or costs.

We could also include here feasibility studies, which aim to analyze whether the test we are about to validate applies to our target population. Feasibility studies also consider the time it takes to administer our test, which is very important in our clinical

context, in where we have a limited time per patient, and a test may have an excellent potential diagnostic but not be suitable for our outpatient clinic context.

There are only a few applicability studies due to the methodological design's complexity and the results' interpretation.

Fundaments

Based on the assumptions set out above and after the review carried out in the introduction, it has been shown that **the neuropsychological examination is an essential component in the diagnosis and planning of treatment in patients with mild cognitive impairment.** For this, it is necessary to have adequate, sensitive, valid measuring instruments with appropriate normative data, competent to reliably detecting mild cognitive changes.

One of the vital **challenges** in our clinical context are **illiterate and low-educated patients.** The usual neuropsychological evaluation procedures are neither possible nor reliable in this group of patients. The normative data and the classical cognitive tests' validations include reading and writing tasks, representing a real challenge due to the lack of adequate tools [210-211].

Recently developed memory tests use **specific hippocampal involvement paradigms** and, therefore, confer specificity for diagnosing amnesic MCI. Among these concepts, the **lack of efficiency of the semantic track or the learning loss by "binding"** could be evaluated using tests such as the "Free and Cued Selective Reminding Test" [174] or "The Memory Binding Test" [186]. However, both assessments use verbal material, which is again a problem for people with low education. These drawbacks turn low-educated people to be more challenging to diagnose, which means that they are frequently excluded from potentially disease-modifying drugs' clinical trials, among others.

One chance to overcome these barriers has come through the development of tests that use pictorial material, such as DMS-48 [195], the "Associative Memory Test of the Seine-Saint-Denis district" (TMA-93) [199]; or the picture version of "Free and Cued Selective Reminding Test, immediate recall" (FCSRT + IR) [174].

RESEARCH JUSTIFICATION

In Spain, and particularly in Andalusia, the memory examination faces multiple problems. We have a **high percentage of low-educated elderlies**, for whom classical tests based on recalling stories or word lists are not feasible. There is **limited face-to-face time per patient in primary care and neurology outpatient clinic settings.** There is an **overuse of short screening tests** that do not specifically evaluate memory. Finally, there is a need for an easy-to-administer memory test for non-specialized personnel. These setbacks limit an early AD diagnosis. **Identifying a memory test feasible for its use at diverse settings and different educational levels should be a primary aim for the Public Health System.**

The candidate test to fill this gap must be identified and developed following the steps to demonstrate the mentioned properties. **It might cover accuracy** to discriminate prodromal AD patients from healthy controls (validation studies), suitable **reliability** (internal consistency and inter-rater and test-retest reliability), **and feasibility** (ease of administration and scoring in the target setting). Its development also needs to include **normative studies** to analyze the effect of the sociodemographic variables on scoring.

Among the memory tests previously reviewed, the **TMA-93** is a novelty on the international scene that may meet the above requirements. This test **examines binding**, a type of memory early disordered in Alzheimer's disease. **It uses images instead of words, an advantage for low-educated patients.** It could be **easily administrable** by non-specialized personnel and its **administration time seems to be shorter** than those of other picture memory tests.

This research will be focused on validation, reliability, feasibility, and normative studies for the TMA-93 in the Spanish population.

Hypotheses

The hypotheses of this Doctoral Thesis are:

Chapter I

1. TMA-93 is as discriminative as the FCSRT for diagnosing aMCI patients.

Chapter II

2. TMA-93 has good reliability (internal consistency and inter-rater and test-retest reliability) and feasibility (task-tolerability, short-time, and simple administration and scoring).

Chapter III

3. TMA-93 total score does not depend on educational attainment.

Chapter IV

4. TMA-93 has high sensitivity for AD diagnosis and improves the biomarker's prediction when added to the FCSRT results.

Hypotheses

Objectives

The general aim of this Doctoral Thesis is to properly validate a new diagnostic tool for amnestic Mild Cognitive Impairment, suitable for illiterate and low-educated patients.

The specific objectives of each chapter are the following:

Objectives of chapter I:

1. To compare the diagnostic accuracy of the TMA-93 against the FCSRT to differentiate patients with amnestic Mild Cognitive Impairment from Healthy Controls in a sample including low-educated patients.

Objectives of chapter II:

2. To study the reliability (internal consistency and inter-rater and test-retest reliability) of the TMA-93.
3. To study the TMA-93 feasibility, through a register of the participants' percentage who completed the test, and measuring the administration time.

Objectives of chapter III:

4. To provide normative values for the TMA-93 in cognitively unimpaired older educationally-diverse Spanish population.

Objectives of chapter IV:

5. To validate the TMA-93 using Alzheimer's Disease biomarkers as gold-standard.
6. To compare TMA-93 diagnostic characteristics against FCSRT ones on a Biobank sample of patients who initially consulted concerning memory complaints.

Objectives

Methods and Results

Chapter I. Article I.

Rodrigo-Herrero. S, Carnero-Pardo. C, Méndez-Barrio. C, Miguel-Tristancho. M, Graciani-Cantisán. E, Bernal Sánchez-Arjona. M, Maillet. D, Jiménez-Hernández. MD, Franco-Macías. E (2019) **TMA-93 for Diagnosing Amnestic Mild Cognitive Imapirment: A Comparison With the Free and Cued Selective Reminding Test.**

American Journal of Alzheimer's Disease & Other Dementias 34(5): 322-328

Chapter II. Article II.

Franco-Macías. E, **Rodrigo-Herrero. S**, Luque-Tirado. A, Méndez-Barrio. C, Medina-Rodríguez. M, Graciani-Cantisán. E, Bernal Sánchez-Arjona. M, Maillet. D (2020) **Reliability and Feasibility of the Memory Associative Test TMA-93.**

Journal of Alzheimer's Disease Reports 4: 431-440

Chapter III. Article III.

Rodrigo-Herrero. S, Sánchez-Benavides. G, Ainz-Gómez. L, Luque-Tirado. A, Graciani-Cantisán. E, Bernal Sánzhez-Arjona. M, Maillet. D, Jiménez-Hernández. MD, Franco-Macías. E. (2020) **Norms for Testing Visual Binding Using the Memory Associative Test (TMA-93) in Older Educationally-Diverse Adults.**

Journal of Alzheimer's Disease 75 (2020) 871-878

Chapter IV. Article IV.

Rodrigo-Herrero. S, Luque-Tirado. A, Méndez-Barrio. C, García-Solís. D, Bernal Sánchez-Arjona. M, Oropesa-Ruiz. JM, Maillet. D, Franco-Macías. E (2021) **TMA-93 validation by AD biomarkers. A comparison with the FCSRT on a Biobank sample.**

Manuscript under review, submitted to the *Journal of Alzjeimer's Disease*. Track number JAD 21-0115

Chapter I. Article I.

Current Topics in Research

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TMA-93 for Diagnosing Amnestic Mild Cognitive Impairment: A Comparison With the Free and Cued Selective Reminding Test

Silvia Rodrigo-Herrero, MD[1], Cristóbal Carnero-Pardo, PhD[2,3], Carlota Méndez-Barrio, MD[4], Miguel De Miguel-Tristancho, MD[1], Eugenia Graciani-Cantisán, MD[1], María Bernal Sánchez-Arjona, PhD[1], Didier Maillet, MSc[5], María Dolores Jiménez-Hernández, PhD[1], and Emilio Franco-Macías, PhD[1]

Abstract

Background: TMA-93 examines binding by images, an advantage for the less educated individuals. **Aim:** To compare the discriminative validity of TMA-93 against the picture version of Free and Cued Selective Reminding Test (FCSRT) to distinguish patients with amnestic mild cognitive impairment (aMCI) from normal controls (NCs) without excluding less educated individuals. **Methods: Design:** Phase I diagnostic evaluation study. **Participants:** A total of 30 patients with aMCI and 30 NCs matched for sociodemographics variables. **Statistical Analysis:** The diagnostic accuracy for each test was calculated by conducting receiver operating characteristic curve analysis. Hanley and McNeil method was used to compare diagnostic accuracy of different tests on the same sample. **Results:** Up to 41.7% of the sample had less than a first grade of education. Both tests showed excellent diagnostic accuracy. The comparisons did not show significant differences. **Conclusions:** TMA-93 is so accurate as FCSRT to differentiate aMCI from controls including less educated individuals. The test could be considered as a choice in this sociodemographic context.

Keywords

TMA-93, FCSRT, binding, amnestic MCI, diagnostic accuracy, ROC curves

Introduction

Diagnosis of Alzheimer's disease (AD) in its prodromal phase is a global aim in dementia research. This diagnosis is currently based on memory tests and pathophysiological markers.[1]

When patients have a low level of education or are emigrants from countries with different languages, the usual neuropsychological assessment procedures are not possible or reliable. Classical neuropsychological tests often require abilities that have been acquired at school such as reading and writing and are not useful for the less educated individuals. These patients are more difficult to diagnose and are usually excluded from clinical trials. To overcome this limitation, tests that use pictorial material to evaluate memory could be administered. Between these tests are the picture version of the "Free and Cued Selective Reminding Test" (FCSRT)[2,3] and the more recent "Memory Associative Test of the District of Seine-Saint-Denis" (TMA-93).[4]

Free and Cued Selective Reminding Test is a classical test based on testing the cueing.[2] This test controls for a successful encoding (achieved by cued recall) and it facilitates retrieval processing with the same semantic cues.[3] A low total recall

[1] Memory Disorders Unit, Department of Neurology, University Hospital Virgen del Rocio, Seville, Spain
[2] Memory Disorders Unit, Department of Neurology, University Hospital Virgen de las Nieves, Granada, Spain
[3] FIDYAN Neurocenter, Granada, Spain
[4] Memory Disorders Unit, Department of Neurology, University Hospital Juan Ramón Jiménez, Huelva, Spain
[5] UF Mémoire et Maladies Neurodégénératives, Service de Neurologie, Hopital Avicenne, Bobigny, France

Corresponding Author:
Emilio Franco-Macías, PhD, Memory Disorders Unit, Department of Neurology, University Hospital Virgen del Rocio. Avenida Manuel Siurot s/n, Seville 41013, Spain.
Email: efranco17@gmail.com

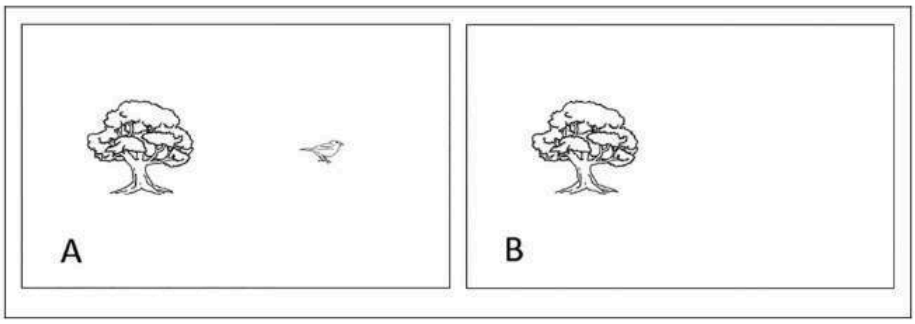

Figure 1. A, A semantically related pair of drawings (a tree and a bird). B, The bird is missing. It is the drawing the participant has to recall.

performance, despite retrieval facilitation with cueing, has an excellent specificity for AD.[5] Dual coding gives advantage to the picture version of the test against the word one.[6] This picture version may be more adequate for patients with a low level of education. There are different ways to administer the test. In one of them,[3] the study phase is followed by 3 recall trials and the usual 30-minute delayed recall is deleted. This deletion improves applicability without losing the more relevant information that is obtained from the 3 recall trials.[3]

TMA-93 is based on testing the binding, the ability to form associations.[4] Binding refers to representational elements in memory that can be recalled together in a unitized way when a specific episode or fact is retrieved.[7,8] Experiments that test binding support the hypothesis that the deficit in binding information in patients with AD is more pronounced than their memory impairment for unrelated information.[8] In animal literature,[9] computational models,[10] neuroimaging studies,[11] and neuropsychological literature,[12] it is posited that associative learning, or relational association, is a low mechanism which is dependent on functional integration in the medial temporal lobe structures, particularly the hippocampus.[7]

On neuropsychological evaluation, binding has been examined in different ways. The Wechsler Memory Scale evaluates it by learning and recalling of verbal paired associates.[13] The subset distinguishes easy (eg, north/south) from difficult (eg, school/cellar) associations.[13] The more recent Memory Binding Test (MBT) examines binding by recalling paired items (eg, flea/ant) from each shared category (eg, insect) from 2 different lists.[14] However, studying binding by images could be more suitable for patients with a low level of education. This is exactly what has been developed by the TMA-93.[4] Drawings of familiar objects of everyday life are displayed in semantically related pairs during the encoding phase (Figure 1A). Then participants have to recall the missing drawing when the associated one is provided (Figure 1B). This retrieval phase is repeated 3 times successively to assess participants' learning abilities. The test has shown diagnostic accuracy to differentiate patients with AD from normal controls (NCs) in a less educated and culturally diverse population.[4]

The aim of this study was to compare the diagnostic accuracy of the recently described TMA-93 against the classical FCSRT to differentiate patients with amnestic mild cognitive impairment (aMCI) from NCs in a sample that does not exclude participants with low educational levels.

Materials and Methods

Design

This study was designed following the guidelines for a preliminary evaluation of a diagnostic test.[15] A cross-sectional, case–control study with convenience sampling and pretest prevalence of 50% was planned. The aim was to compare on the same sample the discriminative validity of 2 picture memory tests (TMA-93 vs FCSRT) to distinguish individuals with aMCI from NCs.

Study Population

The sample consisted of 60 participants from an urban area of Spain. They comprised 2 groups: 30 patients with aMCI and 30 NCs matched for age, gender, and educational level. All participants were older than 60 years and spoke Spanish as their native language. The following sociodemographic variables were considered: age, gender, educational attainment (less than first grade, first grade, and more than first grade), and literacy (illiterate, able to read and write in Spanish but not fluently, and able to read and write fluently in Spanish).

All patients were selected by convenience sampling of consecutive cases who had been diagnosed of aMCI at the Memory Unit of the Hospital Virgen del Rocio (Seville, Spain). The procedures had consisted of general, neurological, neuropsychological, laboratory, and neuroimaging examinations. Neuropsychological evaluation had included "Spanish Version of the Informant-Based AD8 Questionnaire,"[16,17] "Phototest,"[18,19] "Delayed Matching-to-Sample Task 48" (DMS-48),[20,21] "Geriatric Depression Scale 15 items,"[22] and "Interview for Deterioration in Daily Living Activities in Dementia" (IDDD).[23] The diagnosis of aMCI had been made according to the National Institute on Aging and Alzheimer's Association (NIA-AA) recommendations[24] and operationally put into practice as follows: (a) memory complaint corroborated by a reliable informant, (b) objective memory impairment

measured by a score equal to or below the 10th percentile on set 2 of DMS-48 (this score being lower than that on set 1), and (c) no significant functional decline for activities of daily living (score up to 39 on IDDD was allowed).

Normal controls were recruited among the caregivers and relatives of patients attending the center. They met the following inclusion criteria: (a) absence of memory complaints, (b) absence of objective memory impairment (DMS-48 set 2 score equal to or above the 25th percentile), and (c) intact level of independence in activities of daily living (score between 33 and 36 on IDDD).

The following exclusion criteria were considered for both groups: (1) absence of reliable informant, (2) current history of other neurological diseases that potentially cause cognitive impairment, (3) poor vision or hearing despite correction, (4) clinically significant, advanced, or unstable systemic disease that might interfere with cognitive evaluation, (5) current Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (*DSM-V*), diagnosis of active major depression, schizophrenia, or bipolar disorder, and (6) history of abusing alcohol or other substances.

Procedures

Both tests were administered on different days and by different raters blinded to participants' diagnostic group and results of their cognitive testing. TMA-93 was administered following the instructions given by the authors.[4] During the encoding phase, participants were asked to orally name the 10 paired drawings successively and were explicitly told to memorize them (Figure 1A). After this encoding phase, the first cued recall was administered: For each pair of associates, only 1 drawing was displayed and participants had to recall the missing associated drawing (Figure 1B). Following the participant's response, regardless of its accuracy after a 5-second delay, the previously encoded paired drawing was presented again. This procedure was repeated for the 9 other paired associates. If participants did not accurately recall all of the 10 paired associates during the first cued recall (ie, score <10), a second and, in case of obtaining again a score lower than 10, a third cued recall were administered, following the same procedure, resulting in a total score of maximum 30 points (by summing the number of correct responses on 3 recall trials). On the contrary, when participants obtained the maximum score of 10 after the first or the second cued recall, the procedure was stopped and 20 points (or the remaining 10 points) were automatically credited for a total score of 30. Several kinds of errors were distinguished: (i) "errors," all responses corresponding to an object that belonged to 1 of the 9 other paired associates, (ii) "intrusions," responses that did not belong to the 10 paired associates, and (iii) "perseverations," referred to repeatedly produced errors during the whole procedure.

Free and Cued Selective Reminding Test was administered following the instructions given by the author.[3] It begins with a search procedure in which participants are asked to examine a card containing line drawings of easily recognizable objects for an item that goes with a unique category cue. The 16 items to be learned were presented 4 at a time on a card, 1 picture in each quadrant. The participant was asked to search each card and point to and name aloud each item after its cue was aurally presented. After 4 items were identified correctly, the card was removed, and immediate cued recall of just those 4 items was tested by presenting the cues again. The participant was reminded of any item he or she failed to retrieve by presenting the cue and the item together. Once immediate recall for a group of 4 items was completed, the next set of items was presented for studying. The study phase was followed by 3 recall trials, each one preceded by 20 seconds of participants counting backward to obtain recall from long-term memory. Each recall trial consists of 2 parts. First, each participant had up to 2 minutes to freely recall as many items as possible. Next, verbally presented category cues were provided for items not retrieved by free recall. If participants failed to retrieve the item with the category cue, they were reminded by presenting the cue and the item together. The following variables were scored: total free recall (TFR; the sum of free recall from 3 memory trials), total recall (TR; the sum of free and cued recall from 3 memory trials), and Index of Sensitivity of Cueing (ISC), which was determined by the score of (TFR − TR)/(TFR − 48).

