Universitat Autònoma de Barcelona

Early diagnosis of Alzheimer' Disease in different cultural backgrounds: Electrophysiological and cognitive biomarkers

Brenda Nadia Chino Vilca

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UNIVERSIDAD AUTÓNOMA DE BARCELONA
Facultad de Medicina
Instituto de Neurociencias

Early diagnosis of Alzheimer' Disease in different cultural backgrounds: Electrophysiological and cognitive biomarkers

TESIS DOCTORAL

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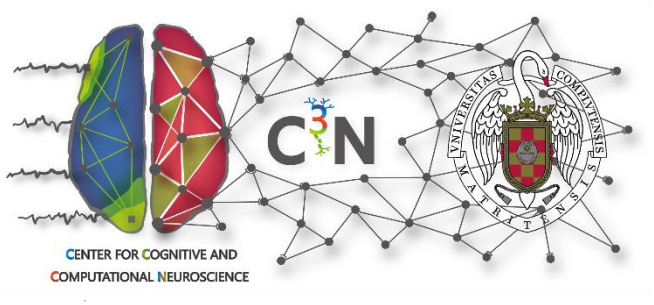

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List of abbreviations

AAL	Automated Anatomical Labeling
AC	Alcohol consumption
ACE-R	Addenbrooke's Cognitive Examination Revised
AD	Alzheimer disease
ADAS-Cog	Alzheimer's Disease Assessment Scale
ANCOVA	Analysis of covariance
AP	Action potentials
APF	Individual alpha peak frequency
APOE	Apolipoprotein E
ATR	Alpha theta ratio
Aβ-42	Amyloid-β 42
BOLD	Blood Oxygen Level Dependent
CBPT	Cluster based permutation test
CBS	Cluster-based statistics
CI	Cognitively intact
CRA	Childhood residence area
CRTs	Choice reaction tasks
CSF	Cerebrospinal fluid
CSS	Current smoking status
CTs	Comparison tasks
CVLT	California Verbal Learning Test
DR	Delayed recall
DSM	Diagnostic and Statistical Manual of Mental Disorders
DWI	Diffusion-weighted images
EC	Eyes close
EEG	Electroencephalography
EM	Episodic memory
EO	Eyes open
ESA	Erlangen Score Diagnostic Algorithm
FA	Fractional anisotropy
FC	Functional connectivity
FDR	False discovery rate
fMRI	Functional magnetic resonance imaging
GDSSF	Geriatric Depression Scale- Short Form
GM	Gray matter volume
IYE	Individual years of education
JCR	Journal Citation Reports

LACs	Latin American and Caribbean Countries
LM	Logical memory
MCI	Mild cognitive impairment
MEG	Magnetoencephalography
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
NDD	Neurochemical dementia diagnostics
NIA-AA	National Institute on Aging and the Alzheimer's Association
PAT	Physical activity time
PEL	Parents' Educational Level
PICO	Patient, intervention, comparison, outcome
PLV	Phase locking value
PRISMA	Preferred reporting items for systematic reviews and meta- analyses
PS	Power spectrum
PSD	Power spectral density
PSP	Postsynaptic potentials
p-tau	Phosphorylated tau
RAVLT	Rey Auditory Verbal Learning test
RBMT	Rivermead Behavioral Memory Test
ROIs	Regions of interests
RSPM	Raven´s Standard Progressive Matrices
RT	Reading time
SART	Sustained Attention to respond task
SCD	Subjective cognitive decline
SD	Standard deviations
SQUIDs	Superconducting quantum interference devices
STM	Short term memory
SWiM	Synthesis without meta-analysis
TMS	Test of Memory Strategies
TMT	Trail making test
t-tau	Total tau
VFT	Verbal Fluency Test
WAIS	Weschler Adult Intelligence Scale
WM	Working memory
WM	White matter volume
WMS	Wechsler Memory Scale
YE	Years of education

Abstract

Aging is a natural process characterized by the progressive accumulation of physiological changes and a slowdown of some cognitive domains. However, some aspects of these cognitive changes are also associated with pathological states, such as the Alzheimer's disease (AD). AD is a progressive neurodegenerative disorder, results of a complex interaction between genetics and environmental factors experienced throughout life. One approach to defining the pattern of the biological mechanism underlying the onset and development of AD is the use of non-invasive tools able to detect changes in the structure and function of the nervous system in humans, which allows characterizing and following the development of AD pathology from preclinical stages. In this sense, electroencephalography (EEG), and magnetoencephalography (MEG) are useful tools since they allow studying the evolution of electrophysiological markers in the brain in a completely non-invasive way. The combined use of these techniques, evaluation brain activity in resting-state, with neuropathological markers of AD and cognitive performance, could help to improve the distinguish pattern of early AD. In this sense, the main objective of this Doctoral Thesis is to identify robust electrophysiological and cognitive markers that allow to distinguish (i.e., probabilistically classify) healthy subjects from patients with mild cognitive impairment, considering as sources of information sociodemographic data, neuropsychological assessment, cerebrospinal fluid (CSF) biomarkers, and EEG/MEG measures extracted from resting activity of multicultural samples.

With this main objective in mind, the thesis is organized into two parts, with five articles focusing on the study of healthy and pathological aging. Regarding healthy aging, the first two studies include (i) the analysis of the impact of sociodemographic and lifestyle characteristics on cognitive performance in Peruvian adults and (ii) a systematic review of previous findings on the association between resting-state electrophysiological profiles and cognitive performance in healthy aging. Concerning pathological aging, the following three studies address (iii) the exploration of the potential association between delayed recall performance and resting-state functional connectivity in cognitively intact subjects and mild cognitive impairment (MCI) patients; (iv) a multicenter study of cerebrospinal fluid markers and their association with episodic memory impairment and executive functions in patients with mild cognitive impairment; and (v) the association of electrophysiological signs of mild cognitive impairment with cerebrospinal fluid biomarkers and the assessment of this relationship according to sex. Finally, chapter eight frames the general discussion and conclusions of the thesis, summarizing the status of the hypotheses and evaluating the degree to which the proposed objectives have been achieved.

Our findings corroborate the relevance of non-modifiable and modifiable factors related with cognitive decline in healthy aging. Although nonmodifiable factors (i.e., residence area during childhood, education level of the parents) impact older adults' cognition, their influence is mediated by other factors that are indeed modifiable (i.e., time spend reading, engagement in physical activity). Furthermore, since electrophysiological point of view, the measure of alpha peak frequency is associated with the cognitive performance and could be considered as an electrophysiological marker of healthy aging. This finding could be the base to support the implementation of initiatives encouraging a healthy lifestyle and promoting brain health activities (for example, through exercise, healthy diet, brain enrichment activities, and social interaction), which could favor reducing cognitive decline in aging.

On the other hand, regarding the electrophysiological profile of MCI, (i) higher values in functional connectivity (FC) of the beta band in the right occipital region were associated with lower delayed recall scores in cognitively intact and MCI subjects. The brain seems to progressively lose the ability to desynchronize beta oscillations, and this process starts to become significant in preclinical stages, at least in participants with AD vulnerability such as the presence of the APOE ε4 allele; (ii) an early executive functioning impairment, which could ultimately affect their performance on episodic memory test could help to discriminate between two different patterns of MCI (positive and negative CSF); and (iii) there is a potential differential association between EEG profiles and CSF markers in male and female participants. These facts reinforce the need for clinical trials focused on a more personalized approach to improve the early detection of AD and the application of pharmacological and non-pharmacological interventions, in addition to supporting the use of neuroimaging techniques for early disease characterization.

Resumen

El envejecimiento es un proceso natural caracterizado por la acumulación progresiva de cambios fisiológicos y la ralentización de los dominios cognitivos. Sin embargo, algunos aspectos de estos cambios cognitivos se asocian a estados patológicos, como la enfermedad de Alzheimer (EA). La EA es un trastorno neurodegenerativo progresivo, resultado de una compleja interacción entre la genética y las exposiciones ambientales experimentadas a lo largo de la vida. Una aproximación para definir el patrón del mecanismo biológico que subyace a la aparición y desarrollo de la EA es el uso de herramientas no invasivas capaces de detectar cambios en la estructura y función del sistema nervioso en humanos, lo que permite caracterizar y seguir el desarrollo de la patología de la EA desde estadios preclínicos. En este sentido, la electroencefalografía (EEG) y la magnetoencefalografía (MEG) son herramientas útiles, ya que permiten estudiar la evolución de los marcadores electrofisiológicos en el cerebro de forma totalmente no invasiva. El uso combinado de estas técnicas, la evaluación de la actividad cerebral en estado de reposo, con los marcadores neuropatológicos de la EA y el rendimiento cognitivo, podría ayudar a mejorar el patrón de distinción de la EA temprana. En este sentido, el objetivo principal de esta Tesis Doctoral es identificar marcadores electrofisiológicos y cognitivos robustos que permitan distinguir (es decir, clasificar probabilísticamente) a los sujetos sanos de los pacientes con deterioro cognitivo leve, considerando como fuentes de información los datos sociodemográficos, la evaluación neuropsicológica, los biomarcadores en líquido céfalo-raquídeo y las medidas de EEG / MEG extraídas de la actividad en reposo de muestras multiculturales.

Con este objetivo principal en mente, la tesis se organiza en dos partes, con cinco artículos centrados en el estudio del envejecimiento saludable y patológico. En cuanto al envejecimiento saludable, los dos primeros estudios incluyen (i) el análisis del impacto de las características sociodemográficas y de estilo de vida sobre el rendimiento cognitivo en adultos peruanos y (ii) una revisión sistemática de los hallazgos previos sobre la asociación entre los perfiles electrofisiológicos en estado de reposo y el rendimiento cognitivo en el envejecimiento saludable. En relación al envejecimiento patológico, los tres estudios siguientes abordan (iii) la exploración de la asociación potencial entre el rendimiento de recuerdo demorado y la conectividad funcional en estado de reposo en sujetos cognitivamente sanos y en pacientes con deterioro cognitivo leve (DLC); (iv) un estudio multicéntrico de los marcadores del líquido cefalorraquídeo y su asociación con el deterioro de la memoria episódica y las funciones ejecutivas en pacientes con deterioro cognitivo leve; y (v) la asociación de los signos electrofisiológicos del deterioro cognitivo leve con los biomarcadores del líquido cefalorraquídeo y la evaluación de esta relación según el sexo.

Nuestros hallazgos corroboran la relevancia de los factores no modificables y modificables relacionados con el deterioro cognitivo en el envejecimiento saludable. Aunque los factores no modificables (es decir, la zona de residencia durante la infancia, el nivel educativo de los padres) afectan a la cognición de los adultos mayores, su influencia está mediada por otros factores que sí son modificables (es decir, el tiempo que se dedica a la lectura, la participación en actividades físicas). Además, desde el punto de vista electrofisiológico, la medida de la frecuencia del pico alfa se asocia con el rendimiento cognitivo y podría considerarse como un marcador electrofisiológico del envejecimiento. Este hallazgo podría ser la base para apoyar la implementación de iniciativas que fomenten un estilo de vida saludable y promuevan actividades de salud cerebral (por ejemplo, a través del ejercicio, la dieta saludable, las actividades de enriquecimiento cerebral y la interacción social), lo que podría favorecer la reducción del deterioro cognitivo en el envejecimiento.

Por otro lado, en lo que respecta al perfil el DCL (i) los valores más altos de la conectividad funcional de la banda beta en la región occipital derecha se asociaron con puntuaciones más bajas de recuerdo retardado en sujetos cognitivamente intactos y con DCL. El cerebro parece perder progresivamente la capacidad de desincronizar las oscilaciones beta, y este proceso empieza a ser significativo en las etapas preclínicas, al menos en los participantes con vulnerabilidad a la EA, como la presencia del alelo APOE ε4; (ii) un deterioro temprano del funcionamiento ejecutivo, que podría afectar en última instancia a su rendimiento en la prueba de memoria episódica, podría ayudar a discriminar entre dos patrones diferentes de DCL (LCR positivo y negativo); y (iii) existe una posible asociación diferencial entre los perfiles EEG y los marcadores del LCR en los participantes masculinos y femeninos. Estos hechos refuerzan la necesidad de realizar ensayos clínicos centrados en un enfoque más personalizado para mejorar la detección temprana de la EA y la aplicación de intervenciones farmacológicas y no farmacológicas, además de apoyar el uso de técnicas de neuroimagen para la caracterización temprana de la enfermedad.

Planteamiento de la tesis doctoral

El envejecimiento es un proceso natural que implica la acumulación progresiva de cambios fisiológicos a lo largo del tiempo. El declive fisiológico va acompañado de una ralentización de los dominios cognitivos, que comienza poco después de que los individuos alcancen la madurez. Algunos aspectos de estos cambios cognitivos se asocian a estados patológicos, como las etapas prodrómicas de la enfermedad de Alzheimer. Sin embargo, quedan aún muchas dudas sobre qué factores juegan un papel de riesgo o protección frente al declive cognitivo asociado a esta enfermedad y cuáles podrían ser los signos que caracterizan estas primeras etapas. La mayor parte de los procedimientos de caracterización de los estadios patológicos de un proceso neurodegenerativo se basan en medidas caras, de difícil acceso en diferentes regiones del mundo o muy invasivas para el sujeto. En ese sentido, el objetivo principal de la tesis es identificar marcadores electrofisiológicos y cognitivos robustos que permitan clasificar probabilísticamente el envejecimiento saludable y el deterioro cognitivo leve, considerando como fuentes de información los datos sociodemográficos, el estilo de vida, la evaluación neuropsicológica, los marcadores de líquido cefalorraquídeo (LCR) y las mediciones de EEG / MEG extraídas de la actividad en estado de reposo de muestras iberoamericanas. Las técnicas neurofisiológicas y la evaluación neuropsicológica constituirán una aproximación disponible en múltiples hospitales (especialmente el EEG) y además a un bajo coste para el diagnóstico.

Para conseguir estos objetivos es esencial la descripción del envejecimiento saludable. En este sentido, la presente tesis enmarca dos estudios. El primero está dirigido a establecer qué factores sociodemográficos y estilos de vida median la relación entre la adquisición de años de escolaridad y el rendimiento cognitivo de adultos sanos. Y el segundo, de corte más teórico, busca establecer, con una revisión sistemática de trabajos previos, cuál es la relación entre el rendimiento cognitivo y los patrones electrofisiológicos en sujetos cognitivamente sanos.

El siguiente paso fue caracterizar cognitiva y electrofisiológicamente el perfil de los pacientes con deterioro cognitivo leve, utilizando técnicas de neuroimagen como la electroencefalografía y magnetoencefalografía, pruebas neuropsicológicas como el rendimiento neuropsicológico, y pruebas bioquímicas como los marcadores de proteínas en líquido cefalorraquídeo. Considerando el amplio uso de la evaluación neuropsicológica para identificar los primeros signos de las EA, y siendo un marcador ampliamente reconocido el rendimiento en recuerdo demorado, el tercer estudio evalúa la relación entre el recuerdo demorado y la conectividad funcional en estado de reposo de sujetos cognitivamente sanos y personas con deterioro cognitivo leve. Adentrándonos un poco más en el debate sobre los dominios cognitivos y su implicancia en el deterioro, el siguiente paso fue valorar qué dominio cognitivo (si la memoria episódica o el funcionamiento ejecutivo) es más sensible

para discriminar entre pacientes con marcadores positivos de LCR en DCL. Finalmente, y considerando los antecedentes sobre los patrones cognitivos y las oscilaciones cerebrales según el sexo, el último estudio pretende responder a la pregunta: ¿Cuál es la relación, según el sexo, entre el espectro de potencia en estado de reposo en EEG y los marcadores de líquido cefalorraquídeo en pacientes con deterioro cognitivo leve?

Chapter 1

Introduction to EEG/MEG hallmarks of healthy and pathological aging

1. Electrophysiological basis of EEG/MEG signal

Neuronal communication in the brain is associated with small electrical currents, which give rise to measurable voltage differences on the scalp and magnetic fields outside the head. Electroencephalography (EEG) and magnetoencephalography (MEG) are neurophysiological techniques that allow us to map, respectively, the brain electrical and magnetic activity through the recording of such quantities in a non-invasive manner. EEG and MEG reflect, in essence, the same elementary neuronal phenomena: the post-synaptic activity of synchronously activated neurons (Lopes da Silva, 2013).

Each neuron –which typically has thousands of synapses with other neurons (Hämäläinen et al., 1993)– continuously integrates information into postsynaptic potentials (PSP), caused in turn by the action potentials (AP) of presynaptic afferent neurons. Although AP and PSP are part of the same process, they represent different underlying mechanisms, and have, therefore, different features: the AP is characterized by a considerable amplitude (~100mV) and a short duration (~1ms), whereas the PSP presents a smaller amplitude (~10mV) but a larger duration (10 ms). This will be an important factor to determine whether the activity of cell assemblies translates to a more likely overlap in time.

Among the different types of neurons, pyramidal neurons –which approximately constitute the two-thirds of the neurons present in the cerebral cortex– possess geometrical properties that foster the detection of post-synaptic activity at a distance from the neuronal sources, when several neurons (in the scale of tens of thousands) activate with a certain degree of synchrony (Buzsáki et al., 2012; Lopes da Silva, 2013).

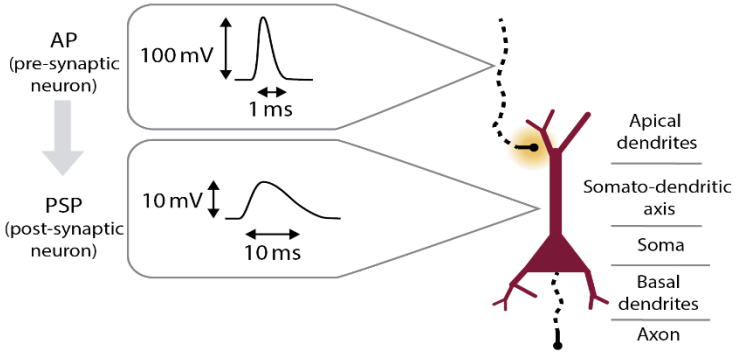

Fig. 1 Schematic drawing of a pyramidal neuron and representation of the two classes of electric potential involved in the information signaling process between neurons: AP (from the pre-synaptic neuron) and PSP (on the postsynaptic neuron).

Indeed, pyramidal neurons present an elongated shape, which constrains the circulation of the intracellular current along the somato-dendritic axis (Baillet, 2017) and can be modeled as a current dipole[1]; further, these neurons are arranged in the form of a palisade, with their main axes parallel to each other and perpendicular to the cortical surface, and with the apical dendrites oriented toward the pial surface of the cortex (Hansen et al., 2010). Such features are ideal for the generation of coherent (and therefore additive) electric and magnetic fields.

The intracellular (primary) current generates a primary magnetic field around it, following the right-hand rule of the electromagnetism (Fig.2A). Such current is compensated by extracellular (volume, or secondary) currents that circulate in the opposite direction elsewhere along the membrane, completing the loop of ionic flow in the surrounding medium (Fig.2B), and able to induce i) voltage differences on the scalp and ii) secondary magnetic fields (usually of smaller amplitude).

This is the reason why the EEG (which measures voltage differences) reflects exclusively the extracellular currents, while the MEG (which measures *magnetic fields*[2]) is more sensitive to the intracellular currents (Lopes da Silva, 2013). Due to the approximately spherical shape of the head, and since magnetic fields generated by pyramidal neurons in the cortex are radial to their axis, the magnetic field generated by intracellular currents oriented tangentially to the skull (e.g., those

[1] *Current dipole*. The activation of a synapse implies a net flow of ions within dendrites and soma of the postsynaptic neuron, producing the intracellular current on the postsynaptic neuron. A current dipole is a popular source model used to approximate the flow of such current in a small area (5, 6).

[2] Two distinct but closely related quantities are referred to as magnetic fields: the H-field (*magnetizing field*, measured in (A/m)) and the B-field (*magnetic flux density*, measured in (T)), commonly called magnetic field (7).

generated by pyramidal neurons in sulcal walls) will be stronger than those generated by currents from radial sources (e.g., pyramidal neurons in gyral crowns) (Baillet, 2017; Hansen et al., 2010; Lopes da Silva, 1991). In fact, in those

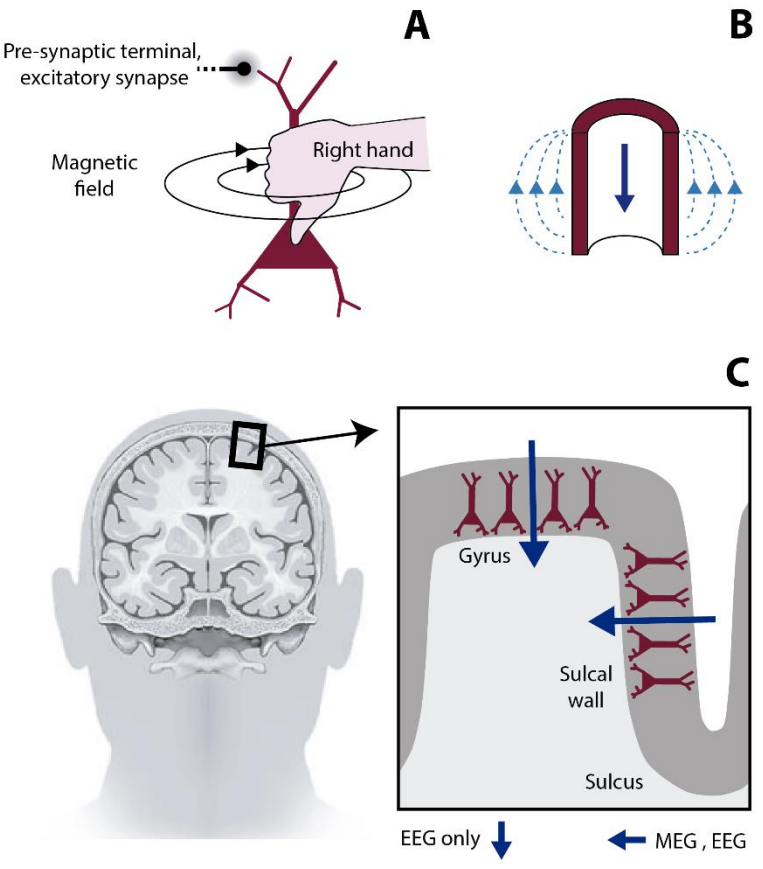

Fig. 2 A) An excitatory synaptic stimulation at the level of the apical dendrites is associated with a magnetic field generated around the somato-dendritic axis, in accordance with the right-hand rule of electromagnetism.

intracellular currents that are oriented radially to the skull the secondary magnetic fields will arrange in such a way that they cancel out the magnetic signal in any point outside of the head and are therefore invisible to MEG. Therefore, since EEG and MEG are sensitive to different aspects of these sources, the combined EEG/MEG source analysis can yield more accurate results than using either method alone (Aydin et al., 2015).

Note that, an inhibitory synapse at the level of the soma will produce the same effect whereas an inhibitory (excitatory) synapse at the level of apical dendrites (soma) will produce an intracellular current upward. This process causes B) the flow of intracellular (primary) current (solid blue arrow) along the somato-dendritic axis and related extracellular (volume or secondary) currents in the surrounding medium (dashed blue arrows). C) Scheme of pyramidal neuron disposition in the cortex (palisade). Since the primary currents flow roughly perpendicular to the cortex, MEG blind to neural currents with a radial orientation with respect to the scalp.

In addition to the observation of the signal measured at the level of the sensors (sensor space), EEG and MEG allow the scientist to estimate the primary currents originating them at the level of neural sources (source space). The inference of the position and activation of the current sources from external sensors (known as the inverse problem) requires the combination of the signal acquired from the sensors with the MRI of the subject, or by using proper existing structural templates if a subject-specific image is not available.

EEG and MEG are particularly appropriate for the study of neurocognitive processes because: 1) they measure neural activity directly, not relying on vascular responses, differently to other in-vivo functional neuroimaging techniques (e.g., functional magnetic resonance imaging (fMRI)); and 2) they are able to capture cognitive dynamics with high-temporal-resolution (i.e., in the order of the millisecond), that is an appropriate time frame for cognition processes. In addition, MEG is superior in some respects to EEG, as it presents a fair spatial resolution (up to 2–5 mm) and lacks interaction with biologic tissues, avoiding smearing and distortion outside of the scalp (Baillet, 2017).

The characteristics of EEG and MEG allow us to study brain activity during the execution of cognitive tasks, and many studies have highlighted the potential of M/EEG as a tool for understanding the resting brain and the nature of the "functional connectivity" that binds together the brain areas (i.e., network nodes). Such techniques represent a useful set of tools to unveil neurobiological mechanisms related to the functional changes observed during aging.

1.1. Brain oscillations captured by EEG/MEG

Among the brain signals captured by EEG/MEG are of special interest those containing rhythmic activity. This rhythmic activity is directly linked to neural oscillations in the cortex produced by fluctuations in the excitation/inhibition of underlying populations of neurons. There are three main features that characterize any oscillation: its power (i.e., the amount of energy per unit time), its frequency (i.e., the number of cycles per second), and its phase (i.e., the position of the "starting point" across time). Some oscillations could be modified by tasks or events, while some others seem to remain stable for longer periods of time.

In the brain, oscillations of multiple frequencies coexist simultaneously, in appearance independently. These frequencies have been historically grouped into bands, usually named delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-30 Hz), low gamma (30-80 Hz), and high gamma (80-150 Hz). These band definitions are not unique, but the most typically related to cognitive processes in the literature, and their boundaries could vary slightly between studies (Lopes da Silva, 1991).

The field of spectral analysis enables the study of the frequency content of brain signals. By means of the power spectral density (PSD) (also referred as *power spectrum* (PS) or *power density spectrum*) one can analyze how the signal power is distributed over the different frequencies or bands. Several studies show that individual differences in the location of the peaks in the spectrum (mainly the alpha peak) have been linked to a number of individual characteristics, highlighting their potential as biomarkers for specific diseases (Başar et al., 2013). In the last decades, studying the frequency content of brain signals dynamically has drawn great interest, revealing promising results in the field of aging (Fernández et al., 2006; Rondina et al., 2016).

Therefore, analyzing the oscillatory components of brain signals is considered a key step to further study the "interaction" between brain regions (i.e., the functional connectivity, FC).

1.2. M/EEG instrumentation.

Both EEG and MEG allow us to measure a large frequency range (in theory up to 1,000 Hz), although bands of interest span typically across 1–80 Hz. This frequency span depends on the technical limitations of the technique; for example, the low-conductivity skull restricts the propagation of high-frequency (higher than 30 Hz) oscillations, affecting the sensitivity of EEG to gamma waves.

While the detection of surface potentials (this is, the measure of EEG) can be made through small electrodes attached to the scalp, without particular constraint, the sensing of tiny magnetic fields implies a more complex system. To this purpose,

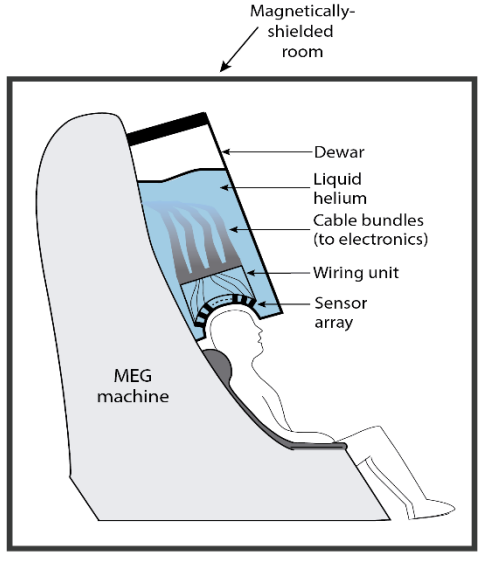

Fig. 3 Schematic drawing of a MEG machine.

classical MEG equipment employs superconducting quantum interference devices (SQUIDs), i.e., specific magnetic sensors (magnetometers and gradiometers) made of superconducting material and based on the so-called Josephson effect, only explainable by quantum mechanics (thus the name). To maintain superconductivity, the entire device needs to operate within a few degrees of absolute zero, and for that are cooled with liquid helium. This need reflects on a much more complex system, sketched in Fig. 3.

The unit of measurement of EEG is the volt (with the signal in the range of the microvolts or μV) while the unit of MEG is the tesla (with the signal in the range of the femtotesla or fT). Differently to MEG, EEG accounts for electric potentials, relative in nature, and the measured values are reported as relative with respect to a reference electrode placed somewhere else, usually on the head (e.g., ear lobe).

The fact that MEG is reference-free electrode greatly simplifies the data interpretation. In addition, the possibility of performing continuous head monitoring for subsequent movement compensation ensures versatility in relation to specific types of subjects, such as infants or patients with movement disorders. On the other hand, MEG technology imposes substantial capital and operating costs. Fortunately, cost-effective solutions are being increasingly used, as helium recycling or helium-free alternatives to SQUIDs (i.e., optically pumped magnetometers) (Tierney et al., 2019).

2. Aging in figures: A current epidemiological overview

There are 7.7 billion people in the world, of whom 12.3% are over 60 years old (Aranco et al., 2018). In 2018, for the first time in history, people over the age of 65 outnumbered children under the age of five. It is estimated that by 2050, one in six humans in the planet will be elderly, which implies a radical increase in the ratio of old-to-young (Department of Economic and Social Affairs, 2020). Aging is a natural process, and it is associated with a series of biological changes that include the gradual decrease in physical and mental capacities, increased risk of disease, and finally death (Harada et al., 2013). This increase in demand can be particularly significant in developing countries, where population aging occurs at a faster rate than in developed countries. For example, in 2010, the global population of people aged 60 and over residing in developing countries was 65%, and this figure is projected to increase to 80% by 2050 (Department of Economic and Social Affairs, 2020). The pace reached by aging is attributed to two aspects: first, to the increase in life expectancy, which in 2019 reached 72.6 years; second, to the decrease in fertility rates, with 2.5 children per fertile women in 2019 (from 3.2 in 1990) (Department of Economic and Social Affairs, 2020).

