Healthy and Pathological Neurocognitive Aging: Spectral and Functional Connectivity Analyses Using Magnetoencephalography

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Summary

Oscillatory activity present in brain signals reflects the underlying time-varying electrical discharges within and between ensembles of neurons. Among the variety of non-invasive techniques available for measuring of the brain's oscillatory activity, *magnetoencephalography* (MEG) presents a remarkable combination of spatial and temporal resolution, and can be used in resting-state or task-based studies, depending on the goals of the experiment.

Two important kinds of analysis can be carried out with the MEG signal: *spectral a.* and *functional connectivity* (FC) *a*. While the former provides information on the distribution of the frequency content within distinct brain areas, FC tells us about the dependence or interaction between the signals stemming from two (or among many) different brain areas. The large frequency range combined with the good resolution offered by MEG makes MEG-based spectral and FC analyses able to highlight distinct patterns of neurophysiological alterations during the *aging process* in both healthy and pathological conditions. Since disruption in spectral content and functional interactions between brain areas could be accounted for by early neuropathological changes, MEG could represent a useful tool to unveil neurobiological mechanisms related to the cognitive decline observed during aging, particularly suitable for the detection of functional alterations, and then for the discovery of potential biomarkers in case of pathology.

The aging process is characterized by alterations in the spectral content across the brain. At the network level, FC studies reveal that older adults experience a series of changes that make them more vulnerable to cognitive interferences.

While special attention has been dedicated to the study of pathological conditions (in particular, mild cognitive impairment and Alzheimer's disease), the lack of studies addressing the features of FC in healthy aging is noteworthy. This area of research calls for future

attention because it is able to set the baseline from which to draw comparisons with different pathological conditions.

Keywords

aging, functional connectivity, magnetoencephalography, dementia, Alzheimer's disease

Neurocognitive Aging

In recent centuries, humanity has undergone a series of changes. In 2009, the United Nations estimated that the proportion of people worldwide over the age of 60 would double between 2000 and 2050, going from 10% to 22% and equaling the proportion of children (up to 14 <years), which would cause the global percentages of old and young people to be the same for the first time in history. The last report published by HelpAge International (World Health Organization (WHO), 2015) supports the aforementioned, stating that in 2015, 12.3% of the population was over 60 years of age. This increase in life expectancy also entails an increase in associated clinical manifestations such as dementia; thus, characterizing the cognitive decline due to aging and differentiating it from clinical conditions such as dementia is a first step in addressing the problem (Martínez Pérez & González Aragón, 2018). It is equally important to identify the changes and adaptations that occur in the aging brain in contrast to those associated with underlying pathological processes, and to find early biomarkers of dementia that will enable diagnosis and prevention in its preclinical stages, such as subjective cognitive decline (SCD) and mild cognitive impairment (MCI).

Introduction to Spectral and Functional Connectivity Analyses Using MEG

How to Measure Neuromagnetic Brain Activity

Neuronal communication in the brain is associated to tiny electrical currents that give rise to magnetic fields outside the head. Magnetoencephalography is a non-invasive neurophysiological recording technique for mapping brain activity through the recording of such magnetic fields. Pyramidal neurons—which represent two-thirds of the neurons present in the cerebral cortex—possess specific geometrical features that make us consider them the key of MEG signal genesis.

Electrophysiological Basis of MEG Signals

[Insert Figure 1]

Each neuron has typically thousands of synapses from other neurons (Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993), and operates a continual integration of postsynaptic potentials, caused by incoming pulses (action potentials) from the afferent neurons. In pyramidal neurons, the elongated shape of the somato-dendritic axis facilitates such contributions giving rise to the circulation of a resulting *intracellular* (*primary*) current, which can be modeled with a *current dipole*.[1] Such current generates a magnetic field around it, in accordance with the right-hand rule of the electromagnetism (Lopes da Silva, 2013; Baillet, 2017) (see Fig. 1a). *Extracellular* passive currents (*volume*, or *secondary* currents) in the surrounding medium complete the loop of ionic flow, spreading even to neighbor regions. Because all currents elicit magnetic fields, secondary currents contribute also to MEG signals,

[1] *Current dipole.* In MEG research the dipole is a popular source model used to approximate the flow of electrical current in a small area (Hämäläinen et al., 1993).

although to a lesser extent (Haueisen, Ramon, Czapski, & Eiselt, 1995; Rezaie, Simos, Fletcher, Denton, & Papanicolaou, 2012).

Pyramidal neurons are arranged in the form of a palisade, with their main axes parallel to each other and perpendicular to the cortical surface, and the apical dendrites oriented toward the *pial* surface of the cortex (Hansen et al., 2010; Lopes da Silva, 2009; Snell, 2010). Such features are ideal for the generation of coherent magnetic fields when adjacent neurons activate with a certain degree of synchrony (Buzsáki, Anastassiou, & Koch, 2012; Lopes da Silva, 2013). Since magnetic fields generated by pyramidal neurons in the cortex are radial to their axis, intracellular currents that have a component oriented tangentially to the skull (e.g., those generated from pyramidal neurons in sulcal walls) will produce stronger contributions to MEG signal than currents generated from radial sources (e.g., pyramidal neurons in gyral crowns) (Hansen et al., 2010; Lopes da Silva, 2009; Baillet, 2017).

MEG Signal Detection

Magnetic fields emerging from cortical sources exit and re-enter the scalp, giving rise to neuromagnetic signals that are typically in the order of 10^{-13}T, about 10^{8} times less than the earth's steady magnetic field. To detect such magnetic fields, very sensitive *flux-to-voltage transducers* are employed, so that such tiny magnetic flux across *pickup coils* (i.e., *magnetometers* or *gradiometers*) can induce readily measurable proportional currents, typically consisting in particular sensors called Superconducting Quantum Interference Devices (SQUIDs), made of superconducting material and based on the so-called Josephson effect (see Jenks, Sadeghi, & Wikswo, 1997; Hari & Puce, 2017; Hämäläinen et al., 1993; Hansen et al., 2010 for a detailed description of technical/electronics aspects).