Ethics

This study was approved by the ethics committee of the Hospital Virgen del Rocio (Seville, Spain) and conducted according to the World Medical Association Declaration of Helsinki. All participants accepted the study procedures by signing an informed consent.

Statistical Study

Comparative analysis between groups included independent sample *t* tests and χ^2 tests, depending on the variables. Descriptive results were shown as frequencies (percentage) or means ($\pm$standard deviation) for categorical or continuous variables, respectively. The diagnostic accuracy of the TMA-93 and the FCSRT was estimated by the area under curve (AUC) using receiver operating characteristic (ROC) curve analysis. The diagnostic accuracy was classified as excellent (>0.9), good (>0.8), fair (>0.7), or poor (>0.6).[25] The Youden index was used to determine the optimum cutoff scores to provide the best balance between sensitivity and specificity.[26] The method suggested by Hanley and McNeil was used to compare AUCs between the memory measures.[27] Analysis was performed using SPSS version 24. Statistical significance was set at $P < .05$ and 95% confidence intervals were calculated.

Results

Sociodemographics characteristics and neuropsychological background for aMCI and NC groups are shown in Table 1. There were no significant differences in age, gender,

Table 1. Sociodemographic Characteristics and Neuropsychological Tests Results by Diagnostic Group.

	NC	aMCI	Total	*P*	Cohen *d* Effect Size
Number of participants	30	30	60		
Gender (female %)	19 (63.3%)	22 (73.3%)	41 (68.2%)	.40	
Age (years)	75.4 (4.7)	73.9 (6.6)	74.7 (5.7)	.32	
Educational attainment					
<First grade	10 (33.3%)	15 (50.0%)	(41.7%)	.29	
First grade	11 (36.7%)	6 (20.0%)	17 (28.3%)		
>First grade	9 (30.0%)	9 (30.0%)	18 (30.0%)		
Degree of literacy					
Illiterate	1 (3.3%)	3 (10.0%)	4 (6.7%)	.43	
R&W not fluently	11 (36.7%)	13 (43.3%)	24 (40.0%)		
R&W fluently	18 (60.0%)	14 (46.7%)	32 (53.3%)		
Phototest (total score)	36.2 (5.2)	25.7 (6.1)	30.9 (7.8)	<.001	1.85
DMS-48					
Set 1 score	46.6 (1.5)	37.7 (4.5)	42.2 (5.6)	<.001	2.65
Set 2 score	46.3 (1.7)	32.2 (4.1)	39.2 (7.8)	<.001	4.49
TMA-93					
Total score	27.4 (3.8)	11.2 (7.6)	19.3 (10.1)	<.001	2.70
Errors	0.3 (0.6)	2.1 (3.6)	1.2 (2.7)	<.001	−0.48
Intrusions	0.7 (2.3)	3.7 (5.1)	3.7 (5.1)	<.001	−0.76
Perseverations	0.1 (1.4)	1.4 (2.4)	1.4 (2.4)	<.001	−0.66
FCSRT					
TFR	28.1 (5.2)	11.0 (6.2)	19.5 (10.3)	<.001	2.99
TR	46.8 (1.3)	31.0 (10.9)	28.9 (11.1)	<.001	2.04
ISC	0.94 (0.06)	0.57 (0.24)	0.76 (0.26)	<.001	2.11

Abbreviations: NC, normal controls; aMCI, amnestic mild cognitive impairment; DMS-48, Delayed Matching-to-Sample Task 48; FCSRT, Free and Cued Selective Reminding Test; ISC, Index of Sensitivity of Cueing; R&W not fluently, able to read and write in Spanish but not fluently; R&W fluently, able to read and write fluently in Spanish; TFR, total free recall; TR, total recall.

educational attainment, or degree of literacy between groups. Up to 41.7% of the sample was comprised of individuals with less than a first grade of educational attainment.

All the participants were able to complete both TMA-93 and FCSRT tests. With respect to TMA-93, the aMCI group had significantly lower TMA-93 total scores than the NC group (11.2 ± 7.6 vs 27.4 ± 3.8, $P < .001$; Cohen $d = 2.7$) and made significantly more errors (2.1 ± 3.6 vs 0.3 ± 0.6, $P < .001$; Cohen $d = 0.4$), intrusions (3.7 ± 5.1 vs 0.7 ± 2.3, $P < .001$; Cohen $d = 0.7$), and perseverations (1.4 ± 2.4 vs 0.1 ± 1.4, $P < .001$; Cohen $d = 0.6$; Table 1). In the NC group, 21 of 30 participants needed only 1 or 2 trials to complete the test. On the contrary, all 30 of 30 patients needed all 3 trials. Of 30, 18 individuals in the NC group scored 29 or 30 on the test. The ROC curve analysis determined an AUC of 0.97 (95% CI, 0.89-1.00, $P < .001$) for the TMA-93 total score (Figure 2). A score of 19/20 (Youden index, $J = 0.83$) was revealed as the optimal threshold to distinguish between patients with aMCI and NC with a sensitivity of 0.87 (95% CI, 0.69-0.96) and a specificity of 0.97 (95% CI, 0.83-1.00).

With respect to FCSRT, the aMCI group had significantly lower TFR (11.2 ± 6.2 vs 28.1 ± 5.2, $P < .001$; Cohen $d = 2.9$), TR (31.0 ± 10.9 vs 46.8 ± 1.3, $P < .001$; Cohen $d = 2.0$), and ISC (0.57 ± 0.24 vs 0.94 ± 0.06, $P < .001$; Cohen $d = 2.1$) scores than NC group (Table 1). The ROC curve analysis determined an AUC of 0.99 (95% CI, 0.92-1.00) for TFR, 0.95 (95% CI, 0.86-0.99) for TR, and 0.93 (95% CI, 0.83-0.98) for ISC. A score of 21/22 (Youden index, $J = 0.93$) was shown as the best cutoff for TFR to discriminate between groups with a sensitivity of 1.00 (95% CI, 0.88-1.00) and a specificity of 0.93 (95% CI, 0.78-0.99). A score of 43/44 (Youden index, $J = 0.83$) was revealed as the optimal threshold

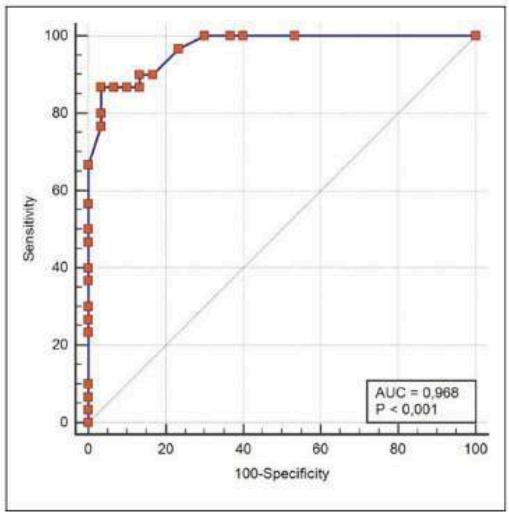

Figure 2. TMA-93 total score: receiver operating characteristic (ROC) curve. Area under the curve (AUC) of 0.97.

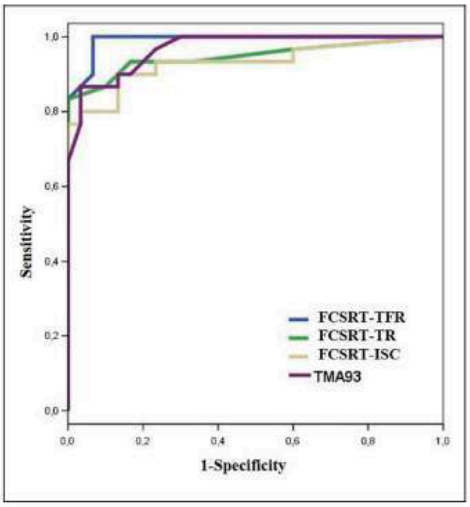

Figure 3. Comparison of receiver operating characteristic (ROC) curves: total score TMA-93 (purple); total free recall of Free and Cued Selective Reminding Test (FCSRT-TFR; blue); total recall of FCSRT (FCSRT-TR green); and Index of Sensitivity of Cueing of FCSRT (FCSRT-ISC, gray).

Table 2. Comparison of aROC between TMA-93 and FCSRT by Hanley and McNeil Method.

	aROC	FCSRT-TFR	FCSRT-TR	FCSRT-IS
TMA-93	0.97 (0.02)	0.02 (0.02); ns	0.02 (0.03); ns	0.04 (0.03); ns
FCSRT-TFR	0.99 (0.01)		0.04 (0.03); ns	0.06 (0.03); ns
FCSRT-TR	0.94 (0.03)			0.02 (0.01); ns
FCSRT-ISC	0.93 (0.04)			

Abbreviations: aROC, The area under curve (AUC) using receiver operating characteristic (ROC) curve analysis; FCSRT, Free and Cued Selective Reminding Test; FCSRT-ISC, Index of Sensitivity of Cueing on FCSRT; FCSRT-TFR, Total Free Recall on FCSRT; FCSRT-TR, Total Recall on FCSRT; ISC, Index of Sensitivity of Cueing; ns, not significant.

for TR with a sensitivity of 0.83 (95% CI, 0.65-0.94) and a specificity of 1.00 (95% CI, 0.88-1.00). For ISC, the best cutoff was <0.77 (Youden index, $J = 0.76$) with a sensitivity of 0.77 (95% CI, 0.58-0.90) and a specificity of 1.00 (95% CI, 0.88-1.00).

The ROC curves comparison showed an apparent superiority for TFR (Figure 3) but, following the Hanley and McNeil method, the comparisons of AUC between TMA-93 total score and each variable FCSRT did not show significant differences (Table 2).

Discussion

Even in the most developed countries, there are patients with memory complaints who have a low educational attainment or are migrants from other cultures and have a different native language. It seems inappropriate to use classical memory tests based on list learning or memorizing paragraphs in these patients. Diagnostic delays and exclusions from clinical trials are consequences of this handicap. Picture memory tests seem more suitable in this context.

Here, TMA-93 diagnostic accuracy was first tested to differentiate patients with aMCI from NC without excluding less educated participants (up to 41% of the sample). Results showed an optimal diagnostic accuracy of 0.97, not different from that obtained by the picture version of the FCSRT on the same sample. This result indicates that TMA-93 may be so reliable as FCSRT to assist in the diagnosis of aMCI in this sociodemographic context.

This study also supposed the preliminary validations of the TMA-93 and the picture version of the FCSRT in Spain. The best cutoff scores for both tests were lower than the previously described.[4,28] Total scores on TMA-93 for patients with aMCI here were similar to those previously reported for patients with dementia in the French validation study.[4] Apparently, this result could indicate that while TMA-93 can be useful in differentiating patients with aMCI or dementia from NC, it may not be so useful in distinguishing patients with aMCI from patients with dementia. With respect to FCSRT, the best cutoff (43/44) for TR was also lower than that recently reported for American population (45/46).[28] So, it is probable that the relatively low cutoff scores for both tests in this study could be better explained by differences in the sociodemographic features of the population or by differences in the method used for the validation.

High total scores with a relatively small standard deviation suggest a ceiling effect for the TMA-93 in the control group. This ceiling effect could be an advantage for the test in diagnosing aMCI since a small number of errors can be a worrisome result for a patient. In some way, this ceiling effect has also been described for FCSRT and has been considered as a problem in studies focused on the preclinical phase of AD.[29] In fact, MBT has been recently developed to overcome this problem with the FCSRT.[14,29] This ceiling effect seems to be even most robust for the TMA-93. Normative studies should be undertaken to explore whether this ceiling effect for controls remains when only the oldest or the less educated individuals are considered.

The strength of the FCSRT is its validation with AD biomarkers.[30,31] TMA-93 has not been validated using AD biomarkers yet. Unavailability of biomarkers is a limitation for this study. The diagnosis of aMCI was based on clinical criteria according to NIA-AA recommendations.[24] The evidence obtained from this preliminary validation study highlights the need for inclusion of biomarkers in the design of future studies focused on validations or comparisons of these picture memory tests in order to increase the specificity of the diagnosis.

Another important question is about the applicability and acceptability of these tests. Both FCSRT and TMA-93 were well tolerated by the participants in this study including those with less than a first grade of educational attainment. The acceptability usually emerges as a problem when patients have severe memory impairment and there is a floor effect for the

test. In this situation, a short test that requires less examination time is better tolerated by the patients. Applicability is very important in contexts that are not so specialized as dementia units where patients with memory complaints are usually first attended. The shorter the test, the more applicable it will be. Right there, in terms of acceptability and applicability, TMA-93 would have an advantage since it takes shorter time than FCSRT and DMS-48 to be administered. Future studies comparing these picture memory tests should also focus on applicability or acceptability, not only on diagnostic accuracy.

This study presents some limitations. In relation to design, there may be a selection bias. Convenience sampling is not representative of the normal population or the population with dementia. However, for a preliminary evaluation of a diagnostic test, the main requirement is that the 2 groups that are compared, patients and NC, do not differ in the sociodemographic variables and only differ in the diagnosis.[32] Here, this requirement was fulfilled.

The standard Mini-Mental State Examination (MMSE) was not used here as screening test before making the diagnosis by the DMS-48. The MMSE scores may have better defined the cognitive status of the sample and would have allowed comparisons with other studies. However, MMSE may be not reliable for participants with low educational level[33,34] and was deliberately avoided in this study. The Phototest,[18,19] a picture screening test with normative data collected in Spain,[35] was used instead. This test was shown to be robust to educational level.[36]

In conclusion, the difficulty to evaluate the memory in emigrants or individuals with a low educational attainment can be solved by using picture memory tests. TMA-93 may be as discriminative as FCSRT for diagnosing aMCI. Future studies including AD biomarkers will strengthen the validity of the test. Studies focused on applicability and acceptability could place this new test as a good choice in some sociodemographic and clinical care contexts.

Authors' note

Didier Maillet is now affiliated with Service de Neurologie, Hôpital Saint-Louis (AP-HP), Paris, France.

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Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Carnero-Pardo is the author of the Phototest. Maillet is the author of the TMA-93.

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ORCID iD

Cristóbal Carnero-Pardo https://orcid.org/0000-0003-3415-6727
Didier Maillet https://orcid.org/0000-0001-5190-6548
Emilio Franco-Macías https://orcid.org/0000-0003-4186-1037

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Chapter II. Article II.

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Research Report

Reliability and Feasibility of the Memory Associative Test TMA-93

Emilio Franco-Macías[a,*], Silvia Rodrigo-Herrero[b], Andrea Luque-Tirado[a], Carlota Méndez-Barrio[b], Manuel Medina-Rodriguez[a], Eugenia Graciani-Cantisán[a], María Bernal Sánchez-Arjona[a] and Didier Maillet[c]
[a]*Unidad de Memoria, Servicio de Neurología, Hospital Universitario Virgen del Rocío, Seville, Spain*
[b]*Unidad de Memoria. Servicio de Neurología, Hospital Universitario Juan Ramón Jiménez, Huelva, Spain*
[c]*Service de Neurologie, Hôpital Saint-Louis (AP-HP), Paris, France*

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Abstract.
Background: Memory tests focused on binding may be more sensitive to diagnose Alzheimer's disease (AD) at an early phase. TMA-93 examines relational binding by images.
Objective: Evaluate the reliability (internal consistency and inter-rater and test-retest reliability) and feasibility of the TMA-93 in a clinic setting with low-educated individuals and limited face-to-face time per patient.
Methods: The study was undertaken in a neurology outpatient clinic of a hospital in Southern Spain. The internal consistency of the TMA-93 was estimated in 35 patients with amnestic mild cognitive impairment (aMCI) and 40 healthy controls (HCs). The inter-rater reliability (by two raters) and feasibility (by recording the percentage of participants who completed the test, and by timing the administration time) were evaluated in HCs ($n = 16$), aMCI patients ($n = 18$), and mild dementia patients ($n = 15$). The test-retest reliability for the TMA-93 total score was studied in 51 HCs tested by the same examiner 2–4 months apart. The internal consistency was estimated by Cronbach's alpha. The inter-rater and test-retest reliability was quantified by the intraclass correlation coefficient (ICC). The administration time was compared by diagnosis.
Results: The internal consistency was "optimal" (Cronbach's alpha = 0.936). The test-retest reliability was "good" [ICC = 0.802 (CI 95% = 0.653–0.887)]. The inter-rater reliability was "optimal" [ICC = 0.999, (CI 95% = 0.999–1)]. All participants completed the test. The administration time ranged from less than 3 min in HCs to 6 min in aMCI patients, and 7 min in mild dementia patients.
Conclusion: Good feasibility and reliability support using the TMA-93 for examining visual relational binding, particularly in the context of low-educational attainment and limited time per patient.

Keywords: Binding, feasibility, inter-rater reliability, internal consistency, mild cognitive impairment, test-retest reliability, TMA-93

INTRODUCTION

In cognition, binding is the function that supports the integration of multiple elements together [1–3]. Errors in conjunctive binding (the integration of features within an object) and also in relational binding or associative memory (the ability to remember novel

*Correspondence to: Emilio Franco-Macías, Unidad de Memoria, Servicio de Neurología, Hospital Universitario Virgen del Rocío, Avenida Manuel Siurot s/n, Seville 41013, Spain. Tel.: +34 609732041; Fax: +34955012593; E-mail: efranco17@gmail.com.