On the other hand, Latin America and the Caribbean do not constitute, at the moment, an aging region. According to data from the United Nations, adults over 65 years represent 15.2% of its population. This value is lower than that observed in Europe, North America, Oceania, where we found figures like 32%, 28.5%, 22.6%, respectively, similar to Asia (14.8%), and higher only than Africa (7.7%) (*World Population Prospects 2019 Volume II: Demographic Profiles | Population Division*, 2020). However, regional data hides strong heterogeneities. Countries such as Belize, Bolivia, Guatemala, Guyana, and Haiti have a population profile similar to that of China, with around 15% of the population over 60 years of age. Contrary, Bahamas, Barbados, Brazil, Chile, Colombia, Costa Rica, Jamaica, Trinidad and Tobago, and Uruguay can be compared to Germany, Finland, and even Japan, with a proportion of older adults close to 30% (Aranco et al., 2018).

This panorama has also led to a growth in the prevalence of various diseases related to older age, such as dementia, which directly affects the independence and quality of life of the older population (Mukadam et al., 2019; Sperling et al., 2011).

In a systematic review of data obtained in 195 countries between 1990 and 2016 and published by the Global Burden of Disease Study, the analysis of mortality, prevalence, and incidence of cases with this pathology concluded that, in 2016, the global number of people living with disease was 43.8 million. This figure increased by 20.2 million from 1990 (GBD 2016 Dementia Collaborators, 2019). In the same way, the latest report from Alzheimer's Disease International (2018) indicates that there 50 million people worldwide live with dementia (Alzheimer's Association, 2018). This implies that there is a new diagnosis of dementia somewhere in the world every 3 seconds. This figure will more than triple to reach 152 million by 2050. With these numbers, dementias are a pressing problem for global public health, with costs that exceed $160 billion annually (Prince et al., 2012), being even more pressing in low/middle-income countries (Wimo et al., 2017; Xu et al., 2017).

In Latin America, in a study by Nitrini et al., (2009), the prevalence of dementia in older adults (≥65 years) was determined to be 7.1%, a score similar to that found in developed countries. Among the causes for dementias, Alzheimer's disease was the most frequent, from 49.9% in Maracaibo, Venezuela, up to 84.5% in Concepción, Chile. Vascular dementia was the second most prevalent disease, from 8.7% in Lima, Peru, up to 26.5% in Maracaibo, Venezuela. It is noteworthy that a high prevalence of dementia is evident in relatively young individuals (2.40% 65 to 69 years of age), significantly high compared to that seen in developed countries (Nitrini et al., 2009). In the Andean region alone, 250,000 people are estimated to live with dementia (Custodio et al., 2015).

In recent years, many investigations of Alzheimer's dementia (AD) concluded that interventions must be started in the early stages of the pathology (Contador et al., 2010; Gomez & White, 2006; Olazarán et al., 2016), before the neurodegeneration starts affecting the integrity of the brain (Silverberg et al., 2011; Skoog et al., 2017). This intervention will reduce the costs of institutionalization, time of care, and medication, that in Peru, for example, exceeds up to 2.5 times the minimum wage (Rojas et al., 2011).

Thus, the call to combat dementia has become global (Parra et al., 2018), aiming to transform health systems to provide timely care with affordable diagnostic tools to the general population, which favors the early identification of AD cases and promotes a preventive approach to the disease.

3. Cognitive complains associated with healthy aging

Aging is a natural process and involves the progressive accumulation of physiological changes over time (Carmona & Michan, 2016). The physiological decline is accompanied by a slowdown in cognitive processes, which begins shortly after individuals reach maturity (Ferreira et al., 2015; Nikolai et al., 2018). Complex processes are more vulnerable to aging. Between 61 and 96 years old, there is a decline of 0.04 to 0.05 standard deviations (SD) in general performance per year, much more pronounced than that found in people younger than 60 years (0.02 to 0.03 SD per year) (Salthouse, 2009).

However, not all aspects of cognitive functioning exhibit early declines comparing between age. Crystallized skills such as vocabulary and general knowledge, based on accumulated knowledge, remain stable or gradually improve at a rate of 0.02 to 0.03 SD per year during the sixth and seventh decades of life (Harada et al., 2013; Salthouse, 2009). For example, when compared their performance to that of people between 20 and 40 years, older with adults of 70 and 80 years old obtained higher vocabulary scores (Harada et al., 2013; Salthouse, 2019).

In contrast, fluent intelligence declines with age. This is referred to skills used for problem-solving and reasoning in a new context, independently of previous learning. Psychomotor ability and processing speed are included in this category, and peak in the third decade of life and then decreases at an estimated rate of 0.02 standard deviations per year (Harada et al., 2013; Salthouse, 2009, 2012). The last one usually appears as an early sign of normal aging (Ferreira et al., 2015), and its decrease negatively impacts performance in many specific neuropsychological tests used to evaluate other cognitive domains (for example, working memory) (Harada et al., 2013; Laurence & Michel, 2017).

Attention, memory, and executive function are also affected by aging. The decrease in attention is especially patent in activities that depend on more complex levels of care (Luo & Craik, 2008), for example, when engaging in conversation in a noisy environment (selective attention) or cooking while talking on the phone (divided attention). On the other hand, the simple listening attention, evaluated classically, with the repetition of a string of digits, shows only a slight decline in late life (Harada et al., 2013).

The decline in memory performance is a common complaint in the elderly. However, it remains stable until before the 60s, and then starts decreasing with age (Salthouse, 2019). The alteration of the memory is characterized by difficulties in the acquisition and/or free recovery of the information but not in consolidation (Ferreira et al., 2015; Salthouse, 2012). For example, in free recall tests, the support provided by the task is minimal and the demand for self-initiated processes is maximum, and the effects of age are easy to observe. On the other hand, in the recognition task, the older people receive greater environmental support and less need for self-initiated processing, decreasing differences by age (Luo & Craik, 2008).

Executive function can also be altered with aging. Components of the executive function like concept formation, abstraction, and flexibility usually decrease after the 70s (Harada et al., 2013). Contrary, other types of executive functions, such as the ability to identify similarities, describe the meaning of proverbs, and reason about familiar material remain stable throughout life.

These changes have practical implications. Age-adjusted cognitive data and longitudinal assessments are essential to define impairment and detect deviations in the clinic practice that may herald the presence of neuropathology.

4. What can neuroimaging techniques (EEG/MEG) tell us about the aging process?

Brain oscillations changes with aging. Recent literature describes EEG/ MEG as the ideal tool for evaluating the progressive loss of efficiency of the neuronal networks in normal aging, and also the dysfunctions at the synaptic level that occur in the early stages of pathological aging (Maestú et al., 2019; Mufson et al., 2012; Rossini et al., 2006). Two cognitive scenarios are used to study these changes: resting state paradigms, where participants do not have to engage in any cognitive activity; and task paradigms, where participants have to perform a specific perceptual or cognitive task. In the next lines, we only report findings resulting from studies about the resting state condition, as this is the cognitive state that aligns with the studies included in the thesis.

4.1. The electrophysiological pattern of healthy aging: What happens in resting state condition?

Relating to power spectrum, the evidence found in EEG studies suggests that a decrease in delta (Babiloni et al., 2006) and theta power are associated with healthy aging (Dias et al., 2015; Duffy et al., 1984; Pollock et al., 1990). Duffy and collaborators (1984) described a negative correlation between age and the power of delta and theta waves, indicating that the amount of slow activity on the EEG does not increase with age in the context of a good state of health. In contrast, one study has shown the opposite scenario, this is, that relatively higher theta power correlates with healthy cognitive aging in subjects aged between 56 and 70 (Finnigan & Robertson, 2011).

Alpha and beta bands showed an inverse pattern with age. One study describes a decrease in beta band associated with age (Pollock et al., 1990), meaning more age was characterized by less beta power. Regarding alpha band, some studies reported an inverse association between alpha power and aging (Dias et al., 2015), similar to that observed by Babiloni and collaborators (2006) in parietal, occipital, temporal, and limbic areas. Ponomareva and colleagues (2013) described a decrease in alpha 3 (10.9- 12.9 Hz) in the occipital ROI in older adults compared with young adults. This change was observed in alpha two relative power (10-12 Hz), where the decrease in the parietal area with associated with an increase in age (Reichert et al., 2016).

On the other hand, MEG studies on healthy aging in resting state indicate a general shift from low- to high-frequency bands of the power spectral density (PSD) distribution until the end of middle age (Vlahou et al., 2014), then followed by an opposite behavior for group over 60 years old (Gómez et al., 2013), similar than observed in the relative power of higher frequency bands (alpha and beta) (Gómez et al., 2013). Vlahou and colleagues (2014) highlight that for older adults, but not younger participants, higher delta and theta relative power in central and temporal regions was associated with improved cognitive performances (separately assessed with cognitive tests).

Regarding to functional connectivity (FC), several studies have explored differences in FC networks associated with non-pathological aging. For instance, Duffy and collaborators (1996) evaluated 371 healthy adults between 20 and 80 years old with EEG, finding age-related reductions in interhemispheric coherence between temporal lobes, particularly in theta, alpha, and beta bands. Similarly, Smith and colleagues (2012) reported weakened functional connectivity in delta, theta, alpha, and beta bands in subjects above 50 years old when compared with younger adults (in a sample of 1675 healthy individuals).

Studies combining fMRI and EEG have reported a reduction in beta band connectivity between the default mode network (DMN) (particularly, the anterior part) and hippocampus and between the DMN and the supplementary motor area in older adults (65-78 years old) when compared with young adults (age 18-28) (Balsters et al., 2013).

Other studies found changes in the patterns of the alpha band. Shinosaki and collaborators (2003) described a decrease in functional interdependence in alpha band over left temporal occipital areas in subjects between 50 to 80 years old, and additional reductions of alpha interdependence in the right inferior frontal areas for ages from 70 to 80 years old. This finding could be indicative of a progressive alteration of alpha FC as regular aging advances. In the same line, Schlee et al., (2012), using MEG, found several age-related changes characterized by a lower FC inflow in posterior cingulum and precuneus, together with increased FC within temporal lobes. The last one was inversely correlated with cognitive performance.

In a M/EEG study with 48 EEG (18 – 72 years old), and 31 MEG (20 – 75 years old) recordings using transfer entropy, McIntosh and colleagues (2014) reported an age-related reduction of distributed entropy across hemispheres.

One study carried out by Vysata and collaborators (2014) analyzed a large sample of healthy adults (17,722) using EEG coherence. They reported reductions in global coherence in theta and alpha bands, accompanied by an increase in the coherence of beta band. Conversely, Nakamura and collaborators (2017) found increased low frequency FC between precuneus and the bilateral inferior parietal lobules in healthy aging, correlating with amyloid-β deposition.

The novel machine learning methodologies allow to identify the common features that define a particular brain state. Moezzi and collaborators (2019) employed support vector machine to sort the FC features, measured with imaginary part of coherence, of a group of young adults (19 to 37 years old) and a group of older adults (63 to 85 years old). They found that older adults presented decreased FC in the alpha band, involving frontal, temporal and parietal electrodes. These findings were interpreted as reduced connectivity in the networks which govern attention and awareness. In contrast, increased beta FC was reported for this same group in sensorimotor functional networks.

Some of these findings in the FC of older adults has been also related with differences in the individual alpha peak frequency (IAPF). Scally and collaborators (2018) found a lower alpha band FC in older adults (N = 32; mean age 69) compared with younger adults (N = 37; mean age = 20). However, these differences disappeared when the band definition was individually adapted to each IAPF.

Altogether, the study of the variation of RS networks with healthy aging seem to shed consistent evidence: age-related changes are generally characterized by a reduction in the synchronization of spontaneous brain activity among diverse cortical areas. This reduced FC is particularly seen in slow frequency bands, together with increases of beta band synchronization within sensorimotor networks. However, there are different methodologies to estimate FC patterns, giving rise to different results, a fact that must be borne in mind when drawing conclusions.

4.2. How does pathology modify the electrophysiological footprints of the aging brain? The Alzheimer's Disease continuum

One of the most relevant age-related disorders affecting the brain is Alzheimer's disease. AD is a neurodegenerative disease characterized by progressive and fatal cognitive impairment resulting from the abnormal accumulation of proteins in the brain parenchyma, which starts 20 years before the earliest signs of the disease. This process which includes the preclinical, prodromal, and dementia stages, is called AD continuum. The first of these is known as Subjective Cognitive Decline (SCD) (Riedel-Heller et al., 1999; Roberts et al., 2009) and is followed by Mild Cognitive Impairment (MCI) (Albert et al., 2011). There is a high rate of progression from this state to AD, while a significant percentage is not progressing into dementia at all, and some revert to a cognitively normal state (Petersen, 2004; Petersen et al., 2014). After this long process, the final stage will be reached, accompanied by a formal diagnosis of AD.

E/MEG studies build upon our knowledge on how the electrophysiological properties of the aging brain are affected by AD neuropathology. The characterization of the power spectrum has yielded highly consistent outcomes, where a general slowing of the oscillatory activity characterizes the AD continuum, including prodromal and preclinical stages of the disease (Engels et al., 2017; López et al., 2014; Poza et al., 2007).

This profile features an increase in power in low frequencies (delta and theta bands) together with a decrease in higher frequency bands (alpha and beta) (Besthorn et al., 1997; López et al., 2014; Mizuno et al., 2010; Moretti et al., 2004; van der Hiele et al., 2007; Verdoorn et al., 2011). According to de Waal and collaborators (de Waal et al., 2013), it is possible to observe an increase in delta and theta power in the temporal, parietal and/or occipital region in patients with AD even after a 3-year follow-up. These changes can be observed bihemispherically even in the early stages of the disease in anterior and posterior areas (Czigler et al., 2008; Moretti et al., 2004). Some studies also indicate an alteration of the gamma power; however, the results are still contradictory, likely to the lower sensitivity of EEG to these frequencies. McBride and colleagues (2014) point, for example, to a decrease in

gamma in the right frontal and left temporal regions along the continuum, while Sharma et al., (2019) indicate increased gamma power in AD.

The most robust finding in the literature is the reduction in the alpha power, which is strongly linked to the slowing in the brain activity. This reduction is associated with worse cognitive functioning in AD patients (de Haan et al., 2008), and is even more exacerbated among multi-domain MCI patients (MCI cases showing alterations in more than one cognitive domain) compared to single-domain MCI patients, hinting that is a marker of severity of the disease. Similarly, in an EEG study, van der Hiele and colleagues (2007) described an increase in theta and a decrease in alpha relative power in AD patients, also related to worse performance in several cognitive domains.

In the stage of MCI, the findings are controversial. According to Hsiao and colleagues (2013), the cortical activity of resting-state oscillations is altered during the transition from MCI to AD. However, one year later, the same authors concluded that there was no significant difference between the spectra of AD and MCI patients, but that averaged power values in AD were larger in low frequencies (theta and delta bands) and smaller in higher frequencies (alpha and beta bands) (Hsiao et al., 2014). On the other hand, longitudinal studies on MCI, such as the ones by Rossini and colleagues (2006, 2008) and Musaeus and collaborators (2018), point out to a decrease in power in the alpha and beta band in temporal and frontal areas both in AD and MCI compared with control subjects. Moreover, progressive MCI (this is, MCI patients later progressing to AD) was characterized by decreased beta power in parietal, temporal and central regions, a feature that could be considered a good classifier to distinguish between MCI progressive and MCI stable at 2 years follow up. Additionally, high spectral power in slow rhythms (delta and theta) in frontotemporal areas can also be considered a sign of warning of "conversion from MCI to AD" (Jiang, 2005) and as a biomarker of the disease (Dimpfel, 2014). Altogether, the reported evidence indicates that an early increase in theta power and a decrease in beta power, followed by a subsequent decrease in alpha and a late decrease in delta power would be the process of conversion of normal adults to AD (Smailovic et al., 2018). Altogether, this sequence of changes can be considered as a progressive slowing of the brain waves, with is consistent with the changes in the EEG activity of AD patients when compared to healthy controls.

On the other hand, brain connectivity alterations play a fundamental role in the study of the mechanisms underlying disturbances in cognition. AD has often been defined as a disconnection syndrome (Delbeuck et al., 2003). Abnormal interactions between brain areas in AD could be linked to early neuropathological changes, which degenerate white matter tracts and synaptic transmission, even decades before the first clinical symptoms appear (Braak & Braak, 1991; Villemagne et al., 2013). Therefore, alterations in FC could be detectable in early stages of the disease,

such as in MCI or event SCD, using in-vivo functional and structural connectivity. In this sense, hyper synchronization has been suggested as an AD biomarker of synaptic dysfunction, showing abnormal excitation/inhibition levels in the brain (Berendse et al., 2000; Pusil et al., 2019; Stam, 2010; Stam et al., 2002).

In the continuum of the disease, people with SCD and MCI, when compared to HCs, present a hyper-synchronization in the anterior network and a hypo-synchronization in posterior regions in resting state, being the latter significantly more marked in MCI patients as compared to SCD subjects (Bajo, Castellanos, Cuesta, et al., 2012; Bajo, Castellanos, López, et al., 2012; Bajo et al., 2010; Lopez-Sanz, Bruna, et al., 2017; Lopez-Sanz, Garces, et al., 2017). This hypo-synchronization between different areas is often interpreted as a network disruption and a loss of the network communication, while the hyper-synchronization is often attributed to a pathological process related to AD due to the progressive loss of cognitive function. At the same time, network-based studies in MCI have revealed that these changes of connectivity occur often more randomly and inefficiently. These disruptions are also present in SCD subjects, but to a lesser degree (Lopez-Sanz, Garces, et al., 2017; Stam, 2004).

In AD, MEG papers usually report decreases in FC (Berendse et al., 2000; Stam, 2010; Stam et al., 2002). These changes seem to affect especially to higher frequency bands (e.g., Alonso et al., 2011; Stam et al., 2002, 2006, 2009), which may reflect local or small-range connectivity changes (Engels et al., 2017). Some studies have also found an increased connectivity in slow frequencies (3-7 Hz), particularly in posterior regions, but this kind of patterns have been less reported (e.g., Alonso et al., 2011; Escudero et al., 2011; Stam et al., 2006). Connectivity between long-range regions have been reported to be diminished in the left hemisphere, involving main frontal, temporal regions, while the small-range connectivity within a region was primarily decreased in the right frontal and parietal areas (for a review, see Engels et al., 2017; Maestú et al., 2019; Stam, 2010). Findings of studies using network analyses help integrating some of the previous results reported in AD: lower and more vulnerable hubness (Yu et al., 2017), weaker connections between modules (De Haan et al., 2012), and a more random configuration in several bands (Franciotti et al., 2006; Pusil et al., 2019; Stam et al., 2009).

Regarding the progressive MCI, Pusil and colleagues (2019) compared the FC resting state networks of MCI patients who remained 'stable' after several months of evaluation and MCI patients that converted into AD in the same time lapse, using MEG. Two characteristic networks were identified in the theta and beta bands, involving fronto-temporal and fronto-occipital connections, with lower levels of FC in the progressive MCI group after conversion to AD. However, at baseline (i.e., before conversion), patients of this group presented higher synchronization than patients with stable MCI. These results suggest an 'X' form model where the

hypersynchrony predicts conversion, but once it occurs it leads to a network breakdown (Pusil et al., 2019).

Despite the different approaches used to estimate FC and cognitive function in the different studies, cognitive impairment usually correlates with modification of functional connectivity (e.g., López-Sanz, Bruna, et al., 2017; Stam et al., 2002, 2006; Yu et al., 2017). This is in line with previous findings from other neuroimaging techniques (Teipel et al., 2016) and with neuropathological studies that found that synapses disturbances lead to connection impairment (Coleman et al., 2004), supporting the notion of AD as a disconnection syndrome.

In summary, different reports of FC in the AD continuum using MEG confirm the existence of an anteroposterior dual pattern in the network failures that occur in pre-dementia and AD stages. There seems to be an early loss of synchronization in posterior regions accompanied by an increase in anterior regions when the cognitive impairment is still not perceptible by neuropsychological assessments. This is followed by a similar pattern but with a more decreased synchrony in posterior networks at the MCI phase, and a final network desynchronization when the patient reaches the AD stage. However, it is still unclear if this pattern is specific of AD, and it is necessary to unravel the network disturbances that occur in different types of dementia.

5. Conclusions

Non-pathological brain aging involves several neurobiological changes which, in turn, affect neuro-physiological functioning. As exposed, the consequences of these changes can be explored under the framework of brain power spectrum and brain synchronization.

Resting state EEG / MEG studies on healthy aging coincide in pointing out a generalized reduction of the relative power of low frequency (delta and theta bands) with increasing age until late middle age. Opposite pattern than observed with the relative power of the higher frequency bands (alpha and beta increasing with age). Regarding FC, FC analysis methodologies applied to E/MEG recordings have proved valuable and reliable in identifying age-related variations. In general, RS studies reported reduced synchronization in slow frequency bands (delta, theta, alpha) and increased sensorimotor synchronization in the beta band. Such alterations could be associated with the loss of integrity of the white matter tracts and with non-pathological processes of neural degeneration. Some authors have proposed different "compensatory mechanisms" models as a potential explanation for increased FC usually observed in older adults. The brain would engage additional neural resources to develop a particular cognitive task successfully. However,

drawing firm conclusions becomes challenging considering the relatively low number of works addressing this topic and the techniques employed.

On the other hand, electrophysiological studies on AD find an exacerbated slowing of brain activity and alterations within the alpha band. The study of the power spectrum suggests an increase in low frequencies (delta and theta bands) and a decrease in higher frequency bands (alpha and beta). FC pattern was characterized by an anterior hyper-synchronization and posterior hypo-synchronization in SCD and MCI individuals, whose is more intense in MCI compared with HC sample. This hyper-synchronization in MCI patients can predict conversion to dementia, as patients with higher FC levels are more likely to progress to AD in a short amount of time. So, AD could be considered a disconnection syndrome at the end of the spectrum, where a widespread decreased FC is the most remarkable feature.

6. References

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Chapter 2

Objectives and hypothesis

1. Main objective

The main objective of the thesis is to identify robust electrophysiological and cognitive markers that allow for the discrimination of healthy subjects and patients with mild cognitive impairment. For such a goal, we will be considering as sources of information sociodemographic data, neuropsychological assessment, and EEG/MEG measurements extracted from resting-state activity of multicultural samples.

2. Specific objectives and related hypotheses

To achieve the general objective of this work, we stablish the next five secondary objectives, with the related hypotheses:

- To assess the mediation role of sociodemographic characteristics and lifestyle factors in the cognitive performance of older adults.

  Hypothesis 1: The relationship between the area of residence during childhood and years of education is mediated by the parents' years of formal education.

  Hypothesis 2: Lifestyle factors play a mediator role of the relationship between the years of education and the cognitive profile of healthy adults.

- To review and summarize the findings about the spectral properties and connectivity patterns of frequency bands in resting state conditions related to cognitive performance during healthy aging.

  Hypothesis: The cognitively healthy aging profile is associated with a reduction of the power in low frequency (delta and theta bands) and an

increase in the power in higher frequency bands (alpha and beta bands).

- To explore the potential association between memory (specifically delayed recall) performance and functional connectivity of resting-state brain activity in both healthy volunteers and MCI patients.

  Hypothesis: The subjects with MCI will show a differential relation between their functional connectivity profile related to cognitive performance than the cognitively intact individuals, indicating preliminary signs of belonging in the AD continuum.

- To evaluate and analyze the possible relationship between EEG spectral power in resting state and CSF markers in MCI patients when taking into account the sex of the participant.

  Hypothesis: The impairment in executive functioning plays a crucial role on the performance of verbal learning tasks, even more important that what has been previously reported for MCI patients. Furthermore, we expect an improvement on the performance of verbal learning tasks when the use of executive functions is diminished. These phenomena would be in close correlation with levels of proteins found at CSF.

- To assess and analyze which cognitive measures are most sensitive to discrimination among participants with mild cognitive impairment (MCI) with positive and negative CSF biomarkers.

  Hypothesis: The relation between the spectral power profile and he cognitive function and CSF biomarkers in MCI patients will be different in men and women.

Chapter 3

Study 1: Impact of sociodemographic features and lifestyle in cognitive performance of Peruvian adults

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Abstract

Background: Cognitive impairment and dementia may result from a combination of modifiable and nonmodifiable risk and protective factors, such as the environment, educational attainment, time devoted to cognitively stimulating activities, and physical activity.

Objective: This study aimed to investigate the mediating role of sociodemographic characteristics and lifestyle factors in the years of education and cognitive performance in Peruvian adults.

Methods: This cross-sectional study included 1,478 subjects assessed by Addenbrooke's Cognitive Examination Revised (ACE-R). Using mediation models, we evaluated the mediation role of parents' educational level, reading time (RT), and physical activity time (PAT) in the years of education (IYE) and cognitive performance.

Results: People who reported having lived in an urban area during their childhood are estimated to have, on average, 2.085 years more formal education than those who lived in rural areas. In addition, 49% of cognitive performance scores are explained by the mediation effect of reading and physical activity time in the IYE. This implies that higher levels of education, mediated by RT and PAT per week, are 1.596 units associated with higher scores on the ACE-R.

Conclusion: Despite the fact that nonmodifiable factors (i.e., childhood residence area, parents' educational level) seem to exert an effect on older adults' cognition, their influence is mediated by other factors that are indeed modifiable (i.e., reading time, physical activity engagement). In this sense, lifestyle changes could help prevent or decrease the risk of cognitive impairment and reduce the disease's impact on vulnerable environments in Latin American and Caribbean countries.

Keywords: aging, cognitive performance, lifestyle, sociodemographic characteristics, vulnerable populations

1. Introduction

In recent years, differences in dementia rates across diverse populations have drawn the attention of scientists around the globe (Custodio et al., 2017; GBD 2016 Dementia Collaborators, 2019; Prince et al., 2013). Cognitive impairment results from a combination of modifiable and nonmodifiable risk and protective factors. Some of the most widely studied protective modifiable factors include educational attainment, time devoted to cognitively stimulating activities (e.g., reading), and physical activity (Clare et al., 2017; Foubert-Samier et al., 2012; Stern, 2009; Stern et al., 2019). In fact, a recent publication shows that up to 56% of the dementia burden in Latin American and Caribbean countries (LACs) could be attributable to a wide range of modifiable risk factors (Livingston et al., 2020). On the other hand, it has been well established that higher socioeconomic status is associated with a healthier lifestyle (World Health Organization, 2018) through a combination of increased purchasing power and understanding of the implications of unhealthy behaviors. In this context, the study of the impact of socioeconomic inequalities and other social determinants of health on brain health and cognitive function across the lifespan has drawn increasing attention (Deckers et al., 2019; Yaffe et al., 2013). This approach takes particular importance in LAC, characterized by poor access to health care, lower education rates, heterogeneity, diversity, unstable economy,and political instability (Parra et al., 2021), which affect the establishment and implementation of prevention and promotion policies.

The elevated level of inequity in LAC countries might contribute to the diverse estimations of dementia prevalence across countries. Along this line, it is crucial to consider additional risk factors associated with cognitive decline that are particularly common within these regions. For example, access to education in LAC is still concentrated in the wealthier social strata of societies, and the most impoverished strata have fewer opportunities to complete secondary or superior education (UNESCO-IESALC, 2020). Access to education influences cognitive abilities, especially in early life, and protects against the development of dementia (Chen et al., 2019; Lövdén et al., 2020). This factor represents the 7.1% risk factor prevalence in early life to develop dementia (Livingston et al., 2020).

Even if recent economic analyses reflect a better current situation for certain LAC countries, moderate poverty increased from 21% to 27%, and extreme poverty rose from 7% to 11% by 2015 (Helwege & Birch, 2007), affecting primarily rural and suburban areas in the access to education or the possibility to educate the children owing to the lack of financial resources. In this sense, estimating the prevalence of risk factors should consider the lifetime of elderly subjects in LAC.

Beyond sociodemographic factor data, other risk factors, such as diabetes (Athanasaki et al., 2022; Ferguson et al., 2021), obesity (Dye et al., 2017), physical inactivity (Scarmeas et al., 2004; Song et al., 2022), and hypertension (Reitz et al., 2007), could contribute to increasing the risk of cognitive decline and dementia (Avilés-Santa et al., 2020), suggesting that lifestyle changes could be critical. Poor access to health care, treatment, cultural influences on nutrition, and physical activity aggravates the picture, and all these factors influence the development and increase of dementia in LAC. The lifestyle changes could be critical to reducing this situation, although the evidence remains mixed and inconclusive about the amount of dementia that can be prevented with lifestyle changes (Montero-Odasso et al., 2020).

In the specific case of Peru, inequality has been associated with several factors, including migration, poverty, and centralism (i.e., centralization of health and economic resources in large cities such as Lima, with the concurrent decrease in health or educational services in the periphery of the city and rural areas) (Carrillo-Larco et al., 2022; Rougeaux et al., 2022). These factors impact the social determinants of health across the territory and act in combination with a lack of effective public health policies and programs (Allen et al., 2014; Carrillo-Larco et al., 2022). In this sense, the absence of specific policies, the difficulty of health services delivery to specific targets, such as the elderly population, and the deficient design of health care programs (Yamada & Castro, 2012) are likely to negatively impact the brain health of the Peruvian population. Therefore, assessing these features could be the first step in the prevention of cognitive decline and its associated reduction in the quality of life of Peruvian older adults.

In Peru, living in a rural or urban environment could determine access to a healthier lifestyle, negatively affecting cognitive performance during aging. Some studies suggest large inequalities between rural and urban areas in low-income countries in contextual, cognitive, nutritional, and academic opportunities (Fagbamigbe et al., 2020; Goodburn, 2014; Tine, 2017). Some reports suggest that socioeconomic inequalities are related to dementia risk differences and modifiable health conditions and lifestyle factors (Deckers et al., 2019). Nonetheless, the specific social determinants that influence cognitive performance are not well understood, especially in LAC countries. Considering all of the evidence presented above, the present study aimed to investigate sociodemographic characteristics and lifestyle factors specifically influencing cognitive function in Peruvian older adults, applying mediation modeling to assess their contribution.

2. Materials and methods

2.1. Participants

The baseline sample consisted of 1,689 subjects of both sexes who were recruited from 14 public health centers in Arequipa, Perú, as part of the following Survey in Health Services of Primary Attention. Participants were volunteering county dwellers, members of the aging center, who could participate in approximately 60 min of neuropsychological evaluation under appropriate conditions. The aging center is a governmental program associated with public institutions to promote the physical, mental, and social well-being of older adults across the country. General inclusion criteria were as follows: age between 50 and 90 years, a short form Geriatric Depression Scale score ≤ 5, capable of speaking in Spanish, with no verbal comprehension or expression problems, and no history of psychiatric or neurological disorders. The institutional review boards of aging centers approved the study protocol, and the procedure was performed according to the guidelines of the Helsinki Declaration. The participants gave written informed consent to participate in the study.