The notable spatial resolution achievable with MEG data is due to the properties of the magnetic field and its lack of interaction with biologic tissues, avoiding smearing and distortion outside of the scalp (Baillet, 2017).

MEG systems acquire brain signals through a sensor array (more than 300 independent channels in state-of-the-art MEG machines) that is aligned to the scalp surface and embedded in a thermally insulated tank (*dewar*) at very low temperatures, required for the proper operation of the sensors.

Since magnetic signals from the brain are extremely weak compared with those from the ambient (earth's geomagnetic field variations, vehicles, power-line fields, radio-transmitter devices, etc.), a properly multilayered shielded room is necessary to carry out MEG recordings.

MEG sensors allow us to measure a large frequency range (up to 1,000 Hz), although bands of interest span typically across 1–80 Hz. MEG is particularly useful when the user is interested in obtaining signals at the level of neural sources (*source space*), instead of those measured at the level of the sensors (*sensor space*). The reconstruction of the neuromagnetic sources can be achieved by combining the MEG signal acquired from the sensors with the magnetic resonance imaging of the subject, or by using proper existing structural templates.

MEG allows us to study brain activity both in resting state and during the execution of cognitive tasks (see Appendix 1).

MEG Pros and Cons

On the one hand, MEG offers plenty of advantages with respect to other functional imaging methods. MEG measures neuronal activity directly, not relying on vascular responses like other in-vivo functional neuroimaging techniques (e.g., functional magnetic resonance imaging (fMRI)), offering a good combination between spatial (2–5 mm) and temporal

resolution (1 ms). Unlike electroencephalography (EEG), MEG does not require a reference electrode; this greatly simplifies the data interpretation and facilitates the modeling of the functional network and the connectivity analysis. The fact of having gel-free sensors and 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 some kinds of movement disorders.

On the other hand, MEG technology imposes substantial capital and operating costs (installation and maintenance, in addition to the machine itself). Fortunately, more cost-effective solutions are emerging, such as onsite helium recycling or helium-free alternatives to SQUID-based technology (i.e., Optically Pumped Magnetometers (Boto et al., 2017)).

Oscillations, Frequency Bands, and Power Spectral Density

[Insert Figure 2]

[Insert Figure 3]

Brain signals contain rhythmic activity. This rhythmic activity, which can be captured by MEG, is a direct reflection of neural oscillations in the cortex produced by fluctuations in the excitability of underlying populations of neurons, and can be observed even in raw, unprocessed data. In general, oscillations are characterized by three features: their frequency (cycles per second), their power (amount of energy per unit time) in specific frequency bands, and their phase (position along the cosine wave) (see fig.2). We can find some oscillations that are modified by task events, and some that seem to remain unchanged.

Multiple frequencies coexist simultaneously in the brain. These frequencies have been historically grouped into bands (see fig.3), which include delta (2–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (15–30 Hz), low gamma (30–80 Hz), and high gamma (80–150 Hz).

The presented rhythms are not the only ones, but they are those most typically associated with cognitive processes in the literature, and their boundaries may vary slightly between studies.

Spectral analysis can be studied by estimating the *power spectral density* (PSD) (also called *power spectrum*, or *power density spectrum*). The PSD shows how power is distributed in the different frequency components. It has been found that individual differences in peak frequencies have been linked to a number of individual characteristics, and could act as biomarkers for certain diseases (Başar, Başar-Eroğlu, Güntekin, & Gülmen Yener, 2013). The importance of studying the frequency content dynamically has generated interest in recent decades, showing promising results in the field of aging (Rondina et al., 2016; Fernández et al., 2006).

Since PSD gives us an idea of the oscillatory components, it is mainly under this framework that it makes sense to speak of the "interaction" between brain regions at the different frequency bands.

Functional Connectivity

Brain connectivity or the connectomics (Sporns, 2013; Maestú, del Pozo, & Pereda, 2015) is a new field in brain functional activity research, based on the concepts of structural connectivity (SC) and functional connectivity (FC). SC refers to the white matter fibers connecting different brain regions, while FC studies the synchronized neural networks co-activation which has been proposed to reflect communication between different specialized brain regions, supporting the majority of cognitive functions (Varela, Lachaux, Rodriguez, & Martinerie, 2001; Mesulam, 1990, 1998).

[Insert Figure 4]

The physiological mechanism underlying brain regions' synchronized activity can involve the brain oscillations' changes in frequency, patterns, or strength of their rhythmic fluctuations (Fries, 2015; Bastos & Schoffelen, 2015). Commonly, MEG signal can be quantitatively measured using two related metrics: interaction analysis between the time series of couples of sensors or brain regions (commonly referred to as FC) and analysis of the brain network organizational properties, based on FC networks (Engels, van der Flier, et al., 2017). The first can be subdivided into two groups of methods, depending on whether directionality of the interaction is measured (see the list of methods in Table A1 of Appendix 2). The second uses graph theory (see fig.4) to discover patterns in the FC measures quantifying the interrelationship (edges) between areas (nodes) (see the list of methods in Table A2 of Appendix 3).

The properties of brain networks have been robustly described. They are characterized by the presence of modularity, local clustering, and "hubs"—brain regions that function as important connectors (Sporns, 2011) (see Fig. 4). Healthy brain is often characterized as a "small world" network that exhibits a balance between segregation (specialized clusters) and integration (connectivity between clusters) (Stam, 2004a; Watts & Strogatz, 1998).

What Can Meg Tell Us About the Aging Process?