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associations between words or pictures) have been reported in Alzheimer's disease (AD) at an early phase [4]. Conjunctive binding is supported by the entorhinal and perirhinal cortex and seems more sensitive than the relational one to early AD [5, 6]. The "Short-Term Memory Binding Test" is the most used tool for examining conjunctive binding. This test, one of the most promising neuropsychological tools, has been incorporated into trials to predict who among those with mild cognitive impairment will go on to develop AD [7]. There is also evidence that relational binding, that relies on the hippocampus, parahippocampal cortex, and default mode network regions (posterior cingulate cortex/precuneus/lateral parietal and medial frontal cortex) [5], declines in the prodromal stages of late-onset sporadic AD [8–10]. Even more, asymptomatic individuals with greater amyloid-β burden on amyloid imaging have shown abnormal scores on relational binding tests when the performance on other standardized episodic memory test is still preserved [11]. In neuropsychology, the relational binding ability can be examined by different tests. The "Wechsler Memory Scale" (WMS) assesses binding through learning and recall of paired associated words [12]. This WMS subtest discerns between easy (i.e., North/South) and complex associations (i.e., School/Cellar) [12]. The "Memory Binding Test" (MBT) examines associative memory through the recall of pairs of items that belong to the same semantic category (i.e., flea/ant = insects) but presented in two different lists of words [13]. The "Face Name Associative Memory Exam" is a cross-modal associative test based on a functional magnetic resonance imaging (fMRI) task that pairs pictures of unfamiliar faces with common first names [14].

Testing relational binding only by images rather than words could be more feasible for low educated individuals. The "Memory Associative Test of the district of Seine-Saint-Denis" (TMA-93) was recently developed in France for the early diagnosis of AD among low educated immigrants [15]. Briefly, during the encoding phase, the patient is shown ten pairs of drawings of common and easy to recognize objects from daily life that are semantically related (Fig. 1A). Only one of the two items is shown in the recall phase, and the patient is asked to recall the missing item (Fig. 1B) [15]. In the original paper, the test demonstrated high diagnostic accuracy for discriminating AD patients from healthy controls in a sample of immigrant residents from a district in Paris (France) [15]. In that study, the cutoff of 24 of 30 showed a sensitivity of 88% and a specificity

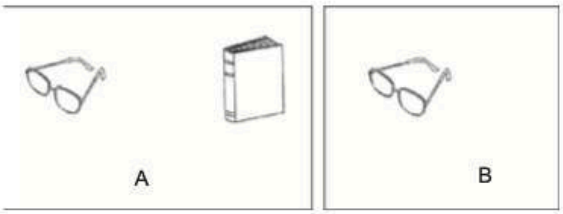

Fig. 1. Pairs of semantically-related drawings of the TMA-93. In the codification phase, the semantically-related drawings are presented in pairs (A). In the recall phase, the subject has to recall the missing object (B).

of 97% for distinguishing AD patients from healthy controls [15]. A posterior validation study in older educationally-diverse Spanish people demonstrated that the test is so sensitive as the picture version of the Free and Cued Selective Reminding Test (FCSRT) in discriminating between amnestic mild cognitive impairment (aMCI) patients and healthy controls (HCs) [16]. In that study, the receiver operating characteristic (ROC) curve analysis determined an optimal area under the ROC curve (AUC) of 0.97 (95% CI, 0.89–1.00, $p < 0.001$) to distinguish between aMCI patients and HCs [16].

On the other hand, the most used memory tests are based on learning and recalling two paragraphs or a list of words and often include a final step of facilitation with verbal cues or recognition among distractors that have to be administered 15–30 min later [17, 18]. These tests take too long time to be used in busy primary care and general neurology outpatient settings with limited face-to-face time per patient. On the contrary, the TMA-93 is a relatively short test that may be more suitable in that context.

These potential uses and advantages of the TMA-93 encourage the completion of the development of the test. There are no previous studies focused on the reliability or feasibility of the TMA-93. There is a need to validate the test-retest reliability of binding tasks to detect and monitor AD-related populations [4]. Tests providing such reliability will be appropriate for use in longitudinal research. On the other hand, feasibility has been considered a crucial prerequisite by a consensus document on neuropsychological assessment [19]. The aim here was to study the reliability (the internal consistency and the inter-rater and test-retest reliability) of the TMA-93 and its feasibility (by recording the percentage of participants who completed the test, and by timing the administration time).

METHODS

Study population

The studies were undertaken in a general neurology outpatient clinic at the University Hospital Virgen del Rocio, a tertiary referral academic center in Seville, in the Southern Spanish region of Andalusia. Many older people of this region had limited access to primary school and are not skilled in reading or writing. In the region, time availability for examining patients with memory complaints is limited: from 5 min in busy primary care to 20 min in a general neurology outpatient setting.

The internal consistency was studied in an extension of the phase I validation study for the TMA-93 [16]. Here, the sample was increased to 75 individuals (35 patients with aMCI and 40 HCs) to meet the required sample size for studying the internal consistency of a test composed of 10 items. Procedures for this cross-sectional study has been previously described [16] and included Phototest, a brief cognitive test developed in Spain with high diagnostic accuracy for diagnosing cognitive impairment and dementia [20], and the "Delayed Matching-to-Sample Task 48" (DMS-48), a visual recognition memory task on which the diagnosis of aMCI was based [21]. The diagnosis of aMCI had been made according to the National Institute on Aging and Alzheimer's Association (NIA-AA) recommendations [22] and operationally put into practice as follows: 1) memory complaint corroborated by a reliable informant; 2) objective memory impairment measured by a score equal to or below the 10-percentile on set 2 of DMS-48 (this score being lower than that on set 1); and 3) no significant functional decline for activities of daily living [score up to 39 on "Interview for Deterioration in Daily Living Activities in Dementia" (IDDD) (23)]. We recruited HCs among the caregivers and relatives of patients attending the center. They met the following inclusion criteria: 1) absence of memory complaints; 2) absence of objective memory impairment (DMS-48 set 2 score equal to or above the 25-percentile); and 3) intact level of independence in activities of daily living (score between 33 and 36 on IDDD).

For the test-retest reliability, HCs were recruited among the participants in the Spanish normative study for the TMA-93 [24]. The inclusion criteria for this study were: 1) age equal to or above 50; 2) no cognitive complaints; 3) score equal or above 10-percentile according to normative data for the Phototest in Spain [25]; and 4) independent level of functioning. 51 randomly selected HCs were invited to repeat the TMA-93 conducted by the same examiner (SRH) between 2 and 4 months after the initial examination.

For studying the inter-rater reliability and feasibility, an ad-hoc sample composed of 16 HCs, 18 patients with aMCI, and 15 patients with mild dementia due to probable AD ($n = 15$) was recruited. Both groups of patients had been diagnosed according to NIA-AA recommendations [22, 26]. The diagnosis of mild dementia due to probable AD was based on core clinical criteria for AD [26]. Amnestic presentation and classification at stage 4 according to the Global Deterioration Scale were required [27]. All available information had been used for this diagnostic process including history, blood tests, brain imaging (head CT or brain MRI), and the following battery of neuropsychological tests: the Spanish version of the Informant Questionnaire AD8 [28], the Phototest [20], the picture version of the FCSRT [29], the Stroop Color and Word Test [30], the ADAS-Cog subtest of constructive praxis [31], the 12-item Boston Naming Test [32], the VOSP subtests of Dot Counting and Number Location [33], the IDDD [23], and the 15-item Geriatric Depression Scale [34]. The TMA-93 was conducted by two examiners (1 = EGC and 2 = SRH), who followed an alternating order for its administration and timing on the same subjects, and were blinded to both the subject's diagnosis and the score obtained by the other examiner.

Instrument: TMA-93

The TMA-93 was administered following the instructions given by its authors [15]. During the encoding phase, subjects were shown and asked to name 10 pairs of real-life semantically-related objects presented as drawings in cards (tree/bird, bed/bedside lamp, boat/fish, dog/sheep, foot/trousers, knife/apple, glasses/book, hand/watch, car/car keys, flower/sun). The examiner specifically asked the participants to memorize the pairs of drawings (Fig. 1A). Next, the first associative memory trial was administered: examinees were shown only one of each pair's drawings and asked to recall the missing one (Fig. 1B). After each subject's response (regardless accuracy) or a period of up to 5 s, we displayed the pair again. This protocol was repeated for the 9 remaining pairs.

The maximum score of 30 points was granted only when the participant produced 10 out of 10 correct

responses in this first trial, in which case, the second and the third trials were omitted. Otherwise, the participants were scored from 0 to 9 based on their number of correct answers in this first trial and were administered a second similar trial with the same 10 pairs of drawings. If a subject correctly recalled the 10 missing objects in this second trial, s/he was given 20 points: 10 points corresponding to the second trial, and 10 more corresponding to the third trial, which was cancelled. The score of each of the 10 items of the TMA-93 ranged from 0 to 3 and these scores were used for estimating the test's internal consistency.

Three types of incorrect answers were recorded: 1) error, when the subject recalls an object that belongs to a different pair; 2) intrusion, when the subject recalls an object that was never shown to him/her; and 3) perseveration, when the subject repeated the same error [15].

Ethics

The studies were approved by the ethics committee of the Hospital Virgen del Rocio (Seville, Spain) and conducted according to the World Medical Association Declaration of Helsinki. All participants accepted the study procedures by signing informed consent.

Statistical analyses

Descriptive results are shown as frequency (percent) for dichotomous and categorical variables, mean (±SD, range) for normally-distributed continuous variables, and median [interquartile range (IQR), range] for non-normally distributed continuous variables. Between-group comparisons of continuous variables were performed with Student's *t*-test or one-way ANOVA (or their non-parametric alternatives Mann-Whitney U test and Kruskal-Wallis ANOVA, respectively). Between-group comparisons of categorical variables were performed with the Chi square test.

Internal consistency was estimated by Cronbach's alpha. Values of Cronbach's alpha above 0.70 were considered acceptable, between 0.90 and 0.95 were considered "optimal", and above 0.95 were interpreted as indicative of "item redundancy" [35, 36]. In addition, "split-half reliability" was analyzed considering the first five pairs of drawings of the TMA-93 as a half and the last five ones as the other half and estimating the correlation between each other by the Spearman-Brown coefficient. "Corrected item-total correlations" were calculated, and a value below 0.40 was considered indicative of item redundancy [35]. Item redundancy was also evaluated by "Cronbach's alpha if item deleted", considering an item as redundant if the Cronbach's alpha increased at deleting it [37].

Test-retest reliability for the TMA-93 total score was estimated by the intra-class correlation coefficient (ICC). In addition, we also created the variable "total score time 2 minus total score time 1" and analyzed its distribution.

Inter-rater reliability for the TMA-93 total score and number of errors, intrusions, and perseverations were estimated by the ICC.

According to the ICC, reliability was categorized as: optimal (ICC > 0.90), good (ICC 0.71–0.90), moderate (ICC 0.51–0.70), mediocre (ICC 0.31–0.50), or bad/null (ICC < 0.31) [21].

The feasibility was analyzed by recording the number of participants who completed the test, and comparing the administration time according to diagnosis, and educational attainment.

Statistical significance was set at a $p < 0.05$, and all estimates were obtained with a 95% confidence interval (CI 95%).

All statistical analyses were run in SPSS version 25 (IBM, USA).

RESULTS

Socio-demographics characteristics and neuropsychological background for the extension of the cross-sectional study focused on internal consistency are shown in Table 1. For the total sample ($n = 75$), 46 participants were females. Their average age was 74.6 (SD = 5.9, range = 51–84). Regarding educational attainment, 31 individuals (41.3%) had not completed primary studies (Table 1). There were no significant differences in age, gender, or educational attainment between aMCI and HCs groups (Table 1). aMCI patients scored significantly lower than HCs on Phototest, DMS48, and TMA-93 (Table 1). Internal consistency was "optimal" (Cronbach's alpha = 0.936). Split-half reliability was also high (Spearman-Brown coefficient = 0.911). Corrected item-total score correlations ranged from 0.661 for the pair "hand-watch" to 0.837 for the pair "flower-sun" (Table 2). There was no redundancy of any item as the Cronbach's alpha did not increase at deleting anyone (Table 2).

Table 1
Socio-demographics characteristics and neuropsychological background of the internal consistency study

	Total, $n=75$	HCs, $n=40$	aMCI, $n=35$	p
Age	74.6 ± 5.9 (51–84)	74.7 ± 6.3 (51–83)	74.6 ± 5.4 (65–84)	0.706
Gender				
Female	46 (61.3%)	21 (52.5%)	25 (71.4%)	0.093
Male	29 (38.7%)	19 (47.5%)	10 (19.6%)	
Educational attainment				
<first grade	31 (41.3%)	12 (30%)	19 (54.3%)	0.052
First grade	19 (25.3%)	14 (35%)	5 (14.3%)	
>first grade	25 (33.3%)	14 (35%)	11 (31.4%)	
Phototest (total score)	31.8 ± 7.5 (13–52)	36.3 ± 5.7 (26–52)	27.1 ± 6.3 (13–41)	<0.001
DMS48				
Set 1 score	45, (41–47), (31–48)	47, (46–47), (41–48)	41, (35–44), (31–47)	<0.001
Set 2 score	43, (36–47), (26–48)	47, (45–48), (40–48)	36, (30–39), (26–45)	
TMA-93 (total score)	24, (14–29), (0–30)	29, (25–30), (14–30)	13, (6–20), (0–28)	<0.001

Results are shown as median, (interquartile range), and (range) for non-normal distributed variables and mean ± SD, and (range) for normal distributed variables.

Table 2
Corrected Item-Total Correlations and Cronbach's alpha if item deleted

	Item-Total Statistics			
	Scale Mean if Item Deleted	Scale Variance if Item Deleted	Corrected Item-Total Correlation	Cronbach's Alpha if Item Deleted
tree/bird	18,6667	67,793	0,773	0,927
bed/bedside lamp	18,4933	69,199	0,773	0,928
boat/fish	18,5067	68,929	0,744	0,929
dog/sheep	18,4800	71,253	0,677	0,932
foot/trousers	18,7200	68,366	0,722	0,930
knife/apple	18,5867	68,921	0,770	0,928
glasses/book	18,9333	68,441	0,719	0,930
hand/watch	18,6267	70,940	0,661	0,933
car/car keys	18,6400	70,098	0,754	0,929
flower/sun	19,1867	65,262	0,837	0,924

Corrected Item-Total Correlation was never lower than 0.400. Cronbach's alpha was not above 0.936 at deleting any item. Both results demonstrated no redundancy of any item.

Socio-demographics characteristics and neuropsychological background for the test-retest reliability study are shown in Table 3. Their average age was 64.8 (SD = 8.9, range = 50–86). 13 subjects (25.5 %) had not completed primary studies, and 30 (58.8%) were females (Table 3). Test-retest reliability for the TMA-93 total score was "good" [ICC = 0.802 (CI 95% = 0.653–0.887)]. The "total score time 2 minus total score time 1" variable showed a non-normal, right asymmetric, and leptokurtic distribution (median = 0, IQR = 0–1, Range = –3–3). There were four atypical observations: two of them scored three points higher at the retest and the remaining two scored two and three points lower, respectively (Fig. 2). We analyzed the TMA-93 total score at time 2 by the TMA-93 total score at time 1: the variability was greater for scores below 28, and some practice effect could be detected in the range 27–29 (Fig. 3).

Table 4 shows the characteristics of the sample for the inter-rater reliability and feasibility study. Their

Table 3
Socio-demographic characteristics and neuropsychological background of the test-retest study

Age	64.8 ± 8.9 (50–86)
Gender	
Female,	$n=30$ (58.8%)
Male,	$n=21$ (41.2%)
Educational attainment	
<first grade,	$n=13$ (25.5%)
First grade,	$n=16$ (31.4%)
>first grade,	$n=22$ (43.1%)
Phototest (total score)	37.8 ± 4.8 (27–47)
TMA-93 (total score)	29, (28–30), (23–30)

Results are shown as median, (interquartile range), and (range) for non-normal distributed variables and mean ± SD, and (range) for normal distributed variables.

average age was 68.7 (SD = 7.2, range = 55–81). 16 subjects (32.7%) had not completed primary studies, and 32 (65.3%) were females. There were statistically significant differences in the TMA-93 scores across the three diagnostic groups

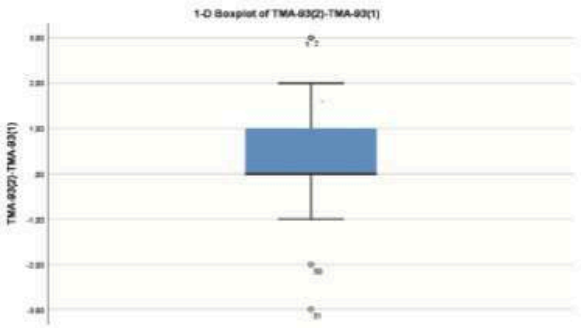

Fig. 2. Boxplot chart showing the distribution of the "total score time 2 minus total score time 1" variable. There are four outliers.

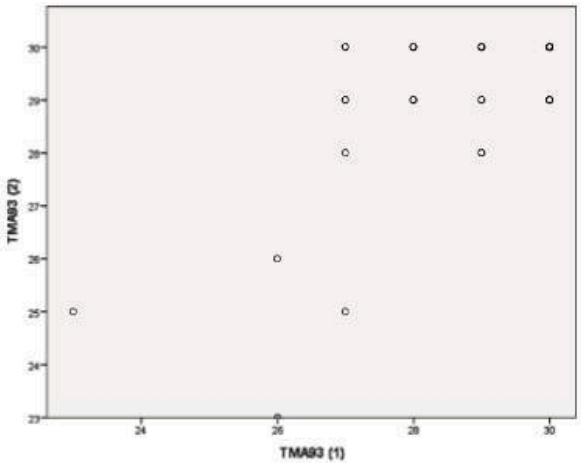

Fig. 3. Scatterplot with Time 1 performance on the x axis and Time 2 performance on the y axis. The variability in the measure was greater for scores below 28, and some practice effect could be detected in the range 27–29.