For the present analysis, we excluded subjects with a Geriatric Depression Scale score > 5 because of the relationship between depression and worse cognitive performance (Ganguli, 2009) (n = 120), those living in institutions (n = 30), and those with missing cognitive test scores (n = 61).

The sample for this study, therefore, included 1,478 participants (64.7% female). The results of the descriptive analysis of participants' performance are displayed in Table 1.

2.2. Measures

Sociodemographic features, lifestyle factors, and clinical history were analyzed through a detailed survey administered via a 20-min face-to-face interview in which data about demographics, lifestyle, and comorbidities were collected. This survey was composed of questions about sociocultural variables such as sex, age, education, socioeconomic status, and lifestyle factors. These measures were categorized as binary, tertial, or quartile variables based on their frequency distributions. Education was reported by the number of Years of Education (YE). Marital status was classified as single, cohabitant, married, widowed, or divorced. The parent's educational level was treated as a dichotomous variable (yes-no) and then displayed a list divided into no schooling, between one and six YE, between seven and 11 YE, and more than 11 YE. Medical history was answered with yes (one or more chronic medical conditions) or no (absence of chronic medical condition),

and then multiple options were provided to define the disease, including cardiovascular, metabolic endocrine, psychiatric, oncological disease, and others. The childhood residence area (CRA) was evaluated with an open question about where the participants lived before they were six years old. Then, we classified the location between urban and rural areas.

Regarding lifestyle factors, reading time was evaluated considering the number of hours per week in the last month. The information about physical activity per week was determined by the reported frequency of hours per week of physical activity, including walking at a moderate pace, dancing, floor or stretching exercises, jogging, gym, and other relative activities. Current and ex-smokers were identified using two questions: "Do you smoke?" and "How often do you consume?" Then, self-reported information on the frequency of smoke consumption was used to classify participants into four groups according to the Likert scale: not consume (never consume), very rarely (once a month or less), rarely (2-3 times a month), occasionally (1-2 times per week), and frequently (1-2 times a day). The same questions were used with alcohol and drug consumption.

We included these factors (educational level, childhood residence area, individual years of education, parents' education level, reading time per week, physical activity time per week) based on previous reports that explain how they impact cognition (Chen et al., 2019; Lövdén et al., 2020; Mandolesi et al., 2018; Peterson et al., 2020).

To evaluate cognitive performance, participants were screened using Addenbrooke's Cognitive Examination - Revised (ACE-R). This test was applied to explore their cognitive functioning in different domains, such as verbal memory, attention and executive functions, language, and praxis. The ACE-R is a screening test that assesses six cognitive areas (orientation, attention, memory, language, verbal fluency, and visual construction functions). The version of the test used here is a linguistic cross-cultural adaptation of Torralva et al., (2011). The maximum score is 100 points, and the most commonly used cutoff point is 88, with lower scores indicating the presence of cognitive impairment. The internal consistency analysis for the ACE-R in this study showed a Cronbach's alpha coefficient of 0.904 (elements = 24), which is considered acceptable.

2.3. Statistical analysis

To ensure the quality and reliability of the data, we conducted several preliminary analyses prior to the formal analyses. First, we use descriptive statistics to assess the frequencies, percentages, central tendency, and dispersion measures. Nonparametric contrast tests (χ^2, U Mann–Whitney) were used considering the distribution of the data (checked using Kolmogorov–Smirnov test) and homogeneity

of variances (Levene test). Second, Spearman's correlation test examined how cognitive performance was associated with age, educational level, reading time, and physical activity time. Then, extension of simple linear regression was used to investigate the overall associations between each factor and cognitive function, adjusting for the covariables (age, sex, and chronic conditions).

Mediation analysis investigated the mechanisms underlying observed relationships between sociodemographic factors, lifestyle, and cognitive performance and examined additional hypothesized variables on the causal pathway. Therefore, the final model was constructed considering two steps: Step 1. To evaluate the mediation role of parents' educational level (PEL) between the individual's years of education (IYE) and childhood residence area (rural versus urban; CRA), we used a simple mediation analysis, where CRA is the independent variable and IYE the dependent variable. The model construction is presented in Table 3. Step 2: Regarding the lifestyle factors, we evaluated the influence of reading time per week, physical activity time per week, current smoking status, and alcohol consumption as mediators between educational level and cognitive performance (see Table 4). The mediation models in both cases were constructed as a function of the variance explained in every step for the independent variable (i.e., in step 1: individual level of education, and in step 2: cognitive performance), as illustrated in Fig. 1, exploring covariables such as age, sex, and chronic illness and the overall indirect effect of cognitive scores using Process Macro. Process Macro is a bootstrapping statistical computed tool written by Andrew Hayes as an extension for SPSS and computes X's direct, indirect, and total effects on Y and unstandardized and standardized regression coefficients, standard errors, t, p values, and R^2. Adjusted R-squared indicated the proportion of variance explained by the independent variables (Hayes, 2017). Additionally, previous regressions and a final mediation model were run to confirm predictors with 95% bias-corrected bootstrapped confidence intervals with 10000 repetitions (to correct for nonnormally distributed data). The SPSS V. 22.0 statistical package was used for this analysis.

3. Results

Among the sample, the mean age was 67.30 years old (± 9.98), and 64.7% of the participants were females. The largest group (43.1%) had between one and six years of education; no schooling represented 15.7% of the sample. Approximately 50% of the participants' parents (fathers and mothers) had attained fewer than seven years of formal education (43.2% and 52.7%, respectively). Regarding lifestyle factors, the mean Reading Time (RT) per week was 1.95 h (± 3.96), and the Physical Activity Time (PAT) per week was 0.67 h (± 1.71). Finally, the mean ACE-R score was 63.77

(±19.09), and we found significant differences in this score between rural and urban areas (59.66 ± 18.61; 68.63 ± 18.53). See Table 1.

Table 1 Sociodemographic characteristics of the sample

		All (n= 1478)	Rural (n= 800)	Urban (n= 678)	*p-value**
Age (y)		67.30±9.98	67.88±9.32	66.49±10.66	**0.001[a]**
Sex (%)	Female	64.7	65.4	63.9	0.59[b]
	Male	35.3	34.6	36.1	
Individual's educational level (y)		6.69±5.06	5.11±4.47	8.55±5.08	**<0.001[a]**
Parent's educational level (%)	Illiterate	40.6	50.4	29.0	**<0.001[b]**
	Fewer than 7 y	37.6	35.8	39.9	
	Between 7 and 11 y	17.4	11.8	24.0	
	More than 12 y	4.3	2.0	7.1	
Medical history (%)	Yes	49.4	53.6	44.4	**<0.001[b]**
	No	50.6	46.4	55.6	
Reading time per week (h)		1.95±3.96	1.40±3.10	2.59±4.70	**<0.001[a]**
Physical activity time per week (h)		0.67±1.71	0.55±1.39	0.80±2.03	0.102[a]
Current smoking status (%)	Do not consume	93.9	95.3	92.3	0.069[b]
	Very rarely	0	0	0	
	Rarely	5	4	6.2	
	Occasionally	1.1	0.8	1.5	
	Frequently	0	0	0	
Alcohol consumption (%)	Do not consume	0	0	0	0.069[b]
	Very rarely	81	82.8	78.9	
	Rarely	15	12.9	17.6	
	Occasionally	3.7	4	3.4	
	Frequently	0.3	0.4	0.1	
ACE-R score		63.77±19.09	59.66±18.61	68.63±18.53	**<0.001[a]**

Table 1 provides the mean values ± standard deviations (in the case of continuous variables) or percentages (in the case of categorical and ordinal variables) for relevant sample characteristics. The results are provided for the whole sample and stratified by childhood residence area (rural or urban). Group comparisons were performed for all variables of interest (rural versus urban), where (a) the Mann–Whitney test was applied in the case of continuous variables and (b) the chi-squared test was calculated for categorical and ordinal variables. *p values were corrected using the false discovery rate (FDR) to account for multiple testing. Significant p values are shown and marked in bold.

The association between sociodemographic variables and lifestyle factors is reported in Table 2; we can see that all variables are related to cognitive performance. Older age is associated with lower scores on the ACE-R (Coeff. -0.506; p<0.01). Fewer years of education are related to lower performance in ACE-R (Coeff. 0.641; p<0.01), reading time (Coeff. 0.458; p<0.01), and physical activity (Coeff. 0.191; p<0.01); also, physical activity per week (Coeff. 0.191; p<0.01) is also associated with cognitive performance (Coeff. 0.213; p<0.01).

Table 2 Associations between sociodemographic characteristics and lifestyle factors

	1	2	3	4	5	6
1. Age	1					
2. IYE	**-0.402****	1				
3. PEL	**-0.224****	**0.541****	1			
4. RT	**-0.157****	**0.458****	**0.277****	1		
5. PAT	-0.046	**0.191****	**0.126****	**0.358****	1	
6. ACE-R	**-0.506****	**0.641****	**0.366****	**0.504****	**0.213****	1

Spearman's correlation test was used to define the associations between age, individual years of education (IYE), parents' education level (PEL), reading time per week (RT), physical activity time per week (PAT), and ACE-R scores. **p<0.001.

The final model was constructed in two steps. Step 1: To evaluate the mediation role of parents' educational level (PEL) between years of education (IEL) and childhood residence area (rural versus urban; CRA), we used a simple mediation analysis, where CRA is the independent variable and ILE the dependent variable. The unadjusted model explained 35% of the variance; including age and sex as covariables increased that percentage up to 45% of variance explained in the full model, as shown in Fig. 4 Step 1. Chronic illness did not report meaningful results related to IELs.

Table 3 Model Construction: Educational level and childhood residence area

	Model 1		Model 2		**Model 3**	
Antecedent	Coeff.	*p*	Coeff.	*p*	Coeff.	*p*
X_CRA	2.13	<0.001	2.08	<0.001	2.08	<0.001
M1_PEL	2.97	<0.001	2.50	<0.001	2.50	<0.001
C1 (age)	-	-	-0.1518	<0.001	-0.15	<0.001
C2 (sex)			1.7666	<0.001	1.76	<0.001
C3 (chronic illness)			-0.0552	0.78		
Constant	3.16	<0.001	13.26	0.00	13.15	<0.001
R^2	0.352	<0.001	0.459	0.000	0.459	<0.001

Table 3 provides coefficients (Coeff.) and p values for the individual's educational level assessed during the model construction process, including variables such as childhood residence area (X_CRA), parents' education level (M1_PEL), and covariables such as age, sex, and chronic illness. The final model was constructed considering the influence of the covariables on the result. Model 1: unadjusted; Model 2: adjusted for age, sex, and chronic illness, F (5,1472) =249.7334. Model 3: Adjusted for age and sex, F (4, 1473) =312.3429. The use of chronic illness as a covariable did not show any significant result in the final model.

In this sense, people who reported having lived in an urban area during their childhood are estimated to have more than 2.085 years of formal education, on average, compared to those who lived in rural areas. The direct effect is c = 3.117 (CI: 2.681-3.554), and the indirect effect ab = 1.032 (CI: 0.799-1.273); two effects are significant. The direct effect is c = 3.117 (CI: 2.681-3.554), and the indirect effect ab = 1.032 (CI: 0.799-1.273); two effects are significant.

Regarding lifestyle factors, we evaluated the impact of mediators such as reading time per week, physical activity time per week, current smoking status, and alcohol consumption on the cognitive performance of the participants. Table 4 provides the coefficient (coeff.) and *p* values for the cognitive performance (dependent variable) of four models considering covariables such as age, sex, and chronic illness. We identified an effect of chronic illness on physical activity time per week (Coeff. -0.357; p<0.01); we did not find any significant association with cognitive performance (Coeff. -0.257; p=0.73). The final model includes RT and ST as mediators between years of education (independent variable) and cognitive performance (dependent variable). This model explains 49% of the variance and considers covariables such as age, sex, and chronic illness (Fig. 4 Step 2). This means that higher levels of education, mediated by RT and ST per week, are 1.596 units associated with higher scores on the ACE-R. The direct effect (c= 1.596; CI: 1.430-1.763) and the indirect effect (ab=0.02; CI: 0.005-0.037) are significant.

Table 4 Model Construction: Lifestyle factors, educational level, and cognitive performance

	Model 1		Model 2		Model 3		**Model 4**	
Antecedent	Coeff.	*p*	Coeff.	*p*	Coeff.	*p*	Coeff.	*p*
X_IEL	2.06	<0.001	1.60	<0.001	1.6	<0.001	1.62	<0.001
M1_RT	0.73	<0.001	0.79	<0.001	0.8	<0.001	0.8	<0.001
M2_PAT	0.48	0.04	0.52	0.02	0.53	0.02	0.54	0.02
M3_CSS	-1.36	0.31	-0.47	0.71	-	-	-	-
M4_AC	2.42	<0.001	0.69	0.35	-	-	-	-
C1 (Age)	-	-	-0.58	<0.001	-0.58	<0.001	-0.57	<0.001
C2 (Sex)	-	-	0.86	0.28	0.98	0.20	-	-
C3 (Chronic illness)	-	-	-0.28	0.70	-	-	-	-
Constant	47.76	<0.001	89.97	<0.001	89.93	<0.001	89.7	<0.001
R^2	0.4163	<0.001	0.4889	<0.001	0.4885	<0.001	0.4879	<0.001

Table 4 provides the coefficient (Coeff.) and p values for cognitive performance tested during the model construction process, including variables such as individual educational level (in years; X_ IEL), reading time per week (M1_RT), physical activity time per week (M2_PAT), current smoking status (M3_CSS), and alcohol consumption (M4_AC), and covariables such as age, sex, and chronic illness. Model 1: unadjusted including all variables, F (5,1472) = 209.9829, Model 2: Includes all variables, adjusted for age, sex, and chronic illness, F (8,1469) =175.6224; Model 3: Including IEL, RT and ST, adjusted for age and sex, F (5,1472) =281.1679; and Model 4: Including IEL, RT and ST, adjusted for age, F (4,1473) = 350.9081. The use of chronic illness as a covariable did not show any significant result in the final model.

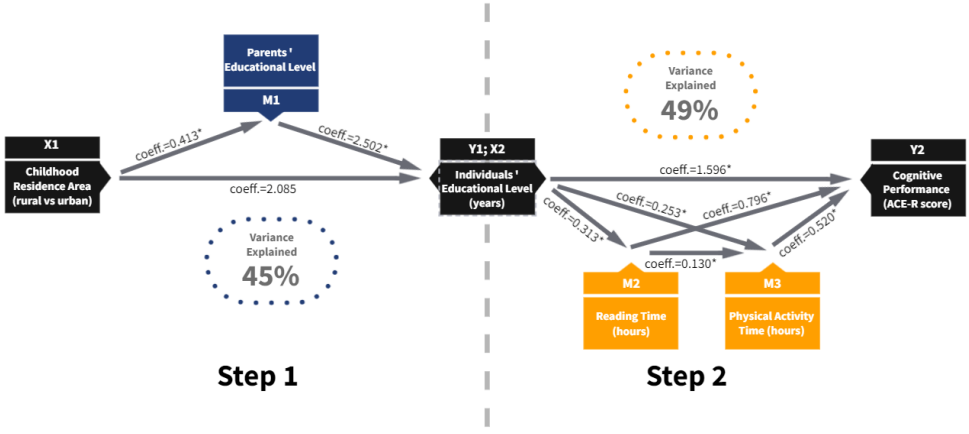

Fig. 4 Mediation analyses

Fig. 4 Represents the two final models combined, where there is a significant effect from childhood residence area on the individual's educational level, which is mediated by the parent's educational level. Moreover, there is a significant effect of the individual's educational level on the individual's cognitive performance, which is mediated by time spent both reading and practicing physical activity. Finally, reading time also predicts physical activity time. In both models, age, sex, and chronic illness were used as covariates. Coefficient values (coeff.) are included in the figure, and significant relationships are marked with an asterisk (*).

4. Discussion

The evidence regarding which factors contribute to the promotion of healthy aging and prevent cognitive decline at an advanced age remains mixed and inconclusive, especially when we refer to the lifestyle changes that can successfully prevent dementia through aging. Among the list of potentially modifiable lifestyle factors associated with reduced risk levels, we find years of education, cognitive activity, and physical activity (Scarmeas & Stern, 2003; Song et al., 2022). According to the *Lancet* Commission Report, modifiable risk factors, including low education and physical inactivity among several others, could account for as much as 56% of the dementia burden in LAC (Livingston et al., 2020). Nevertheless, most of the studies looking at the protective effect of lifestyle factors are based in certain world regions (e.g., Europe and North America). As a result, the effect of these variables on late-life cognition in diverse populations remains to be elucidated. Given that both genetic makeup and engagement in diverse risk and protective activities vary across diverse populations (Dhana et al., 2021; O'Bryant et al., 2013; Raj et al., 2017; World Health Organization, 2018), it is crucial to understand to what extent the results found in Western societies can be replicated in other regions. Moreover, the risk of pathological aging results from the complex interaction between genetics and environmental exposures experienced throughout life (Dunn et al., 2019; Finch & Kulminski, 2019), and thus focusing on a single aspect of lifestyle may be insufficient to reduce the risk of cognitive decline. Therefore, the present study is focused on selected risk and protective factors of cognitive decline grouped under two categories: sociodemographic and lifestyle factors. Our objective was to investigate the potential mediating effect of these factors on the cognitive function of Peruvian older adults who had been raised in either rural or urban environments.

The impact of sociodemographic factors has been studied extensively in the literature. The place where people live define many aspects of their health and well-being, especially during the early years' development. These conditions, influenced also by economic, social, political, and environmental forces, are called social determinants (Allen et al., 2014; Borenstein & Mortimer, 2016) and impact the populations across the LAC (Nitrini et al., 2009; Parra, 2014; Parra et al., 2021), where the inequities are visible even within the same country. The residence area during childhood is strongly associated with intrauterine growth and development, mediated by nutrition, living conditions, access to education, and early stimulation at home (Borenstein & Mortimer, 2016; Fagbamigbe et al., 2020). However, these adverse conditions are potentially modified by parenting support, education, and the inclusion of lifestyle protective factors (Borenstein & Mortimer, 2016; Deckers et al., 2019).

Our results confirm the effect of sociodemographic factors on years of formal education, which in later life predicts cognitive performance. Importantly, our study also provides a deeper analysis of the complex relationships that emerge among these key variables. First, nonmodifiable sociodemographic factors (i.e., childhood residence area) predict the participant's education level, an effect mediated by the parent's formal education level. In this sense, people who reported having lived in a rural area during their childhood and who had less educated parents are estimated to have on average 2 points lower formal education than those who lived in urban areas. Second, the effect of years of formal education on late-life cognitive performance appears to be mediated by modifiable factors (i.e., reading time per week and physical activity time per week), explaining 49% of the variance in ACE-R scores. These protective factors could exert their effects by means of increasing cognitive reserve, which has been described as the ability of the brain to preserve its normal functioning despite the presence of underlying structural damage (Borenstein & Mortimer, 2016; Stern, 2009), and represent behaviors related to cognitive enrichment, which may stimulate neurotrophic factors in the brain (Fernandez et al., 2018). Nevertheless, we should bear in mind that the individual's educational level might have also affected the participant's ability to comprehend and navigate the cognitive test, which could have influenced our overall results (de Azeredo et al., 2015).

Interestingly, even though there has been straightforward evidence that alcohol consumption (Sudhinarase et al., 2016; Baumgart et al., 2015) and smoking (Chen et al., 2009; GBD 2016 Dementia Collaborators, 2019; Rusanen et al., 2011) are independent risk factors for dementia, these two factors were not significantly associated with cognitive performance in our study. The probable reason is the low consumption levels in the sample, whose percentage is lower than that reported in 2016 on consumption in the last 30 days (17.4% versus 20.7%) of older adults consuming alcohol. Something to consider here is the sociocultural validation and the roots of alcoholic beverages in the Andean region and rural areas. It is possible that its consumption is not considered a health problem and is underestimated (Rusanen et al., 2011).

Finally, projections suggest that by 2050, the prevalence of dementia in Latin America would quadruple (Custodio et al., 2017), while in Europe and the US, it is expected to double (Alzheimer Europe, 2019; Alzheimer's Association, 2022). Furthermore, the economic burden attributable to dementia in low- and middle-income countries has also been estimated to increase between 47-71% over the next 15 years (Kenne et al., 2021; Parra, 2014; Parra et al., 2020; Reyes-Marin et al., 2021). In this context, our results might aid in the design of science-based strategies

to partially prevent or alleviate the impact of such burdensome predictions. Nevertheless, better estimations are needed considering the limited reliable epidemiologic data, socioeconomic and sociocultural differences, reduced access to mental health facilities, and the absence of specific policies and protocols for the early diagnosis and treatment of dementia (Parra et al., 2020).

This study is not exempt from limitations. For example, although participants underwent extensive cognitive screening, the present study lacks the utilization of proper diagnostic tools that would have enabled us to identify cases of mild cognitive impairment or dementia. Along this line, lifestyle characterization relied solely on self-reported measurements. Moreover, participants were recruited from urban settings, and information regarding childhood residence areas after the age of 6 was not available. This means that the exact timing when rural children moved to the city was not collected, which could have been used in secondary analyses. Furthermore, future studies could aim to include the analysis of social determinants at different ages as well as their influence on cognitive performance at different life stages (i.e., before the age of 10 and between 35 and 45 years old). Nevertheless, the utilization of mediation analyses contributed to deepen our understanding of the relationships among the variables included in the model. Beyond the statistical approach, this study presents several strengths, for example, the sample size and the thorough characterization of an understudied population in the wider literature.

Finally, our results suggest that there is room for the implementation of evidence-based public policies that could restrict the detrimental effects of nonmodifiable factors, reducing cognitive decline and dementia risk in the Peruvian population. Along this line, the political support for the elderly and dementia prevention in Peru is visible in two laws focusing on the improvement of the quality of life of the elderly (Law N° 30490) and on the prevention and treatment of Alzheimer's disease and other dementias (Law N° 30795). Despite these initiatives, their full implementation is far from complete, especially considering the absence of specific mental health facilities or governmental budgets for dementia (Custodio, 2016).

4.1. Conclusions

Altogether, this study fosters our understanding of the interaction between modifiable and nonmodifiable sociodemographic and lifestyle factors on cognitive performance in late life. Here, we show that although nonmodifiable factors (i.e., childhood residence area, parents' educational level) have an impact on older adults' cognition, their influence is mediated by other factors that are indeed modifiable (i.e., reading time, physical activity engagement).

For instance, there is no effective pharmacological treatment currently available to prevent or cure dementia and cognitive decline. It is appropriate that more initiatives encouraging a healthy lifestyle and promoting brain health activities (for example, through exercise, diet, brain enrichment activities, social interaction) and other factors be promoted by the government and other organizations. In addition, more studies are needed to identify lifestyle protective factors that reverse the influence of nonmodifiable factors that impact cognition.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/jad-000000.

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Chapter 4

Study 2: Electrophysiological profiles under resting-state paradigm and its relationship with cognitive performance in healthy aging: A systematic review

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Abstract

Aging is a complex and natural process. The physiological decline related to aging is accompanied by a slowdown in cognitive processes, which begins shortly after individuals reach maturity. These changes have been sometimes interpreted as a compensatory sign and others as a fingerprint of deterioration. Thus, disclosing the mechanisms underlying and supporting normal cognitive functioning of the brain in the later stages of life is the first approach to defining healthy aging. A systematic literature search was conducted using PubMed, Scopus, and Web of Science databases. We included studies that examine the brain oscillations pattern in resting-state conditions associated with cognitive performance in healthy aging. Despite the different characterization of healthy aging across the studies and the several approaches to analyzing brain activity, our review suggests a relationship between alpha peak frequency with neuropsychological scores in healthy aging. A higher alpha peak frequency (APF) is linked with higher scores in intelligence, memory, and general cognitive performance, and could be considered good electrophysiological marker of cognitively healthy elderly and easy-to-assess candidates for defining the first signs of pathological state on resting-state condition.

Keywords: Healthy aging, cognitive performance, resting state, brain oscillations, alpha peak frequency, systematic review

1. Introduction

Not only cognition, but also the brain itself changes, both anatomically and functionally, during ageing. Synaptic transmission efficiency forms the basis of normal cognitive functioning (Terry et al., 1991) and represents the foundational mechanism underlying neural oscillations, which in turn are known to be of critical relevance to cognitive performance (Singer, 2018). Oscillations in the brain are the result of the coordinated electrophysiological activity of relatively large groups of neurons. They coordinate neural processing throughout the cortical surface by a phasic modulation of neuronal firing that largely depends on the amplitude of these oscillations (Jensen et al., 2014). The role of oscillatory activity during task performance has been largely studied and documented, since their amplitude is known to be modulated as a result of cognitive engagement in the task (Buzsáki, 2006). For instance, theta activity during memory paradigms, and in particular, frontal midline modulations of its power, have been systematically associated with increases in task difficulty and memory load (Gevins & Smith, 2000; Mitchell et al., 2008). Similarly, alpha power has been also associated with cognitive effort during memory tasks (Klimesch et al., 1999; Jensen et al., 2002) but also with attentional allocation to the right or left during a somatosensory working memory task (Hari & Salmelin, 1997) and with distraction inhibition (Bonnefond & Jensen, 2012). Even though a more profound review of this topic is out of the scope of the present manuscript, previous literature has systematically reported that modulations of each brain rhythm are associated with performance in several different cognitive tasks (Klimesch et al., 1999).

Contrarily, resting state activity represents the spontaneous modulations occurring in the brain activity while no specific task is being performed. Even though this activity has been traditionally misconceived as noise, it has been repeatedly shown to contain a significant amount of internal structure, exhibiting persistent patterns of long-range coordination between distant brain regions (Fox & Raichle, 2007). Furthermore, these patterns of resting state activity are known to be highly reproducible among different individuals, mental activity states and they have even been used to characterize different clinical and demographical groups (Stevens & Spreng, 2014). Of note, different cognitive abilities have been shown to be consistently associated with these resting state patterns measured by functional Magnetic Resonance Imaging (fMRI) (Stevens & Spreng, 2014). In particular, a more intense activity during resting state in a specific network has been traditionally linked to a better performance in the particular cognitive ability coordinated by that network during a task execution (Stevens & Spreng, 2014). In fact, the behavioral manifestation of cognitive processes has been interpreted as a sign of the renormalization of patterns observed during ongoing oscillatory activity (Fingelkurts

et al., 2010). That is to say, brain activity during active cognitive efforts would be directly linked to resting state activity, which should represent a major driver for cognitive research in resting state.

Interestingly, despite the fact that the relationship between resting state and cognitive abilities has been studied in the field of fMRI in a relatively consistent way, our understanding of this interaction from an electrophysiological point of view is by far scarcer. This gap in the literature is particularly striking with regards to aging, a stage in which cognitive change is particularly marked, as it has already been mentioned. fMRI has been widely used during the last few decades in research given its wide availability and extraordinary spatial resolution, despite its indirect estimation of brain activity based on the Blood Oxygen Level Dependent response (BOLD). However, magnetoencephalography (MEG) and electroencephalography (EEG) are techniques able to directly measure the result of the synaptic communication between neuron populations. Furthermore, M/EEG are able to track brain activity not only with good spatial resolution but also with incomparable temporal resolution up to the millisecond scale, orders of magnitude better compared to the nonetheless very useful fMRI technique. This difference makes these techniques able to capture the activity in a timescale much closer to the actual behavior of neural populations, and thus, can greatly contribute to increase our understanding of cognitive processing in the brain. This article aims to review and summarize the findings of previous literature studying the relationship between cognitive performance and electrophysiological activity in the context of healthy aging. Since cognitive aging is an extremely relevant phenomenon for modern societies and given the interplay between resting state activity and cognition, electrophysiology, which directly captures the result of neuronal activity, might represent a useful tool to delve into the mechanisms underlying cognitive decline in healthy aging.

Thus, unveiling the mechanisms underlying and supporting normal cognitive functioning in the brain in the later stages of life is of key relevance. This understanding could be crucial for future global policy making strategies trying to take into consideration not only prevention or treatment of cognitive impairment, but also healthy ageing promotion.

2. Methods

2.1. Literature search

A systematic search of the literature was conducted on 07 June 2021 using Pubmed, Scopus, and Web of Science databases according to the Patient, Intervention, Comparison, Outcome (PICO) search strategy (Miller & Forrest, 2001) in order to

systematize articles addressing the topic of interest. Keywords included in the literature search were:

Table 5 Search terms

KEY CONCEPT	SEARCH TERMS USED
Healthy Aging	"Healthy*" OR "healthy aging" OR "healthy adults" OR "normal aging" OR "older adults" OR "elderly" OR "aging" OR "normal adult"
Cognitive performance	"cognition" OR "neuropsychology" OR "cognitive markers" OR "cognitive functioning" OR "cognitive domains" OR "brief cognitive screening" OR "screening test" OR "cognitive battery" OR "neuropsychological evaluation" OR "Cognitive Assessment" OR "Screening Instrument" OR "Neurocognitive Tests" OR "cognitive test" OR "assess*" OR "screen*"OR "neuropsychological performance" OR "neuropsychological test" OR "neuropsych*" OR "cognitive screening"
Resting state	"rsfc" OR "resting state" OR "resting-state" OR "resting" OR "ongoing activity" OR "task- free" OR "task free"
Signal analysis	"power" OR "spectral density" OR "oscillations" OR "synchronization" OR "network" OR "topological" OR "graph" OR "complexity" OR "non-linear dynamic" OR "functional connectivity"
Neuroimaging technique	"EEG"OR "electroence*"OR "MEG" OR "magnetoence*" OR "electrophysio*"

Lists the key concepts and search terms employed in PubMed, Scopus, and Web of Science (June 2021)

2.2. Article's inclusion and exclusion criteria

Articles included were limited to those published within the last ten years (2011 to 2021) in journals indexed in the Journal Citation Reports (JCR), following peer-review process, written in English and in which study participants were human. In addition, the evaluation protocol should have been consistent, meaning that it should have been conducted on healthy participants excluding those with any relevant medical diagnosis. Clinical studies, case report journal articles, and empirical studies were also included in the revision procedure.

In addition, articles including i) participants younger than 50 years old, ii) those in which evaluation was not conducted in the participant's native language, and/ or iii) information regarding power spectral analysis or functional connectivity in M/EEG was not reported were excluded.