In this section we report the main effects of healthy and pathological aging found with MEG, both for PSD and FC. In addition to a general summary, a list of the single effects found by different authors is provided in thematic summary tables.

Note that in the tables participants are grouped in age ranges: children (<10 years old), adolescents (10–18), young adults (18–35), middle-aged adults (35–55), and older adults (>55); where no information about the age range is given, older adults are intended.

With regard to pathological aging, we will review SCD, MCI, and Alzheimer's disease (AD), as well as some brief results from Parkinson's disease (PD).

Power in Healthy and Pathological Aging Using MEG

MEG studies about **healthy aging** in resting state indicate a general shift from low- to high-frequency bands of the PSD distribution until the end of middle age, followed by an opposite behavior for subsequent age stages (Gómez, Pérez-Macías, Poza, Fernández, & Hornero, 2013). In addition, a widespread reduction in low-frequency relative power (delta and theta bands) with increasing age is reported until the end of middle age. For older adults, some authors report a perpetuated and linear relative power decrease (e.g., Vlahou, Thurm, Kolassa, & Schlee, 2014), while an increase is highlighted in other studies involving a greater number of subjects (e.g., Gómez et al., 2013), individuating a quadratic trend across the lifespan (discrepancies among the findings may be due to the different power normalization methods used). The relative power of higher frequency bands (alpha and beta) follows an opposite trend with respect to that of low-frequency bands (Gómez et al., 2013). Vlahou et al. (2014) highlight that for older adults, but not for younger participants, higher delta and theta relative power in central and temporal regions is associated with higher cognitive performance (separately assessed with cognitive tests).

With regard to task execution, some studies highlight that older adults show greater activation power in the beta band with respect to younger participants during the early phase of the task. Nevertheless, these results cannot be generalized due to the limited number of comparative studies and the differences between the experimental designs.

As for **pathological aging**, AD is the most widespread brain pathology linked to aging and, in turn, that on which more neuroimaging studies have focused. The most robust finding in MEG studies that aim to characterize power spectrum patterns in people with both AD and

prodromal stages such as MCI is an accentuated slowing of the MEG signal (Fernández et al., 2002; Fernández et al., 2006; Engels, van der Flier, et al., 2017; López, Cuesta et al., 2014; Poza, Hornero, Abásolo, Fernández, & García, 2007; Verdoorn et al., 2011), a power increase in low frequencies (delta band), and a power decrease in higher frequency bands (alpha and beta bands) (Verdoorn et al., 2011; López, Cuesta et al., 2014) with respect to healthy subjects. These distinctive effects have been found to be exacerbated in multi-domain MCI (i.e., MCI cases in which more than one cognitive domain is affected) in comparison with single-domain MCI, and to correlate with worse cognitive performance in the second subtype (López, Cuesta et al., 2014).

The decrease in alpha power has generated particular interest in the scientific community, since it is the most robust finding in neurophysiological research on AD. Such decrease can be explained by the functional roles ascribed to the alpha rhythm, including the support and modulation of attentional states and facilitation of communication between different neuronal populations (Lopes da Silva, 2013; Hari & Puce, 2017). Many parameters have been used to describe such dynamics. In this way it has been found that MCI patients show a lower alpha peak frequency than both healthy controls (HC) and SCD (Garcés et al., 2013; López-Sanz et al., 2016), correlated with a lower hippocampal volume, a key area in memory processing and one of the first regions affected by AD pathology. Interestingly, a decrement in the alpha band activity across broad regions characterizes elders with SCD in comparison with age- and sex-matched counterparts without any cognitive concern (López-Sanz et al., 2016). In addition, patients suffering AD have decreased alpha band *reactivity* (i.e., the result of a comparison between the power at eyes-open resting state and eyes-closed resting state) compared with healthy elders (Franciotti et al., 2006). Table 1 lists the most representative findings on MEG-based PSD.

<COMP: INSERT TABLE 1 NEAR HERE>

Functional Connectivity in Healthy and Pathological Aging Using MEG

Several studies have been conducted applying the FC metrics to the study of the brain in healthy and pathological aging cohorts. In general, MEG studies about **healthy aging** in resting state show an inverse correlation between cognitive performance and information inflow into the posterior cingulum/precuneus and the medial temporal lobe (Schlee, Leirer, Kolassa, Weisz, & Elbert, 2012). Nakamura et al. (2017) found increased FC in low-frequency bands between precuneus and the bilateral inferior parietal lobules. Similarly, López, Aurtenetxe et al. (2014) have found that a lower CR is associated with higher FC, due to the fact that participants with low CR need a greater "effort" than those with high CR to achieve the same level of cognitive performance. Studies of participants performing an interference-based working memory task show that older adults require higher synchronization between cortical brain regions in order to achieve a successful recognition; in this scenario, the main differences between age groups arise during the interference window, where older participants present reduced ability to reorganize their brain functional network (Ariza et al., 2015). Given the few studies dedicated to FC in healthy aging, and the different metrics used in each of them, results have to be carefully interpreted.

In the case of **pathological aging,** as in AD, abnormalities at the network level have become paramount in the study of brain mechanisms underlying disturbances in cognition. Disturbed functional interactions between brain areas in AD could be accounted for by early neuropathological changes (beta-amyloid accumulation and tau protein phosphorylation) that produce degeneration of white matter tracts and affect synaptic transmission even decades before the initial clinical symptoms appear (Braak & Braak, 1991b; Villemagne et al., 2013). In this line, it has been suggested that AD can be viewed as a disconnection syndrome

(Delbeuck, Van der Linden, & Collette, 2003) that could be detectable in early stages of the disease, such as in SCD and MCI, using in-vivo FC and SC methods.