(Table 4). The inter-rater reliability was "optimal" for the TMA-93 total score [ICC = 0.999, (CI 95% = 0.999–1)], number of intrusions [ICC = 0.985 (CI 95% = 0.974–0.992)], and number of errors [ICC = 0.996 (CI 95% = 0.993–0.998)]. The inter-rater reliability for the number of perseverations was "good" [ICC = 0.853 (CI 95% = 0.738–0.918)].

All participants, including mild AD dementia patients, completed the test. There were statistically significant differences in the TMA-93 duration across the three diagnostic groups (Table 4). *Post-hoc* multiple comparison analyses revealed that the duration of the administration (in minutes) was significantly lower in healthy controls (median = 2.2, IQR = 2.0–4.0, range = 1.5–5.5) than in aMCI (median = 6.2, IQR = 4.7–7.8, range = 2.3–11.7, $p < 0.05$) and mild AD dementia patients (median = 7.5, IQR = 5.9–9.4, range = 5.0–17.2, $p < 0.001$). The

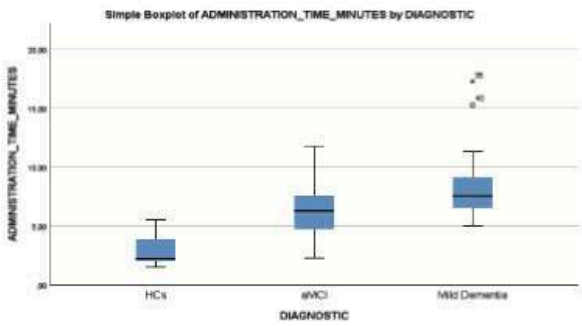

Fig. 4. Boxplot chart depicting the differences in "Administration Time" (in minutes) among the three diagnostic groups of the inter-rater reliability and feasibility study.

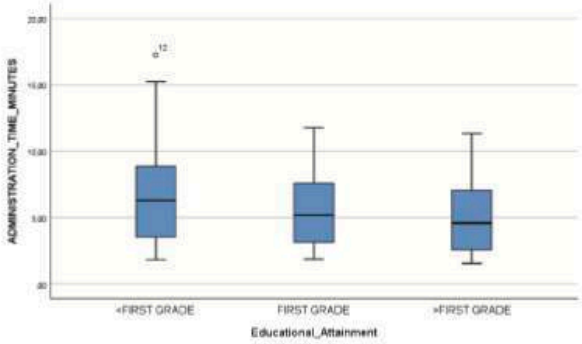

Fig. 5. Boxplot chart depicting no significant differences in "Administration Time" (in minutes) by educational attainment in the inter-rater reliability and feasibility study.

aMCI and mild AD dementia groups did not differ significantly ($p = 0.337$). There were two outliers from the mild dementia group, with an administration time longer than 15 min (Fig. 4). There were no statistically significant differences in the TMA-93 administration time by educational attainment in the inter-rater reliability study (<first grade: median = 6.28, IQR = 2.94–9.00, range = 1.82–17.25; first grade: median = 5.18, IQR = 2.63–7.58, range = 1.85–11.78; >first grade: median = 4.58, IQR = 2.43–7.10, range = 1.53–11.33; $p = 0.399$) (Fig. 5). To better analyze the educational attainment effect on the administration time, we went back to the test-retest study and evaluated differences in administration time by educational attainment among the HCs at test 1. Again, there were no significant differences (<first grade: median = 2.47, IQR = 1.77–3.40, range = 1.37–4.59; first grade: median = 2.23, IQR = 1.44–2.46, range = 1.38–3.16;>first grade: median = 2,26, IQR = 1.88–3.15, range = 1.46–4.11; $p = 0.352$) (Fig. 6).

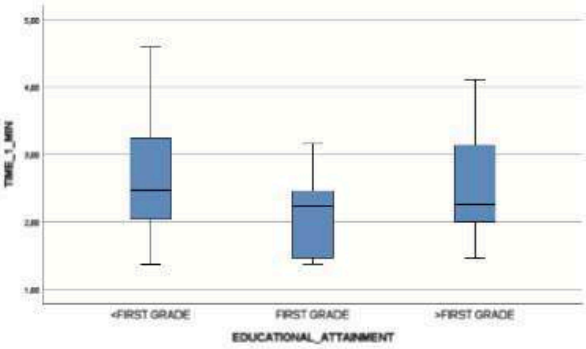

Fig. 6. Boxplot chart depicting no significant differences in "Administration Time" (in minutes) by educational attainment in the test-retest reliability study at time 1.

DISCUSSION

To our knowledge, this is the first study focused on the reliability and feasibility of the TMA-93, the French visual relational binding test [15]. The test has already demonstrated high diagnostic accuracy in validation studies [15, 16] and has normative studies from French and Spanish populations [24, 38].

Internal consistency among the 10 pairs of semantically-related drawings of real-life objects that compose the TMA-93 was "optimal" (Cronbach's alpha = 0.936). This result means the 10 items of the test are highly correlated each other and measure the construct of interest, visual relational binding, in a similar way [39]. By comparison, an "acceptable" internal consistency has been reported for the FCSRT, a standard memory test (Cronbach's alpha = 0.810) [40].

"Corrected Item-Total Correlation" is the correlation of the item designed with the summated score for all other items. A rule-of-thumb states that this value should be at least 0.40 to rule out item redundancy [35]. Every item of the TMA-93 fulfilled the rule. In the same way, the Cronbach's alpha did not increase at deleting any of the ten pairs, so, again, redundancy of any item could not be demonstrated.

Split-half testing is another measure of internal consistency. This method measures the extent to which all parts of the test contribute equally to what is being measured. We found a strong correlation between the two virtual halves of the TMA-93, indicating that HCs and aMCI patients performed equally well (or as poorly) on both halves of the test.

The TMA-93 showed a "good" test-retest reliability [ICC = 0.802 (CI 95% = 0.653–0.887)]. By comparison, this reliability is similar to that reported for the "Mini-Mental State Examination" (MMSE) (0.80) [41] and suggests stability in performance over time. The test-retest reliability studies' design varies by the time considered between test 1 and test 2, and by the selection of participants (only HCs or mixed sample of HCs and patients). Here, we considered 2–4 months for administering the retest and only HCs. The time interval seems to be short enough to pre-

Table 4
Characteristics of the sample for the inter-rater reliability and feasibility study

	Healthy Controls	aMCI	Mild dementia due to AD	*p*
N	16	18	15	
Age	66,6 ± 6,4 (56–75)	69,8 ± 6,4 (58–80)	69,7 ± 8,8 (55–81)	0.38
Gender (F/M)	12 (75%)/4 (25%)	10 (55,5%)/8(45.5%)	10 (66,6%)/5 (33.3%)	0.48
Education				
<first grade	4/16 (25%)	7/18 (38.8%)	5/15 (33.3%)	0.93
First grade	7/16 (43.7%)	7/18 (38.8%)	6/15 (40%)	
>first grade	5/16 (31.2%)	4/18 (22.2%)	4/15 (22.2%)	
Duration of test (min)	2.2, (2.0–4.0), (1.5–5.5)	6.2, (4.7–7.8), (2.3–11.7)	7.5, (5.9–9.4), (5.0–17.2)	<0.001
TMA-93 (1)	30, (28–30), (24–30)	20, (6–27), (4–30)	6, (4–19), (0–24)	<0.001
TMA-93 (2)	30, (28–30), (24–30)	20, (6–27), (4–30)	6, (4–19), (0–24)	<0.001
Errors (1)	0, (0–0), (0–0)	0, (0–1), (0–12)	1, (0–2), (0–6)	<0.005
Errors (2)	0, (0–0), (0–0)	0, (0–1), (0–11)	0, (0–2), (0–7)	<0.01
Perseverations (1)	0, (0–0), (0–0)	0, (0–1), (0–2)	0, (0–1), (0–8)	0.074
Perseverations (2)	0, (0–0), (0–0)	0, (0–1), (0–2)	0, (0–1), (0–6)	0.075
Intrusions (1)	0, (0–0), (0–1)	2, (0–3), (0–18)	0, (0–3), (0–12)	<0.05
Intrusions (2)	0, (0–0), (0–1)	2, (0–3), (0–18)	0, (0–2), (0–13)	<0.05

aMCI, amnestic mild cognitive impairment; TMA-93 (1); TMA-93 total score by examiner 1; TMA-93 (2); TMA-93 total score by examiner 2; Errors (1) errors score by examiner 1; Errors (2), errors score by examiner 2; Perseverations (1), perseverations score by examiner 1; Perseverations (2), perseverations score by examiner 2; Intrusions (1), intrusions score by examiner 1; Intrusions (2), intrusions score by examiner 2. Age is expressed in mean ± SD and (range). Scores and duration of the TMA-93 are expressed in median, (interquartile range), and (range).

vent the effect of an eventual cognitive impairment on the sample, particularly from participants with lower scores, and long enough to prevent a practice effect. With a similar design, the MBT demonstrated ICC values ranged from 0.64 to 0.76 [42]. Analyzing the distribution of the "total score time 2 minus total score time 1" variable, there were four atypical observations that probably precluded this reliability could be upgraded to "optimal". Two of them scored 3 points more at the retest. On the opposite side, two outliers scored 2 and 3 points less, respectively. The former could be explained by practice effect and the latter by cognitive decline, but a more global explanation could be that binding is somewhat changeable and dynamic, making it difficult for a test to achieve an "optimal" test-retest reliability [43]. The variability in the measure were greater for scores below 28 at time 1. The test-retest reliability could be supported by scores above 28 at time 1 and, thus, overestimated due to ceiling effect. To clarify this issue, future test-retest reliability TMA-93 studies should recruit enough HCs scoring below 28 at time 1 and consider participants' AD biomarker status to understand eventual score changes over time.

Inter-rater reliability of the TMA-93 was "optimal" for the total score and the number of errors and intrusions, and "good" for the number of perseverations. We noted that the administration and scoring are relatively simple, but that classifying the incorrect responses in errors, intrusions or perseverations can lead to disagreements between examiners and requires some training. Individually, perseverations—scored as the number of times that an error (a response that corresponds to a different drawing pair) is repeated—were the main source of disagreement between examiners.

Regarding TMA-93 feasibility, all participants, including mild AD dementia patients, were able to complete the test. Participants' task-tolerability was good, including that of those who scored the minimum (4 out of 30) or whose administration time was the longest (17.2 min). There were significant differences in administration time by diagnosis: cognitively impaired patients spent more time on recalling the missing drawing, made more mistakes, and usually needed the maximum of three memory trials.

The average time required to complete the test was 2–3 min for HCs, 6 min for aMCI patients, and 7 min for mild AD dementia patients, so this test is relatively short despite being a specific memory test and not a brief cognitive screening test as MMSE or MoCA. By comparison, the time of passing the MMSE in cognitively impaired patients is, on average, 4 min 51 s [44]. Busy primary care and general neurology outpatient settings with limited face-to-face time per patient need a short but specific memory test. The TMA-93 could fill the gap. The test runs with a ceiling effect in HCs and is highly discriminative for diagnosing patients with aMCI or mild dementia [16]. However, a floor effect should be expected in patients with moderate dementia and may could be already present in some patients with mild dementia, here represented by the outliers for whom the administration of the test took longer than 15 min. The target of the TMA-93 are mainly patients with memory complaints and no functional impairment when total scores on MMSE or MoCA are around the cutoffs and are not conclusive [24]. Studies comparing the diagnostic accuracy and feasibility of the TMA-93 against screeners, as MMSE or MoCA, in settings with limited face-to-face time per patient are needed.

The samples here tested were composed of a relatively high percentage of low-educated participants. Lack of education remains a limitation in many elderly Spanish people since they had limited primary school access in the aftermath of the Spanish Civil War (1936-1939). Although the situation has significantly improved in recent years, 59% of the population over 65 years of age in Spain did not complete primary studies [45]. Low-education is also a limitation for people in many developing countries in the world. In most developed countries, multicultural individuals with a different primary language, not proficient in the host country one, also have this limitation. The neuropsychological examination must comply with this handicap. Here, the TMA-93 was again demonstrated feasible to be administered to low-educated individuals. In fact, there were no significant differences in administration time by educational attainment. Despite this feasibility, the TMA-93 total score should be expected lower in low-educated individuals. Feasibility does not mean that the test is free of educational bias. Associative learning is also trained and acquired at school and, accordingly, normative studies show lower TMA-93 total score in less educated groups [24, 38].

In addition to optimal diagnostic accuracy previously reported for the TMA-93, the good reliability and feasibility here demonstrated encourages the completion of the test´s development. The next steps will be phase II and III validation studies, including AD biomarkers and comparing the diagnostic accuracy of the test with that of the standard mem-

ory instruments on samples organized by educational attainment.

Conclusion

In summary, our findings of good reliability (internal consistency and inter-rater and test-retest reliability) and feasibility (task-tolerability, short administration time, and simplicity of administration and scoring after some training) make the TMA-93 a brief relational binding memory test suitable to be administered to patients with memory complaints, particularly in settings with limited face-to-face time per patient and low-educated population.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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Chapter III. Article III.

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Norms for Testing Visual Binding Using the Memory Associative Test (TMA-93) in Older Educationally-Diverse Adults

Silvia Rodrigo-Herrero[a], Gonzalo Sánchez-Benavides[b], Leire Ainz-Gómez[a], Andrea Luque-Tirado[a], Eugenia Graciani-Cantisán[a], María Bernal Sánchez-Arjona[a], Didier Maillet[c], María Dolores Jiménez-Hernández[a] and Emilio Franco-Macías[a,*]
[a]*Unidad de Memoria, Servicio de Neurología, Hospital Universitario Virgen del Rocío, Seville, Spain*
[b]*Barcelonaβeta Brain Research Center, Pasqual Maragall Foundation, Barcelona, Spain*
[c]*Service de Neurologie, Hôpital Saint-Louis (AP-HP), Paris, France*

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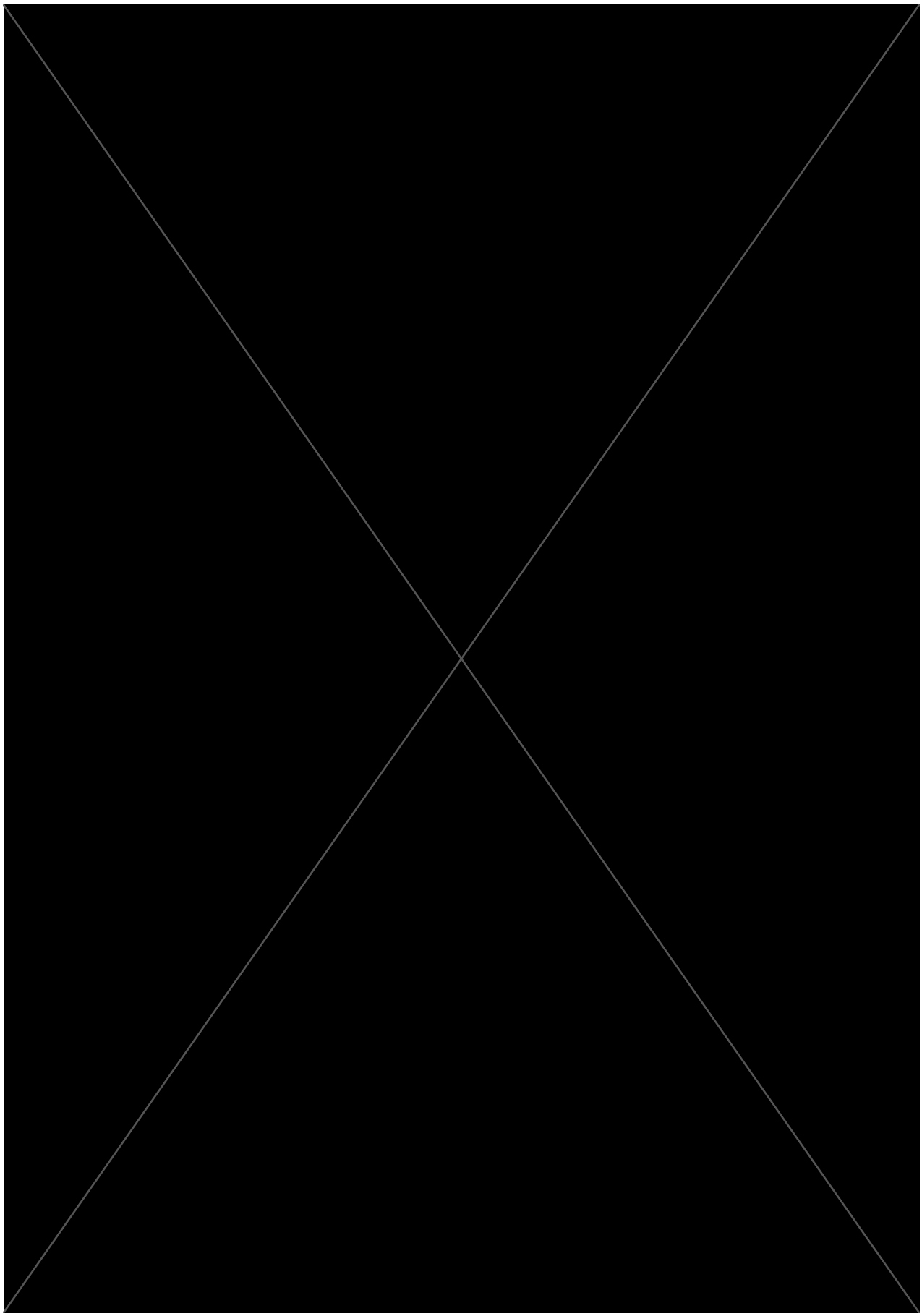
Abstract.
Background: TMA-93 examines binding by images, a potential advantage for less-educated individuals.
Objective: To obtain norms from older Spanish adults for TMA-93.
Methods: A cross-sectional normative study was undertaken in a general neurology outpatient clinic of a university hospital in the Southern Spanish region of Andalusia. Partners of patients who attended the clinic were systematically recruited when eligible: aged 50 and over, no memory complaints, and a total score equal or above percentile 10 on Phototest. Age, gender, and educational attainment were considered as sociodemographic variables. TMA-93 was administered and the total score was registered.
Results: The final sample contained 1,131 participants (mean age = 65.7, SD = 9.2), including 305 individuals (27%) who did not completed primary studies. The total score on TMA-93 showed a non-normal, left asymmetric, and leptokurtic distribution (median = 29, interquartile range = 27–30, range = 16–30) mitigated by lower education and older age. Stratified analysis by age and education showed wide variations of the scores for the 5-percentile.
Conclusion: TMA-93 runs with a ceiling effect in non-cognitively impaired older Spanish adults. The score for the 5-percentile depends on age and education. The test is feasible for low-educated individuals.