2.3. Screening protocol

In order to avoid duplication, ensure the reliability of the process, and follow a standard systematic review protocol, this review was registered in PROSPERO (publication code: CRD42021279382). Selected articles were imported into COVIDENCE (Veritas Health Innovation, n.d.). The revision process was conducted by two reviewers (BC and DLS), as recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews (Moher et al., 2009), attending to the above-mentioned exclusion and inclusion criteria. Firstly, the articles' abstracts were screened. For those manuscripts selected in the first stage, full texts were obtained and subsequently reviewed. Disagreements were resolved in specific meetings to review each conflicting decision (screening protocols and final selection are depicted in Figure 2).

2.4. Quality assessment

Three independent reviewers (BC, LT, and SD) assessed the quality of the selected articles using the tool for cross-sectional studies using biomarker data (BIOCROSS) (Wirsching et al., 2018). The specific assessment of the items was performed under the adaptation described in Torres-Simon et. al., (2022), as some of the original items could not be easily applied due to the nature of the specific research field studied. This information included: neurophysiological technical specifications, research, or data processing protocols modeling details. Furthermore, we incorporated additional specifications to improve quality standards within our study population, healthy controls (for more details, see "Quality Assessment" in Appendix A). Quality assessment was conducted over the 13 selected studies. No articles were excluded based on the quality assessment (the three reviewers' final scores for the 13 articles for each quality item are reported in Appendix Table 1) (See Appendix A for further information).

2.5. Data extraction

The information extracted for each full text article reviewed is summarized in two tables according to the type of signal analysis performed (spectral analysis, Table 1; and connectivity analysis, Table 2). In these tables the most relevant information was extracted for each of the articles following the same structure:

Authors and publication date.

Sample characteristics: including number of subjects and basic demographic information (age and distribution by sex).

Methods: referring to the neuroimaging technique used in each article (MEG or EEG). Signal acquisition condition (eyes close resting, eyes open) and cognitive test (classified by cognitive process) were also included.

Main findings: where main *results*, *conclusions* and *limitations* were reported.

2.6. Data synthesis

Due to the diversity in recording conditions and analysis methods, we employed the synthesis without meta-analysis (SWiM) guidelines described by (Campbell et al., 2020). Data synthesis was conducted by attending to the main type of analysis employed (i.e., spectral analysis vs connectivity analysis) and the cognitive process involved. In the case of connectivity studies, the division according to cognitive domains was not possible considering the small number of studies. Figure 5 shows the number of papers included in each category.

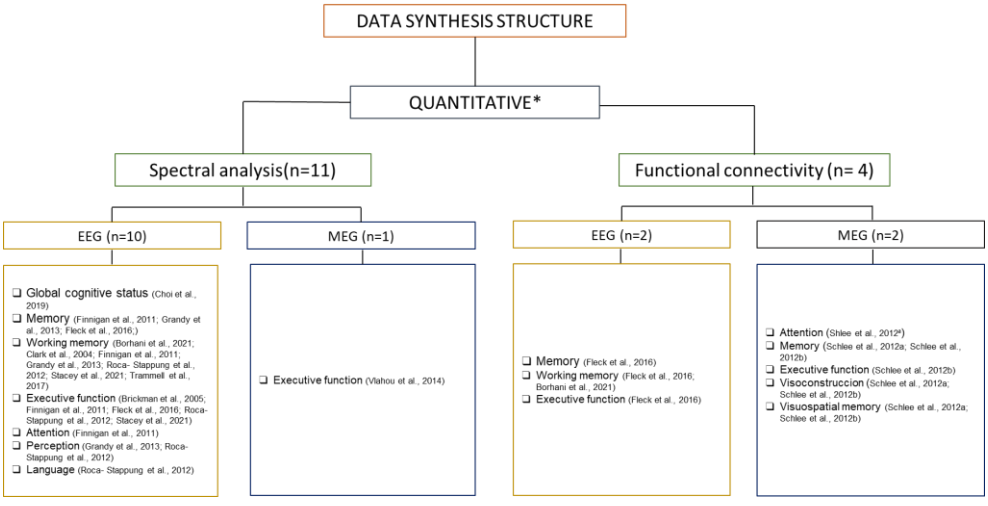

Fig. 5 Data synthesis structure

*Fig. 5 Include in the box the number of papers considered in each category. *Ones of the articles selected analyze the signal from both perspectives (spectral analysis and functional connectivity).*

3. Results

After conducting a literature search in the specified datasets, five hundred forty-nine articles were imported for screening. After removing those duplicated and those irrelevant for this systematic review, 22 studies were assessed for eligibility. Nine studies were excluded based on the exclusion criteria: six were excluded for incompatible study designs, and three due to the age range studied. Finally, 13 studies with 2081 participants were considered for analysis in the systematic review (see Figure 6).

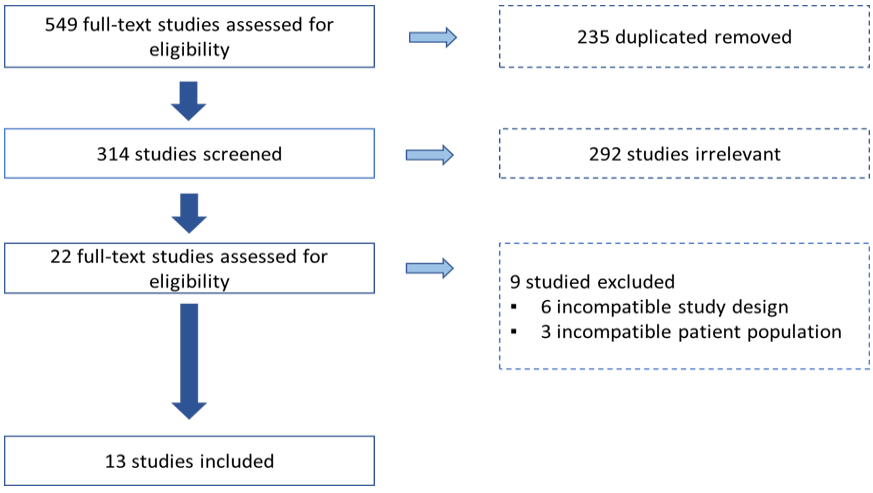

Fig. 6 Selection process overview

Fig. 6 shows a flow chart of included and excluded articles through the screening process following the PRISMA presentation guidelines.

3.1. Healthy aging: Inclusion and exclusion criteria across the studies selected

Before discussing neural oscillations and their relationship to cognitive domains, a brief review on the inclusion and exclusion criteria considered in the 13 articles examined is warranted, as it could aid in the understanding of the patterns observed in our results.

The studies were included using several criteria related to recruitment and sample selection. Ten of them used fliers and advertisements to incorporate participants, considering as inclusion criteria: 5/13 normal or corrected normal vision, 5/13 right-handed, and 2/13 native speakers. Only two studies consider the evaluation of the global deterioration scale or quality of life as an important aspect in the selection of the sample.

Several exclusion criteria were taken into account in each study to define the final sample. The most important criteria comprised the exclusion of individuals with a personal history of mental illness or symptoms of anxiety/ depression (11/13), neurological disorders (10/13), and traumatic brain injury (7/13). Six studies considered the history of drug or alcohol addiction or use of antiseizure/ psychopharmacological medication by selection. Other medical conditions (such as diabetes), or performance in screening tests (such as MMSE or ADAS-Cog) were considered in five studies. Only three articles mentioned the loss of consciousness, history of the family disorder, or metal objects in the body as criteria. Other aspects

explored were: 2/13 heart attack, 2/13 DSM IV-TR, 1/13 learning difficulties, 1/13 nurses' opinion, and 1/13 deformity on electrode contact sites.

3.2. Spectral analysis

All the studies mentioned in this section are summarized in detail in Table 6.

Eleven articles were included in this section; ten used EEG and one MEG to record the electrophysiological brain signal during resting state. The methodologies used to analyze the signal spectrum included the estimation of absolute and relative power of the signal in each frequency band, the ratios between the power found in the theta and alpha band and the APF and the measure of distribution across the brain.

Concerning the *memory domain*, Finnigan & Robertson (2011) evaluated the memory performance associated with task-free EEG recordings with only four channels located over frontal, central and parietal areas. Immediate recall scores were positively associated with theta band amplitude in frontal and parietal sites in both, relative and absolute power. A similar tendency was observed in delayed recall scores, where higher absolute theta power in parietal areas was related to better performance. Fleck et al., (2016) described a pattern in which decreases in delta and beta absolute power in posterior and frontal areas were related to better immediate and delayed recall performance, despite evaluating the same cognitive domain, this might unveil that there is a different association with memory depending on the area and the frequency band analysis. Furthermore, regarding the APF Grandy et al., 2013 reported a positive increase in APF power associated with episodic memory, commonly related in cognitive neuropsychology with delated and immediate recall scores (Huo et al., 2018), in young and older adults.

Working memory was the focus of the interest in seven studies. Three studies showed that higher working memory scores were associated with higher APFs (Grandy et al., 2013; Richard Clark et al., 2004; Stacey et al., 2021). This result is particularly relevant considering the large sample included (683 subjects). The same tendency was observed related to delta relative power in frontal, parietal, and central areas, meaning that an increase in delta relative power is associated with better performance in short-term memory tasks (Trammell et al., 2017).

However, Roca-Stappung et al., (2012) and Borhani et al., (2021), reported contradictory results, showing an inverse correlation between delta power, and working memory score and reaction time in the task, respectively. Similarly, lower values of alpha power (Borhani et al., 2021; Trammell et al., 2017), beta band, over parietal site (Borhani et al., 2021; Finnigan & Robertson, 2011), and gamma band (Borhani et al., 2021) in parietal and frontal sites, respectively, have been recently reported in association to better working memory performance.

On a different note, Finnigan & Robertson, 2011 evaluated the relationship between *executive functions* and signal power across frequency bands considering both, resting state and tasks condition. In eyes-closed condition, better performance in executive function (verbal fluency test) was associated with more relative theta power over frontal areas. The association with delta band and executive function, was described in two studies: A faster completion of TMT B was related with an increase in delta power over central areas (Stacey et al., 2021); on the contrary, Fleck et al., (2016) reported a positive tendency between delta power and time in TMT over posterior areas, both in the eyes-closed condition. In addition, Roca-Stappung et al., (2012) reported a positive relation between beta band and this cognitive domain. specifically, a positive association between processing speed index and beta absolute power and an inverse pattern emerged for beta relative power. In eyes-open condition, one study in MEG described an inverse tendency in delta and theta power and completion time in TMT B, meaning that increase in both bands involved a less completion time in the task (Vlahou et al., 2014). Moreover, more theta power over frontal and temporal areas was related with a better performance in semantic fluency test (Brickman et al., 2005).

Perception was reported in two studies, one focused on reaction times, and the other one on the perceptual organization index (derived from Picture Completion, Block Design, and Matrix Reasoning subtests). In the first case, the results suggested that higher APF was associated with better task performance speed, i.e., faster perceptual skills (Grandy et al., 2013). Similarly, in the second study, an increase in beta power (absolute and relative) was found to be predictive of higher perceptive index score (Roca-Stappung et al., 2012). The inverse tendency was observed for theta power over frontal areas (Roca-Stappung et al., 2012).

The association between both; *attentional processing* and *language*, with power spectral measures has been poorly described in the literature. Only one study found an inverse association between relative theta power during resting state and reaction times obtained during a sustained attention to response task in frontal areas (Finnigan & Robertson, 2011). Similarly, for the language domain, Roca-Stappung et al., (2012) also described an inverse relationship between verbal scores in WAIS III and theta relative power over left temporal and bilateral central and parietal regions; as well as a positive association between beta-band power and scores in the verbal comprehension index.

Finally, one study evaluated the relationship between *global cognitive performance* using the Mini-Mental State Examination (MMSE) and activity in prefrontal areas in a sample of 496 subjects. Choi et al., (2019) found significant differences between individuals scoring less than 25 points and those scoring between 25-27 points in MMSE (adjusting by age and years of education). Their results suggest that median frequency, peak frequency, and alpha-theta ratio were higher in individuals scoring

25-27 points than in patients with lower scores. They also found that higher performance in time and place orientation were associated with increased in the three measures.

Table 6 Summary of studies included in power spectral analysis

Authors (Year)	N	Mean Age± SD (Range)	Sex (M/F)	Neuroimaging Technique	Experimental condition	Cognitive domain	Type of signal analysis	Main Findings	Quality Assessment Score- Classification
Borhani et al. (2021)	43	71.6 ±7	20/23	EEG (14 channels)	**EC (60 sec.)**	**Working memory** (Short term memory STM)	Absolute power	• *Reaction time:* (+) δ (Left parietal site – P7) (-) reaction time in memory task (+) θ band (left parietal) Faster reaction time in memory task (no significant; p = 0.07) • *Accuracy (Short- term memory task-STM)* (-) β band over the right parietal site (+) accuracy STM. (-) α (-) β (Right parietal site) and (-) γ (right frontal) – Higher ability to correctly distinguish between target and distractor images in a STM.	15.67 (VG)
Brickman et al. (2005)	**471** 196 87 72 61 35 20	**21-82** 21-30 31-40 41-50 51-60 61-70 71-82	**231/240** 94/102 53/34 27/45 27/34 17/18 44755	EEG (32 channels)	**EO (2 min)**	**Executive function** (Verbal Fluency Test)	Absolute power	(+) θ band over frontal and temporal areas (+) Semantic fluency. (+) age (-) θ power θ power not moderate the relationship between age and fluency performance.	14.33 (VG)
Choi et al. (2019)	**496** T3= 162 T2= 179 T1=155	**67.84±9,77** 63.05±8,37 66.54±8,24 74.34±9,31	**165/331** 68/94 64/115 33/122	EEG (2 channels; Fp1. Fp2)	**EC (5 mins)**	**Global Cognitive status** (MMSE scores) was divided by MMSE terciles: T3 (28 ≤ MMSE ≤ 30) T2 (25 ≤ MMSE ≤ 27) T1 (MMSE ≤ 24)	Median frequency Alpha Peak Frequency (APF) Alpha Theta Ratio (ATR)	Males: Differences in Alpha-Theta Ratio between T1-T2 (t= -5.19). Females: (+) Median frequency (+) MMSE. MMSE & EEG decreased with age and less education ((+) in females). (+) Median frequency (+) peak frequency (APF) and (+) Alpha-Theta Ratio (ATR) correlated with (+) orientation time and place.	16.00 (VG)
Clark et al. (2004)	**550** 140 160 150 100	**33 (11-70)** 17 ± 2.5 (11-20) 24.6 ± 2.8 (21-30) 40.3 ± 6 (31-50) 58 ± 5.7 (51-70)	Balanced	EEG (10 channels)	**EC (2 min)**	**Working Memory** (Digit span, reverse digit span)	Alpha Peak Frequency (APF)	(-) Alpha peak frequency (APF) (+) Age: Stronger at anterior than posterior regions. (+) APF (+) working memory (independent of age). ↑ 1 Hz in APF frontal is associated with ↑ 0.21 scores in reverse digit span.	12.67 (G)

Authors (Year)	N	Mean Age± SD (Range)	Sex (M/F)	Neuroimaging Technique	Experimental condition	Cognitive domain	Type of signal analysis	Main Findings	Quality Assessment Score- Classification
Finnigan et al. (2011)	73	60.76 (56-70)	25/48	EEG (4 channels; CZ, FZ, PZ, and M1)	**EC (4 min)**	**Memory** (Rey Auditory Verbal Learning test- RAVLT and Rivermead Behavioral Memory Test- RBMT immediate and delay recall) **Intelligence** (Raven´s Standard Progressive Matrices- RSPM) **Working Memory** (Digit span) **Attention** (Sustained Attention to respond task- SART)	Absolute power / Relative power	• In Fz: (+) θ relative power (+) List A Recall RAVLT (+) RSPM, (+) category fluency, and (-) SART reaction time. • In Pz: (+) θ band – (+) recall immediate and (+) delayed RBMT scores. (-) β band -- (+) RSPM and (+) backward digit span scores.	15.67 (VG)
Fleck et al. (2016)	66	67.15± 9.16 (50-88)	24/42	EEG (19 channels)	**EC (3 min)**	**Memory** (California Verbal Learning Test- CVLT II) **Executive Function** (Trail Making Test TMT)	Absolute power	• (-) posterior δ power – (+) Immediate memory and (+) delayed recall • (-) posterior δ power – better performance in TMT A • (-) β power at frontal and posterior electrode sites (+) CVLT II- immediate and delay recall (no significant at the 0.01 significance threshold)	15.33 (VG)
Grandy et al. (2013)	**Interv 58** Young 30 Old 28 **Control 27** Young 15 Old 12	25.3± 3.1 (20-31) 71.8± 4.0 (65-80) 24.8± 2.3 (22-29) 69.2± 3.5 (66-79	13/17 18/10 8/7 6/6	EEG (64 channels)	**EC (2 min.)**	**Perceptual speed.** Choice reaction tasks (CRTs). Comparison tasks (CTs: Digits, letters, or lines) **Working Memory** (WM: numerical memory updating task)	Alpha peak frequency	In both groups: (+) APF (+) speed tasks (CRT, CT, digit symbol). In young adults: (+) APF (+) complex tasks (WM. EM, RSPM). APF: Lower in older adults relative to younger adults. APF with eyes closed is highly reliable and stable with regard to the rank order of individuals across a test- retest interval of 6.6 months.	16.33 (VG)

Authors (Year)	N	Mean Age± SD (Range)	Sex (M/F)	Neuroimaging Technique	Experimental condition	Cognitive domain	Type of signal analysis	Main Findings	Quality Assessment Score- Classification
						Memory (Episodic Memory- EM: word list task) **intelligence** (Raven´s Standard Progressive Matrices- RSPM)			
Roca-Stappung et al. (2012)	27	67.2± 6.70 (60-84)	12/15	EEG (19 channels)	**EC (20 min)**	**Intelligence** (Wechsler Adult Intelligence Scale WAIS-III). Including too:	Absolute power / Relative power	(-) δ Absolute power (AP) (+) WAIS III index scores (+) WM index (-) δ (frontal site) (-) θ (fronto polar). Lateral prefrontal cortex (Left hemisphere) is activated during WM task. (+) alpha values – (+) cognition. (-) θ Relative power (RP) (+) verbal scores (Left temp. and bilateral central and parietal regions) (-) θ in frontal areas (+) perceptual organization index (+) β (+) verbal comprehension index, processing speed index, perceptual org. index. (+) β RP: (-) processing speed index (+) perceptual organization index.	15.67 (VG)
Stacey et al. (2021)	**75** Young 31 Old 44	**18-90** 23.96± 4.52 (18-30) 71.47±6.49 (61-90)	**26/49** 10/21 16/28	EEG (128 channels)	**EC (2.5 min per two times)**	**Working memory** (Digit span, Spatial span) **Executive function** (Trail Making Test TMT)	Alpha peak frequency / Absolute power	β power: Older > Young APF: Young > Older EC: (+) APF Frontal (+) WM (no significant then of multiple comparison). Older: (+) central δ power (-) time in TMT.	15.67 (VG)
Trammell et al. (2017)	**36** Young 16 Old 20	- 20,7± 0.9 (20-19) 72,9 ± 2.5 (70-79)	14/22 8/8 6/14	EEG (19 channels)	**EC (5 min per two times)**	**Working memory** (Short term Memory- STM) **Intelligence** (Raven´s Standard Progressive Matrices- RSPM)	Theta alpha Ratio Relative power Absolute power Alpha peak frequency	RP: relative Power Cz: TAR dependent upon cognitive performance only after accounting for age. With constant cognitive performance: young adults had greater θ and α than old adults ***Age:*** (+) age (-) iPAF FZ: (-) Relative δ (+) age. Fz and Cz: (-) Relative θ (+) age.	16.00 (VG)

Authors (Year)	N	Mean Age± SD (Range)	Sex (M/F)	Neuroimaging Technique	Experimental condition	Cognitive domain	Type of signal analysis	Main Findings	Quality Assessment Score- Classification
								(+) α (+) cognitive ability in general (Aging: no sig.) (-) RSPM (+) TAR (Constant: Age, STM, and task) All sample: (+) STM (-) θ and (-) α (+) iAPF (+) RSPM. (+) δ RP (+) STM (Fz, Pz, Cz) Young: (+) TAR (+) STM (+) TAR (+) RSPM (no sig.). (+) α (+) RSPM (+) δ RP (+) STM (Fz) Older: (-) α (-) θ (+) RSPM (+) δ RP (+) STM (Pz). No sign. results in theta power and performance.	
Vlahou et al. (2014)	53 Young 26 Old 27	53.1 ± 20.1 (18-89) (18-54) (55-89)	23-30	MEG (148 channels)	**EO (5 min)**	**Executive Function** (Trail Making Test A and B- TMT)	Absolute power	(+) age (-) 0.5-6.5 Hz. Age* slow wave power (δ and θ) at temporal and central regions -> Predictor of performance in the trail making test. For older: (+) δ in central (+) θ in temporal regions- > Best performance in TMT B (Less time).	16.33 (VG)

3.3. Connectivity

Described in Table 7.

Brain connectivity (Maestú et al., 2019b; Sporns, 2013) is a relatively new field compared with power spectrum analyses in brain activity research. Probably because of this, only four studies were found that analyzed brain connectivity during resting state in association with cognitive performance, using two different metrics: magnitude-squared coherence and partial directed coherence with EEG and MEG data. In the following lines, the main results of these studies are presented.

The approaches to memory assessment were diverse, including verbal and visuospatial tasks to characterize the pattern of brain activity associated with this domain. Fleck et al., (2016) reported only a positive relationship between false positive recognition scores and delta coherence in frontal and posterior areas as measured by the California Verbal Learning test in eyes-closed condition, meaning that less false positive scores in the recognition task involved lower delta coherence in the above-mentioned regions. On the other hand, in eyes-opened condition, visuospatial memory evidenced a negative relationship with connectivity intensity in both beta and gamma bands over temporal regions (Schlee et al., 2012).

Concerning working memory, very little is known regarding its relationship with resting state functional connectivity patterns. One study suggested a positive association between accuracy in working memory and delta and theta coherence between frontal and temporal areas (Borhani et al., 2021). Frontal areas involvement has been also highlighted by Fleck et al., (2016) who reported a positive association between beta and gamma coherence in frontal areas and scores in digit span forward scores. However, this pattern is no longer followed by the results reported in the same study where gamma coherence over frontal areas was negatively associated with scores in digit span sequencing. Coherence over posterior brain regions showed in general negative associations in this study with the performance in the same digit span sequencing test for all delta, theta, beta, and gamma bands.

In the eyes-opened condition, visuoconstructive skills showed a negative correlation with connectivity in the high-frequency range (> 16 Hz) within temporal regions. Moreover, this negative pattern found in temporal regions also appears in association with the recall of these visuoconstructional material as well (Schlee et al., 2012a; Schlee et al., 2012b).

Two studies reported neural oscillations patterns in task-free paradigms associated with executive function. In eyes-closed, Fleck et al., (2016) found a positive relationship between executive function and coherence the connectivity measured in delta and beta bands over frontal regions, and also with coherence in the theta

band between frontal and posterior brain regions. This tendency was observed too in the eyes-opened -condition, showing a positive association between medial temporal and posterior cluster and executive function scores (Schlee et al., 2012).

Regarding attention processes, two studies in the open-eyes condition reported a negative pattern of association between attention scores and coherence in the temporal region in high frequencies (beta-gamma) (Schlee et al., 2012) and also a medial temporal cluster positively related with age. The inverse pattern was observed when evaluating a posterior cluster, negatively related to age (Schlee et al., 2012).

Table 7 Summary of studies included in functional connectivity analysis

Authors (Year)	N	Mean Age± SD (Range)	Sex (M/F)	Neuroimaging Technique	Experimental condition	Cognitive domain	Type of signal analysis	Main Findings	Quality Assessment Score- Classification
Borhani et al. (2021)[a]	43	71.6 ±7	20/23	EEG (14 channels)	**EC (60 sec.)**	**Working memory** (Short- term memory)	Coherence analysis	(+) α coherence between right parietal and left frontal sites (+) reaction time in WM task. (+) θ & (+) δ coherence between frontal and temporal sites (+) accuracy scores in memory retrieval.	15.67 (VG)
Fleck et al. (2016)	66	67.15± 9.16 (50-88)	24/42	EEG (19 channels)	**EC (3 min.)**	**Working memory** (Digit Span) **Memory** (California Verbal Learning Test- CVLT II) **Executive Function** (Verbal Fluency Test VFT, and the Trail Making Test TMT)	Coherence analysis	(+) Digit span forward (+) β frontal coherence (+) γ frontal coherence (+) Digit span sequencing (+) frontal β coherence (-) posterior γ coherence (+) Memory (-) Frontal posterior θ coherence (+) CVLT-False Positive scores (+) Frontal and posterior δ coherence (+) category fluency (+) frontal coherence in the δ. (+) Trail B scores (+) frontal coherence δ & β frequency bands (+) Trail A scores (+) θ coherence between frontal and posterior brain regions.	15.33 (VG)
Schlee et al. (2012a)	53	53.06± 20.1 (18-89)	-	MEG (148 channels)	**EO (5 min)**	**Visuo-constructional praxis** (CERAD Figure recall; the mosaic subtest- WAIS) **Visuospatial memory** (Benton Visual Retention Test- revised form)	Partial directed coherence	*In high- frequency network size:* Right temporal regions: (+) FC (-) concentration (-) visuospatial memory (Benton) (-) constructive praxis (CERAD figure copy & Mosaic Test). *Left temporal lobe:* (+) FC (-) Visuospatial memory (Benton test) (-) constructive praxis memory (CERAD figure copy).	14.67 (VG)

Authors (Year)	N	Mean Age± SD (Range)	Sex (M/F)	Neuroimaging Technique	Experimental condition	Cognitive domain	Type of signal analysis	Main Findings	Quality Assessment Score-Classification
Schlee et al. (2012)[b]	53	53.06± 20.07 (18 – 89)	23/30	MEG (148 channels)	**EO (5 min)**	**Visuo-constructional praxis** (CERAD Figure recall; the mosaic subtest-WAIS) **Executive function** (Trail Making Test TMT A B **Attention** (Digit symbol) **Visuospatial memory** (Benton Visual Retention Test- revised form)	Partial directed coherence	• Inflow: Inflow in Medial and inferior temporal lobes was stronger with higher age (8-100 hz). Cluster 5: Posterior cingulate cortex and precuneus was stronger for younger Reduced for elderly in 1-100 Hz frequency range. ↑ *inflow* ↑*age in medial temporal areas associated with:* (-) Attention (Digit symbol) (+) Executive function (Trail making test) (-) Visoconstructional praxis (Figure recall) (-) Visuospatial memory (Benton test) ↑ *inflow* ↓ *age in posterior zones associated with:* (+) Attention (Digit symbol) (-) Executive function (Trail making test) (+) Visoconstructional praxis (Figure recall) (+) Visuospatial memory (Benton test) Inflow into medial temporal region no correlates with working memory.	15.33 (VG)

4. Discussion

Neuropsychological assessments to differentiate between the cognitive changes that occur as a normal consequence of aging and those that signal other pathological states are common in health care attention. Thus, unveiling the mechanisms underlying and supporting normal cognitive functioning in the brain in the later stages of life could help to define a cognitive biomarker associated with well-being in aging. In this line, our purpose was to identify, considering the available literature, the electrophysiological fingerprints during resting state associated with cognitive performance in healthy aging, as reflected by the spectral and connectivity properties of brain activity in the different frequency bands. Despite the many inconsistencies in the selected studies related to the heterogeneity in the definition of healthy aging, the relatively small sample sizes, and the different analytical approaches, a thorough analysis reveals consistently several resting-state brain oscillation patterns associated with cognitive skills.

Power spectral analysis reveals a strong relationship between APF and cognitive capacity. Higher APF is associated with better performance in several cognitive domains, such as perception, working memory, fluid intelligence, and even with orientation (Choi et al., 2019; Grandy et al., 2013; López-Sanz et al., 2016; Richard Clark et al., 2004; Stacey et al., 2021; Trammell et al., 2017). A possible explanation of this finding is to consider the APF as a state of cognitive preparedness (Angelakis et al., 2004). According to Angelakis et al. (2004), the APF predicts cognitive performance and reflects the brain state in healthy subjects. This idea was tested by comparing a group of traumatic brain injury (TBI) patients with healthy controls matched by age, sex, and education. Their results showed that TBI patients had lower APF in the post-test rest condition than the control group. Also, despite the evidence about APF decrease with age (Knyazeva et al., 2018), this measure is considered a highly stable individual marker of central nervous system functioning (Grandy et al., 2013), so that slowness of APF in the power spectrum could be a predictor of cognitive impairment in several cognitive domains (Garces et al., 2013), even before the dementia stage (Fernández et al., 2006). The consistent findings of relationship between APF and cognitive performance in healthy older adults, adds to the reports on the role of APF as a potential alternative to assess the impact of intervention on lifestyle behaviors (de Frutos-Lucas et al., 2018), makes it a good candidate as a biological marker to assess healthy aging in different aspects.

Moreover, we only find a negative tendency between working memory and absolute power across frequency bands, meaning that higher working memory is related to less power throughout the frequency spectrum (Borhani et al., 2021; Finnigan & Robertson, 2011; Roca-Stappung et al., 2012; Trammell et al., 2017). This finding could be interpreted considering that the opposite pattern is observed in task paradigms, where working memory performance has been related to an

increase in alpha/beta power during the early encoding phase (Proskovec et al., 2016).

Concerning brain connectivity, four studies reported results on the topic. Despite the differences between the analysis approach and the resting condition evaluated (eyes-closed or eyes-opened) severely limiting the possibility of establishing general conclusions in terms of stable and reliable patterns associating cognitive performance and functional connectivity, we found a positive association between working memory and coherence across all frequency bands in frontal areas in eyes-closed condition (Borhani et al., 2021; Fleck et al., 2016). This pattern was also observed using task paradigms in the theta and alpha band. Tóth et al., (2014) found an increased theta FC strength between the frontal midline and temporal areas associated with better working memory performance. Similarly, Ariza et al., (2015) showed that older adults require higher alpha synchronization between cortical brain regions to achieve a successful recognition. The similarity between resting state and task paradigms results could be explained by the high resources required in working memory execution by the association with other domains; however, this finding must be taken with discretion, considering the small sample, the different time analyzed, the methods used and the paradigms of the study.