In comparison with HCs, SCD population shows a hypersynchronization in the anterior network, while the posterior network decreases in FC in resting state (López-Sanz, Bruña, et al., 2017). In studies of patients with MCI, the subjects show two characteristic patterns: (a) a hypersynchronization between anterior regions (during a memory task (Bajo et al., 2010) and while at rest (Bajo, Castellanos, Cuesta, et al., 2012; López-Sanz, Bruña, et al., 2017); and (b) a hyposynchronization in posterior regions (López-Sanz, Bruña, et al., 2017; López-Sanz, Garcés, et al., 2017). Both these patterns have also been found in SCD participants. However, the decreased FC in posterior areas was significantly lower in MCI in comparison with SCD subjects. This hyposynchronization between different areas is often interpreted as the disruption and loss of network communication, while the hypersynchronization is often attributed to a compensatory recruitment of brain areas for the progressive loss of cognitive function. On the other hand, network-based studies in MCI have revealed that these changes of connectivity are often more random and inefficient. MCI patients present a loss of *small worldness* and clustering, disruptions that SCD subjects also present, but in a smaller degree (Stam, 2004b; López-Sanz, Garcés, et al., 2017).

At the stage of the diagnosis of AD, overall MEG papers describe a decrease of FC (Stam, 2010). This decreased synchronization seems to affect especially higher frequency bands (e.g., Stam et al., 2002, 2006, 2009; Alonso et al., 2011), which may reflect local connectivity changes (Engels, van der Flier, et al., 2017). Some studies have also found an increased connectivity in slow frequencies (3–7 Hz), particularly in posterior regions, but these have been less reported (e.g., Stam et al., 2006; Alonso et al., 2011; Escudero, Sanei, Jarchi, Abásolo, & Hornero, 2011).

Connectivity between long-range regions was predominantly diminished in the left hemisphere, involving main frontal and temporal regions, while the connectivity within a region was primarily decreased in the right hemisphere frontal and parietal areas (for a review, see Stam, 2010; Maestú, Solesio-Jofre, & Bajo, 2014; Engels, van der Flier, et al., 2017). Findings of studies using network analyses confirm the previous data in AD: lower and more vulnerable hubness (Yu et al., 2017), weaker connections between modules (de Haan, van der Flier, W. M., Wang, H et al., 2012; de Haan, Van der Flier, W. M., Koene, T. et al., 2012), and a more random configuration in several bands (Franciotti et al., 2006; Stam et al., 2009).

Despite the different measuring approaches to FC and cognitive function of the cited studies (see Table 2), cognitive impairment is correlated with the modification of functional connectivity (e.g., Stam et al., 2002, 2006; López-Sanz, Bruña, et al., 2017; 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, Federoff, & Kurlan, 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 along the network failures that occur in pre-dementia and AD stages (Maestú et al., 2014). There seems to be an early loss of synchronization in posterior regions but an increase in anterior regions (López-Sanz, Bruña, et al., 2017), when the cognitive impairment is still not perceptible by neuropsychological assessments, 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 is diagnosed as AD. However, still more research in neurodegenerative diseases other than AD

is necessary to unravel the patterns of network disturbances that occur in dementia. Table 2 lists the most representative studies on MEG-based FC.

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Conclusions

MEG is a powerful tool that enables us to study how such changes could alter neural communication in the brain and give rise to the typical cognitive effects that we commonly find in the old population. This technique provides us with a window to the study of brain activity in vivo and in a completely non-invasive manner, which is unrivaled by other techniques, as MEG is characterized by a notable combination of spatial and temporal resolution. One of the most prominent features of MEG is that it allows us to understand how different brain regions coordinate and synchronously work together. This enables the pursuit of the unraveling of cognitive states and processes. Moreover, the fact that no damage could result from participating in a MEG study makes this the ideal tool to conduct longitudinal studies.

The aging process is characterized by an initial shift from low- to high-frequency bands of the PSD distribution, and a widespread decrement (increment) of low- (high-) frequency relative power with increasing age. During middle age a trend reversal seems to happen: a slowing of MEG activity begins, accompanied by an increment (decrement) of low- (high-) frequency relative power. This pattern is even more pronounced in MCI and AD. Alpha band power (both magnitude and peak position) has been found to be highly representative of the aging quality, catching the attention of many scientists; consequently, many metrics have been applied to untangle such phenomena, especially in the study of MCI and AD. Interestingly, a decrement in the alpha band activity characterizes the power dynamics of old

individuals with SCD compared with their healthy counterparts, indicating that AD-related alterations may start in the SCD stage.

At the network level, there is a great diversity of results with different connectivity metrics, and more confirmatory studies need to be done. However, there is some consensus that FC studies have shown that older adults experience a series of changes that make them more vulnerable to cognitive interferences. At the neurophysiological level, some alterations in the organization of functional networks seem to emerge, allowing us to build a continuum from healthy to pathological aging: neurocognitive aging would be characterized by a decrease in FC in posterior areas and an increase in FC in anterior regions, probably the result of a compensatory mechanism or reflecting a primary sign of the loss of inhibitory synapses. Interestingly, older individuals with lower cognitive reserve exhibit higher FC as well. As for pathological aging, most studies show widespread congruity, and the most widely accepted model involves an early loss of synchronization in posterior regions and an increase in anterior regions at preclinical stages, a pattern that persists but with a more decreased synchrony in posterior networks in MCI, and a final network desynchronization in AD, leading scientists to catalogue AD as a disconnection syndrome.

All these findings point to MEG as a very useful tool to both better understand the neurophysiological dynamics that characterize different diseases, as well as to keep track of the progression of such neuropathological processes. So far, AD has been the most broadly studied pathology in aging employing MEG, and for that reason it has received special attention in this article. Years of research in this field have allowed us to deepen our knowledge about the different stages of the disease, covering a wide range that goes from healthy aging to AD through SCD and different subtypes of MCI. However, more long-term longitudinal studies, potentially commencing in non-clinical phases, are required to accurately

depict the progression of changes in the neurophysiological patterns that characterize the aging brain.