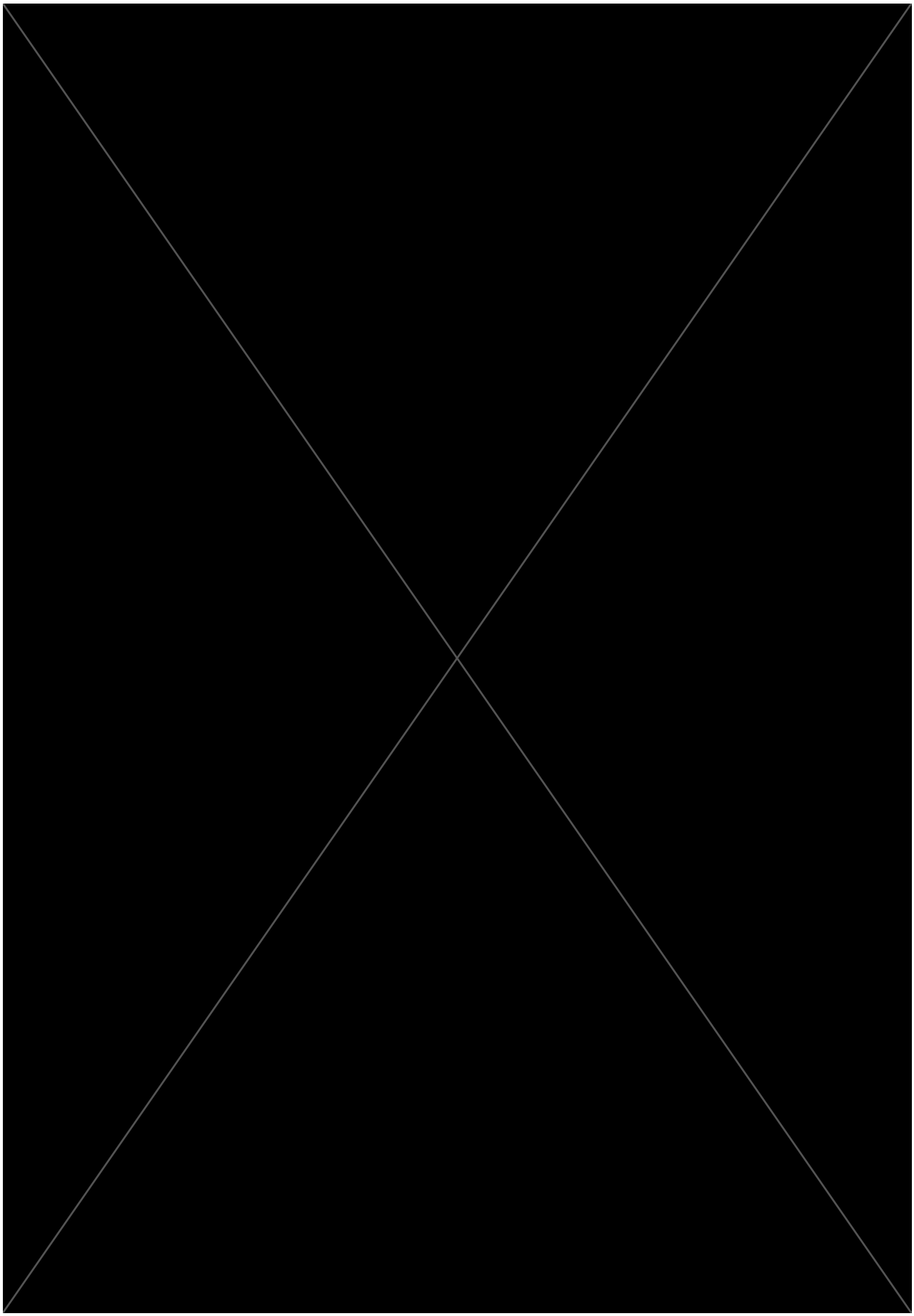
Keywords: Associative memory, cognitive assessment, cross-cultural neuropsychology, memory test

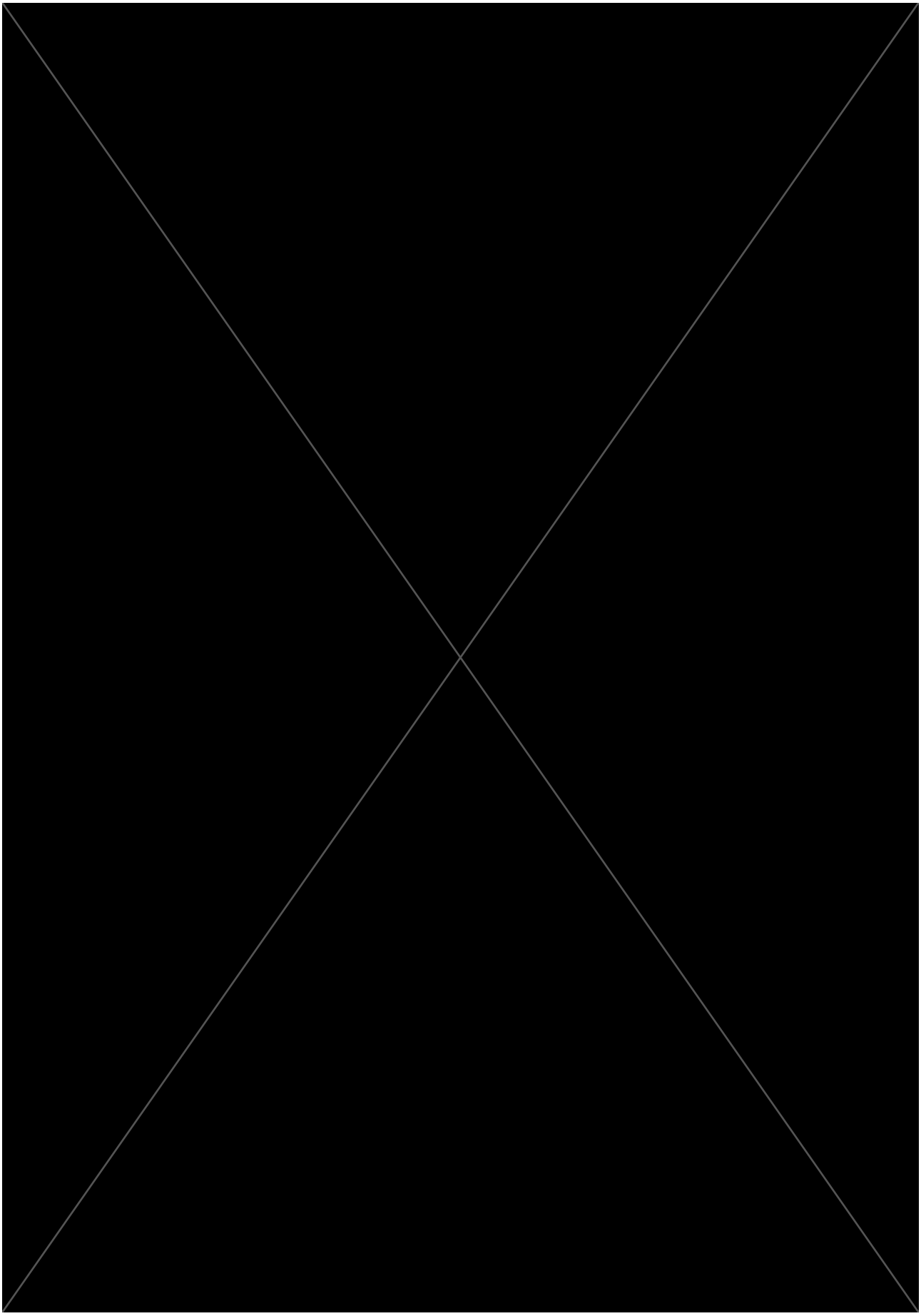
INTRODUCTION

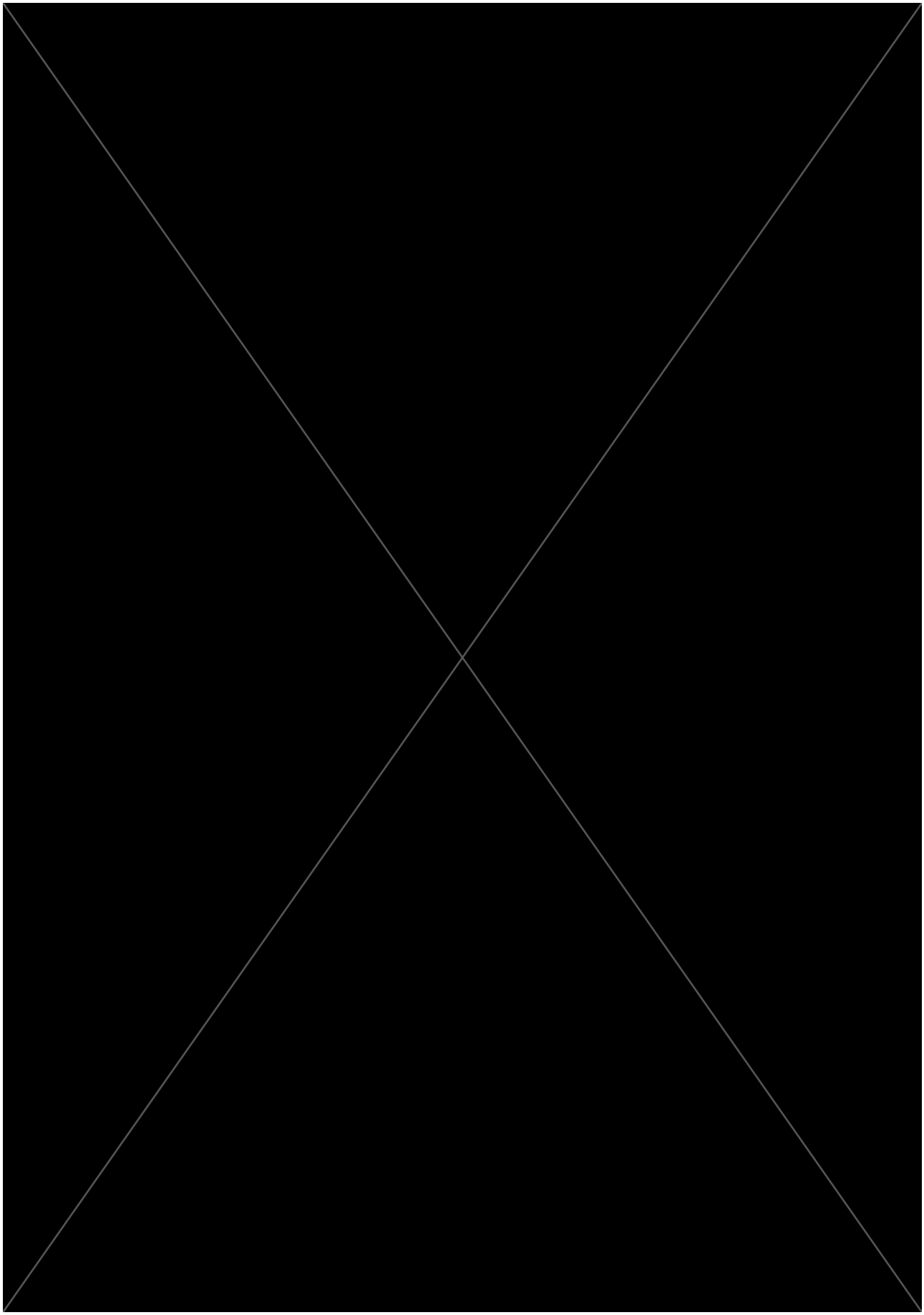
Diagnosing Alzheimer's disease (AD) at an early phase is a challenge for physicians who evaluate patients with memory complaints [1, 2]. Examinations may be done in very different settings, from busy primary care or general neurology offices to more specialized academic centers, with variable face-to-face time per patient. Illiteracy or lack of proficiency in a second language are limitations for memory tests based on learning and recalling of words or stories. Picture memory tests thought to overcome these limitations of both time and lack of verbal skills are welcome and, in this background, The "Memory Associative Test of the District of Seine-Saint-Denis" (TMA-93) is a novelty [3]. In the original study, the test demonstrated optimal diagnostic accuracy to differentiate patients with AD from normal controls in a low educated and culturally diverse population [3].

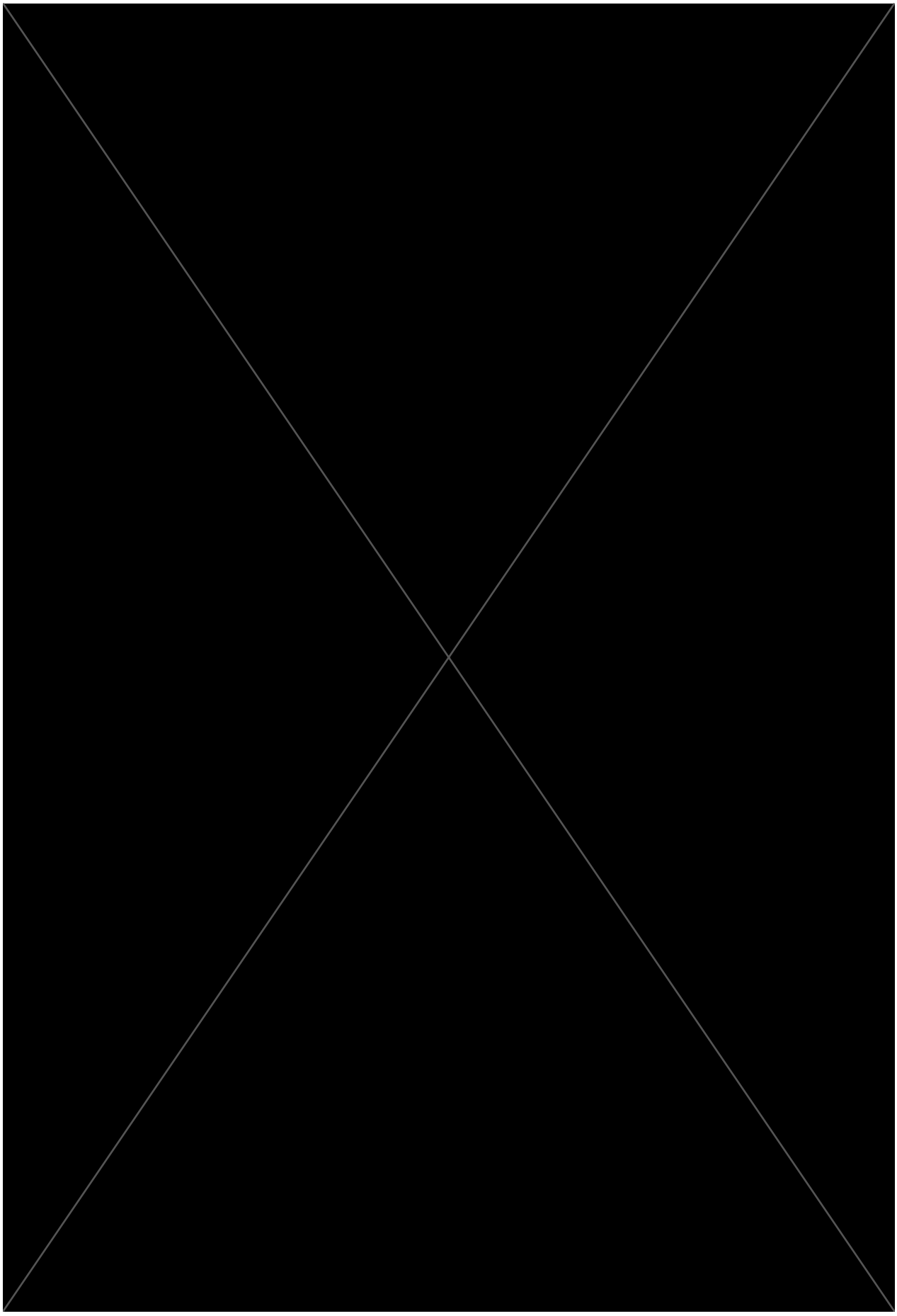
*Correspondence to: Emilio Franco-Macías, Unidad de Memoria, Servicio de Neurología, Hospital Universitario Virgen del Rocío, Avenida Manuel Siurot s/n, Seville 41013, Spain. Tel.: +34 609732041; Fax: +34 955012593; E-mail: efranco17@gmail.com.