Another aspect to consider when interpreting the results is the different criteria using to define healthy aging across the studies. The articles included in the review are based on exclusion criteria such as history of mental illness, neurological disorders, and traumatic brain injury. Only five studies consider the performance in screening tests as include criteria. It is possible that this process misclassified a proportion of subjects. There is also the potential for some of the participants to later develop or even already have undiagnosed mild cognitive impairment or underlying pathology. This would severely modify the behavior of their neural communication, thus altering its relationship to cognition. This could also partially explain some of the variability in the results observed in the literature, and henceforth represent an important caveat that the field should seriously consider addressing in the future. Another aspect to consider is the scarce literature about the use of MEG in this field, despite its particularly appropriate use for studying neurocognitive processes. The hundreds of sensors used in MEG recordings have made possible to identify and locate the source of brain oscillations (Maestú et al., 2019a), due to the lack of interactions between de MEG signal and biological tissues, avoiding smearing and distortion outside of the scalp (Baillet, 2017). An improved signal to noise ratio and easier and more reliable source reconstruction process could also improve the consistency of future results.

To sum up, according to our review, previous literature on the topic consistently suggests that the APF could be considered good approximations to establish an electrophysiological marker of cognitively healthy aging (Drago et al., 2011). They

are easy-to-assess markers for monitoring deviations from central nervous system functioning (Grandy et al., 2013), with the advantages that both measures could be registered during the resting-state condition, which is an easily replicable set-up, accessible to most populations. In this sense, assessing the resting state brain signal has wide appeal because this measure can be acquired in individuals whose cognitive ability or native language hinders testing with standard neuropsychological assessments (Rosazza & Minati, 2011). Furthermore, electrophysiological recordings, particularly using EEG, are relatively cheap and easy to transport, which makes this technology well-suited for most countries regardless of their economic power.

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Chapter 5

Study 3: Episodic memory dysfunction and hypersynchrony in brain functional networks in cognitively intact subjects and MCI: a study of 379 individuals

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Abstract

Background: Delayed recall (DR) impairment is one of the most significant predictive factors in defining the progression to Alzheimer's Disease (AD). Changes in brain functional connectivity (FC) could accompany this decline in the DR performance even in a resting state condition from the preclinical stages to the diagnosis of AD itself, so the characterization of the relationship between the two phenomena has attracted increasing interest. Another aspect to contemplate is the potential moderator role of the APOE genotype in this association, considering the evidence about their implication for the disease.

Method: 379 subjects (118 mild cognitive impairment (MCI) & 261 cognitively intact (CI) individuals) underwent an extensive evaluation, including MEG recording. Applying network-based statistics, we identified a cluster of differences in FC and studied which connections drove such an effect in DR. The moderation effect of APOE genotype between FC results and delayed recall were evaluated too.

Results: Higher FC in beta band in the right occipital region is associated with lower DR scores in both groups. A significant anteroposterior link emerged in the seed-based analysis with higher values in MCI. Moreover, *APOE* genotype appeared as a moderator between beta FC and DR performance only in the CI group.

Discussion: An increased beta FC in the anteroposterior brain region appears to be associated with lower memory performance in MCI. This finding could help discriminate the pattern of the progression of healthy aging to MCI and the relation between resting state and memory performance.

Keywords: Delayed recall, MCI, cognitively normal, functional connectivity, MEG.

1. Introduction

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder that can develop unnoticed for several years prior to the manifestation of clinical symptomatology. Along with executive functioning, episodic memory impairments are the hallmark of the cognitive dysfunction associated with the disease (Corey-Bloom, 2002; Reed et al., 2007), which accompany histopathological and morphological changes. In particular, delayed recall (DR) of meaningful information is notably affected in AD, with recall of stories showing the sharpest deterioration in longitudinal studies (Locascio et al., 1995). Moreover, episodic memory declines are well documented in people not yet diagnosed with AD (Chen et al., 2001) (see also Bäckman et al., 2005, for meta-analytic evidence), suggesting that individual performance on tests evaluating this cognitive domain may help to identify people either at risk of developing AD or even in prodromal stages as Mild Cognitive Impairment (MCI) (Locascio et al., 1995). Moreover, the genotype for the apolipoprotein E (*APOE*) is known to be the major genetic risk factor for AD, and carriers of ε4 allele show greater impairments on episodic memory performance in the form of poorer DR (e.g., Wolk et al., 2010).

On the neurophysiological level, the last decades have seen the emergence of functional connectivity (FC) and its identification as a potential neuromarker for the diagnosis of AD (Habeck et al., 2008; Han et al., 2012). Disrupted synchronization is considered as a sign of synaptic dysfunction in AD, consequence of abnormal neural excitation/inhibition balance (Maestú et al., 2021). Indeed, people with MCI tend to show hyper-synchronization of anterior networks, in combination with hypo-synchronization of posterior areas (Bajo et al., 2012; López-Sanz et al., 2017). Given that episodic memory impairments could be accompanied by changes in brain FC from the preclinical stages of the disease to the diagnosis of AD itself, the characterization of the functional relationship between the two phenomena has attracted increasing interest. Rather than focusing on task-related FC measures, which can be affected by variability in experimental designs and task difficulty (Rosazza & Minati, 2011), neuroimaging research in the last years has focused on the study of resting-state (RS) functional connectivity patterns and how they relate to individual differences in cognitive performance (e.g., del Río et al., 2012). Indeed, increased FC, measured during functional Magnetic Resonance Imaging (fMRI), has been associated with reduced episodic memory in patients with MCI and AD (Pasquini et al., 2015). However, fMRI-based FC estimates are an indirect measure of brain activity. Furthermore, they provide limited information on the frequency of neural oscillations, particularly those in the fast ranges, considered one of the core

neural mechanisms for cognition, and more relevant to this study, for episodic memory (Buzsáki & Draguhn, 2004; Fell & Axmacher, 2011). Therefore, neurophysiological measures such as Magnetoencephalography (MEG) or Electroencephalography (EEG), having a high temporal resolution, are able to capture the brain dynamics in the frequency domain providing an enriched information for network analysis.

Considering all the evidence provided above, in this study we explore the potential association between delayed recall performance and FC of resting-state brain activity in healthy volunteers and MCI patients. As a second step, the role of *APOE* genotype as a potential moderator of the relation between FC and delayed recall was evaluated, under the hypothesis that this genotype can increase brain vulnerability to damage. We expect that subjects with MCI will show a differential functional connectivity profile than Cognitively Intact (CI) participants related to memory performance, indicating preliminary signs of conversion in the AD continuum.

2. Methods

2.1. Participants

The sample consisted of 379 individuals divided into 118 MCI (aged from 58 to 87) and 261 CI participants (aged from 41 to 82). The participants were recruited from the Hospital Universitario San Carlos (Maestú et al., 2015) and from "Centro para Mayores del Distrito de Chamartín'', both located in Madrid (Spain). General inclusion criteria were as follows: a modified Hachinski score ≤ 4, a Geriatric Depression Scale (short form) score ≤ 5, and T1, T2, and diffusion-weighted MRIs within 54 weeks before the MEG recordings (on average, the time period between the MEG and MRI recordings was three months) without an indication of infection, infarction, or focal lesions (rated by two independent experienced radiologists (Bai et al., 2012). In addition, the criteria for the MCI diagnosis were established according to the NIA-AA clinical criteria (Albert et al., 2011). For more information about the diagnostic criteria for MCI, see López et al., (López et al., 2020). For CI participants, we exclude subjects with evidence of significant hippocampal atrophy in a T1-weighted MRI scan within two months before MEG acquisition, as hippocampal atrophy is considered a brain marker associated with neurodegeneration (Jack et al., 2016). No one of the participants exhibited a history of psychiatric or neurological disorders other than MCI. Furthermore, we advised subjects to avoid medications that could affect MEG activity, such as benzodiazepines, for 48 hours before recordings.

Table 8 Descriptive measures of the final sample

Variable	Whole sample	CI	MCI	*p*-values
Sex (M/F)	135/244	91/170	44/74	
Age	68.00±8.59	65.96±8.48	74.28±5.26	<0.001
Education	13.24±5.54	14.30±5.49	9.99±4.33	<0.001
Depression	2.23±2.74	1.63±2.33	4.05±3.09	<0.001
Delayed recall	40.46±23.21	49.98±17.18	11.14±12.20	<0.001
eTIV	1384457.31±8190.08	1395275.80±154063.19	1359214.17±148921.36	0.224
Total GM	558888.08±545633.32	567118.08±53093.03	533530.78±51447.00	<0.001
Total WM	424346.04±64360.58	432579.60±64658.18	398977.79±56705.69	<0.001
Hippocampus	6829.66±952.96	7132.30±846.21	6123.50±805.16	<0.001
Left Cingulum	0.41±0.04	0.41±0.03	0.39±0.04	<0.001
Right Cingulum	0.41±0.40	0.41±0.03	0.39±0.04	<0.001
Forceps mayor	0.55±0.03	0.55±0.03	0.53±0.04	<0.001
Forceps minor	0.54±0.04	0.54±0.04	0.52±0.03	<0.001

Note. We present values as mean ± standard deviation (SD) for the characteristics of the participants as well as variables used for correlation analyses. These include sex (male/female), age (in years), education (expressed in years of education), depression (measured by Global depression scale), delayed recall (Weschler Scale- Logical Memory II Index) and structural measures such as: estimated Total Intracranial Volume (eTIV), total gray matter volume (GM), cerebral white matter volume (WM), hippocampus volume, left and right cingulum along the hippocampal cortex fractional anisotropy, forceps major fractional anisotropy, forceps minor fractional anisotropy. Results are displayed for the whole sample and for each subsample of interest (CI and MCI).

Standard Protocol Approvals, registrations, and patient consents

All participants were native Spanish speakers and provided written informed consent. The Institutional Review Board Ethics Committee at Hospital Universitario San Carlos approved the study protocol, and the procedure was performed following the Helsinki Declaration and National and European Union regulations.

2.2. Neuropsychological assessment

All participants were screened using standardized diagnostic instruments and received a thorough neuropsychological assessment as formerly detailed in López et al., (López et al., 2020). The screening consisted of standardized tests that included the Spanish version of the Mini-Mental State Examination (MMSE; Tombaugh et al., 1996), the Geriatric Depression Scale-Short Form (GDSSF; Greenberg, 2007), and the Logical Memory (I and II) subtest (Wechsler Memory Scale III, WMS-III; Tulsky et al., 2003).

Due to its effectiveness as a measure of verbal episodic memory, Logical Memory is one of the most frequently administered subtests in the Wechsler Memory Scale-III (LM-WMS-III) (Tulsky et al., 2003). In the LM test the participants are presented a text, and the memory ability is divided into immediate recall, delayed recall, and recognition. Our study only included the analysis of the delayed recall score, which consisted of free recall of the passages after a 20 to 30 minutes delay after the presentation. The narrative nature of the task is sensitive to discriminate between normal aging, MCI (Chapman et al., 1997), and early dementia, due to its tight relationship with other high-level cognitive functions such as episodic memory, conceptual organization, and schema formation (Dunn et al., 2002).

2.3. MRI acquisition and Volumetric Analyses

We used a General Electric 1.5 T system with a high-resolution antenna and a homogenization PURE filter (Fast Spoiled Gradient Echo sequence, TR/TE/TI = 11.2/4.2/450 ms; flip angle 12°; 1 mm slice thickness, 256x256 matrix and FOV 25 cm) to obtain T1-weighted images of our participants. The resulting images were processed using Freesurfer software (version 5.1.0) and its specialized tool for automated cortical parcellation and subcortical segmentation (Fischl et al., 2002). The measures that were included in further analyses were total gray matter, total cerebral white matter, and hippocampus (in mm3). The volumes of bilateral structures were collapsed in order to obtain a single measure for each region.

2.4. Diffusion Tensor Imaging

The same scanner was also used to collect diffusion-weighted images (DWI). Single-shot echo planar sequence, TE/TR 96.1/12,000 ms; NEX 3 for increasing the SNR; 2.4 mm slice thickness, 128 × 128 matrix and 30.7 cm FOV). We acquired 1 image with no diffusion sensitization (i.e., b0 images) and 25 DWI directions (b = 900 s/mm^2).

DWI images were processed using probabilistic fiber tractography was run on the automated tool AutoPtx (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/AutoPtx) as in Verdejo-Román et al. (Verdejo-Román et al., 2019). Due to its relation to memory performance, we studied the relation between FC, DR and the fractional anisotropy (FA) at the uncinate, forceps mayor and forceps minor.

2.5. Magnetoencephalography

MEG data was recorded using a 306-channel whole-head MEG system (Vectorview, Elekta AG, Finland), placed in a magnetically shielded room located at the Center for Biomedical Technology in Madrid, following the protocol described in de Frutos-

Lucas et al., (2020). First, we applied Maxfilter software (temporal extension of the signal space separation method, correlation window of 10 s and correlation limit of 0.9) to remove external noise. Then we used Fieldtrip software 28 to automatically scan the data for artifacts, which were visually confirmed by an MEG expert. Artifact-free data were segmented in 4 seconds epochs, plus 2 seconds of real data at each side as padding.

Afterwards, we estimated the source level activity for each individual. As source model we used a 1 cm homogeneous grid of source positions defined in MNI space and labeled according to the Automated Anatomical Labeling (AAL) atlas. This source model consisted of 1202 positions in 78 cortical areas and was transformed to subject space using a linear transformation between the template and the T1-weighted MRI of the participant. This image was also used to generate a single-shell head model defined by the inner skull surface. Then, we combined the head model, the source model, and the sensor definition to create a lead field using a modified spherical solution. As last step, we used a linearly constrained minimum variance beamformer as inverse method.

We estimated FC by means of the phase locking value (PLV), a phase synchronization metric that evaluates the distribution of the phase difference between two-time series. Briefly, after source reconstruction, the dataset consisted of matrices of 1202 nodes by 4000 samples by epochs for each of the 4 frequency bands studied here. Then, for each frequency band and epoch, we calculated the PLV (Mormann et al., 2000) via the following procedure: firstly, we used the Hilbert transform to extract the instantaneous phase ϕj(t) for each node j = 1…1202 and time t = 1…4000 ms:

$$z_j(t) = x_j(t) + i \cdot Hilbert\left(x_j(t)\right) = A_j(t) \cdot e^{i\varphi_j(t)}$$

Secondly, we estimated the synchronization between each pair of signals j, k by means of their difference of phases $\varphi_j(t)$ and $\varphi_k(t)$ using the following expression:

$$PLV = \frac{1}{M}\left|\sum_{m=1}^{M} e^{i(\varphi_j(t_m)-\varphi_k(t_m))}\right|$$

where T = 4000 is the number of samples in the time series (4 seconds per epoch at 1000Hz sampling rate). Lastly, we averaged the PLV matrices across epochs to obtain a more robust estimator of resting-state FC.

This algorithm provided symmetrical whole-brain matrices of 1202x1202 nodes per participant and frequency band (theta, between 4 and 8 Hz; alpha, between 8 and

12 Hz; beta, between 12 and 30 Hz; and gamma, between 30 and 45 Hz) (Lopes da Silva, 2013). Then, we calculated the nodal strength (also known as weighted global connectivity), which is defined for each node as the sum of its FC with the rest of the nodes. To account for the number of links, the strength of each node was then normalized by dividing the number of links connected to it. This procedure resulted in one brain map of normalized node strengths per each participant and frequency band.

2.6. APOE genotype

Genomic DNA was extracted from 10 ml blood samples in ethylenediaminetetraacetic acid. Detection of APOE genotype was performed with TaqMan technology using an Applied Biosystems 7900 HT Fast Real-Time PCR machine (Applied Biosystems, Foster City, CA). See the genotyping method previously described in Cuesta et al. (2015) for more information. All the sample was included independently of *APOE* genotype in the initial analysis. Then, to evaluate the potential moderation role of genotype, the participants were classified as *APOE* ε4 carriers and non-carriers (i.e., ε3ε3). Participants who presented less frequent allele combinations (i.e., ε2ε2, ε2ε3, ε2ε4 and ε4ε3ε4) were excluded from the sample.

2.7. Statistical Analyses

Functional Connectivity Strength (Strength FC)

Cluster based permutation test (CBPT) were carried out separately for each frequency band (Zalesky et al., 2010). We defined a cluster as a set of spatially adjacent nodes that presented a significant partial correlation (Spearman correlation using age as a covariate, $p < 0.001$) in the same direction between Strength FC values and each DR variable. In this framework, a cluster can be considered as a functional unit. Only clusters including at least 1% of the grid (i.e., a minimum of 12 nodes) were considered. The Spearman rho values were transformed into Fisher Z values, and the cluster-mass statistics were computed as the sum of the Z values of all nodes within the cluster. The p-value for each cluster was calculated in a non-parametric fashion, using a null distribution generated by the mass of the main cluster obtained over 5000 random permutations (shuffled versions) of the data (Maris & Oostenveld, 2007). Only those clusters that resulted significant ($p < 0.05$) after this step were considered in further analyses. Then, we used the average of the Strength FC values of the members of the cluster to obtain a representative FC marker. Of note, this FC marker would be indicating that the

global FC of the possible significant clusters appeared to be associated with memory performance.

Seed-based analyses (Seed link FC)

To examine whether the Strength FC results were caused by global or region-specific effects, we performed complementary seed analyses, using the previous clusters as seeds. For it, we calculated the average FC of each source position with the sources in the cluster. Then, we repeated the statistical CBPT analysis using these seed-based FC values instead of the Strength FC values.

Correlations between FC and measures of white matter integrity and brain volume

We used the aforementioned cluster markers in subsequent correlation analyses with measures of AD-specific signatures (the complete list is shown in Table 4). As to this, we used both the whole sample and a stratification of the cohort by diagnosis (MCI and CI). To account for multiple comparisons the resulting *p*-values were corrected using a false discovery rate (FDR). All statistical analyses were carried out using Matlab R2020b (Mathworks Inc).

Moderation analysis

Additionally, we analyzed the impact of FC on DR focusing on the possible influence exerted by *APOE* genotype. Each group was divided into ε4 carriers and ε4 non-carriers to evaluate multiple regression analysis (using age and years of education as covariates), and we calculated the increase in variance explained after including the interaction into the model. Then, we examined the effect of FC on delayed recall scores in the *APOE* genotype subgroups and used the Johnson-Neyman technique to identify the threshold where the synchronization shows a dysfunctional pattern in CI (CI33/CI34) and MCI (MCI33/MCI34). Statistical analyses were carried out using Process Macro, an extension for SPSS that calculates X's direct, indirect, and total effects on Y and unstandardized and standardized regression coefficients, standard errors, t, p values, and R^2 for the models (Hayes, 2017).

3. Results

Delayed recall is associated with decreased occipital beta frequency band FC in MCI and CI participants

One significant (CBPT p value = 0.019) primary cluster emerged in the beta band (primary β, Figure 7, A & B), located on the right occipital region (detailed regions within the cluster are showed in Table 9). The correlation between the Strength FC

of this cluster and DR performance was negative, indicating that the higher the Strength FC, the lower the memory performance. In addition, the correlation remained significant when looking at the MCI (rho = -0.236; p = 0.011) and CI (rho = -0.207; p < 0.001) groups separately (Figure 1, B). The Strength FC value was found to be higher in the MCI patients than in the CI individuals, but the difference did not reach significance (ANCOVA with age and education as covariates, p value = 0.150, F value = 2.079. see Figure 7, B).

When exploring the seed-based FC in the brain, using the primary β cluster as seed, we found one significant secondary cluster whose FC with the primary cluster showed to be negatively correlated with DR. The correlation between DR and the seed link FC remained significant when looking at the CI (rho = -0.165; p = 0.008) and MCI (rho = -0.312; p < 0.001) groups separately (Figure 7, A & C). However, the average seed link FC was significantly different between groups (ANCOVA with age and education as covariates, p value = 0.006, F value = 7.591), showing higher values for the MCI patients than for the CI individuals (Figure 7, C).

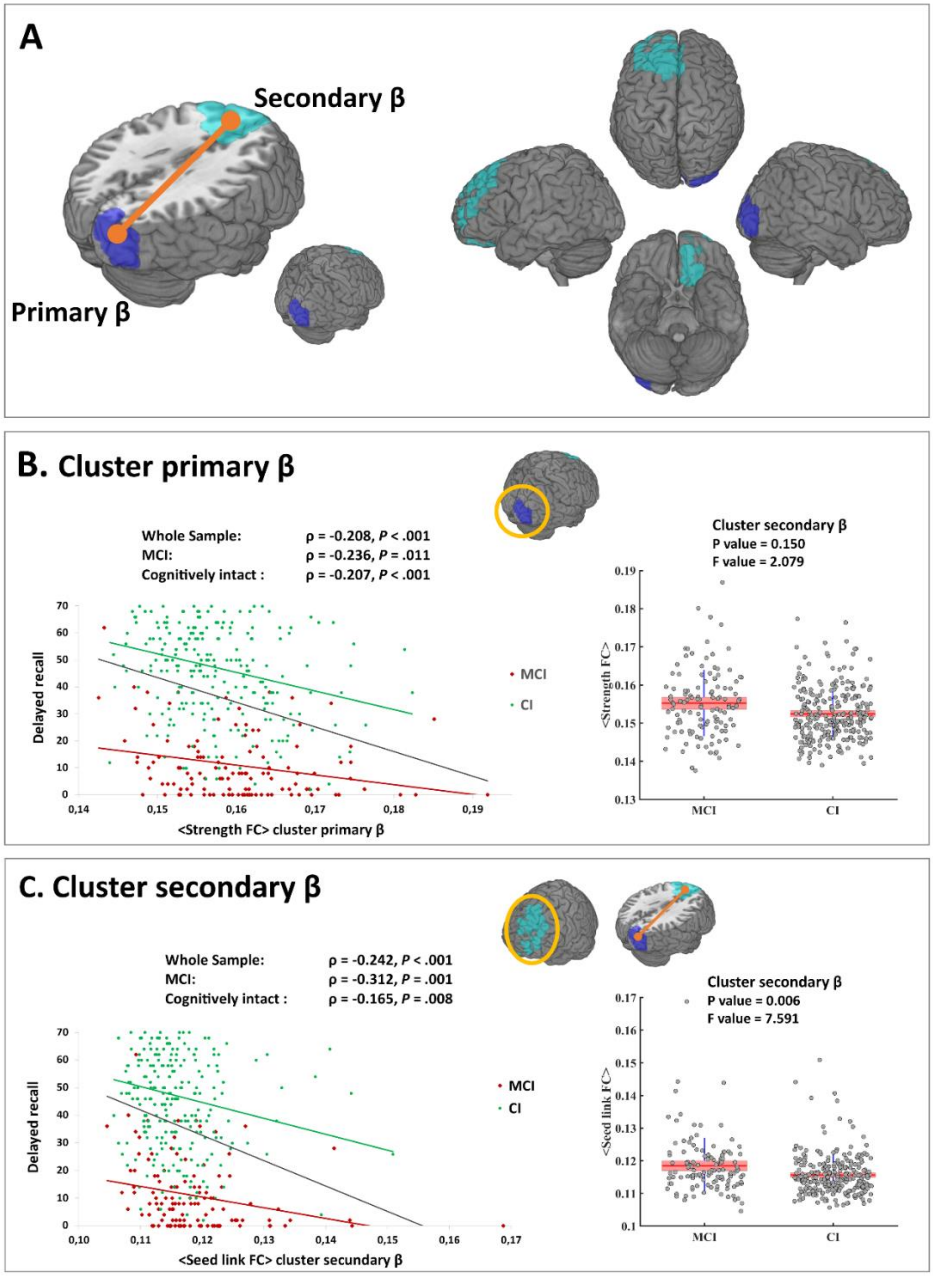

Fig. 7 Functional connectivity strength correlated with delayed recall.

[A]: In dark blue, marked as primary β, is displayed the brain region whose functional connectivity strength (Strength FC) was found inversely correlated with Delayed recall (DR). In light blue are depicted the region, marked as secondary β, whose FC with the primary β cluster was found to inversely correlate with DR. [B] Scatter plot shows the correlation between primary β cluster Strength FC and DR computed with the whole sample (grey), MCI patients (red) and cognitively intact (CI) participants (green). Boxplot graphic shows the average Strength FC of the primary β cluster for each group. [C] Scatter plot shows the correlation between primary β <--> secondary β FC and DR computed with the whole sample (grey), MCI patients (red) and cognitively intact (CI) participants (green). Boxplot graphic shows the average seed link FC of the secondary β cluster for each group. In boxplot graphics, vertical blue line indicates 95% confidence interval, whereas salmon boxes depict avg ± sd.

Table 9 Main cluster and seed analyses presented increased in FC at less DR performance

Cluster	mβDR	%	sβDR	%
ROIs	Right Middle Occipital lobe	29.41	Left Superior Frontal gyrus. Medial	58.82
	Right Cuneus	15.38	Left Middle Frontal gyrus	44.12
	Right Superior Occipital lobe	20.00	Left Superior Frontal gyrus	48.15
	Right Inferior Occipital lobe	40.00	Left Cingulate gyrus. Anterior part	42.11
			Left Superior Frontal gyrus. Medial Orbital	50.00
			Left Gyrus Rectus	37.50
			Left Superior Frontal gyrus. Orbital	66.67

Note. Beta main cluster whose functional connectivity strength (FC) was significantly correlated with DR was used a seed in a seed-based analysis. List of regions of interests (ROIs) from the AAL atlas that were captured for each significant cluster. % Depicts the percentage of the ROI that fall within the cluster (only show the ROIs above 15 %).

Lower occipital beta FC is differently associated with brain structure in MCI and CI patients.

To better understand our results, we explored the relationship between the Strength FC and structural measures (see Table 10). About MCI, white matter (r = -0.24; p = 0.01) and gray matter volume (r = -0.22; p = 0.02) exhibited negative association with primary β electrophysiological activity. The same direction was observed with right cingulum in the hippocampal area (r = -0.25; p = 0.01) and forceps major fractional anisotropy (r = -0.24; p = 0.02). In contrast, only one inverse correlation was found for the FC of the link mβ-sβ related to the right grey matter volume (r = -0.19; p = 0.04). On the other hand, the CI group's association in primary β with structural measures was only expressed inversely with forceps minor fractional anisotropy (r = -0.14; p = 0.03).

Table 10 The relationship between the strength FC and structural measures

	MCI			CI		
	Structure	*r*	*p* value	Structure	*r*	*p* value
mβDR	Total WM	-0.2431	0.0086	Forceps minor	-0.143	0.0253
	Right cingulum	-0.2462	0.0122			
	Forceps mayor	-0.2365	0.0161			
	Total GM	-0.2152	0.0204			
sβDR	Right total GM	-0.1923	0.0386			

Note. Results for Spearman correlation analyses between the FC of the edge <main-β. seed2-β> and brain structural integrity scores. Total gray matter volume (GM) and total cerebral white matter volume (WM) in mm3; right cingulum along the hippocampal cortex fractional anisotropy. forceps major fractional anisotropy. forceps minor fractional anisotropy.

Moderation effect of APOE-ε4 genotype, beta FC link in delayed recall scores.

After we had described how lower levels of DR related to a distinctive Strength FC profile, we analyzed the impact of APOE genotype as a moderator (W) between the pattern of FC in right occipital and left anterior areas in beta band (X) and the DR scores (Y) separately for each group. Our results showed a significant regression coefficient different from zero (b3 = -1428.07, t (209) = -3.10, p = .002) for XW only for the CI group, meaning that the effect of the network on episodic memory scores depends on the APOE genotype in cognitively intact participants. Once we defined the moderator effect of the APOE genotype, we tried to identify what was the threshold in FC that differentiated the episodic memory performance in carriers vs non-carriers. The Johnson-Neyman technique allowed the exact calculation of the conditions and the limit values in which a moderator obtains statistically significant slopes. Our results showed significant differences in FC values higher than 0.116, which means that the effect of APOE genotype on episodic memory scores was expressed only when the value of FC was above 0.116.

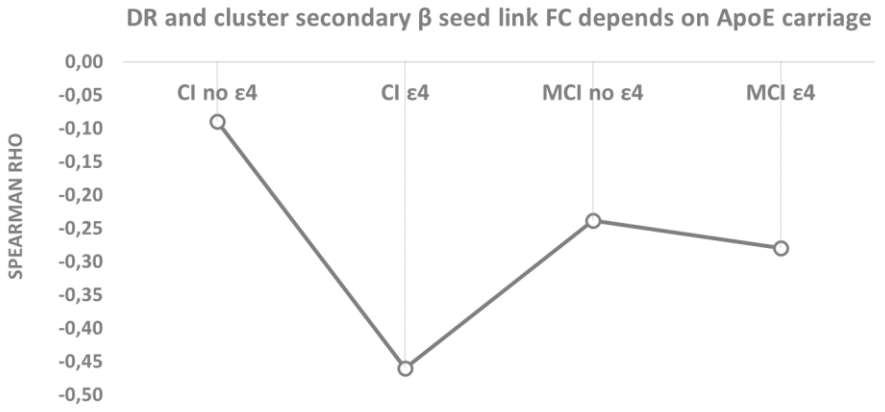

Fig. 8 Variation of the Spearman rho scores (age and education as covariates) for the correlation between delayed recall (DR) and secondary β seed link FC with ε4 ApoE carriage

In order to show qualitatively the dependence of APOE in the relationship between DR and the FC of the link primary β <-> secondary β clusters, we have depicted the Spearman rho scores (computed with age as covariate) obtained for four groups: CI/MCI with and without any allele ApoE4. As it can be seen, the influence of the allele 4 of the ApoE is notorious in the CI ε4 group. The solid black line that connects all groups is just indicative of the Rho's variance.

4. Discussion

Episodic memory dysfunction and altered functional connectivity patterns are among the most important features associated with cognitive decline in AD and its prodromal stages (Bäckman et al., 2005). Together with the genetic risk posed by the presence of the ε4 allele of the *APOE* gene, these variables can provide valuable information on the identification of individuals with a higher risk of developing AD. With this aim, we evaluated these variables in a large sample of participants either healthy or diagnosed with MCI. Firstly, we analyzed the relationship of FC and delayed recall, considering, in a second step, the potential moderator effect of the *APOE* genotype on this relationship. Results from our analysis identified a cluster of right occipital regions whose global beta band functional connectivity were negatively associated with delayed recall scores. Moreover, a post-hoc seed-based analysis showed that the left frontal cortex was the primary region contributing to this effect.