With respect to the biological causes of signal alteration during aging, many hypotheses have been made but the general picture is still not clear. The slowing of the spontaneous background activity can be explained by the reduced cholinergic projections to the cortex (as hypothesized in both MEG and EEG studies) (Neufeld et al., 1994; Osipova et al., 2003; Riekkinen, Buzsaki, Riekkinen, P., Soininen, & Partanen, 1991; Riekkinen, Sirviö, & Riekkinen, 1990; Moretti et al., 2004), caused, in turn, by dendritic, synaptic, and axonal degeneration (Schliebs & Arendt, 2011). Regarding the alpha frequency shift in particular, some studies support the idea that the alpha band is especially sensitive to damage in inhibitory interneurons in the thalamus (Bhattacharya, Coyle, & Maguire, 2011), and the exacerbated trend reported in pathological cases can be related with amyloid β, since its deposition has been shown to contribute to synaptic loss in AD (Reddy & Beal, 2008; Bate & Williams, 2011). The reduction of amplitude and synchronization of gamma oscillations in resting state can be attributed to the modification of the balance between excitatory–inhibitory neuronal activity (Buzsáki & Wang, 2012), in turns due to a disruption of the GABAergic circuits (Li et al., 2016).

Beyond that, in order to describe these results as truly distinctive features of disease in particular and not a simple non-specific biomarker of disease, more work needs to be done to better portray other pathological processes as well as to discriminate between AD and other neurodegenerative diseases. Another field of research that should be further developed is that of FC connectivity in healthy aging, as presently studies that analyze aging in the healthy population are scarce. More work needs to be done comparing brain activity of younger and older adults, both at rest and during the execution of diverse cognitive tasks, in order to fully understand the brain dynamics of healthy aging and define the hallmarks of the healthy older

brain. In line with this, it would be interesting to see how different lifestyle factors could promote a "healthier aging brain," such that its neurophysiological patterns more closely resemble those of younger individuals.

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Appendix 1: Experimental Paradigms

Both normal and pathologic aging are accompanied by cognitive changes (Harada, Natelson Love, & Triebel, 2013). In turns, cognition results from interactions among functionally specialized but widely distributed brain regions (Siegel, Donner, & Engel, 2012). Since MEG allows us to identify specific functional patterns of alteration observed during aging, it offers the possibility to map cognitive decline at a functional level, and the opportunity to unveil the underlying neurobiological mechanisms.

In this direction many works in the literature describe MEG as an ideal tool for evaluating the progressive loss of efficiency of the neuronal networks in normal aging and the dysfunctions at the synaptic level that occur at early stages of pathological aging (Maestú et al., 2014; Mufson et al., 2012; Rossini, Rossi, Babiloni, & Polich, 2007).

These studies can be differentiated into two main classes:

Resting-state studies record brain activity while the subject is "at rest," that is, not performing a directed task or exposed to an external stimulus. This class of recordings

provide us with information on the brain's baseline activity (Raichle et al., 2001). Patterns of brain activation recorded in this condition are not random, showing correlated activity across different brain areas (Deco et al., 2013). Resting-state FC has gained particular importance because it is shaped by the underlying network structure (Deco et al., 2013; Shen, Hutchison, Bezgin, Everling, & McIntosh, 2015), and it reflects structural abnormalities. Resting-state recordings are characterized by the considerable ease of acquiring (and comparing) data without any complicated task design, representing an ideal paradigm for children, the old, and patients. The study of age-related changes in spontaneous brain activity by means of MEG has generated widespread interest since the high temporal resolution offers the possibility of analyzing a wide range of oscillatory brain activity (see Maestú at al., 2014 for a review), and opens up novel possibilities for the study of cross-frequency interaction (i.e., the interaction of oscillations pertaining to different bands; see Wang et al., 2017). Different settings can be adopted by patients for resting-state recordings (e.g., eyes open/closed and body position supine/upright), although the trend is to standardize such specifications in the near future, in order to facilitate comparison and to improve interpretability.

Task-based studies consist of the recording of brain activity while individuals perform a task. Through comparison with the baseline activity, this kind of paradigm can shed light on underlying cognitive processes as well as their disruption with aging. A wide variety of tasks can be performed during a MEG recording, thus enabling the study of different brain processes such as memory, language, or visual perception. Once again, the main advantage of MEG in this class of paradigms resides in the high temporal resolution offered (in the order of typical neural communication processes), which enables many possibilities for recording the real *dynome,* that is, the dynamical network structure associated with cognitive processes (Kopell, Gritton, Whittington, & Kramer, 2014). The rich spatio-temporal information emerging from this technique can shed light on directionality and timing of information flow

among brain regions. However, the limitation of task-based studies is the main assumption that baseline activity is stationary, which may not be the case.

Appendix 2: Description of the Most Frequently Used FC Indices

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Appendix 3: Description of the Most Frequently Used Graph Theory Measures

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Figure 1. (a) Primary ionic current (in red) and related magnetic field (black circles) evoked by an excitatory PSP arising in the apical dendrites of a pyramidal neuron, in accord with the right hand rule. **(**b) Primary current and associated secondary currents (dashed blue arrows) schematized as current paths that connect the two ends of a pyramidal neuron. (c) Scheme of pyramidal neuron disposition in the cortex (*palisade*). The primary currents flow roughly perpendicular to the cortex. As a consequence of the right hand rule of the electromagnetism, MEG is much less sensitive to neural currents with a radial orientation with respect to the scalp.

Figure 2. Characterization of an oscillation.

Figure 3. Decomposition of brain signal captured by a MEG sensor into different frequency bands. Y-axis indicates signal amplitude. X-axis represents time in seconds.