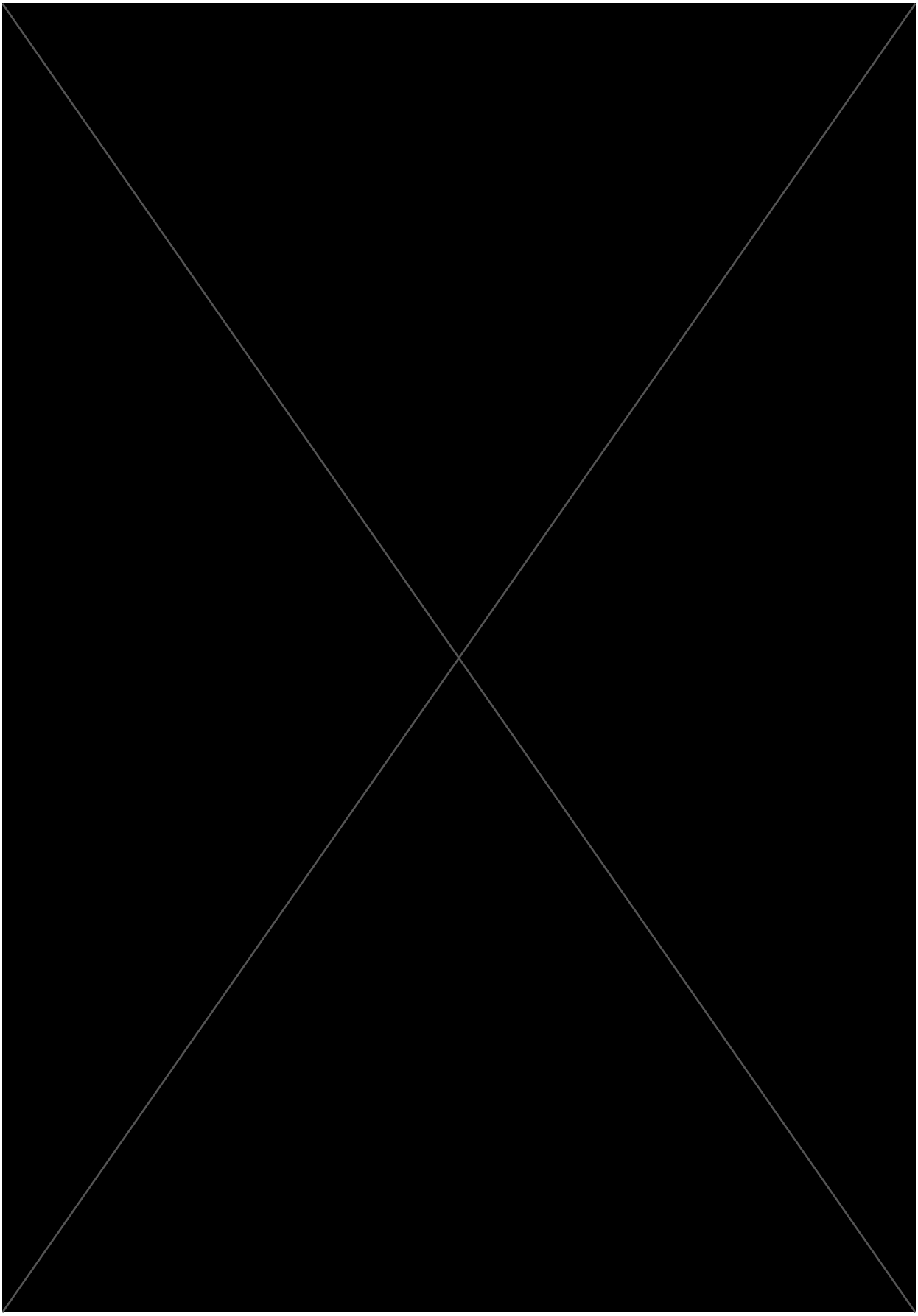












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TMA-93 Validation by Alzheimer's Disease Biomarkers: A Comparison with the Free and Cued Selective Reminding Test on a Biobank Sample

Silvia Rodrigo-Herrero[a,*], Andrea Luque-Tirado[b], Carlota Méndez-Barrio[a], David García-Solís[c], María Bernal Sánchez-Arjona[b], Juan Manuel Oropesa-Ruiz[a], Didier Maillet[d] and Emilio Franco-Macías[b]
[a]*Memory Unit, Juan Ramón Jiménez University Hospital, Huelva, Spain*
[b]*Memory Unit, Virgen del Rocio University Hospital, Seville, Spain*
[c]*Nuclear Medicine Unit, Virgen del Rocio University Hospital, Seville, Spain*
[d]*Neurology Service, Saint-Louis Hospital (AP-HP), Paris, France*

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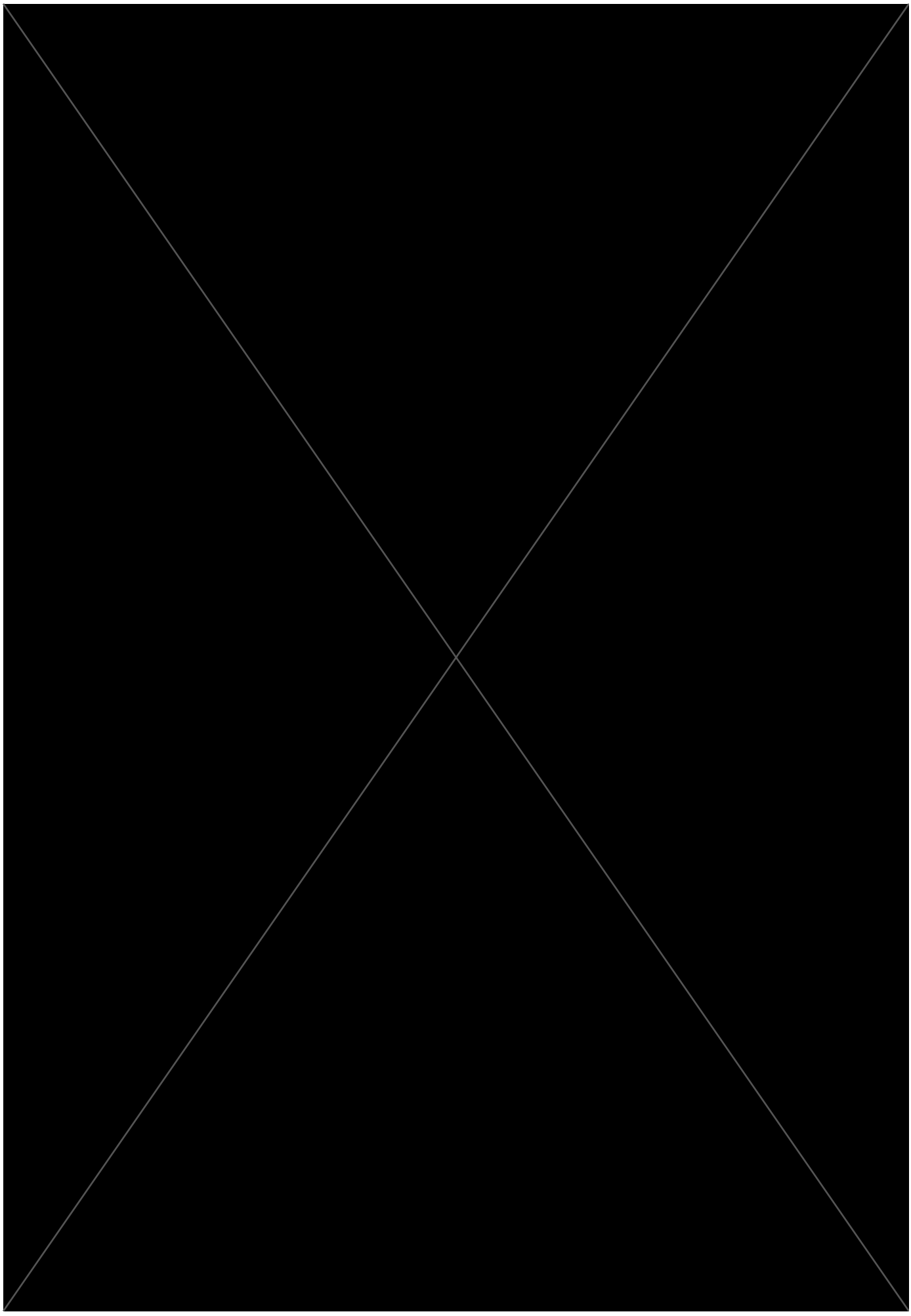
Abstract.
Background: The Memory Associative Test TMA-93 examines visual relational binding, characteristically affected in early-AD stages.
Objective: We aim to validate the TMA-93 by biomarkers determination and compare its diagnostic characteristics with the Free and Cued Selective Reminding Test (FCSRT).
Methods: Retrospective analysis of a Biobank database. Patients' records initially consulted for memory complaints, scored MMSE $\geq$ 22, had TMA-93 and FCSRT tested, and AD biomarker determination (Amyloid-PET or CSF), either positive or negative, were selected. As cutoffs, we considered the 10-percentile for TMA-93 (P10/TMA-93), and "total free recall" (TFR) 21/22, total recall (TR) 43/44, and Cued Index < 0.77 for FCSRT from previous Spanish validation and normative studies. Diagnostic utilities were calculated using ROC curves and compared by the DeLong method. We studied if one test improved the other test's prediction, following a forward stepwise logistic regression model.
Results: We selected 105 records: 64 "positive" and 41 "negative" biomarkers. TMA-93 total score diagnostic utility (AUC = 0.72; 95%CI:0.62–0.82) was higher than those of the FCSRT: TFR (AUC = 0.70; 95%CI: 0.60–0.80), TR (AUC = 0.63; 95%CI:0.53–0.74), and Cued Index (AUC = 0.62; 95%CI:0.52–0.73). The P10/TMA-93 cutoff showed 86% sensitivity, similar to that of the most sensitive FCSRT cutoff (TFR21/22, 89%) and 29% specificity, lower than that of the most specific FCSRT cutoff (Cued Index < 0.77, 57%). 32.8% of the positive-biomarker group scored above CI/0.77 but below p10TMA-93. The addition of TMA-93 total score to FCSRT variables improved significantly the biomarkers results' prediction.
Conclusion: TMA-93 demonstrated "reasonable" diagnostic utility, similar to FCSRT, for discriminating AD biomarker groups. TMA-93 total score improved the AD biomarker result prediction when added to FCSRT variables.

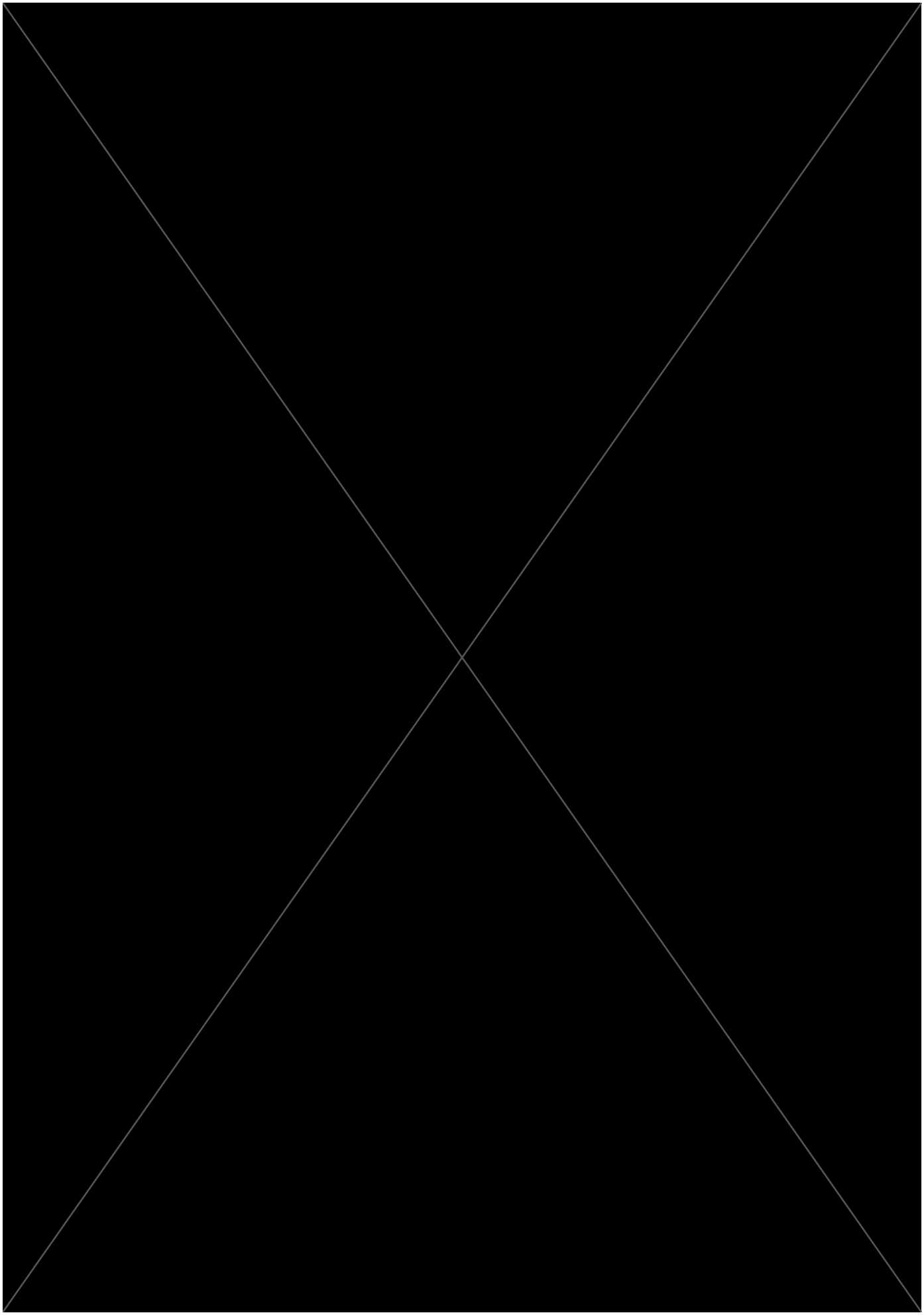
Keywords: Alzheimer's disease, amyloid-PET, biomarker, cerebrospinal fluid, free and cued selective reminding test, TMA-93

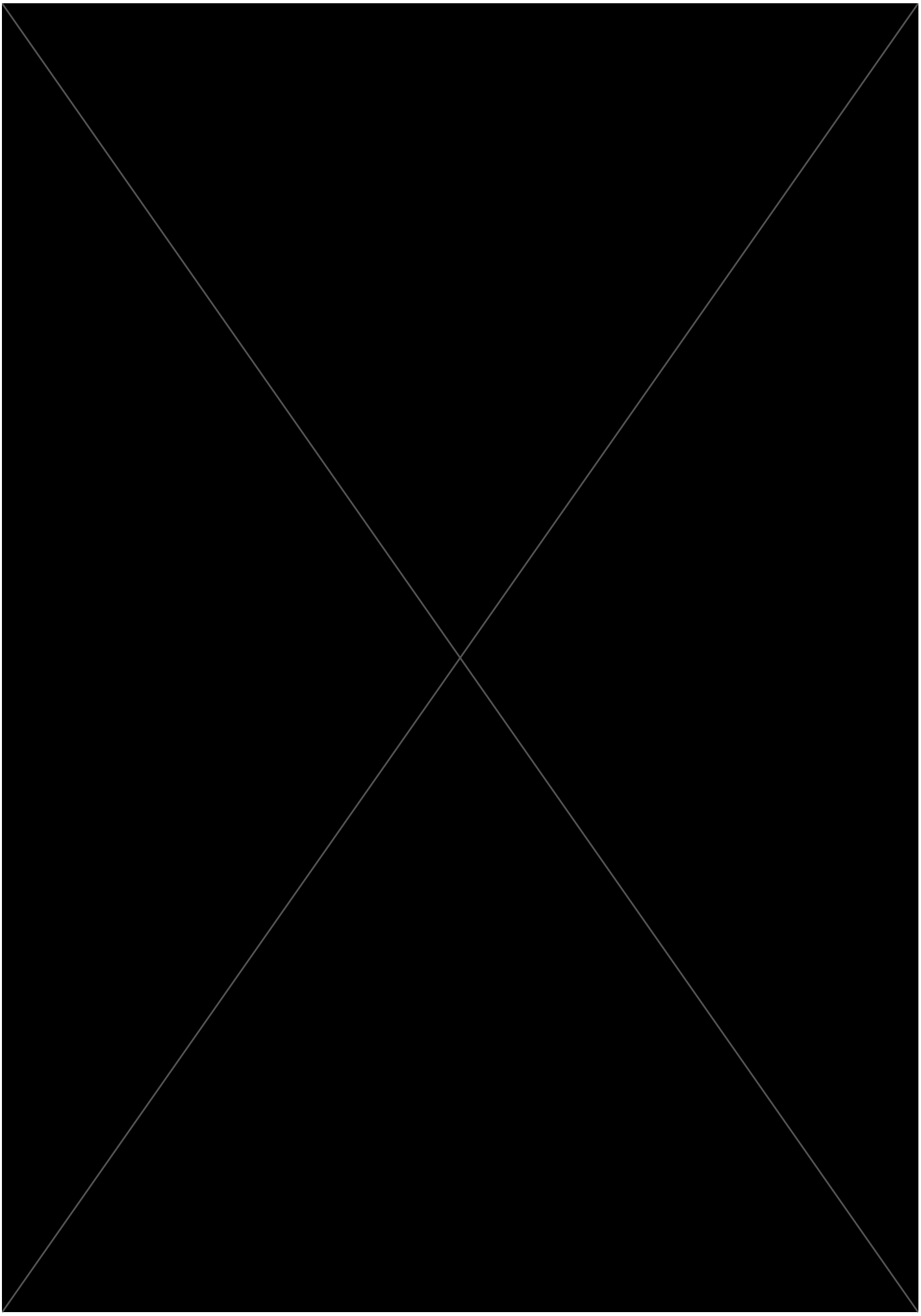
*Correspondence to: Silvia Rodrigo-Herrero, Neurologist and Neuropsychologist consultant, Atlantic Senior Fellow for Equity and Brain Health, Global Brain Health Institute, Juan Ramon Jimenez University Hospital, Ronda Exterior Norte s/n, First floor, Secretary of Neurology, 21005 Huelva, Spain. E-mail: silvia.rhgi@gmail.com.