Previous studies have linked hyper-synchronization in the beta band with early stages of pathological aging (Bajo et al., 2012). In task, there is evidence showing that MCI patients who later progress to AD present higher values of functional connectivity in the beta band than those who will remain stable (Bajo et al., 2012). Other studies have confirmed that these values can be a good predictor of progression from MCI to AD (Pusil et al., 2019). This hypersynchronization has been proposed to be derived from neuropathology. In particular, high accumulations of

beta amyloid protein are especially toxic to inhibitory neurons, inducing an excess of excitability that can cause spurious synchronization (Garcia-Marin et al., 2009; see also Maestú et al., 2015) for a multicentric study). In this line, our results reveal that an increase of functional connectivity between frontal and posterior regions is associated with reduced delayed recall scores. Of importance, this functional coupling was greater in the MCI group than in the healthy participants, according to the idea of a progressive increase of neuronal excitability along the continuum of the disease, until the network breakdown at AD (Pusil et al., 2019). Moreover, these results can also be interpreted as well as a hampered desynchronization. Beta desynchronization is one of the main electrophysiological features of resting state brain activity, and a higher FC is compatible with the idea of an interruption of the natural desynchronization process at rest, reflecting a dedifferentiation process (Fornito & Bullmore, 2015). Nevertheless, we will refer to our finding as hyper-synchronization, as that is the direct interpretation of the actual results.

Interestingly, when we tested the potential role of the *APOE* ε4 allele as a moderator of the relationship between the identified pattern of FC (between right occipital and left anterior areas in beta band) and delayed recall memory, we found a significant effect in the healthy ε4 carriers. In this subsample, the indirect relationship between beta FC and memory performance was exacerbated, whereas in MCI patients the role of *ApoE* ε4 allele was non-significant, likely due to the more advanced stage of these patients in the AD continuum. These results would be indicating the existence, in the healthy ε4 carriers, of a selective vulnerability in the electrophysiological process of beta hyper synchronization, producing a result that mirrored the one observed in pathological aging. The deleterious effect of having one or two copies of the *ApoE* ε4 allele has been largely described in the literature (Chew et al., 2020). Hence it does not come as a surprise that in ε4 carriers' functional alterations in the brain are more strongly associated with cognitive outcomes than in non-carriers, most likely due to a reduced remodeling and repair capacity resulting from impaired lipid transportation processes in ε4 carriers. Unfortunately, genetic background is a non-modifiable risk factor for cognitive decline, and no therapy can reduce the associated risk directly. However, several modifiable lifestyle factors have been shown to exert an influence on FC (de Frutos-Lucas et al., 2020; Klados et al., 2016). Given that this pattern of increased FC between right occipital and left anterior areas in beta band predicts lower cognitive performance in ε4 carriers, future studies looking into the potential effect of several lifestyle factors to decrease this pattern of FC are warranted.

Episodic memory performance has been traditionally understood as the first clinical

manifestation of an underlying Alzheimer-type neuropathological process (Bäckman et al., 2005; Chen et al., 2001; Locascio et al., 1995). However, the emergence of clinically measurable memory damage occurs in a stage where the brain damage is substantial. Here, we sought for functional integrity markers associated with memory performance that can be used as proxies of the underlying neuropathological process. Since the FC markers can be computed in every participant, this approximation would allow the identification of individuals with a higher risk of developing AD (Duke Han et al., 2013; Sperling et al., 2011). Here we found that beta frontal-occipital hyper synchronization predicts a poor DR performance in healthy and pathological aging. In addition, this FC marker seemed to be more pronounced in MCI patients. A similar finding was reported by Canuet et al. (2015) in an independent sample with abnormal CSF p-tau levels. Furthermore, in a longitudinal study, beta FC was negatively associated with working memory and executive function, and, at the baseline, their levels were highest in progressive MCI compared to stable MCI, showing a high accuracy (71%) to discriminate between the two groups (Pusil et al., 2019). A work similar to ours showed that an increase in beta and gamma frequencies above 16 Hz correlated with lower cognitive performance (Schlee et al., 2012). Finally, the augmentation of beta-band FC with age in healthy aging has been described in a large study (Vysata et al., 2014). In addition to these FC patterns, many works have shown the inverse relationship of beta power with working memory over parietal sites (Borhani et al., 2021; Finnigan & Robertson, 2011) and with immediate and delayed recall in posterior areas (Fleck et al., 2016), supporting the idea of a hampered beta desynchronization at rest is associated with these domains.

When evaluating the relationship between the FC markers and brain structural integrity, the MCI patients showed a negative association between occipital FC with white and grey matter measures, reinforcing the relationship between the FC markers described in this study with the progression of the dementia. This points out that the worsening of the neuropathology in these patients would be captured by their even higher hyper synchronization when compared to controls. This endorses our view of the FC values here reported as possible markers that would help tracking the trajectory a specific patient along the AD continuum.

Considering all the evidence shown so far, a tentative explanation of the present findings is that the hyper-synchronization in beta FC reflects a progressive deterioration of neuronal function that advances at hand with the evolution of the neuropathological process associated with dementia. In healthy aging, the key factor was the presence of the ε4 allele; while the inverse relation between FC and

DR was clearly significant in healthy ε4 allele carriers, it did not reach significance in noncarriers. On the other hand, the MCI patients showed an exacerbation of this malfunction both in ε4 carriers and noncarriers. This process could be understood as maladaptive process of dedifferentiation (Fornito & Bullmore, 2015). The advance of the neuropathology would be altering the ability of the brain to focus its activity, reflected as a lack of beta desynchronization. This would be likely to the lack of inhibitory connection shown in the pathological process related to AD (Canuet et al., 2015; de Haan et al., 2012; López et al., 2014). Moreover, higher synchronization was not associated to better cognitive performance, discarding the classical interpretation as a compensatory mechanism. It is interesting to note here that the occipital lobe has been usually less impaired until the last state of the AD, and the appearance of the beta cluster in our results could be explained by the effect of amyloid pathology in the hippocampus regions that results in a reduction in neuronal input to occipital areas. This decrease that influences the brain organization at the functional level is defined as a functional diaschisis (Campo et al., 2012).

Finally, some limitations of our study should be addressed in future research. The use of a cross-sectional design provides only a snapshot of brain activity, and the picture can be enhanced by the developing of longitudinal studies aimed to track the individual FC changes along the AD continuum. In addition, the combination of these techniques with neuropathological markers of AD, as amyloid or tau pathology, would improve the clarity of the results since we would be able to distinguish whether these results are specific of AD (Ranasinghe et al., 2022).
Nevertheless, our results strongly suggest that the lack of desynchronization (or hypersynchronization) in beta band has the potential to be used for assessment of pharmacological and non-pharmacological interventions. Moreover, the results can be transferred from the costly MEG to the widely available EEG. Altogether, they have the potential to become a widely used non-invasive biomarker of the neuropathological progression underlying the developing of dementia.

5. Conclusion

The goal of the present study was to bridge the gap between measures of cognitive performance and electrophysiological markers in healthy and pathological aging. The results suggest that beta hypersynchronization associated markers could be useful to evaluate brain health. This contrasts with the typical use of RS markers more focused in the assessment of alpha band features. Here, our results indicate that the brain seems to progressively loss the ability to desynchronize beta FC, and that this process would be starting to become significant in preclinical stages, at

least in participants with AD risk factors such as the presence of the *APOE* ε4 allele.

Acknowledgments

Disclosures

Ethical Statement

All participants were informed about the aims of this study and gave written informed consent. The Institutional Review Board Ethics Committee at Hospital Universitario San Carlos approved the study protocol, and the procedure was performed following the Helsinki Declaration and National and European Union regulations.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Chapter 6

Study 4: Understanding the episodic memory and executive functioning axis impairment in MCI patients: A Multicenter Study in comparison with CSF biomarkers

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Article Info:

Under revision

Abstract

Objective: The aim of the present work is to study the association between a verbal learning task that evaluates the potential mutual dependency between memory and executive functions (i.e., the Test of Memory Strategies, TMS) and cerebrospinal fluid (CSF) Alzheimer's Disease (AD) biomarkers.

Method: 47 mild cognitive impairment (MCI) participants were recruited from a multicenter international study in Poland and Spain (mean age: 68.58 ± 10.03 years). The sample was classified according to the Erlangen Score Diagnostic Algorithm (ESA): CSF- (n=16) and CSF+ (n=31). Correlation analyses between the five TMS word-list conditions and CSF biomarkers were conducted. Additionally, an analysis of covariance was performed to define the effect on ESA classification in the sample, using as covariable the country of origin of the participants.

Results: Significant associations between the TMS-3 condition and Aβ42, t-tau and p-tau were observed for the whole sample. Besides, when dividing the participants in CSF- and CSF+, the first ones obtained a higher cognitive performance in the TMS-3 compared to the CFS+ group. This outcome persisted if the groups were divided according to Aβ42 scores, but not with respect to t-tau and p-tau values.

Conclusions: Our results revealed an executive functioning impairment (mostly associated with TMS-3 condition) in patients with positive AD CSF biomarkers. This could be indicating that poor performance on verbal learning tests may be interfered with by executive dysfunctions. These results could influence future intervention plans focused on training executive functions to improve abilities to encode and organize the information in MCI patients

Keywords: CSF biomarkers, neuropsychology, test of memory strategies, executive functions, episodic memory, mild cognitive impairment.

1. Introduction

In recent decades the abrupt increment in life expectancy has led to the population aging. Nowadays, 9% of the worldwide population is over 65 years old and the number of people aged 80 years or over is projected to triple, from 143 million in 2019 to 426 million in 2050 (United Nations: Department of Economic and Social Affairs: Population Division, 2021). This dramatic change in population structure raises the risk of age-related pathologies like dementias.

Alzheimer's Disease (AD) is the major cause of clinical dementia in the elderly (World Health Organization, 2017). From a neuropathological perspective, it is well characterized by the accumulation of amyloid-β (Aβ) neuritic plaques, neurofibrillary tangles formed by hyperphosphorylated tau protein, and the loss of synapses (Blennow et al., 2006; Hampel, 2013). Note that, cerebrospinal fluid (CSF) has been stated as a sensible and validated biomarker for AD diagnosis (Blennow et al., 2015; Molinuevo et al., 2018; Smailovic et al., 2020). For example, it is well reported and extensively replicated that lower CSF Aβ-42 concentrations and higher CSF levels of total and phosphorylated tau (t-tau and p-tau respectively) are typical findings among AD and mild cognitive impairment (MCI) patients (Blennow, 2004; Blennow et al., 2015). Additionally, the relationship between CSF values and the accumulation of amyloid and tau proteins in certain brain regions reported in amyloid Positron Emission Tomography have been already established (Palmqvist et al., 2015). Amyloid deposits are typically found in certain nodes of the default mode network (prefrontal and parietal regions), while tau is associated with medial and neocortical temporal regions in MCI patients (Canuet et al., 2015). Therefore, these two types of deposits are affecting different functional networks involving both, memory and executive functions.

From a neuropsychological point of view, there is typically an important source of confusion regarding the subjective and objective cognitive symptoms in the early stages of AD. Whether they are of executive function or episodic memory nature is still a matter of debate. Performance of classical episodic memory tests involve both cognitive functions, making it difficult to discriminate the origin of the cognitive decline. This is an important issue, as it has been established that episodic memory failure is a proxy for AD, while executive functions impairment could be leading to other types of dementia (Pasquier et al., 2001; Stopford et al., 2012). In this sense, Yubero et al. (2011) developed the Test of Memory Strategies (TMS) specifically for differentiating these two cognitive symptoms with a word learning paradigm. The TMS is formed by five word-list conditions which allows clinicians to easily evaluate two cognitive constructs simultaneously, memory and executive functions. In this sense, conditions 2 to 5 (i.e., from low to high material organization strategies), progressively reduce the need to use executive functions towards evaluating the primary capacity for episodic memory (see section 2.3 for a more detailed

explanation of the test). Based on TMS conditions, discriminant analysis revealed 90% sensitivity and specificity to discriminate between different neurocognitive disorders such as amnestic or multidomain mild cognitive impairment (MCI) or vascular cognitive impairment patients (Yubero et al., 2011). These results indicated how executive functions influence performance on memory tasks in elderly subjects with different neuropsychological profiles. Furthermore, executive and memory functions have been established as independent factors through TMS performance in a sample of Portuguese elderly subjects (Fernandes et al., 2018) and middled-aged Italian healthy adults (Vaccaro et al., 2022).

Numerous studies have invested many resources looking for the relationship between CSF biomarkers and cognitive performance to improve early discrimination of AD and MCI patients. For example, it has been observed that, typically tau load, has been more directly correlated with cognitive decline than total amyloid plaques aggregates (Nelson et al., 2012; Vos et al., 2013). Additionally, CSF tau values seem to be more associated with memory performance, while lower Aβ-42 concentrations predicted fast conversion to dementia (Ivanoiu & Sindic, 2005). Nevertheless, when combining CSF biomarkers with neuropsychological performance, results have evidenced a relationship between both biomarkers (i.e., higher CSF tau and also lower Aβ-42 values) and declining global cognition and episodic memory (Engelborghs et al., 2006; Schindler et al., 2017). In this line, episodic memory deterioration has been closely related to an increased likelihood of developing AD in MCI patients (Albert et al., 2011; Dubois et al., 2014). However, failures in other cognitive processes, such as verbal fluency or executive functions, have also been associated with lower levels of Aβ-42 and very high values of tau and p-tau (Ewers et al., 2012; van der Vlies et al., 2009). Given these CSF biomarker associations with different cognitive domains in classical neuropsychological tests, discriminative tasks like TMS could help in the early differentiation of the origin of the cognitive impairment. However, up to this point there is no literature studying the possible relationship between TMS scores and one of the most clinically established biomarkers in AD (i.e., CSF tau and Aβ42 values).

In order to understand the episodic memory and executive functioning axis impairment in MCI patients, we have used the TMS. To comprehend its linkage with current biomarkers of AD we have computed a series of Pearson correlations between CSF values and TMS scores. We hypothesize that executive functioning impairment plays a crucial role on the performance of verbal learning tasks, even more important that what has been previously reported for MCI patients. Furthermore, we expect an improvement on the performance of verbal learning tasks when the use of executive functions is diminished. These phenomena would be in close correlation with levels of proteins found at CSF.

2. Materials and methods

2.1. Participants

The sample consisted of 135 Caucasian participants (61 to 85 years old) who were consecutively and prospectively recruited from a multicenter international study in two health/research centers, in Spain (48 participants) and Poland (87 participants). The first one, was the Cognitive Disorders Unit of the Hospital Universitari Santa Maria (Lleida, Spain), and the second, the Research Institute for Dementia-Related Diseases (Wroclaw -Poland) of the Medical University of Wroclaw. MCI participants were enrolled in this study after detailed clinical and neuropsychological examination, according to the NIA-AA criteria (Albert et al., 2011). The exclusion criteria consisted of: 1) the presence of visual and/or communication problems that could interfere with the study procedures; 2) illiterate participants, as it would hinder the administration of neuropsychological tests; 3) comorbidities such as cancer, severe renal or hepatic insufficiency, and severe cardiac or respiratory failure; 4) excessive alcohol intake (>280 g/week); 5) Computerized Tomography or Magnetic Resonance Imaging (MRI) evidence of hydrocephalus, stroke, a space-occupying lesion, or any clinically relevant central nervous system disease other than AD; 6) the presence of mental disorders according to DSM-V-TR™ criteria; 7) the presence of untreated (or treated for less than 3 months prior to the screening visit) vitamin B12 or folate deficiency; and 8) the presence of untreated thyroid disease (Jorge et al., 2020).

The patient, the responsible caregiver, and the legal representative (when different from the responsible caregiver), gave written informed consent to participate in the study and participants underwent a neuropsychological evaluation and a CSF lumbar puncture. The ability to generate memory strategies was evaluated using the TMS.

Finally, from the original cohort, only 47 participants (24 females and 23 males) had available and valid data regarding our main variables of interest (CSF markers and neuropsychological assessment), making up our final sample (25 Poland/22 Spain). The sample was divided into two groups, according to CSF values (see a detailed description in section Classification based on CSF cut-offs levels): normal CSF biomarkers, named CSF - (67.38±10.81 years old and 11.00±3.41 years of schooling) and possible AD, named CSF + (69.13±9.73 years old and 10.97±4.56 years of schooling).

2.2. Cerebrospinal Fluid (CSF) acquisition and analysis

CSF determinations

CSF biomarker variables include Aβ42, t-tau, and p-tau levels measured in ng/L. CSF samples were collected between 8:00 and 10:00 a.m. to avoid variations related to

the circadian rhythm (Lucey et al., 2017). The samples were collected in polypropylene tubes, centrifuged at 2000 x g for 10 min at 4 °C, immediately frozen and stored within 4 hours in a -80ºC freezer. Later, they were used for biomarkers analysis. The biomarker variables levels were determined by the enzyme immunoassay method (ELISA) according to the manufacturer's instructions. In this sense, the concentration of Aβ-42, t-tau, and p-tau were measured using the following ELISA commercial kits (In Spain: Innotest® β-Amyloid 1-42 for Aβ-42; Innotest® hTAU Ag for t-tau; and Innotest® Phospho-TAU181P for p-tau, Fujirebio-Europe, Gent, Belgium; In Poland: ELISA kits for Aβ-42, IBL International, Hamburg; and ELISA kits for t-tau and Tau 181P, Fujirebio Europe Gent, Belgium). All samples were measured in duplicate, and the values were expressed in pg/ml. Finally, samples were obtained with support from IRBLleida Biobank (B.0000682) and PLATAFORMA BIOBANCOS PT17/0015/0027 (Targa et al., 2021).

Classification based on CSF cut-offs levels

Each CSF measure was dichotomously classified (i.e., positive, or negative for AD) according to the following validated cut-off values: For t-tau and p-tau, the cut-off scores used were the ones proposed by Sjögren et al. (2001) to Innotest ELISA assays (t-tau ≥ 450 ng/l, and p-tau ≥ 61 ng/l), which were also the same to that reported in other previous and recent multicenter studies [29-32]; the cut-off value for Aβ42 was ≤ 500 ng/l according to Innotest (Sjögren et al., 2001) and IBL International scores. Then, the sample was divided into five categories based on the Erlangen Score Diagnostic Algorithm (ESA) classification which reflects the continuum between the entirely normal and the entirely pathological CSF measures: 0 points if all the CSF biomarkers were normal, 1 point reflects a pattern with marginal alterations in only one of the biomarkers (Aβ or tau, but not both), 2 points establish a clear pathological CSF alteration in either Aβ metabolism (decreased Aβ42 concentrations and/or decreased Aβ42/40 ratio) or tau metabolism (increased concentrations of t-tau and/or p-tau) but not both. On the other hand, a clear alteration in one biomarkers' group (either Aβ or tau) with marginal alterations in other group is scored with 3 points, and up to 4 points are considered when clear alterations were detected in both Aβ and tau/p-tau results (Lewczuk et al., 2015). Lastly, and taking into account the characteristics of our sample, we combined the obtained ESA categories as follows: those participants with 0 or 1 points were considered as CSF - ("neurochemically improbable AD"), and those with 2 or 3 points as CSF + ("neurochemically possible AD").

2.3. Test of Memory Strategies (TMS)

TMS is an immediate verbal memory test in which, through five consecutive conditions, the necessity of using executive functions is progressively reduced. Each list includes 10 words that have been randomly selected according to its linguistic

frequency. The TMS-1 is an incidental learning task with no semantic nor a phonetic relationship between the words, in which the participants are not aware if they are in the context of a memory task. The TMS-2 to TMS-5 are explicit learning tasks, with a progressive organization of the material into semantic categories. Every list/condition reduces the need for memory strategies and, therefore, the recruitment of executive functions.

In the case of TMS-2 and TMS-3, the participants have a greater need to implement internal recall strategies. Specifically, in TMS-3, the words should be recalled in groups based on two different semantic categories (with a low organization of the material), which prompts a higher need for working memory activation. Conversely, in TMS-4 and TMS-5 conditions, the lists of words are grouped and presented in two differentiated semantic categories (i.e., sports and vegetables), diminishing the need of internal cognitive strategies due to the external organization of the material.

The words of every list are read at a pace of one word per second. Each correct answer receives one point, and the score varies from 0 to 10 from each list independently or from 0 to 50 for the total scale (i.e., the sum of the five tasks/lists of words).

2.4. Statistical analyses

For the descriptive statistical examination, central tendency and dispersion analyses were applied. The association between demographic, clinical, and neuropsychological data was evaluated using Spearman's correlation. On the other hand and, as already mentioned, participants were divided according to the reference values in healthy individuals suggested by Sjögren et al., (2001) and the ESA, validated by Lewczuk et al., (2015), which describe the pattern of the Neurochemical Dementia Diagnostics (NDD) biomarkers and distinguish between CSF - (no evidence for organic Central Nervous System disease) and CSF + or possible AD (clearly pathological results of either Aβ or tau/p-tau, or both). As data resulted in non-normal and heteroscedastic, according to the Kolmogorov-Smirnoff and Levene tests, we used non-parametric contrast tests (U Mann Whitney) to compare the groups. Finally, an analysis of covariance (ANCOVA) was performed to define the effect on ESA classification in the sample, using the country of origin of the participants or, otherwise, their spoken language (i.e., Spain and Poland) as a covariate. All the procedures were carried out using SPSS statistical package 22.0.

3. Results

3.1. CSF markers vs TMS

When analyzing the correlation among demographic, clinical, and neuropsychological variables, the concentrations of CSF biomarkers did not

correlate with age, years of education, nor for four of the conditions of the TMS. Only significant associations between TMS 3 and AB42 (r = 0.357; p<0.05), t-tau (r = -0.307; p<0.05) and p-tau (r = -0.337; p<0.05) were observed for the whole sample.

Table 11 Association between demographic, clinical, and neuropsychological data

	Age	Years of education	AB 42	Tau	p tau	TMS I	TMS II	TMS III	TMS IV	TMS V	Fluency Test
Age	1										
Years of education	**-0.626****	1									
AB 42	0.050	-0.005	1								
T-Tau	0.014	0.102	-0.228	1							
P-tau	0.192	-0.027	**-.325***	**.869****	1						
TMS I	**-.367***	.459**	0.257	0.173	0.000	1					
TMS II	0.140	-0.160	0.234	-0.205	-0.125	**.322***	1				
TMS III	0.141	-0.210	**.357***	**-.307***	**-.337***	0.113	**.539****	1			
TMS IV	0.163	-0.085	0.258	-0.151	-0.090	0.077	**.490****	**.499****	1		
TMS IV	0.145	-0.158	0.101	-0.066	-0.040	0.137	**.583****	**.648****	**.397****	1	
Fluency Test	0.276	-0.091	0.189	-0.198	0.010	-0.069	**.356***	0.154	0.244	0.284	1

**. The correlation is significant at the 0.01 level (bilateral).

*. The correlation is significant at the 0,05 level (bilateral).

Moreover, when dividing the sample into CSF - and CSF +, the difference between groups remained significant for the TMS-3 condition (p<.001).

Table 12 Socio-demographic and neuropsychological measures divided by ESA classification

Variable	Mean ± SD	CSF – (n=16)	CSF + (n=31)	*p-value**
Age	68.53±10.03	67.38±10.81	69.13±9.73	0.701
Years of education	10.98±4.17	11.00±3.41	10.97±4.56	0.701
TMS I	4.30±3.17	5.06±3.28	3.90±3.09	0.308
TMS II	2.47±1.37	3.00±1.59	2.19±1.17	0.166
TMS III	3.15±1.50	4.25±1.18	2.58±1.34	<0.001
TMS IV	3.72±1.77	4.25±1.24	3.45±1.95	0.166
TMS V	4.53±1.82	5.25±1.77	4.16±1.75	0.166
Fluency test	8.15±3.63	9.00±4.08	7.71±3.37	0.591

Note. We present values as mean ± standard deviation (SD) for the characteristics of the participants as well as variables used for correlation analyses. These include age (in years), years of education, Test of Memory Strategy (TMS). Mann Whitney U test was used to compare within-group differences.

Table 13 shows the ANCOVA results with the two conditions of classification mentioned above: CFS - and CSF+ using the country of evaluation as a covariate. We observed statistically significant differences between groups in TMS 3 ($F(1, 44) = 17.51$, $p < .001$, partial $\eta 2 = .285$). According to the ESA categorization, participants with normal values for CSF biomarkers have a higher cognitive performance in TMS-3 compared to those in the possible AD group.

Table 13 ESA classification and performance in TMS

Factor	F-statistic	*p value**	Effect size
TMS I	3.9	0.087	0.081
TMS II	3.78	0.087	0.079
TMS III	17.51	**<0.001**	0.285
TMS IV	2.11	0.184	0.046
TMS V	3.87	0.087	0.081
Fluency Test	1.23	0.274	0.027

Note. Statistical results of the ANCOVA used the site as a covariate. Effect size is reported as partial η^2. F-statistic, $F(1, 44)$.

These outcomes persisted if the groups were divided according to Aβ42 scores ($p < .05$), but not concerning t-tau ($p = .50$) and p-tau values ($p = .46$).

Table 14 Aβ42 classification and TMS scores

Factor	F-statistic	*p value**	Effect size
TMS I	0.767	0.673	0.017
TMS II	0.325	0.673	0.007
TMS III	8.74	0.03	0.166
TMS IV	1445,000	0.673	0.032
TMS V	0.211	0.673	0.005
Fluency Test	0.18	0.673	0.004

Note. Statistical results of the ANCOVA used the site as a covariate. Effect size is reported as partial η^2. F-statistic, F (1, 44).

Lastly, we probed the effect of the interaction of CSF biomarkers and site in cognitive performance. The results only were significant in the case of fluency tests in tau ($p < .05$) and p-tau ($p<.001$). FDR corrected the p-values *(See supplementary material).*

3.2. Other significant correlations of interest

Besides TMS and CSF correlations, we found additional interesting associations among age, years of education, TMS and verbal fluency. Respect to age, we showed a negative correlation with years of education ($r = -0.626$; $p<0.01$) and TMS-1 (-0.367; $p<0.05$). Furthermore, TMS-1 was positively associated with years of education ($r = 0.459$; $p<0.01$) and, TMS-2, presented a positive correlation with verbal fluency ($r = 0.356$; $p<0.05$.). For more information, see Table 11.

4. Discussion

The present study is focused on establishing significant relationships between CSF values (i.e., Aβ-42 concentrations, t-tau, and p-tau) and the TMS performance in a sample of MCI patients. TMS manipulates the episodic memory-executive functions axis to discriminate the origin of cognitive dysfunction in the early stages of AD.

Regarding the TMS and its neuropsychological implications, participants were enrolled in an immediate memory test which included a total of 5 lists of words. In the first condition, words did not have any semantic or phonological association between them, and, in the last condition, words were organized in two semantic

categories (e.g., sports or vegetables). Thus, it starts from a condition with a higher need of elaborating memory strategies for the encoding and subsequent retrieval of the information (which more directly depends on the use of executive functions), to an external organization of the material and where the use of complex cognitive strategies is hardly needed (that is, the last conditions were focused on assessing the primary capacity for episodic memory). Thanks to this type of test, the possible overlapping between memory impairment and executive dysfunction, which might hinder an accurate differential diagnosis from normal to pathological aging, could be solved. Additionally, its application has also demonstrated an adequate discriminant power to distinguish among a variety of diagnostic groups (Fernandes et al., 2018; Nelson et al., 2012).

Positive (Aβ-42) and negative (t-tau and p-tau) correlations with the TMS-3 condition were observed for the whole MCI sample. That is, the lower Aβ-42 CSF concentrations and the higher the tau levels, the worse the score in the TMS-3 wordlist. Additionally, when stratifying participants according to the ESA classification, results reflected worst performance in the TMS-3 condition for the CSF + group, essentially correlating with lower Aβ-42 CSF values. As described in the introduction, it is well known the interest in combining CSF values and neuropsychological scores as a useful approach for early AD's detection, discrimination and monitorization of its progression (Engelborghs et al., 2006; Ivanoiu & Sindic, 2005; van der Vlies et al., 2009). In the ESA-based groups comparison, both MCI groups seem to perform cognitively similar across TMS conditions, except in TMS-3. That could mean that executive and memory functions are impaired in a similar way in the possible AD (CSF +) and the other MCI patients (CSF -), so it would be difficult to differentiate them with classical neuropsychological scores, even when they present clearly differences in pathophysiological profiles measured through CSF biomarkers. The key point here is that TMS-3 seems to be sensible and sensitive to discriminate between these cognitively similar patients with different pathophysiological profiles (for a clearer explanation about TMS results and its relationship with CSF measures and other executive function/episodic memory tests, see figure 9). In TMS-3, the two semantic categories included are disorganized and need the subject's intrinsic organization to successfully perform this condition, indicating the implementation of a cognitive strategy. Subjects with executive dysfunction, as vascular patients, perform worse in this task (Yubero et al., 2011). When an external organization is involved, as reflected in TMS-4 and 5 conditions, the group differences disappear. Additionally, it has been observed that in the case of patients with a primary memory deficit such as the amnestic MCI patients, the increase in the external organization of the material did not improve their performance, while patients with multidomain MCI obtained better scores as the material was progressively organized (Yubero et al., 2011). All these is indicating that, executive function deficits, are playing a much

more important role in the performance of episodic memory tasks than previously thought. In other words, and as mentioned by Abellán-Martínez et al. (2019), the typical reduction of cognitive performance related to memory tasks throughout the aging process (which could be more exacerbated in those participants with possible AD), might result from the disruption of executive functions rather than to a primary deterioration of memory.

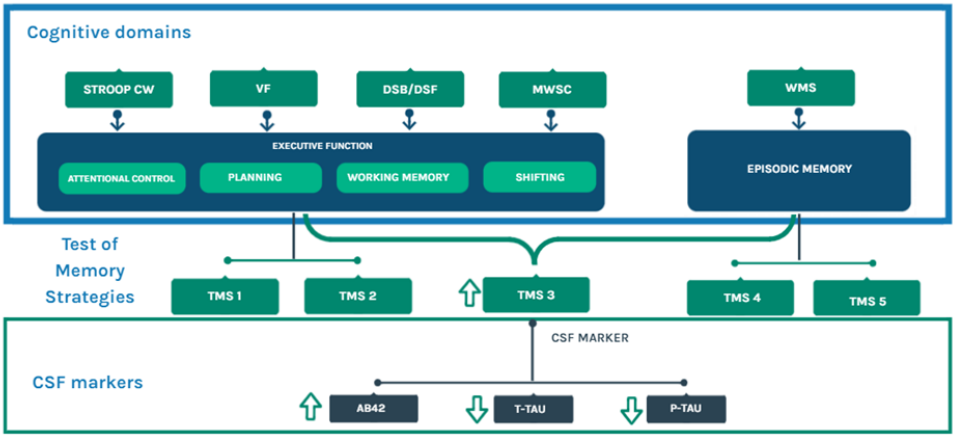

Fig. 9 Cognitive functions associated with the test of memory strategies (TMS) and their link with CSF biomarkers.