Figure 4. Basic graph theory network metrics. A brain network is illustrated in an unweighted graph composed of nodes, which describe neurons or brain regions (blue circles), and links or edges, which describe functional relationships or structural connections (blue lines). (a) A high degree node is a node that has a relatively high number of edges, and a low degree node is a node that has a relatively low number of edges. (b) Clustering is high when the neighbor nodes directly linked to a certain node are highly connected between them. The neighbors of the high clustering node maintain six out of 15 possible edges, giving a clustering coefficient of 0.4. (c) A module is a subset of highly connected nodes with sparser connections to other nodes. A hub is a high degree node that connects nodes within a module (provincial) or modules within a network (connector).

Table 1. Summary table of main articles with PSD results using MEG. Unless otherwise specified, the listed effects have been investigated studying the relative power.

Effect	**Region**	**Task/Rest; sensor/source space**	**Sample**	**Study**
Healthy subjects				
More balanced absolute theta power	Between anterior and posterior areas	Rest, source space	Older adults (9) vs children (8), young and middle-aged adults (25)	(Puligheddu et al., 2005)
Olders are characterized by a slowing of MEG activity in comparison with previous age stages	Averaged	Rest, sensor space	8 age-stages groups from childhood to old adults (220)	(Gómez et al., 2013)
Delta and theta power has a quadratic trend with				

increasing age: decrease until 50~60 y.o., and increase from 60 y.o. onwards. Opposite behavior has been found for higher frequency bands				
Reduced power in slow wave frequencies: linear decrease with increasing age	Widespread over the entire sensor array	Rest, sensor space	Subjects of all ages (53)	(Vlahou et al., 2014)
For older participants, higher delta and theta power is associated with improved cognitive performance (with Trail Making Test)	Temporal and central sensors		Middle-aged and older (27) vs young adults (26)	
a) During the *early encoding* phase, increased alpha/beta	Right hemispheric homologue of Wernicke's area	Modified, Sternberg		

		working memory task, source space	Older (15) vs young adults (31)	(Proskovec, Heinrichs-Graham, & Wilson, 2016)
b) During the subsequent period, and persisting throughout *memory maintenance* phase, increased alpha/beta	Right hemispheric homologue of Broca's area			
c) During *maintenance* phase, stronger alpha activity, occurred earlier, and involving more cortical tissue	Occipital areas			
During the pre-stimulus (baseline) activity, significantly lower theta and greater beta power	Across all brain areas	Visuospatial memory task, source space	Older (16) vs young adults (16)	(Rondina et al., 2016)
Increase in theta power from pre-	Medial/temporal channels			

stimulus to post-stimulus phase			Older adults	
Decrease in alpha power from pre-stimulus to post-stimulus phase	Occipito-temporal regions			
SCD				
Power decrease in alpha band activity	Across broad regions (prefrontal, temporal, occipital)	Rest, source space	SCD (41), MCI (51) vs HC (39)	(López-Sanz et al., 2016)
MCI				
Decrease in average alpha peak frequency. Positive correlation between alpha peak frequencies in several posterior regions and	Posterior regions	Rest, source space	MCI (27) vs HC (24)	(Garcés et al., 2013)

hippocampal volumes				
Increased power in the theta and delta bands; decreased power in the alpha and beta bands	Across all sensors	Rest, sensor space	MCI (69) vs HC (36)	(López, Bruña et al., 2014)
Increased power in the theta and delta bands; decreased power in the alpha and beta bands. Correlation between such effects and poorer neuropsychological performance	Across all sensors	Rest, sensor space	Amnestic Multidomain MCI (36) vs Amnestic Single Domain MCI (33)	
AD				
Increased dipole density in delta and theta bands	Temporoparietal regions of both hemispheres	Rest, source space	AD (15) vs HC (19)	(Fernández et al., 2002)

Right temporoparietal slow-band activity covariated with cognitive performance. Left temporal delta activity covariated with functional status				
Reduced alpha rhythm reactivity in cortical absolute spectral power (changes between open eyes and closed eyes). This effect was larger for moderate AD than for severe AD and Lewy Bodies Dementia (LBD)	Across all sensors	Rest, sensor space	Probable AD (15) and LBD (7) vs HC (9)	(Franciotti et al., 2006)

Positive reactivity (changes between task and open eyes) in the slow-band (3–7 Hz) power spectra	Sensors near inferior lateral areas in moderate AD. Anterior sensors near inferior lateral areas in severe AD	Rest and a simple mental task, sensor space	Probable AD: Moderate (8), Severe AD (7) vs HC (9)	
Lower mean frequency in MCI patients than HC. Lower mean frequency in AD than MCI patients	Across all sensors	Rest, sensor space	AD (22), MCI (22) vs HC (14)	(Fernández et al., 2006)
Spontaneous activity MEG slowing observed employing mean frequency, individual alpha frequency and transition frequency. Irregularity reduction of electromagnetic brain activity	Across all sensors	Rest, sensor space	AD (20) vs HC (21)	(Poza et al., 2007)

employing spectral entropy				
Generalized slowing of brain signaling: Reduction in the centroid frequency of power spectra; Increased power in the theta band; Decreased power in the beta band	Widespread but mainly posterior and lateral cortical sensors	Rest, sensor space	AD (117) vs HC (123)	(Verdoorn et al., 2011)

Table 2. Summary table of main articles with FC results using MEG.