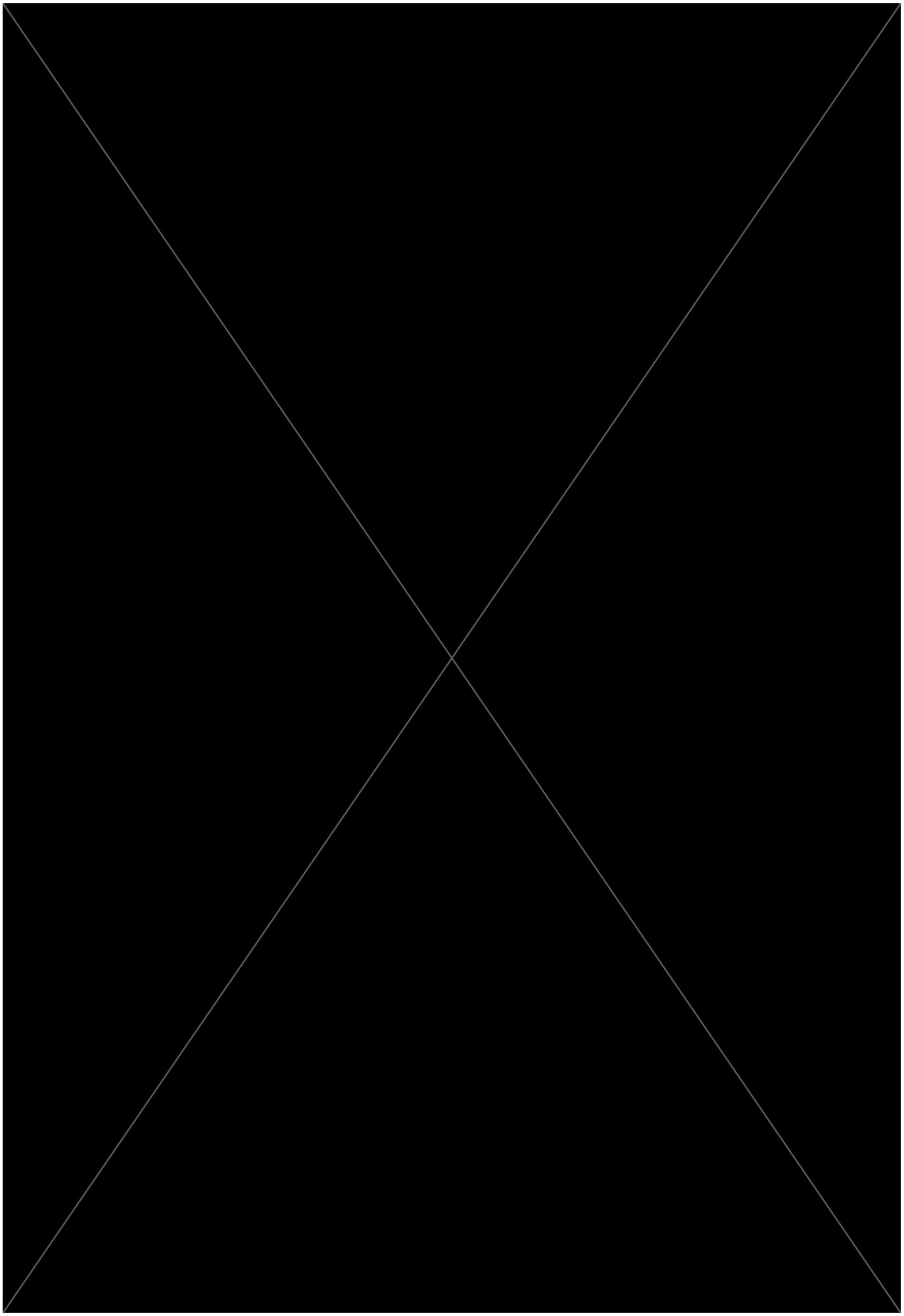
INTRODUCTION

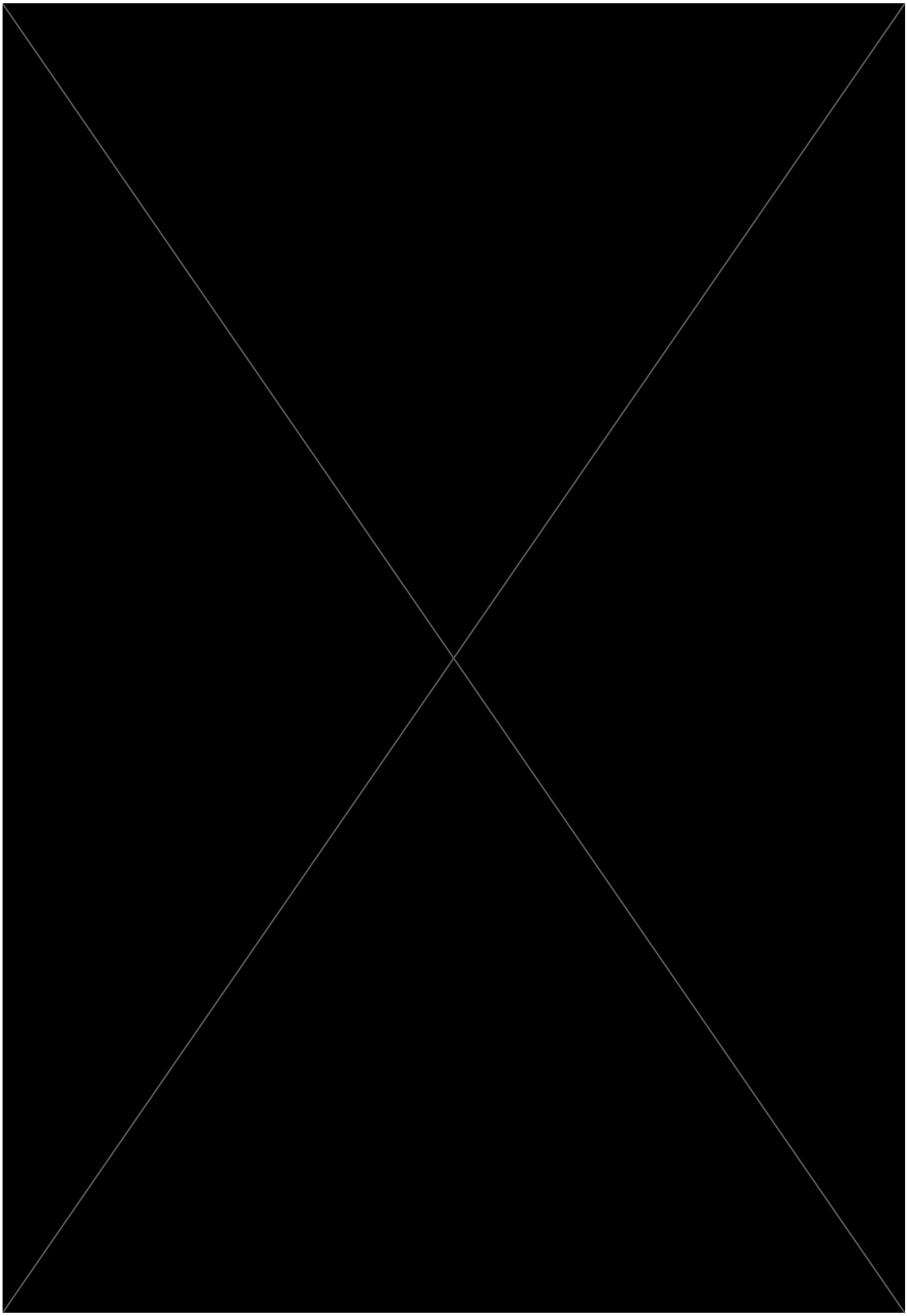
In the past few years, the development of new diagnostic criteria for Alzheimer's disease (AD) has