TMS is an immediate verbal memory test with five consecutive conditions. In each condition, the use of the executive function is progressively reduced, being the TMS-3, the wordlist condition where executive functions and episodic memory could be mainly combined. Interestingly, better performance in TMS-3 is associated with higher scores of Aβ42 and lower levels of t-tau and p-tau classical biomarkers of Alzheimer's Disease (AD). As described in the text, this scenario could lead us to hypothesize that our CSF + participants might be at a very prodromal stage of dementia. Stroop CW: Stroop Color and Word Test; VF: Verbal fluency; DSB: Digit span backward; DSF: Digit span forward; MWSC: Modified Wisconsin Card Sorting Test; WMS: Weschler memory scale. The neuropsychological components included in the figure and their relationship with the TMS, derive from previous works carried out by Fernandes et al. (2018), Vaccaro et al. (2022, and Abellán-Martínez et al. (2019).

Similar to our study, van der Vlies et al. (2009) formed clusters based on CSF biomarkers and their association with different cognitive profiles in a cohort of patients with AD. They described that, depending on the CSF concentrations, patients presented a severe or minor cognitive impairment which could not be explained by disease severity. For instance, those patients with low levels of Aβ-42 and extremely high CSF levels of tau and p-tau (cluster 3) exhibited a worse memory performance, mental speed, and executive functioning. However, participants belonging to cluster 1 with less abnormal biomarker values, showed less impairment of naming and memory. This cluster 1 could be more comparable to our sample according to the CSF markers values and the results of the correlation with cognitive

performance. Specially, findings regarding the Aβ-42 measures are crucial to our study, as this difference found between groups in TMS-3 essentially correlates with lower Aβ-42 CSF values. Furthermore, amyloid plaques are typically located in prefrontal and parietal regions disturbing the fronto-parietal networks classically associated with executive functioning (Palmqvist et al., 2017; Sepulcre et al., 2016). Therefore, it is natural to think that lower values of Aβ-42 at CSF could be indicating higher accumulation of amyloid in these cortical fronto-parietal regions, generating difficulties in the performance of a challenging verbal learning task such as TMS-3. Indeed, TMS-3 condition has been mostly associated with executive functioning as revealed by factor analyses (Abellán-Martínez et al., 2019; Fernandes et al., 2018). TMS-3 is demanding the mobilization of the patient's own strategies to perform this condition successfully. Therefore, this is highlighting the importance of the role of executive dysfunction in the performance of episodic memory tests in MCI patients. Moreover, it could be also indicating the notion that although the prefrontal cortex and, consequently, executive functioning is progressively affected by age (Cabeza & Dennis, 2013; Raz, 2004), its early impairment in the dementia process has not been adequately addressed. TMS-3 correlates as well with tau and p-tau values. While tau has been mainly associated with the medial temporal lobe, amyloid tends to be spread through the whole cortex including anterior cingulate cortex and parietal regions. It has been proposed that tau proteins are prone to brain regions where the amyloid deposits have been already established, linking the network of the proteins (Vogel et al., 2020). This could be a reason why the TMS-3 condition correlates with both proteins at the stage of MCI. It would be of interest if in earlier stages of the disease a similar correlation would be found.

These findings open the possibility of considering the TMS as a non-invasive and appropriate neuropsychological tool that could serve for identifying which is the primary source of cognitive dysfunction in MCI patients. Work is still needed to identify whether these cognitive changes are just a product of a particular stage of the disease or could be already existing at preclinical stages as well. Additionally, the fact that TMS correlates with current biomarkers, makes it more suitable for clinical use, specifically in patients in the process of AD. Episodic memory and executive functions are the two cognitive domains primarily affected in AD's (Dickerson et al., 2007) and, also, the strongest cognitive predictors for the development of dementia in MCI patients (Rozzini et al., 2007; Sarazin et al., 2007). Therefore, the ability of TMS to discriminate between them in a single test could reinforce the idea of contemplating the TMS as a valuable and reliable instrument that might be applied in the very early stages of the AD's diagnosis.

Finally, it is worth noting the other significant associations between certain conditions of the TMS and the verbal fluency task or demographic data relative to our sample. Specially, the positive correlations obtained between TMS-2 and verbal

fluency on the one hand, and TMS-1 and years of education on the other. Furthermore, we could see a negative correlation between TMS-1 and age. It is widely accepted that verbal fluency is closely related to executive functioning (Amunts et al., 2020). TMS-2 is another condition of this test that, similarly to the TMS-3, is strongly related to an executive functioning recruitment. Hence, the positive association between verbal fluency and TMS-2, supports and reinforces this relationship. In the same vein, the negative correlation between TMS-1 and age and the positive one between TMS-1 and years of education, together with the lack of significant differences between groups in TMS-1 performance, could emphasize the role of cognitive reserve and its protective effect against brain damage (Groot et al., 2018; Stern, 2002, 2009; Stern & Barulli, 2019). Specifically, to those cognitive processes (e.g., episodic memory and executive functions) that, as has been exposed, are more vulnerable to the aging process (Abellán-Martínez et al., 2019; Beaudoin & Desrichard, 2017; Fortin & Caza, 2014; Grady, 2012).

4.1. Limitations and future directions

Besides the Spanish version of the TMS (Abellán-Martínez et al., 2019; Yubero et al., 2011), this test was also validated in Portuguese in 2018 (Fernandes et al., 2018). Correlations with classic neuropsychological tests supported convergent and discriminant validity of the TMS scores. Furthermore, internal consistency and reliability for the test was reported for both languages. However, one of the main weaknesses of the present investigation could be related to the fact that the Polish version of the TMS is still being validated, although the obtained preliminary results are being quite robust. The length of words, phonology, pronunciation, semantic category, or the frequency of use (especially in word-list tests), could be critical on the way the words are organized for encoding and retrieval (Baddeley, 1975; Cowan, 1992). Nevertheless, in the ANCOVA analyses to compare the performance in the TMS between the CSF + and CSF - participants, we introduced the country of origin/spoken language as a covariate with the aim of avoiding the effect of this confounding factor. Likewise, besides language, the effects of age and education on test performance have been widely known for several decades (Ardila et al., 2000; Branco et al., 2014; Opdebeeck et al., 2016). Considering this, and taking into account the purposes of this study, these two variables were controlled.

Another important issue could be that shared neuropsychological tests between the Polish and the Spanish participants were scarce (i.e., we only had CSF biomarker measures, the TMS and verbal fluency scores). Despite this, and following the outcomes shown by Schindler and co-workers (Schindler et al., 2017), this mightnot be a disadvantage given the characteristics of our sample. Furthermore, besides the Spanish version of the TMS (Yubero et al., 2011; Abellán- Martínez et al., 2019), correlations with classic neuropsychological tests in other recent validated versions of the test such as the Portuguese (Fernandez et al. 2018) or the Italian (Vaccaro et

al., 2022) ones, support a good convergent and discriminant validity, as well as an adequate internal consistency and reliability for the three languages. Anyway, future studies should try to include a similar multicenter neuropsychological battery to test other potential influences of languages and cultures.

Finally, in line with the CSF cut-offs levels for distinguishing AD patients from healthy controls (Sjögren et al., 2001), and considering that the different diagnostic categories established by Engelborghs and co-workers (Engelborghs et al., 2006) are in support by the reported CSF biomarkers profiles, it is important to contemplate that although our MCI participants might be at a very prodromal stage of the disease as reflected by the obtained CSF concentrations (i.e., higher Aβ-42 and lower t-tau and p-tau levels), it might be possible that they would not manifest a "typical" CSF biomarker profile consisting of lower Aβ-42 values and higher t-tau and p-tau levels. In other words, maybe, they would not ever progress to a "pure" or "typical" AD in the future. On the other hand, although there are multiple studies that demonstrate the correlation between Aβ levels in CSF and PET amyloid, on this occasion, a PET-amyloid study has not been performed. In this sense, we cannot draw conclusions about the location of the Aβ plaques and their correlation with the neuropsychological deficits of the patients. Additionally, our CSF + group was only made up of 36 MCI participants which is a relatively small sample size, but with a high clinical value for the CSF data included in the study. Therefore, upcoming research studies would require higher sample sizes focusing on the identification of meaningful subtypes of the disease (i.e., multi-domain MCI or vascular cognitive impairment) and, to this end, carrying out exhaustive follow-ups to a better characterization of the recruited participants are absolutely necessary.

5. Conclusions

Our study reveals how the TMS-3 condition of the TMS test correlated with typical CSF biomarkers of AD. Having in mind that this condition is associated with needs of executive functioning, this fact could be indicating an early executive functioning impairment in MCI patients, which, ultimately, could be affecting their performance on episodic memory tests (verbal learning lists). This could have important implications not only at the neurochemical level given the possibility of replacing the use of an invasive technique such as the lumbar puncture, but also at the neuropsychological scenario when distinguishing different subtypes of MCI and, therefore, the potential implementation of more precise/ personalized rehabilitation programs. It is typically established that MCI patients' needs essentially episodic memory training interventions. However, our results exhibited the need of an additional and early intervention over the executive functioning process as it could be affecting the participants' abilities to encode and organize the information in memory. Future studies should address how executive training in MCI patients improve the scores on TMS-3 as well as in daily living activities.

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Chapter 7

Study 5: Sex Electrophysiological Signatures Associated with Cerebrospinal Fluid Biomarkers in Mild Cognitive Impairment

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Abstract

Objective: The use of the electroencephalography (EEG) technique in Alzheimer's disease (AD) diagnosis is scarce due to a lack of validation of its neurophysiological information with current biomarkers. Therefore, our goal was to assess correlations between brain spectral power signatures and cerebrospinal fluid markers (CSF) such as amyloid-β 42 load (Aβ-42), total tau (t-tau), and phosphorylated tau (p-tau) in a mild cognitive impairment (MCI) population. Furthermore, given the AD sex-dependent vulnerability related to CSF biomarkers, we went a little forward looking for different electrophysiological correlations for males and females independently.

Methods: A data-driven approach was employed to determine bidimensional spectral power signatures (space-frequency) that correlated (Spearman) significantly with any of the three CSF markers in 27 patients with MCI in any of the two sex-dependent subsamples (i.e., 12 females and 15 males).

Results: Our main significant outcomes evidenced 1) a negative correlation of Aβ-42 load with central-posterior theta power and a negative correlation of t-tau with widespread alpha power within the male subsample, and 2) a significant negative correlation between t-tau and widespread beta power in the female subgroup.

Conclusions: There is a distinctive profile of correlations between resting-state electrophysiological signatures and CSF markers in male and female individuals.

Significance: The combination of these two measures would be pointing out the need of a more personalized approach to promote early AD diagnosis.

Keywords: Mild cognitive impairment, Cerebrospinal fluid, Biomarkers, electroencephalography, Brain oscillations, Neuropsychology

1. Introduction

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder described, at the neuropathological level, by the accumulation of amyloid-β 42 (Aβ-42) neuritic plaques and neurofibrillary tangles formed by hyperphosphorylated tau protein (Blennow et al., 2015; Hampel et al., 2010). The interaction of both pathological biomarkers could trigger a synaptic dysfunction (Crimins et al., 2013), leading to neural communication deficits, which have ultimately contributed to define AD's as a disconnection syndrome (Brier et al., 2014; Delbeuck et al., 2003).

In recent years, the growing interest in AD's early detection has motivated the searching for specific biomarkers which could help to characterize the disease (Dubois et al., 2016; Jack et al., 2011). Considering this, cerebrospinal fluid (CSF) has been established as a sensible and validated biomarker for AD diagnosis (Blennow et al., 2010, 2015; Molinuevo et al., 2018; Smailovic et al., 2019). Lower CSF Aβ-42 concentrations and higher CSF levels of total and phosphorylated tau (t-tau and p-tau respectively) have been extensively reported findings among AD and mild cognitive impairment (MCI) populations (Blennow, 2004; Blennow et al., 2015; Vlassenko et al., 2012). When combining these measures with neuropsychological performance, results have evidenced poorer cognitive performance for those patients with higher CSF tau/Aβ-42 values (Schindler et al., 2017), although tau load has been more strongly related with cognitive decline than total amyloid plaques aggregates (Nelson et al., 2012; Vos et al., 2013). Nevertheless, CSF collection involves a highly invasive procedure since it implies carrying out a lumbar puncture.

In this vein, electrophysiological signatures, measured with the electroencephalography (EEG) technique, have been stated as a useful and low invasive approach to evaluate the progressive loss of neuronal functioning efficiency throughout the AD continuum (Babiloni, Lizio, et al., 2016; Maestú et al., 2019; Susi et al., 2019). Accordingly, and compared to healthy elders, previous literature reliable describe a decrease in relative power of the alpha band in the central, parietal, and limbic brain regions, and an increase in the theta and delta oscillations in frontal, temporal and occipital brain areas in AD's patients (Aghajani et al., 2013; Besthorn et al., 1997; de Waal et al., 2013; Mizuno et al., 2010; Moretti et al., 2004; van der Hiele et al., 2007). Despite the abovementioned outcomes, EEG is not currently included in clinical diagnosis protocols due to the scarce number of studies validating its findings with current established biomarkers, such as CSF parameters (see Maestú et al., 2019 for a literature review).

On the other hand, it is important to keep an eye on the fact that the main risk factor for AD is advanced age (Guerreiro & Bras, 2015), with females being the most

vulnerable group to manifest this disease (Andersen et al., 1999; Hebert et al., 2013; Perera et al., 2018). Furthermore, different studies have reported sex differences regarding the severity and progression of clinical and neuropathological manifestations of AD's (Buckley et al., 2018; Caldwell et al., 2019; Ferretti et al., 2018). This may be explained by women's longer life expectancy (about 4.5 years) compared to men (Masters et al., 2015). Nevertheless, different studies have evidenced an increased female vulnerability to CSF AD biomarkers linked to greater hippocampal atrophy and faster aged-related cognitive decline (Barnes et al., 2005; Koran, Wagener & Hohman, 2017; Li & Singh, 2014; Lin et al., 2015).

Under this framework, the purpose of this investigation was twofold: 1) to assess possible correlations between resting-state EEG spectral power and CSF markers in a sample of MCI patients and for each of the corresponding sex-dependent subsamples, and 2) to provide useful information that could help in the development of a non-invasive clinical protocol able to track the AD-related neuropathology. Moreover, this protocol would be accessible in most dementia units thanks to the widespread availability of EEG systems.

2. Materials and methods

2.1. Participants

A sample of 48 MCI participants were consecutively and prospectively recruited from the Cognitive Disorders Unit of the Hospital Universitari Santa Maria (Lleida, Spain) from March to June 2019. All the participants were white Caucasian and Spanish speakers. This study was conducted in accordance with the Declaration of Helsinki, and it was approved by the care ethics committee of Hospital Arnau de Vilanova de Lleida (CE-1218). A team of expert neuropsychologists ensured that individuals willing to participate met inclusion criteria as follows: age from 61 to 85 years old, with an MCI diagnosis according to the National Institute on Aging and the Alzheimer's Association (NIA-AA) criteria (Albert et al., 2011). The exclusion criteria consisted of: 1) the presence of visual and/or communication problems that could interfere with the study procedures; 2) illiterate participants; 3) comorbidities such as cancer, severe renal or hepatic insufficiency, severe cardiac or respiratory failure; 4) excessive alcohol intake (>280 g/week); 5) Computerized Tomography or Magnetic Resonance Imaging (MRI) evidence of hydrocephalus, stroke, a space-occupying lesion, or any clinically relevant central nervous system disease other than AD; 6) the presence of mental disorders according to the Diagnostic and Statistical Manual of Mental Disorders (DSM; latest edition: DSM-5-TR) criteria; 7) the presence of untreated (or treated for less than 3 months prior to the screening

visit) vitamin B12 or folate deficiency; and 8) the presence of untreated thyroid disease (Jorge et al., 2020).

The patient, the responsible caregiver, and the legal representative (when different from the responsible caregiver), gave written informed consent to participate in the study and underwent a neuropsychological evaluation, CSF lumbar puncture, and EEG recordings. In order to evaluate the global cognitive status, participants were screened using the Mini-Mental State Examination (MMSE) (Lobo et al., 1979). Additionally, a neuropsychological assessment was applied in order to explore their cognitive functioning in different domains such as verbal memory, attention and executive functions, language and praxis. The tests used for the evaluation were: the Alzheimer's Disease Assessment Scale (ADAS-Cog) (Doraiswamy et al., 1997; Rosen et al., 1984), forward and backward digit span test (Wechsler Adult Intelligence Scale IV, 2012), immediate and delayed logical memory and recognition (Wechsler Memory Scale, WMS-IV, 2013) and phonemic and semantic fluency (Peña-Casanova et al., 2009).

Finally, from the original cohort, we included the 27 participants who had available and valid data regarding our main variables of interest (CSF markers, neuropsychological assessment, and validated EEG data). A detailed list of the sample characteristics can be found in Table 15.

Table 15 Descriptive characteristics of the final sample.

Variable	*Mean ± SD*	*Female (n=12)*	*Male (n=15)*	*p-values*
Age	75.48±5.57	74,08 ± 6.48	76.60±4.64	0.251
Years of education	8.04±2.04	8.17±2.16	7.93±2.01	0.775
Aβ 42 (pg/ml)	670.19±444.77	658.58± 575.28	679.47±327.33	0.906
t-tau (pg/ml)	574.74±398.66	677.67 ± 402.27	492.40±389.45	0.237
p-tau (pg/ml)	74.81±36.83	81.75± 44.39	69.26±29.93	0.392
MMSE	25.07±3.29	25.08±2.93	25.06±3.65	0.990
ADAS-Cog	15.40±5.90	15.83±5.33	15.07±6.48	0.745
Forward digit	6.59±1.84	5.83±2.12	7.20±1.37	0.54
Backward digit	5.44±1.78	5.25 ±2.09	5.60±1.54	0.622
FAS-phonemic	7.18±3.63	6.41±3.36	7.8±3.82	0.334
FAS- semantic	10.26±4.93	9.25± 5.47	11.07±4.47	0.352
Immediate recall	14.67±6.41	13.00± 5.73	16.00±6.79	0.234
Delayed recall	7.11±8.20	5.67±6.03	8.27±9.64	0.424
Recognition	17.81±5.86	15.67±7.37	19.53±3.71	0.118

We present values as mean ± standard deviation (SD) for the characteristics of the participants as well as variables used for correlation analyses. These include sex (male/female), age (in years), years of education, amyloid-β 42 (Aβ-42), Total Tau (t-tau), Phosphorylated Tau (p-tau), Mini Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale (ADAS-Cog), working memory (Digit Span Index: forward and backward), Verbal Fluency Test (FAS- Phonemic and FAS- Semantic), episodic memory (Logical Memory II Index: immediate recall, delayed recall, and recognition). Student's t test was used to compare within group differences.

2.2. Cerebrospinal Fluid (CSF) biomarkers

CSF samples were collected between 8:00 and 10:00 a.m. to avoid variations related to the circadian rhythm (Lucey et al., 2017). The samples were collected in polypropylene tubes, centrifuged at 2000 x g for 10 min at 4 °C, immediately frozen and stored within 4 hours in a -80ºC freezer. Later, they were used for biomarkers analysis.

The concentration of Aβ-42, t-tau, and p-tau were measured using commercial kits (Innotest® β-Amyloid1-42; Innotest® hTAU Ag; and Innotest® Phospho-TAU181P, Fujirebio-Europe, Gent, Belgium). The levels of CSF Aβ-42 (Innotest® β-Amyloid (1-42), t-tau (Innotest® hTAU Ag) and p-tau (Innotest® Phospho-Tau (181P) were determined by the enzyme immunoassay method according to the manufacturer's instructions. All samples were measured in duplicate, and the values were expressed in pg/ml. Samples were obtained with support from IRBLleida Biobank (B.0000682) and PLATAFORMA BIOBANCOS PT17/0015/0027 (Targa et al., 2020).

2.3. Electroencephalography

Neurophysiological data was acquired using a NuAmps portable 32 channel EEG amplifier at the Cognitive Disorders Unit of the Hospital Universitari Santa Maria (Lleida, Spain). EEG data was collected in the morning (from 8:30 a.m. to 12:30 p.m.), at a sampling frequency of 1000Hz and online band-pass filtered between 0.1 and 330 Hz.

All participants underwent a 5-minute eyes-closed resting-state EEG recording while sitting comfortably inside of an electrically shielded room. They were requested to stay awake and to minimize their body movements. The arousal level of each participant was monitored by the EEG operator and also checked via a conversation immediately following the measurement session. If a participant reported feeling sleepy during the session, the operator gave him/her sufficient time to feel more awake and performed the measurement again. The analysis pipeline mirrors the procedure followed in previous studies conducted by our research group (de Frutos-Lucas et al., 2020). To facilitate the comprehension of the methodological specifications, hereby, we described the main key points. EEG data was automatically examined to detect ocular, muscle, and jump artifacts using the Fieldtrip package (Oostenveld et al., 2011), which were visually confirmed by an EEG expert. The remaining artifact-free data was sectioned into four-second segments. Afterwards, Independent Component Analysis-based procedure (ICA) was applied to remove heart electric field artifacts and electrooculogram components. Only those recordings with at least 15 clean segments (60 seconds of brain activity) were utilized in subsequent analyses. EEG clean time series were band-pass filtered (2 second padding) between 2 and 45Hz.

Power spectrum of each EEG's sensor was computed by means of Fast Fourier Transform using Hanning tapers with 0.25 Hz of smoothing. For each sensor, relative power was calculated by normalizing by total power over the 1.5- to 45-Hz range. Trials were averaged across individuals ending up with a power matrix of 30 channels x 133 frequency steps x 27 participants.

2.4. Statistical analyses

Power analysis. The aim of this study was the detection of any robust correlation between power values derived from clusters of sensors and CSF markers. Such analysis relied on cluster-based statistics (CBS) (Maris, 2011; Zalesky et al., 2010). Clusters were built according to a criterion of spatial and frequency adjacency. Each cluster consisted of several adjacent sensors, which systematically showed a significant partial correlation (with age as covariate) in at least 4 consecutive frequency steps (a 1-Hz interval) between their power values and the corresponding

CSF markers (Spearman correlation p-value < 0.05). Importantly, all sensors within a cluster must have shown the same sign of the correlation coefficient, indicating that the cluster might be deemed as a functional unit. Only clusters involving at least 1% of the nodes (i.e., a minimum of 3 sensors) in each frequency step were considered. Cluster-mass statistics were assessed through the sum of the Spearman rho values across all sensors and significant frequency steps. Then, to control for multiple comparisons, the entire analysis pipeline was repeated 5000 times, shuffling the correspondence between power estimates and CSF markers across subjects. At each repetition, the maximum statistic of the surrogate clusters (in absolute value) was kept, creating a maximal null distribution that would ensure control of the family-wise error rate (FWER) at the cluster level. Cluster-mass statistics on each cluster in the original data set was compared to the same measure in the randomized data. The CBS p-value represents the proportion of the permutation distribution with cluster-mass statistic values greater or equal than the cluster-mass statistic value of the original data. Power values were averaged across all sensors and frequencies that belonged to the cluster. Such an average was considered as the representative EEG marker value for that cluster, and further subjected to new correlation analyses. Therefore, the statistics presented in the results section derived from the correlation between the averaged power value of each significant cluster and the corresponding CSF marker for each participant. As it has been mentioned above, correlations were first performed within the whole sample. In a second step, correlations between power and CSF markers were performed independently for each sex. Finally, average power values were correlated with measures of cognitive performance traits that are known to be affected in AD's. These analyses were only carried out for those subgroups showing a significant correlation between any CSF marker and average power.

3. Results

CSF markers vs neuropsychological performance

When evaluating possible correlations between CSF markers and neuropsychological performance in the whole population, we found that Aβ-42 load significantly correlated with ADAS-Cog (rho = -0.390, p = 0.0445), delayed recall (rho = 0.459, p = 0.018), forward span (rho = 0.455, p = 0.020), and semantic fluency (rho = 0.425, p = 0.030). In the case of p-tau, the significant correlations emerged for ADAS-Cog (rho = 0.437, p = 0.023), delayed recall (rho = -0.437, p = 0.026), and age (rho = 0.398, p = 0.040). Finally, for the t-tau burden, the correlations were found for ADAS-Cog (rho = 0.578, p = 0.002) and delayed recall (rho = -0.549, p = 0.004). These correlations analyses were also performed for each sex independently. On

one hand, in the male population, the Aβ-42 load correlated significantly with ADAS-Cog (rho = -0.615, p = 0.019) and delayed recall (rho = 0.740, p = 0.002), and t-tau correlated with ADAS-Cog (rho = 0.617, p = 0.019) and delayed recall (rho = -0.540, p = 0.046). On the other hand, in the female sample only t-tau showed significant correlations with delayed recall (rho = -0.602, p = 0.050) and age (rho = 0.586, p = 0.045).

CSF markers vs electrophysiological power signatures

When the power correlation analysis was performed using the whole population, we did not find any significant results. Then, we repeated the same analysis for each sex population separately. Importantly, in each result (power cluster), we depict the values of the corresponding cluster for the three populations (i.e., whole, males and females) to enhance the information of the possible sex differences and to check whether would be a whole population effect.

Amyloid. Using the male population, a significant power cluster (CBS p-value < 0.05) was found in the theta frequency interval [5.25 – 6.50 Hz] mainly comprising central-posterior regions off the EEG helmet (see Figure 1). The theta power values negatively correlated with CSF Aβ-42 load (rho = -0.801, p < 0.001). This result pointed out that the augmentation of theta power in the central-posterior electrodes (Figure 10) was associated with higher amyloid burden in the brain as indicated by the CSF Aβ-42 reduction. The maximum cluster size was found at 6 Hz (16 sensors). The cluster size oscillates between a minimum of 4 sensor nodes at the beginning of the frequency range and 7 at the end of that frequency range.

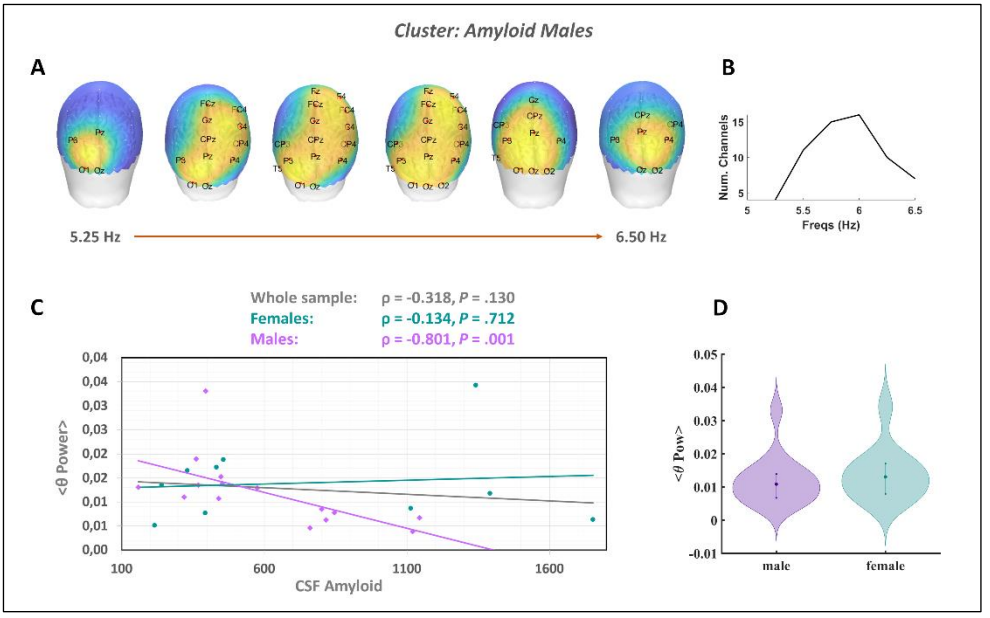

Fig. 10 Results for the theta cluster found when spectral power correlations with CSF amyloid load (Aβ-42) were assessed in the male sample.

A: *sensors labeled and highlighted in yellow color show the cluster configuration in each significant frequency step.* ***B:*** *number of sensors within the cluster in each significant frequency step.* ***C:*** *scatter graphic shows the correlation between the average power of the cluster across all significant frequency steps and the CSF Aβ-42 load for the three populations (although it was found using only the male sample).* ***D:*** *violin plot with the distribution of the power marker used in the scatter plot for each sex-based subsample. Data distributions did not differ significantly.*

When the topology and the frequency range of this cluster were evaluated in the whole sample and in the female sample, we found that neither of them showed significant results. Importantly, there were no significant differences in power in the [5.25 – 6.50 Hz] range between males and females. The average power value of the significant cluster was used for new correlation analyses in the male population. The theta cluster power significantly correlated with ADAS-Cog (rho = 0.562, $p < 0.037$), delayed recall (rho = -0.612, $p < 0.020$) and t-tau (rho = 0.538, $p < 0.049$).

For the female group we did not find any significant results with Aβ-42 load.

Total tau. Using the male population, a significant power widespread cluster (CBS p-value < 0.05) was found in the alpha frequency interval [13 – 14.25Hz] (see Figure 11). The average power values of the cluster negatively correlated with t-tau CSF load (rho = -0.832, $p < 0.001$). This result pointed out that the reduction of alpha power was associated with higher tau accumulation in the CSF. The maximum cluster size was found at 13.25 Hz (7 sensors). When this result was evaluated using the whole sample, the average cluster power correlated with the t-tau score (rho = -0.501, $p < 0.013$). This was not accomplished by the female group. As in the previous result, there were no significant differences in power in the alpha range between males and females.