Effect	**Region**	**Task/Rest; sensor/source space**	**Sample**	**Papers**
Healthy subjects				
Reduced information input (PDC) in different frequency bands. If Stronger → better cognitive performance	Posterior cingulum/precuneus	Rest, source space	Healthy subjects from 18 to 89 years old (53)	(Schlee et al., 2012)

Enhanced information inflow (PDC) in different frequency bands. If stronger → weaker cognitive performance	Medial temporal lobe			
Subjects with lower CR presented higher FC than those with higher CR (PLV, PLI) in different frequency bands	Sensors	Modified version of the Sternberg's letter probe task, sensor space	Healthy old with low (12) vs high CR (9)	(López, Aurtenetxe et al., 2014)
Older adults require higher synchronization between cortical brain sites in order to achieve a successful recognition (PLV)	Sensors network	Interference-based working memory task, sensor space	Old (11) vs young adults (9)	(Ariza et al., 2015)
The main differences between age groups arise	Sensors network			

during the interference window (PLV)				
Older adults show reduced ability to reorganize network topology when interference is introduced (PLV)	Sensors network			
Young adults: decreased coupling between the sensorimotor network and the cortico-striato-cerebellar network is associated with better motor learning (seed-based beta-band power envelope correlation, with the seed located in the right primary sensorimotor cortex)	Sensorimotor network and the cortico-striato-cerebellar network	Resting state before and after a motor sequence learning, source space	Old (14) vs young adults (14)	(Mary et al., 2017)

Old adults: decreased coupling between the sensorimotor, the dorsal-attentional and the *default mode networks* (DMNs) is associated with better motor learning (seed-based beta-band power envelope correlation, with the seed located in the right primary sensorimotor cortex)	Sensorimotor, the dorsal-attentional and the DMNs			
Age-related correlational differences were found in the dorsolateral prefrontal cortex, known to subtend attentional and controlled processes	Dorsolateral prefrontal cortex, known to subtend attentional and controlled processes			
With age, motor skill learning becomes more dependent on subtle	Resting-state networks, motor networks			

interactions between resting-state networks subtending motor activity and controlled and attentional processes	and controlled and attentional networks			
Decreased FC in delta	Within precuneus	Rest, source space	Healthy old with amyloid-β, PiB-positive (13) and PiB-negative (32)	(Nakamura et al., 2017)
Increased FC in low frequency bands	Between precuneus and the bilateral inferior parietal lobules			
Significant correlations between DMN FC links (Delta & Theta bands) and amyloid-β	Links between DMN areas			
SCD				
SCD subjects showed a hypo-synchronization (SL) compared with HC in alpha and beta bands	Anterior and posterior sensors	Rest, sensor space	MCI (19), SCD (12) vs HC (25)	

MCI showed higher synchronization (SL) in all frequency bands	Anterior and central regions, interhemispheric temporo-frontal sensors			(Bajo, Castellanos, Cuesta, et al., 2012)
MCI showed lower SL in all bands	In centro-posterior channels			
SCD hyper-synchronization (PLV)	Anterior LH network: inferior temporal gyrus, paracingulate and anterior cingulate	Rest, source space	SCD (41) vs HC old (39)	(López-Sanz, Bruña, et al., 2017)
SCD decrease in FC (PLV)	Posterior network: intra- and inter-hemispheric temporal medial structures (hippocampi),			

	parietal, and occipital areas			
MCI showed a hyper-synchronization (PLV)	Anterior network		MCI (51) vs HC (39)	
Decrease in FC in MCI and SCD, but more pronounced in the MCI group (PLV)	Posterior network			
MCI showed decreased smallworldness and clustering in theta and beta bands	All network	Rest, source space	MCI (69), SCD (55) vs HC (63)	(López-Sanz, Garcés, et al., 2017)
MCI showed increased M in theta and beta bands				
SCD, like MCI, showed a decrease in smallworldness and clustering (although less pronounced)				

MCI showed decreased nodal degree in theta and beta bands	Posterior regions			
MCI showed decreased nodal degree in theta and beta bands	Anterior regions			
MCI				
Higher interhemispheric synchronization (SL) in all frequency bands	Left and right anterior temporofrontal sensors	Memory task, sensor space	MCI (22) vs HC (19)	(Bajo et al., 2010)
Higher interhemispheric synchronization (SL) in the gamma band	Posterior sensors			
Clusters of lower synchronization (SL) in all frequency bands	Among left temporal and central sensors			
Lower synchronization (SL) in gamma band	Between central-posterior and frontal-posterior sensors and in posterior regions			

Higher synchronization (SL) values in alpha and beta frequency bands	Parieto-occipital sensors	Memory task, sensor space	MCI (19), from which 5 converted to AD	(Bajo, Castellanos, López, et al., 2012)
FC (amplitude correlation method) of the DMN was functionally disrupted in the alpha band	DMN	Rest, source space	MCI (26) vs HC (31)	(Garcés et al., 2014)
Higher synchronization (PLV) in pMCI patients exhibit in the alpha band, inversely correlated with cognitive function, left entorhinal volume and both hippocampal volumes	Between the right anterior cingulate and temporo-occipital regions	Rest, source space	Progressive MCI (19) vs Stable MCI (30)	(Lopez, Bruña et al., 2014)
AD				
Decrease of coherence in all frequency bands	Global sensors	Rest, sensor space	AD (5) vs HC (5)	(Berendse, Verbunt, Scheltens, van Dijk,

				& Jonkman, 2000)
Lower synchronization in alpha, beta, and gamma bands (SL)	Occipital and temporal sensors	Rest, sensor space	AD (20) vs HC (20)	(Stam et al., 2002)
Loss of FC in alpha and beta band (SL)	Left fronto-temporal and fronto-parietal connections	Rest, sensor space	AD (18) vs HC (18)	(Stam et al., 2006)
Increased FC in theta band (SL)	Centro-parietal sensors			
Increased FC in beta and gamma band (coherence)	Occipito parietal sensors			
Positive correlations between alpha and beta band synchronizations and cognitive function (SL)	Interhemispheric average			
FC decreased in the lower alpha band (coherence) in AD	In left (moderate AD) and bilateral	Rest, sensor space	AD (15) and LBD (7) vs HC (9)	(Franciotti et al., 2006)