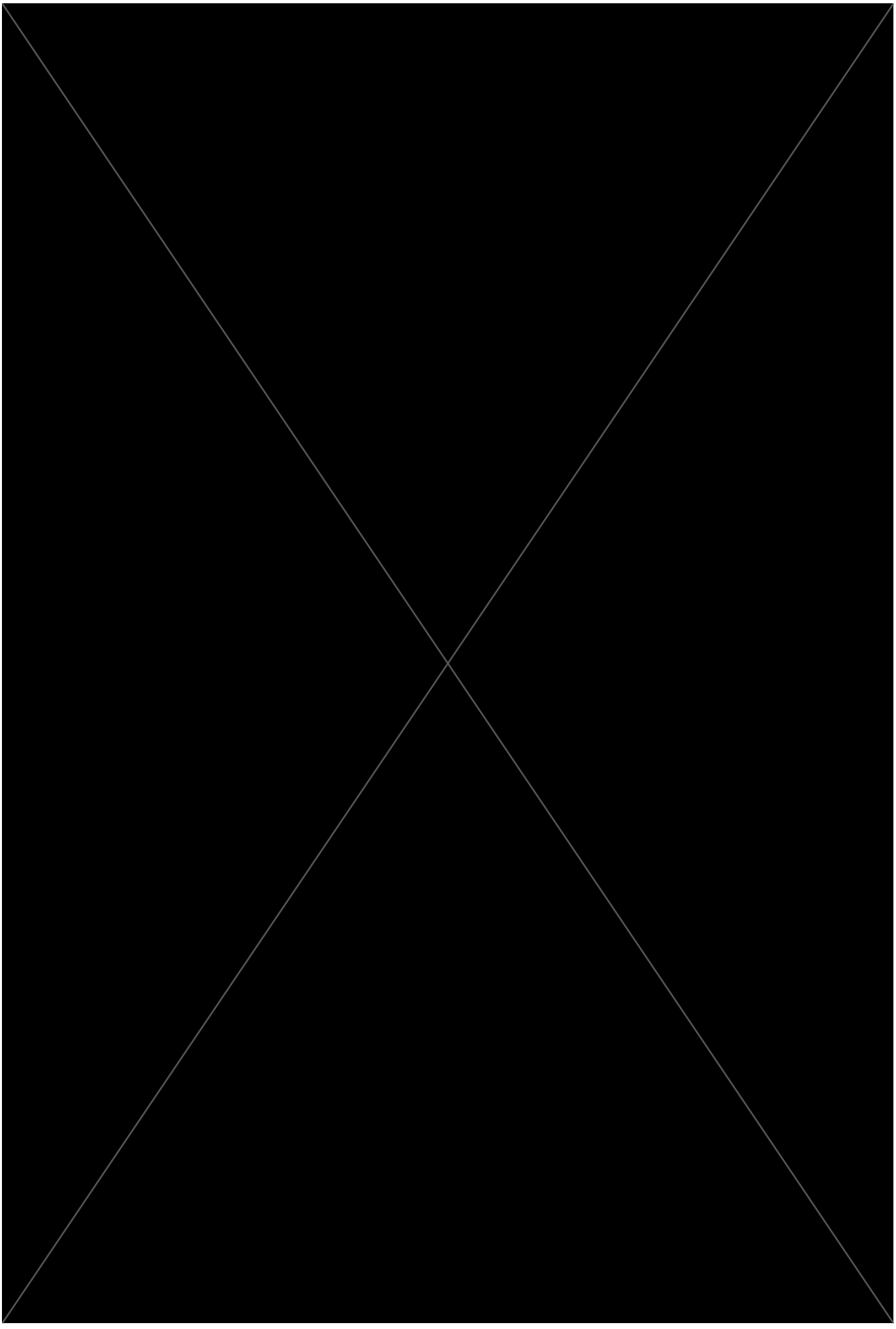


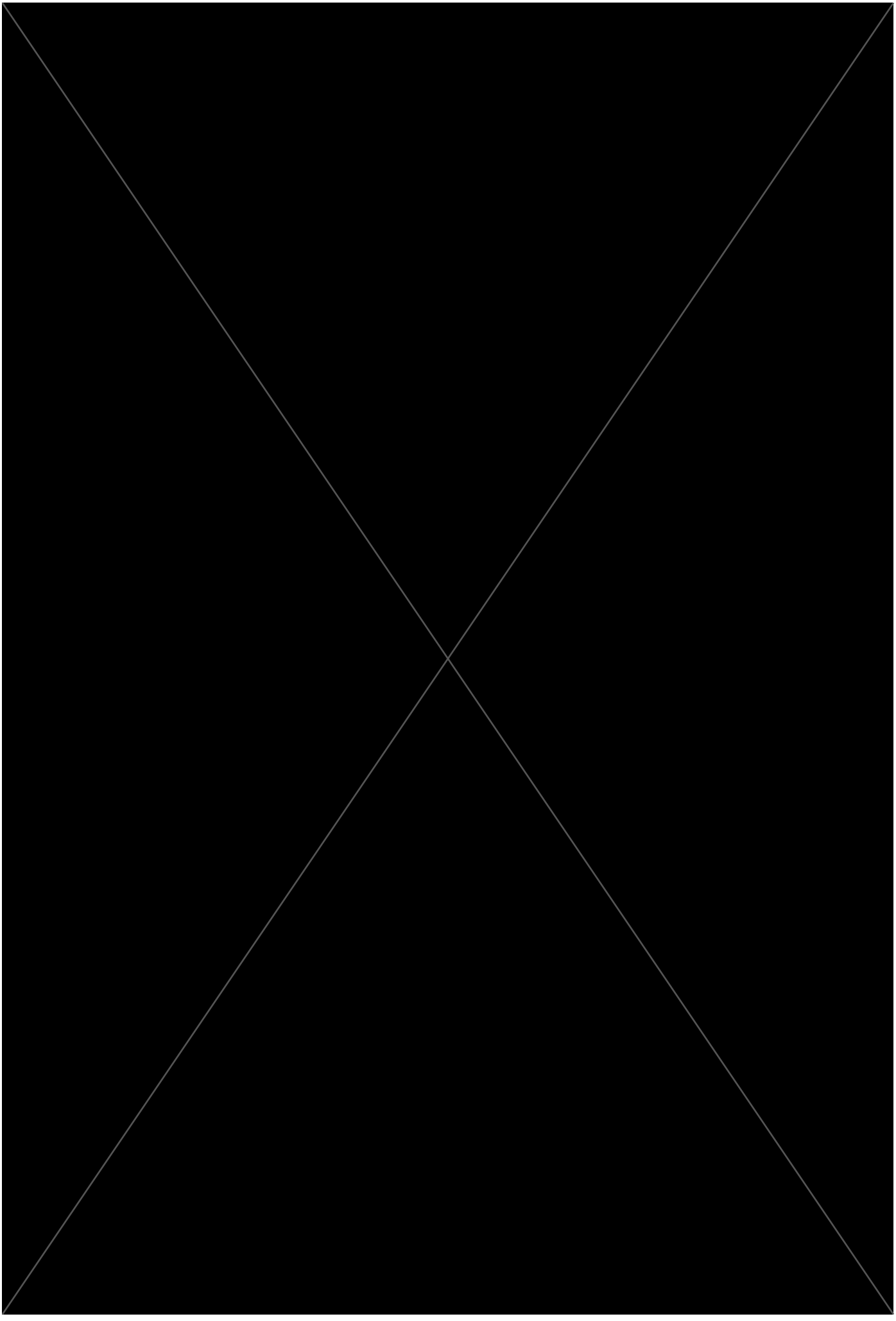


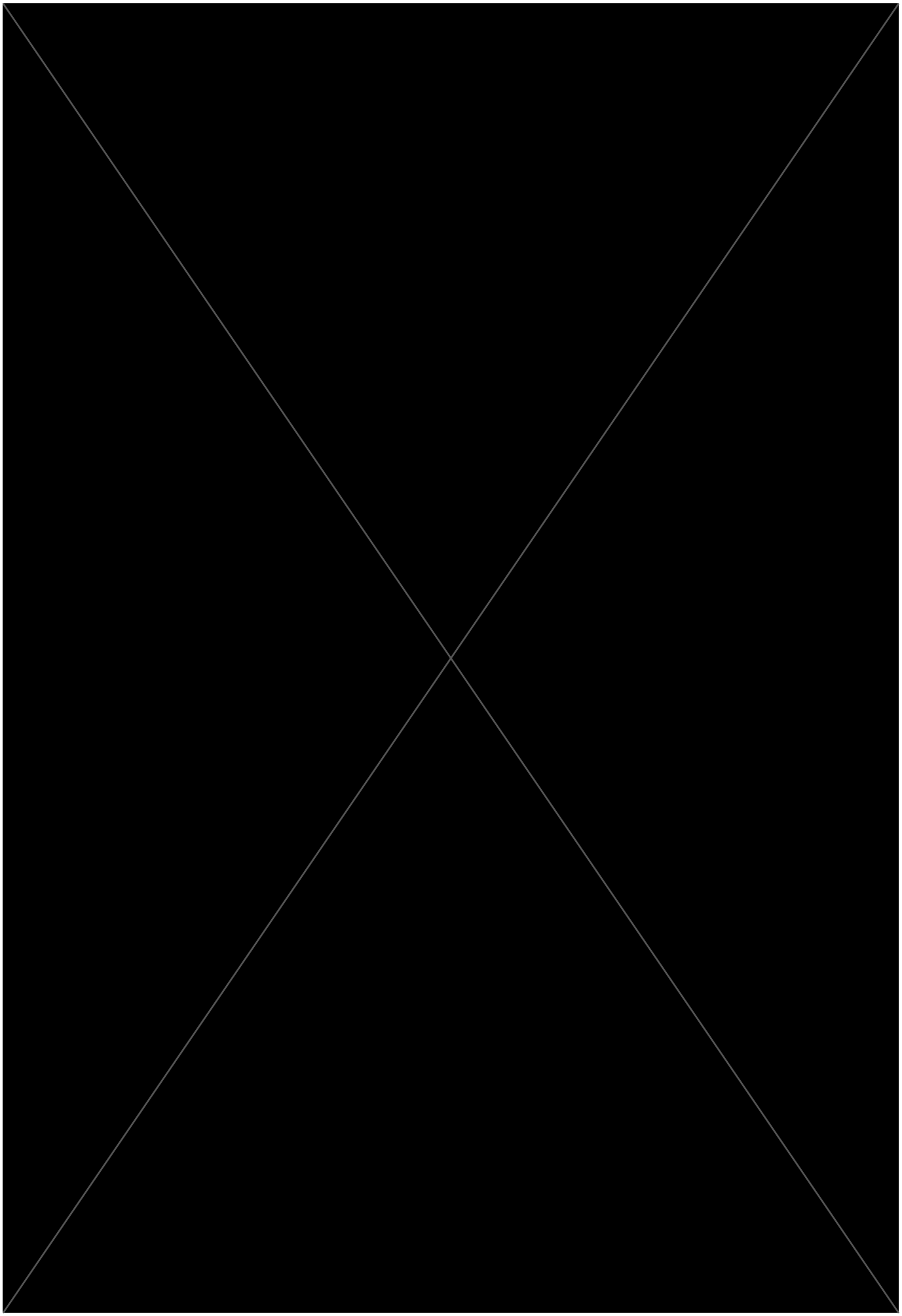


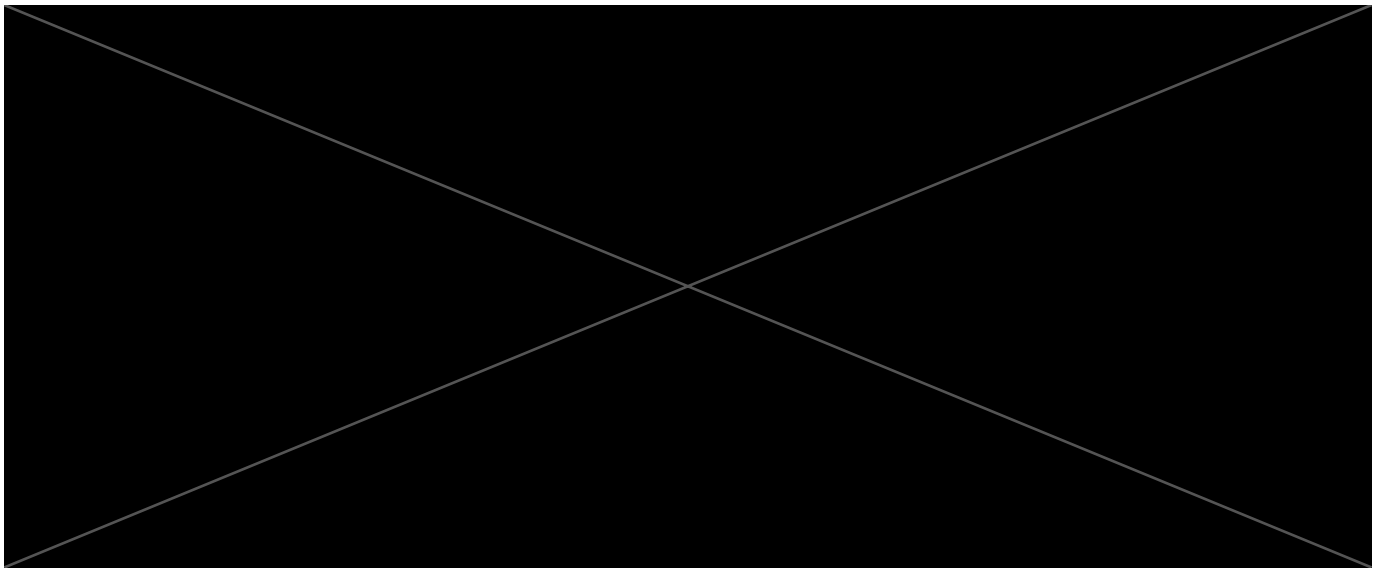












Discussion

The new AD diagnostic criteria allow an earlier diagnosis. The suspicion is established by the clinical and neuropsychological examination and the confirmation by imaging biomarkers or cerebrospinal fluid [52-55].

From the neuropsychological point of view, **aMCI and prodromal AD characteristically show an early episodic memory impairment** [212], classically confirmed by verbal memory tests such as the **Free and Cued Selective Reminding Test (FCSRT), the gold-standard for testing** [174]. However, in recent years, other tests emerged to evaluate episodic memory. Those new tests avoid some of the challenges we find with the FCSRT, such as its moderate sensitivity due to a ceiling effect or its long administration time for primary care or general neurology settings (11 minutes on average) [185]. Among these **new memory tests**, those based on binding stand out. Binding, the ability to remember new associations between words or images, a**ppears to be more sensitive in achieving AD-related memory impairment** [29, 213-214].

In this context, we have chosen as our test to validate the **"Associative memory test of the Seine-Saint-Denis district" (TMA-93), which examines "visual relational binding."** This is a recently developed test for the **early diagnosis of AD among immigrants with a low educational level** [199]. It may be appropriate in our clinical setting, where we have a very high percentage of patients over 65 with a very low educational level who did not complete their primary studies.

As we previously mentioned in the introduction, a new diagnostic test's correct development **includes validation studies, reliability** (internal consistency and inter and test-retest reliability), and a **normative** study [200]. In our case, once we had decided

which test we wanted to validate and what its target population and diagnosis would be, we proceed with the validation phases.

THE CHOSEN TEST: TMA-93

TMA-93 uses ten semantically-related pairs of drawings, assessing binding. Binding ability (or associative learning) is the memorization of an image/word facilitated by exposure to a second image/word, with which the first was previously paired and encoded [185, 215-216].

The ***"relational binding"*** **studies the association between objects or words and has its anatomical basis in the hippocampus, parahippocampal cortex, and network regions.** It decreases in the **prodromal AD** [217-219]. Asymptomatic individuals with a higher amyloid burden have shown abnormal scores on relational binding tests when episodic memory is still preserved [220].

TMA-93 is a specific memory test that provides us with several potential advantages:

1. It is **suitable for elderly and low-educated patients**. It is probably more accurate for diagnosing aMCI than others testing episodic memory.
2. Its **short administration time** turns the test suitable for Primary Care or General Neurology outpatient clinics, in which there is limited time per patient.

Preliminary validation. Article I

"TMA-93 for Diagnosing Amnestic Mild Cognitive Impairment: a comparison with the Free and Cued Selective Reminding Test"

We carried out **a preliminary validation** (phase I) of the TMA-93 test through this first study. **We compared its diagnostic accuracy with the classic FCSRT to differentiate patients with amnestic mild cognitive impairment (aMCI) from HCs.** The 60 participants' sample consisted of 30 patients and 30 HCs. The 41.7% had a low educational level.

Regarding the TMA-93 diagnostic accuracy, the ROC curve analysis determined an AUC of 0.97 (95% CI: 0.89 - 1.00, p <.001) to distinguish between aMCI patients and HCs. **The TMA-93 accuracy did not show significant differences with the gold-standard FCSRT's pictorial version on the same sample.** This result proves that the TMA-93 can help **diagnose aMCI** in an environment like ours, with a high percentage **of older people with a low educational level.**

From this validation study, we obtained cutoffs to distinguish aMCI patients from controls for TMA-93 total score (19/20) and the three variables of the FCSRT (total free recall, 21/22; total recall, 43/44; cued index, <0.77). These results are helpful for clinical practice.

For healthy controls, the TMA-93 total score was high with a relatively small standard deviation. This may be considered a ceiling effect. This ceiling effect in Healthy Controls may be **advantageous in diagnosing aMCI since a small number of errors can be a poor result for a cognitively unimpaired person.** A subsequent normative

study will explore whether this ceiling effect remains when considering only the oldest or less-educated individuals.

This study supposed the **first validation of the TMA-93 and the FCSRT's picture version in Spain.** Picture-based memory tests may have higher applicability in Spain than verbal ones for patients consulting for memory problems and a low-educated. This study also supposed the first international validation for the TMA-93 to distinguish aMCI against HCs. This step is essential to focus the test on early AD.

All participants, including those less-educated, adequately tolerated both FCSRT and TMA-93, completing both tests. The acceptability usually emerges as a problem when patients have severe memory impairment, and there is a floor effect for the test. In this situation, a short test requiring less time is better completed by patients. The shorter the test, the more applicable it will be.

Reliability study. Article II.

"Reliability and Feasibility of the Memory Associative Test TMA-93"

In this development phase, we aimed to study the reliability and feasibility of the TMA-93. This work is the first reliability and feasibility study for the TMA-93.

Reliability

Within the reliability study, we valued internal consistency and inter-rater and test-retest reliability.

The TMA-93 internal consistency between the ten pairs of semantically related pictures was "optimal" (Cronbach's alpha = 0.936). This consistency implies that the **10 test items are highly correlated, so they similarly measure the interest construct** (the "visual relational binding"). Comparing, the FCSRT internal consistency has been described just as "acceptable" (Cronbach's alpha = 0.810) [221]. The "corrected item-total correlation" was at least 0.40 for each of the TMA-93 items. Cronbach's alpha did not increase when eliminating any of the ten pairs, discarding any redundancy in the ten drawing pairs.

We found a **strong correlation between the two halves of the TMA-93**, indicating that HCs and aMCI patients performed equally well (or as poorly) on both halves of the test.

In the HCs group, the **TMA-93 showed a "good" test-retest reliability at 2-4 months** [ICC = 0.802 (95% CI = 0.653 - 0.887)], **suggesting stability in the over-time performance.** The 2-4 months' interval time chosen seems to be short enough to prevent the effect of an eventual cognitive impairment on the sample, particularly from participants with lower scores, and long enough to prevent a practice effect.

By comparison, this reliability is similar to that reported for the "Mini-Mental State Examination" (MMSE) [222]. This property enables the test for use in longitudinal studies.

The **inter-rater TMA-93 reliability resulted "optimal" for the total score** [ICC = 0.999, 95% CI 0.999 - 1], **number of errors** [ICC = 0.996, 95% CI 0.993 - 0.998], and **number of intrusions** [ICC = 0.985, 95% CI 0.974-0.992]. It was "good" for the number of perseverations [ICC = 0.853, 95% CI 0.738 - 0.918].

Administration and scoring are relatively simple, but classifying incorrect responses in errors, intrusions, or perseverations can lead to disagreements between examiners and require some training.

Feasibility

To demonstrate the test's feasibility, we recorded the **percentage of participants who completed the test and the employed administration time. All participants,** including those in the mild-dementia stage**, completed the test**. The task's tolerability was good, including those patients with lower scores or longer administration-time recorded.

We found s**ignificant differences in the administration time according to the diagnosis**: the average time required to complete the test was 2 to 3 minutes for HCs (IQR = 2.0 - 4.0), 6 minutes for aMCI patients (IQR = 4.7 - 7.8), and 7 minutes for AD-like dementia patients (IQR = 5.9 - 9.4). However, there were **no significant differences in administration time regarding educational level.** An average time of 6 minutes in aMCI

Normative study. Article III

"Norms for Testing Visual Binding Using the Memory Associative Test (TMA-93) in Older Educationally-Diverse Adults"

This one is the **first TMA-93 Spanish normative study**. Through it, we provide normative percentiles data.

Following international recommendations [208], we describe the healthy population's reference scores, with a **broad representation of our region's community in which we are applying the test.** We study how sociodemographic variables (age, gender, and educational level) influence the TMA-93 total score.

To carry out this study, we followed a **systematized recruitment strategy for partners of patients who came to the Memory Outpatient Clinic**. Included cases did not suffer from memory difficulties and were cognitively unimpaired. Following routine clinical practice conditions, we did not exclude any participants due to their educational level, reaching a total sample of **1131 participants**.

TMA-93 total score was influenced by age and educational level, but not by gender. The non-normal distribution of the TMA-93 total score led to a percentile results approximation, with age and educational level stratification.

This normative study showed wide variations of the TMA-93 total scores for 5th and 10th percentile by education and age, lower for the older and less educated groups. This distribution suggests that **the ability to learn by visual association is lower and more sensitive to aging in the low-educated group.**

Compared to its French equivalent (original normative and validation study) [199], the test ran similarly. In both populations, the **test works with a ceiling effect mitigated by age and educational level.** Regarding the whole sample, the 5th percentile score was slightly higher in the French study. This finding cannot be explained because of a younger sample or a higher educational level. It could be due to a cultural effect. **Potential cultural differences corroborate the need for normative studies for each reference population.**

Biomarkers' validation. Article IV

"TMA-93 validation by AD biomarkers. A comparison with the FCSRT on a Biobank sample"

During the last stage of this doctoral work, we carried out the TMA-93 validation with biomarkers. **This work represents the first validation of the test with biomarkers**. We performed a retrospective analysis of patient records on a biobank database. The patients included had memory complaints corroborated by an informant, a total score on MMSE equal to or higher than 22, the neuropsychological examination with the TMA-93 and the pictorial FCSRT included; and they had performed a biomarker test (CSF or Amyloid-PET), either with a positive or negative result.

To evaluate the diagnostic accuracy and the biomarkers' predictive value (CSF or Amyloid-PET), **we compared the TMA-93 and FCSRT variables with the positive or negative biomarkers' result, considered as the Gold-Standard**.

The TMA-93 total score demonstrated "reasonable" diagnostic utility in discriminating between "positive" and "negative" biomarker groups (AUC = 0.72; 95% CI: 0.62 - 0.82, p <.001). This diagnostic utility was higher than that of the FCSRT variables. According to the DeLong method, we found no significant differences between the TMA-93 and pictorial FCSRT variables. It shows that TMA-93 is as useful as the international Gold-Standard FCSRT to discriminate either patients with memory impairment and MMSE ≥ 22 have positive or negative biomarkers.

The study involved the first validation with biomarkers of the 5th and 10th percentile cutoffs obtained in the previous normative study according to age and educational level. **Memory impaired patients with an MMSE ≥ 22 and TMA-93 total score ≤ 5th and 10th percentiles showed 75 and 86% sensitivity and 41 and 29% specificity, respectively, for AD biological diagnosis.** These high sensitivity values position the TMA-93 as a good memory screening test, particularly for limited face-to-face time settings. The low specificity is possibly due to the binding component in other non-AD entities, as Argyrophilic grain disease, TDP-43 limbic-predominant age-related encephalopathy, hippocampal sclerosis, and neurofibrillary tangle dementia.

Therefore, **we propose the patients' memory examination to start with the TMA-93 (as screening), followed by the AD-pathology confirmation with the most specific test at present: biomarkers.**

The sequential use of the TMA-93 after the pictorial FCSRT increased the diagnostic sensitivity up to 95.3%. However, 4.7% of the evaluated patients obtained a TMA-93 total score above the 10th percentile and FCSRT - TFR over the 21/22 cutoff, a "positive" biomarker result. This 4.7% with positive biomarkers and that was not detected with the cutoff points of TMA-93 and FCSRT represents the real challenge in our daily clinical practice. A high cognitive reserve could play an essential role in those cases, perhaps requiring more demanding memory tests, studying semantic interference, such as the Memory Binding Test, or "conjunctive binding" tests.

The main limitation of this validation study was the retrospective analysis. The case study from a Biobank database could have incurred a selection bias. To verify this

hypothesis, a prospective study with systematic recruitment of patients would have to be designed.

TMA-93 improved the prediction of biomarker outcomes when added to the FCSRT variables. We could extrapolate that a memory test evaluating binding can improve the biomarker's prediction when added to another test based on coding by semantic clue.

Conclusions

FINAL CONCLUSIONS

1. The TMA-93 associative visual learning test is **highly discriminative to distinguish patients with amnestic Mild Cognitive Impairment** without excluding low-educated individuals.

2. TMA-93 has a **high internal consistency.** All its items measure the interest's construct ("visual relational binding") homogeneously. None of the ten items is redundant.

3. The test is precise**, with high interobserver and good test-retest reliability**. The good test-retest reliability makes the TMA-93 suitable for longitudinal studies.

4. The **TMA-93 administration spends an average of 3 minutes in healthy controls, 6 minutes in amnestic Mild Cognitive Impaired patients, and 7 minutes in Mild Demented patients.** The test is suitable for General Medicine and General Neurology outpatient clinics.

5. **TMA-93 total score varies with sociodemographic variables.** It must be evaluated according to age and educational level**.** The normative data obtained throughout this doctoral work allow its acceptable use by health staff in Spain.

6. **In patients with memory difficulties and MMSE ≥ 22, the TMA-93 is as accurate as the pictorial FCSRT to discriminate between positive and negative AD biomarkers' results.** Biomarkers' prediction improves by adding the TMA-93 total score to the FCSRT variables.

7. Scores below the 10th percentile own a **86% sensitivity** for a biomarker positivity. Together with the **6 minutes of administration** time in Mild Cognitive Impaired patients, it positions the test as a **good screening tool in limit face-to-face consultations.** The specific AD diagnosis, however, must be confirmed with biomarkers.

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