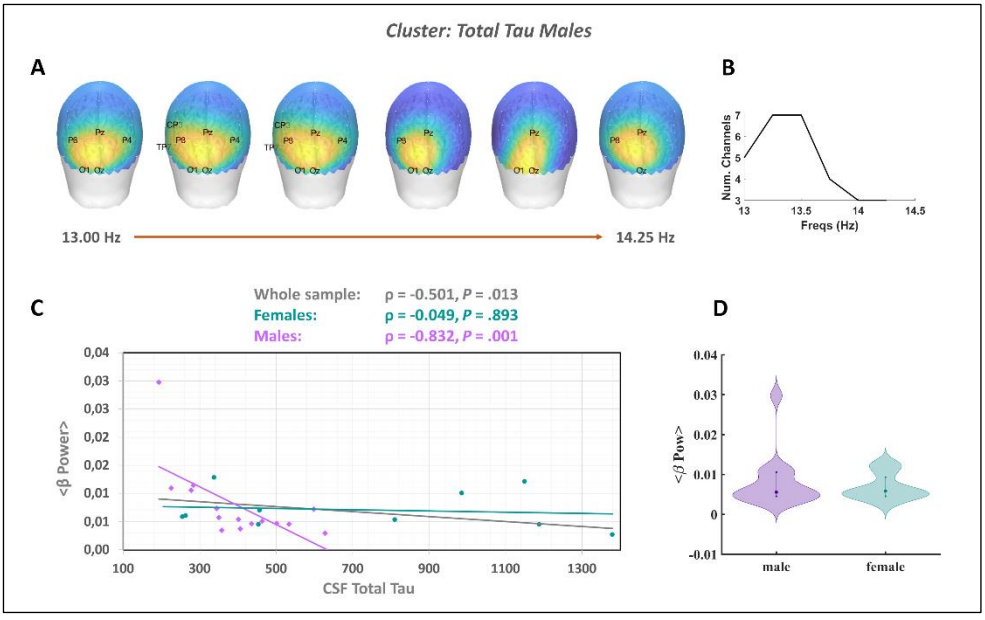

Fig. 11 Results for the alpha cluster found when spectral power correlations with CSF total tau (t-tau) concentration were assessed in the male sample.

***A**: sensors labeled and highlighted in yellow color show the cluster configuration in each significant frequency step. **B**: number of sensors within the cluster in each significant frequency step. **C**: scatter graphic shows the correlation between the average power of the cluster across all significant frequency steps and the CSF t-tau concentration for the three populations (although it was found using only the male sample). **D**: violin plot with the distribution of the power marker used in the scatter plot for each sex-based subsample. Data distributions did not differ significantly.*

When the female sample was evaluated, we found a significant cluster (CBS p-value < 0.05) in the beta range [21.75 – 30.00 Hz] (see Figure 3). The power values negatively correlated with CSF t-tau load (rho = -0.798, p = 0.006). The maximum cluster size was found at 23 Hz (15 sensors). When this result was evaluated using the whole sample, the average cluster power correlated with the t-tau score (rho = -0.413, p = 0.045). This was not accomplished by the male group. Again, there were no significant differences in power in the beta range between males and females. Additionally, the beta cluster average power significatively correlated, in the female sample, with age (rho = -0.621, p = 0.041).

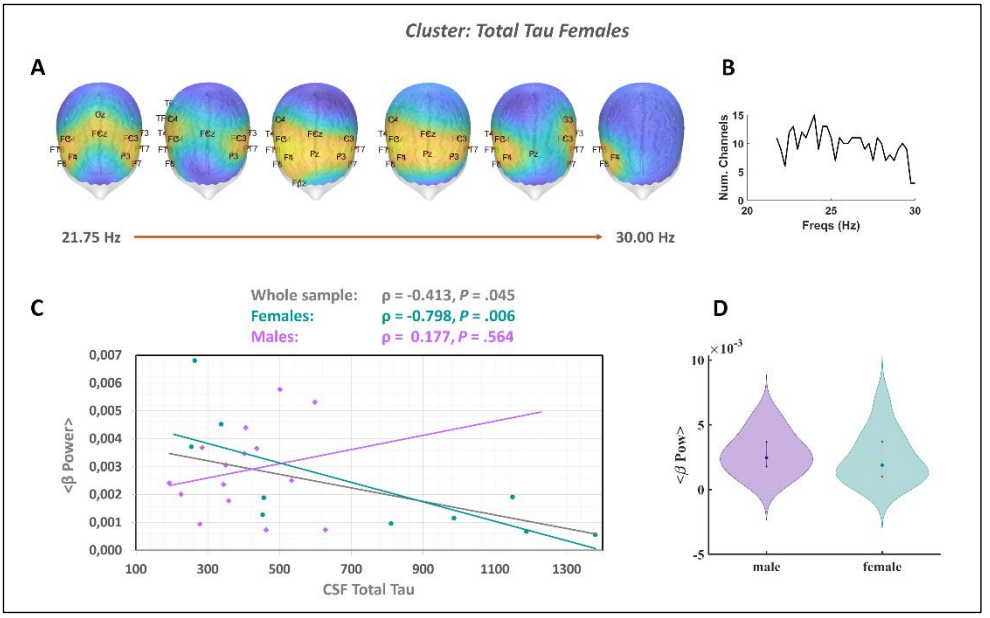

Fig. 12 Results for the beta cluster found when spectral power correlations with CSF total tau (t-tau) concentration were assessed in the female sample.

***A**: sensors labeled and highlighted in yellow color show the cluster configuration in each significant frequency step. **B**: number of sensors within the cluster in each significant frequency step. **C**: scatter graphic shows the correlation between the average power of the cluster across all significant frequency steps and the CSF t-tau concentration for the three populations (although it was found using only the male sample). **D**: violin plot with the distribution of the power marker used in the scatter plot for each sex-based subsample. Data distributions did not differ significantly.*

Phosphorylated tau. When assessing correlations with p-tau, we did not find any significant cluster, neither with males nor with females.

4. Discussion

In order to contribute to the validation of neurophysiological parameters as a valuable tool for AD early diagnosis, we assessed whether spectral power EEG signatures were associated with CSF biomarkers (i.e., t-tau, p-tau, and Aβ-42 concentrations) in patients with MCI. To characterize our sample from a clinical point of view, we started evaluating the possible correlations between neuropsychological tests and CSF markers. We found a solid pattern consisting of a positive relationship between neuropathological status and cognitive performance. When assessing correlation between EEG spectral power signatures and CSF markers, statistically significant results were found when males and females participants were analyzed separately. On the one hand, the men subsample showed a dual pattern consistent with a negative correlation with Aβ-42 load in CSF (i.e., a positive correlation between theta power and higher Aβ levels in the brain), and a negative relationship between the alpha band and t-tau. On the other hand, the female subsample showed a negative correlation between the beta band and t-tau.

As already mentioned in the introductory section, amyloid and tau pathology are well recognized neuropathological signatures of AD (Brier et al., 2014; Delbeuck et al., 2003). Several studies have previously described the correlation between CSF tau levels with the number of neurofibrillary tangles in the brain (Tapiola et al., 2009; Toledo et al., 2015), and their association with worst performance on memory tasks (Ivanoiu & Jm Sindic, 2005). In this sense, and compared to amyloid burden, tau levels have been more directly linked to cognitive impairment (Nelson et al., 2012; Vos et al., 2013). Our results regarding t-tau CSF levels supported previous research findings showing a correlation with poorer cognitive performance in the ADAS-Cog and delayed recall tests, but also pointed out amyloid-related alterations at the neuropsychological level. This finding was marginally explained by the negative correlation between Aβ-42 burden and the ADAS-Cog scores, but not for the rest of the cognitive variables considered in the study (i.e., delayed recall, forward span, and semantic fluency). Interestingly, the delayed recall assessment is one of the neuropsychological tests that showed significant association with both CSF values in our sample. In a recent multivariate approach carried out by our group and related to time to conversion from MCI to AD, this delayed recall memory test was one of the three variables included in the final model that predicted 5.5 times higher risk of progression to AD (López et al., 2020). According to this, our results could highlight the importance of combining markers of different nature that could help predicting times of conversion for this neurodegenerative disease.

At the neurophysiological level, it is well known that the progression through the AD continuum is accompanied by a generalized slowness of brain oscillatory rhythms (Jeong, 2004). The increase in theta power together with a decrease in higher frequency bands (alpha and beta) is part of the process of conversion from healthy aging to AD (Babiloni et al., 2014; Babiloni, Lizio, et al., 2016; Besthorn et al., 1997; de Waal et al., 2013; Garcés et al., 2013; López et al., 2020; López-Sanz et al., 2016; Mizuno et al., 2010; van der Hiele et al., 2007). In addition, the relationship of this electrophysiological patterns with the hippocampal dysfunction and the lower performance on memory functioning, has been already extensively described in the literature (Insel et al., 2018; Musaeus et al., 2018; Stomrud et al., 2010).

Our main findings showed that the average power of the theta cluster correlated not only with lower Aβ-42 CSF levels, but also with neuropsychological scores (i.e., lower cognitive performance in the ADAS-Cog and delayed recall tests). These results agree with previous studies such the one conducted by Stomrud et al. (2010), where the combination of CSF biomarkers, theta activity, and cognitive performance were considered like early markers of abnormal degenerative changes in the brain. Looking at other research focused on the combination of different neuroimaging techniques with CSF measures or EEG independently, we can see the coherence of our findings with the AD underlying physiopathology from different

perspectives. For instance, a recent work carried out by Cecchetti et al., (2021) observed that, compared to healthy subjects, a group of MCI participants that were positive for CSF parameters (CSF p-tau/Aβ-42 ratio) showed an extensive higher theta and a lower beta2 density in parietal and occipital lobes. In addition, they also combined both, EEG and fMRI techniques, in order to identify the networks mostly affected by AD's as well as tracking neurodegeneration across the disease. Their results reported a good accuracy for the alpha2 band in discriminating among AD's patients, MCI's positive and negative for CSF values, and healthy controls. The authors finally concluded on one hand, that the theta band is the first and most sensitive neurophysiological signature of AD's and, on the other, that the alpha2 band could act as a potential neurodegeneration biomarker. Other studies manifest that an increased posterior theta activity has also been linked to glucose hypometabolism in 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) studies (Mosconi, 2005). In this line, and going one step further, Babiloni and co-workers observed a cortical hypometabolism measured by an FDG-PET index (the PALZ score) in ventromedial frontal, bilateral frontal association, posterior cingulate, precuneus, and temporoparietal association areas (Babiloni et al., 2016). This hypometabolism was also associated with an increased EEG delta activity (a very close brain rhythm to the theta band that oscillates at 2–4 Hz) and lower activity of low-frequency alpha in a sample of AD patients in the same cortical regions of interest where the hypometabolism was observed. On another note, lower levels of Aβ-42 in CSF have been related to a typical amyloid-PET pattern with deposits of this protein in the posterior regions of the brain (Palmqvist et al., 2015). Altogether could be indicating that the increased posterior theta activity in MCI patients with lower amyloid levels in CSF are indirect measures of pathological Aβ-42 accumulation in posterior brain regions.

On the other hand, a preceding study which contemplated the association between tau protein and EEG oscillations, exhibited that higher t-tau levels correlated with lower alpha/theta ratio in healthy controls (Jelic et al., 1998). This finding goes in line with our results (i.e., a decreased alpha and beta activity in correlation with higher tau levels for males and females respectively), and the extensive evidence found in the AD continuum consisting of a decreased power in the alpha/beta bands (Babiloni et al., 2009; Lizio et al., 2011; Rossini et al., 2007) In other words, Aβ-42 and tau deposits alters synaptic activity (de Wilde et al., 2016) which could explain the resulting slowing of brain oscillations (D'Amelio & Rossini, 2012). These all could reinforce once again the clinical value of EEG classical parameters given the association of the disruption of brain oscillatory activity with cognitive decline and current neuropathological biomarkers in CSF.

Probably the major finding of this investigation was the distinctive profile of correlations in male and female MCI patients. It is important to notice that there

were no significant differences for Aβ-42, t-tau or p-tau CSF levels between males and females (see table 1). These lack of sex-related differences apply as well for the power analysis. In this regard, several studies have revealed that the prevalence of AD is higher among women (Prince et al., 2015). However, it seems that females are better protected against the disease at the prodromal stages (i.e., the MCI phase), although, as the disease progresses, they suffer greater atrophy and faster cognitive decline (Ferretti et al., 2018). This led us to hypothesize that the MCI men in our study are more vulnerable to AD noxious effects at this pre-dementia stage. This finding is similar to that reported by Roberts and colleagues (2012) and where the authors contemplated the study of different clinical MCI subtypes separately by sex (Roberts et al., 2012). In our case, sex-related different EEG/CSF patterns has been specifically manifested by 1) the two observed altered EEG frequency rhythms (theta-Aβ-42/ alpha-t-tau) for men and 2) the beta-t-tau cluster found in the female sample, an EEG signature which, as opposed to the male subsample, could be indicating that this group is in an earlier stage of the brain functioning deterioration.

5. Limitations

Despite the promising findings for the EEG relationship with CSF biomarkers and sex-related differences, we are aware that our study implies several limitations. Some correlations or group differences could not be reaching statistical significance due to a sample size issue. Assuming this, the results are generally in agreement with previous publications indicating that this aspect is not dramatically affecting our findings. In fact, some of the correlations were pretty high bringing out the robustness of our results. Another limitation could be that, although all the participants met the diagnostic criteria for MCI, absolute confirmation of the AD clinical status for these patients could only be obtained from post-mortem data. In the same vein, and as mentioned by Ewers and co-workers (2012), another important matter that could be tested in future studies is whether our reported results could vary between different subtypes of MCI patients (i.e., multidomain/non-amnestic versus amnestic). Nevertheless, having CSF AD's values is an important biomarker for a more precise characterization of the sample. Moreover, all these patients are being followed up periodically and, therefore, conversion rates and prediction value of the combined CSF EEG markers and neuropsychological performance will be fulfilled accordingly.

6. Conclusions

As a conclusion, the results of the current study provide additional confirmation of the validity of EEG profiles for the early diagnosis of AD. These profiles were supported by CSF biomarkers and neuropsychological scores, which goes in the same direction as the few previous research focused on this topic. Specifically, this work provides additional information about the potential differential association

between EEG profiles and CSF markers in male and female participants. This fact reinforces the need to conduct clinical trials centered on a more personalized approach to enhance the early detection of AD and the implementation of pharmacological and non-pharmacological interventions. Future work should not only confirm these outcomes in a larger population including follow up, but also deepening the development of low cost, availability, and non-invasive wearable EEG measures that can be used as reliable biomarkers of brain electrophysiological activity.

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Chapter 8

General discussion and conclusions

1. General Discussion

The physiological decline and slowdown in cognitive domains are natural processes occurring with aging (Carmona & Michan, 2016; Ferreira et al., 2015; Harada et al., 2013; Salthouse, 2019). However, some aspects of these cognitive changes might associate with pathological states, such as prodromal stages of Alzheimer's disease. Despite the extensive evidence about lower Aβ-42 concentrations and higher levels of total and phosphorylated tau (t-tau and p-tau, respectively) in cerebrospinal fluid (CSF) as a typical finding in MCI and AD patients (Blennow, 2004; Blennow et al., 2015), their use in clinical practice is limited by the high invasiveness procedure, high cost, and interpretational nature. Considering this, the main objective of the thesis was to characterize electrophysiological and cognitive markers that allow discriminate between healthy individuals and patients with mild cognitive impairment, considering as sources of information sociodemographic data, lifestyle indicators, neuropsychological evaluation, and E/MEG measurements extracted from recordings at rest condition of subject samples with different cultural backgrounds.

This thesis is divided into two parts and five studies. First, we tried to identify the mediator effect of modifiable and nonmodifiable factors and, to characterize the brain oscillations related to better cognitive performance in healthy aging. Second, we characterized the cognitive and electrophysiological profile, linked with CSF measures, of MCI patients. Both approaches were framed to distinguish brain activity in resting-state.

Regarding ***healthy aging***, we corroborated our hypothesis about the mediator role of sociodemographic characteristics and lifestyle factors. The people who reported having lived in a rural area during their childhood, and whose parents had lower education levels have, on average, 2 years lower of formal education than those

who lived in urban areas. Moreover, more years of education, mediated by reading time and physical activity time per week, are 1.596 more on the ACE-R score. Well-being is extensively linked with sociodemographic factors (Allen et al., 2014; Borenstein & Mortimer, 2016), and the place where people live define many aspects of their health and well-being, especially during their first years. Intrauterine growth and development, mediated by nutrition, living conditions, access to education, and early stimulation at home, are strongly associated with childhood residence areas (Borenstein & Mortimer, 2016; Fagbamigbe et al., 2020). However, other aspects such as education, parenting support, and lifestyle act as protective factors to combat these adverse conditions (Borenstein & Mortimer, 2016; Deckers et al., 2019) and increase the cognitive reserve, this is, the ability of the brain to preserve its normal functioning despite the presence of underlying structural damage (Borenstein & Mortimer, 2016; Stern, 2009). In this context, our results support the implementation of initiatives focused on healthy lifestyles and brain health activities to promote healthy aging, especially in low-income countries (Nitrini et al., 2009; Parra, 2014; Parra et al., 2021).

The next question was what was the state of the art, this is, what previous studies say about the relationship between electrophysiological traces associated with cognitive performance in healthy aging. Along these lines, the analysis of previous literature suggested that, at resting state, higher APF is associated with better cognitive performance (Choi et al., 2019; Grandy et al., 2013; Richard Clark et al., 2004; Stacey et al., 2021; Trammell et al., 2017). This relationship, coupled with the high stability of APF (Grandy et al., 2013), point to APF as a possible electrophysiological marker of cognitively healthy aging (Drago et al., 2011). On the other hand, despite an inconclusive relationship between specific cognitive domains and the power spectral and functional connectivity pattern in normal aging in this literature, the evidence of episodic memory impairments such a hallmark of the cognitive dysfunction associated with the disease (Corey-Bloom, 2002; Reed et al., 2007) is well documented in people not yet diagnosed with AD (Chen et al., 2001; see also Bäckman et al., 2005).

With the above information in mind, and as a second step in the thesis, we development three studies focus on the ***MCI profile***. When exploring the relationship between delayed recall and brain oscillations activity, our results revealed: First, that *beta frontal-occipital hyper-synchronization predicts a poor delay recall performance, being more pronounced in MCI patients than CI*. Previous studies have linked hyper-synchronization in this band with MCI subjects who later progress to AD (Bajo et al., 2012; Pusil et al., 2019). One possible explanation of this effect is that higher accumulations of beta-amyloid protein have a toxic effect in

inhibitory neurons, inducing an increased excitability that can cause spurious synchronization that advanced at hand with the evolution of the neuropathological process associated with dementia (Garcia-Marin et al., 2009, p.; Maestú et al., 2015). Second, that *healthy APOE ε4 carriers showed a selective vulnerability that mirrored a similar profile observed in pathological aging*. This finding is not surprising, considering the consolidated knowledge about the deleterious effect of having one or two copies of the APOE ε4 allele (Chew et al., 2020). Our results open the door to future studies looking into the potential effect of lifestyle factors in this FC pattern (de Frutos-Lucas et al., 2020; Klados et al., 2016).

On the other hand, considering that episodic memory failure is a proxy of AD, while executive function impairment could be leading to other types of dementia (Pasquier et al., 2001; Stopford et al., 2012), we evaluate the link between the most used CSF biomarkers of AD (Aβ-42 concentrations, total tau, and phosphorylated tau) and the performance in a test of five-word list under different conditions (Test of memory strategies- TMS; Yubero et al., 2011). This test is characterized by the progressively decrease in the use of the executive function (EF) and the increase in the requirements of primary episodic memory (EM). We conclude that *the TMS-3 (a measure primarily associated with EF, with a component of EM) seems to be especially sensitive to differences between cognitively similar patients with different pathophysiological profiles (lower Aβ-42 CSF concentrations and the higher the tau levels).* The outcomes regarding the Aβ-42 could be explained by the typical localization of amyloid plaques in prefrontal and parietal regions disturbing the fronto-parietal networks classically associated with executive functioning (Palmqvist et al., 2015; Sepulcre et al., 2016). Therefore, lower values of Aβ-42 at CSF could be indicating higher accumulation of amyloid, likely in these regions, causing difficulties in the performance of a demanding verbal learning task such as TMS-3 (Abellán-Martínez et al., 2019; Fernandes et al., 2018). Our finding emphasizes the importance of the role of executive dysfunction in the performance of episodic memory tests in MCI patients, and their use for the potential implementation of more specific/ personalized rehabilitation programs that taking account the early intervention over this process. Future studies should address how executive training in MCI patients improves the scores on TMS-3 and daily living activities.

Finally, we verified that *there is a positive relationship between neuropathological status and cognitive performance.* Levels of total tau in CSF show a correlation with poorer cognitive performance in the ADAS-Cog and delayed recall tests, but the levels of amyloid protein also were related to alterations at the neuropsychological level. This finding was marginally explained by the negative correlation between Aβ-

42 burden and the ADAS-Cog scores, but not for the rest of the cognitive variables considered in the study (i.e., delayed recall, forward span, and semantic fluency).

Each sex shows a different spectral power profile associated with CSF markers. The appearance of higher power in the theta and alpha bands in men is related to higher levels of Aβ and total tau in CSF respectively. In contrast, women only showed higher activation in the beta band related to lower total tau, an EEG signature that, unlike the male subsample, could be indicating that this group is at an earlier stage of impaired brain functioning. This assumption is based on the evidence showing the apparently protective role of the women brain in the prodromal stages (i.e., the MCI phase), although, as the disease progresses, they suffer greater atrophy and more rapid cognitive decline (Ferretti et al., 2018).

We also found that *the average power of the theta cluster in men correlated with lower Aβ-42 CSF levels and neuropsychological scores.* These results agree with previous studies such the one conducted by Stomrud and colleagues (2010), where the combination of CSF biomarkers, theta activity, and cognitive performance were considered as early markers of abnormal degenerative changes in the brain. A recent work carried out by Cecchetti and collaborators (2021) concluded, on one hand, that the theta band is the first and most sensitive neurophysiological signature of AD and, on the other, that the high alpha band could act as a potential neurodegeneration biomarker. Moreover, lower levels of Aβ-42 in CSF have been related to a typical amyloid-PET pattern with deposits of this protein in the posterior regions of the brain (Palmqvist et al., 2015). Altogether, this could be indicating that the increased posterior theta activity in MCI patients with lower amyloid levels in CSF are indirect measures of pathological Aβ-42 accumulation in posterior brain regions.

On the other hand, a preceding study which evaluated the association between tau protein and EEG oscillations, exhibited that higher total tau levels correlated with lower alpha/theta ratio in healthy controls (Jelic et al., 1998). This finding goes in line with our results (i.e., a decreased alpha and beta activity in correlation with higher tau levels for men and women respectively), and the extensive evidence found in the AD continuum consisting of a decreased power in the alpha/beta bands (Babiloni et al., 2009; Lizio et al., 2011; Rossini et al., 2006). In other words, Aβ-42 and tau deposits seem to alter synaptic activity (de Wilde et al., 2016), which in turn could explain the resulting slowing of brain oscillations (D'Amelio & Rossini, 2012). These findings could reinforce once again the clinical value of EEG classical parameters, given the association of the disruption of brain oscillatory activity with cognitive decline and current neuropathological biomarkers in CSF.

The studies presented support the idea of a multifactorial scenario in which normal and pathological aging converge with non-modifiable (genetic background) and modifiable (i.e., reading time and exercise time per week) lifestyle factors. Along these lines, our results highlight the importance of combining markers of different nature to help prevent, assess, and predict disease onset and conversion. Our findings also open the door to the implementation of evidence-based public policies that could restrict the detrimental effects of non-modifiable factors, reducing cognitive decline and dementia risk in low-income countries.

1.1. Limitations

The most important limitation across the studies was its cross-sectional design. This design provides only a snapshot of brain activity, and the picture can be enhanced by developing longitudinal studies to track individual changes along the AD continuum. In addition, combining techniques with neuropathological markers of AD, such as amyloid or tau pathology, would improve the clarity of the results since we could distinguish whether these results are specific to AD or general to different types of dementia.

Regarding healthy aging, the different criteria used to define this construct could partially explain some of the variability in the results observed in the literature and, therefore, represent an essential caveat that the field should seriously consider addressing in the future. Another aspect of the review was the scant literature on the use of MEG in the field, despite its recognized use to study neurocognitive processes. This might be explained by the scarcer number of MEG systems available, together with their higher cost, when compared to EEG.

Another limitation is related to the diagnosis criteria used in the clinical practice. Although all the participants met the diagnostic criteria for MCI, absolute confirmation of the AD clinical status for these patients can only be obtained from post-mortem data. In the same vein, and as mentioned by Ewers and collaborators (2012), another critical matter that could be tested in future studies is whether our reported results could vary between different subtypes of MCI patients (i.e., multidomain/non-amnestic versus amnestic). Moreover, all the patients in this thesis are currently being followed up periodically and, therefore, conversion rates will be available in the future. Thus, we will be able to evaluate the prediction value of the combined CSF EEG markers and neuropsychological performance.

Finally, upcoming research studies would require higher sample sizes, focusing on the identification of meaningful subtypes of the disease (i.e., multidomain MCI or vascular cognitive impairment). To this end, carrying out exhaustive follow-ups to a better characterization of the recruited participants is necessary, including variables

such as quantification of CSF levels, neuropsychological batteries, and social determinants.

1.2. Conclusion

The neurobiological and physiological changes associated with aging are the aim of several studies. One approach to exploring the consequences of these changes is in the framework of electrophysiological fingerprints in the brain.

During healthy aging, previous studies are consistent in pointing to a generalized reduction in the relative power of low frequency bands (delta and theta) with increasing age until late middle age, accompanied by an increase in the relative power of higher frequency bands (alpha and beta). Our review of previous researcher also suggests that the higher alpha peak frequency, the most prominent peak in human power spectrum, is associated with a better cognitive performance in this population and could be considered as an electrophysiological marker of healthy aging.

Furthermore, alterations in the electrophysiological profile along the AD continuum have also been addressed in our studies related with cognitive performance. Regarding functional connectivity, higher values in beta band in the right occipital region was associated with lower delayed recall scores in cognitive intact and MCI subjects. In this sense, the brain seems to progressively loss the ability to desynchronize beta oscillations, and this process would be starting to become significant in preclinical stages, at least in participants with AD vulnerability such as the presence of the APOE ε4 allele.

On the other hand, CSF has been stated as a sensible and validated biomarker for AD diagnosis; notwithstanding, their use in clinical practice is reduced, mainly by the cost, invasiveness, and access to the procedure in primary care attention. The validation of neuropsychological measures that differentiate between positive and negative CSF markers is a good option to promote early diagnosis and treatment. The combination of executive function and episodic memory, evaluated by the test of memory strategies, could help discriminate two different patterns of MCI. Our findings suggest an early executive functioning impairment in MCI patients, which could ultimately affect their performance on episodic memory tests (verbal learning lists). This could have significant implications not only at the procedural level, with the possibility of complementing the use of an invasive technique such as the lumbar puncture, but also at the neuropsychological scenario when distinguishing different subtypes of MCI and, therefore, the potential implementation of more precise and personalized rehabilitation programs. It is typically established that MCI patients' essentially need interventions in episodic memory training. However, our

results showed the need for an additional and early intervention over the executive function process, as it could affect the participants' abilities to encode and organize the information in memory.

In the same direction that the previous study, the last research provides additional confirmation of the validity of EEG profiles for the early diagnosis of AD. These profiles were supported by CSF biomarkers and neuropsychological scores, which goes in the same direction as the few previous research focused on this topic. Specifically, this work provides additional information about the potential differential association between EEG profiles and CSF markers in male and female participants. This fact reinforces the need to conduct clinical trials centered on a more personalized approach to enhance the early detection of AD and the implementation of pharmacological and non-pharmacological interventions. Future work should not only confirm these outcomes in a larger population, ideally including follow up, but also deepening the development of low cost, available, and non-invasive wearable EEG systems that can be used to generate reliable biomarkers of brain electrophysiological activity.

Finally, we also explored the non-modifiable and modifiable factors related with cognitive decline. Although nonmodifiable factors (i.e., residence area during childhood, education level of the parents) impact older adults' cognition, their influence is mediated by other factors that are indeed modifiable (i.e., time spend reading, engagement in physical activity). This finding could be the base to support the implementation of initiatives encouraging a healthy lifestyle and promoting brain health activities (for example, through exercise, healthy diet, brain enrichment activities, and social interaction), which could favor reducing cognitive decline in aging.

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APPENDIX - 1

Study 1: Impact of Sociodemographic Features and Lifestyle on Cognitive Performance of Peruvian Adults

Supplementary Table 1. Normality test of the sociodemographic and lifestyle variables.

	Kolmogorov–Smirnov			Shapiro–Wilk		
	Statistic	gl	*p*	Statistic	gl	*p*
Age	0.056	1478	0.000	0.978	1478	0.000
Years of education	0.142	1478	0.000	0.938	1478	0.000
Reading time	0.311	1478	0.000	0.543	1478	0.000
Physical activity	0.423	1478	0.000	0.440	1478	0.000
Cognitive performance	0.064	1478	0.000	0.975	1478	0.000

Supplementary Table 2. Homogeneity of variances of noncategorical variables

	Levene's Test	df1	df2	*p*
Age	0.161	1	1476	0.688
Years of education	0.186	1	1476	0.667
Reading time	59.479	1	1476	0.000
Physical activity	30.344	1	1476	0.000
Cognitive performance	3.465	1	1476	0.063

Study 4: Understanding the episodic memory and executive functioning axis impairment in MCI patients: A Multicenter Study in comparison with CSF biomarkers

Supplementary Tables: Interaction between CSF biomarkers classification and sites and the effect in TMS scores

Ab42*site

Factor	F-statistic	*p-value* corrected	Effect size
TMS I	1.138	0.650	0.026
TMS II	.378	0.650	0.009
TMS III	.004	0.953	0.000
TMS IV	.385	0.650	0.009
TMS V	.483	0.650	0.011
Fluency Test	5.398	0.150	0.112

Tau*site

Factor	F-statistic	*p-value* corrected	Effect size
TMS I	1.048	0.818	0.024
TMS II	0.054	0.818	0.001
TMS III	0.071	0.818	0.002
TMS IV	0.056	0.818	0.001
TMS V	0.060	0.818	0.001
Fluency Test	10.848	0.012	0.201

p-tau*site

Factor	F-statistic	*p-value* corrected	Effect size
TMS I	.004	0.950	.000
TMS II	.281	0.950	.006
TMS III	.076	0.950	.002
TMS IV	.306	0.950	.007
TMS V	.011	0.950	.000
Fluency Test	12.438	0.006	.224

Note. Statistical results of the ANCOVA used the site as a covariate. Effect size is reported as partial η^2. F-statistic, F (1, 44).