	(severe AD) temporo-occipital connections and fronto-occipital connections			
FC decreased in the lower alpha band (coherence) in LBD patients	In right temporo-occipital connections and fronto-occipital connections			
Decreased connectivity in alpha band (PLI)	Left fronto-temporal, fronto-parietal, temporo-occipital and parieto-occipital sensors	Rest, sensor space	AD (18) vs HC (18)	(Stam et al., 2009)

Decreased connectivity in beta band (PLI)	Inter-hemispheric frontal, right fronto-parietal sensors			
Mean FC in alpha and beta band correlated with MMSE scores in all subjects (PLI)	All sensors			
Increase of strength in FC (synchronous neural interactions)	Global, particularly posterior and lateral sensors	Rest, sensor space	AD (117) vs HC (123)	(Verdoorn et al., 2011)
Global loss of network connectivity and disrupted synchronizability in most frequency bands.	Global sensors	Rest, sensor space	AD (18) vs HC (18)	(de Haan, Van der Flier, Wang et al., 2012)
Modularity and number of modules were weakened in most bands and positively related to cognitive impairment	Parietal and temporal sensors	Rest, sensor space	AD (18) vs HC (18)	(de Haan, Van der Flier, Koene et al., 2012)

Node-to-global connectivity decrease in alpha and beta bands	Parieto-temporal regions, source space	Rest, source space	AD (21), old HC (23), young HC (16)	(Koelewijn et al., 2017)
Decreased posterior-to-anterior information flow in the beta band (Phase Transfer Entropy)	From the precuneus and visual cortex towards frontal and subcortical regions	Rest, source space	AD (27), HC (26)	(Engels, Yu, et al., 2017)
Nodal centrality metrics (based on PLI, using a multiplex brain network, integrating frequency-specific networks) consistently showed several vulnerable hubs whose vulnerability correlated positively with perturbed cognitive function and abnormal CSF amyloid-β_{42} levels	Left Hippocampus, posterior parts of the DMN and occipital regions	Rest, source space	AD (27), HC (26)	(Yu et al., 2017)
PD				

FC showed a diffuse increase in the lower alpha band (SL)	Across all sensors	Rest, sensor space	Non-demented PD (70), HC old (21)	(Stoffers et al., 2008)
Positive correlation between disease duration and severity and FC in alpha/beta and theta/beta bands, respectively (SL)	Local, intra- and inter-hemispheric sensors			
In the subgroup of patients who showed the largest improvement, beta band synchronization showed a decrease with levodopa treatment (SL)	Central sensory and motor sensors			
Loss of FC in alpha band (SL)	Intra-hemispherical fronto-temporal sensor connections	Rest, sensor space	Demented (13) vs non-demented PD (13)	(Bosboom, Stoffers, Wolters, Stam, & Berendse, 2008)
Lower FC in delta, theta, and alpha bands (SL)	Intertemporal sensor connections			

Decreased gamma band FC (SL)	Centro-parietal sensors			

Table A1. Summary table of the most frequently used FC indexes. The last four indexes take into account the directionality of the interaction, and in some texts are called *effective connectivity*. For a more detailed description of the metrics, see Pereda, Quiroga, and Bhattacharya (2005) or Niso et al. (2013) (which also offers a freely available Matlab-based toolbox to compute all of them for EEG and MEG data).

FC Index	**Definition**
Pearson's correlation coefficient (COR)	The Pearson's correlation coefficient reflects the degree of (linear) relationship between two signals
Coherence (COH)	The magnitude squared coherence (or simply, the coherence) measures the linear correlation between two signals as a function of the frequency
Phase locking value (PLV)	The phase locking value essentially quantifies how the phase difference between two signals is preserved during the time course (Lachaux et al., 1999)
Phase lag index (PLI)	The phase lag index is similar to PLV, but discards specific phase differences (0 and π), in order to be robust against the presence of common sources (Stam et al., 2007)

Mutual information (MI)	Mutual information quantifies the amount of information that can be obtained about a random variable by observing another
Classical linear granger causality (GC)	For two simultaneously measured signals, if one can predict the first signal better by incorporating the past information from the second signal than by using only information from the first one, then the second signal can be called causal to the first one (Wiener, 1956; Granger, 1969)
Partial directed coherence (PDC)	Partial directed coherence captures the direction of information flow as a function of the frequency (Baccala & Sameshima, 2001)
Synchronization likelihood (SL)	Synchronization likelihood is a general measure of linear and non-linear temporal correlations between time series (Stam & van Dijk, 2002)
Phase transfer entropy (PTE)	Phase transfer entropy estimates the strength and direction of connectivity in a given frequency band (Lobier et al., 2014)

Table A2. Summary table of graph theory indexes. For detailed descriptions, see Rubinov and Sporns (2010), and for a brief summary, see the Supplementary Material in Niso et al. (2015).

Graph theory measures indexes defined for a node	
Index	**Definition**

Degree (D)	The degree (D) of a node is the number of links connected to it
Strength (S)	The strength (S) of a node is the sum of weights of links connected to the node
Graph theory indexes defined for the whole network	
Index	**Definition**
Density (K)	Fraction of present connections to possible connections
Clustering coefficient (C)	Likelihood that neighbors of a node are also connected
Characteristic path length (L)	The characteristic path length (L) is defined as the average shortest path length in the network (Watts & Strogatz, 1998) A “path” consists of a sequence of linked nodes that never visit a single node more than once
Global efficiency (Eg)	The global efficiency (Eg) is related to the L, as it is defined as the average inverse shortest path length in the network, hence they will be inversely correlated
Modularity (M)	Degree to which a network can be subdivided into clearly delineated subgroups or modules