When the time is right: Temporal dynamics of brain activity in healthy aging and dementia

Courtney, S.M.^{1,2,3}, & Hinault, T.^{1,4}

¹Department of Psychological and Brain Sciences, Johns Hopkins University, Baltimore, MD, 21218, USA

²F.M. Kirby Research Center, Kennedy Krieger Institute, MD 21205, USA

³Department of Neuroscience, Johns Hopkins University, MD 21205, USA

⁴U1077 INSERM-EPHE-UNICAEN, Caen, FRANCE

Corresponding author:

Thomas Hinault

INSERM-EPHE-UNICAEN U1077, Neuropsychology and Imaging of Human Memory

2, rue des Rochambelles, 14032 Caen, FRANCE.

Email: thomas.hinault@inserm.fr

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1. Introduction

A central question in cognitive aging research is how the evolution of cognitive functions with age is underpinned by changes of both brain structural characteristics and functional activity patterns. Neuroimaging studies revealed major findings associated with the effects of healthy aging on cognition, the impact of neurodegenerative disease, and variations between individuals. With aging, the brain undergoes several structural and functional changes (see Spreng & Turner, 2019, for a review). Brain structure consistently shows signs of grey matter atrophy and decreases in the microstructural integrity of white matter tracts connecting brain regions. Cortical activity, however, has been observed to either increase or decrease with age, depending on several task and population factors, suggesting either compensation, pathological under- or over-activation, or all of these (see Cabeza et al 2018; Stern et al., 2018, for recent reviews).

Many of these neural changes have been associated with age-related changes in cognitive performance (e.g., Diamond, 2013; Zanto & Gazzaley, 2017; Park & Reuter-Lorenz, 2009). With aging, decreased performance in tasks requiring episodic memory (i.e., memory of events and past personal experience; e.g., Cansino, 2009) or cognitive control (i.e., processes needed to maintain internal goals in changing environments and to suppress irrelevant information; e.g., Courtney, 2004; Manard et al., 2014) are mainly observed (see Box 1, for an overview of the main frameworks of cognitive and brain aging). A prominent part of research on cognitive aging highlighted the specific alteration of inhibition abilities with age and pathology (Diamond, 2013; Hasher & Zacks, 1988; Rey-Mermet & Gade, 2017). Indeed, relative to tasks involving semantic processing, but also compared to attention or working memory processes, healthy older adults show significantly reduced abilities to suppress the interference of irrelevant information and to control the tendency to produce automatic responses (e.g., Diamond, 2013; Sweeney et al., 2001). Importantly, the ability to suppress and recover from distraction is central in cognitive performance (e.g., Feldmann-Wüstefeld & Vogel, 2019; Hakim et al., 2020) and is critically altered with aging (e.g., Clapp & Gazzaley, 2012). Cognitive changes are even more pronounced in pathological aging (e.g., Sjöbeck et al., 2010), with Alzheimer's disease (AD) being the most frequent dementia type (e.g., Baudic et al., 2006). Mild cognitive impairment (MCI) involves cognitive changes beyond what is typical for one's age, without interference with activities of daily

living (Petersen et al., 1999). It is often the prodromal stage of AD, but there are multiple types of MCI and not all cases will progress to AD (e.g., Campbell et al., 2012). Understanding this variability in individual trajectories of brain and cognition changes with age is crucial to preventing and ameliorating age-related cognitive impairment.

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Box 1. Frameworks of cognitive and brain changes with age

Several frameworks have been proposed to explain cognitive and brain changes occurring with age and with age-related pathology (see Anderson & Craik, 2017; Maestú et al., 2014 for reviews). Changes in the frontal lobe figure prominently in several of these frameworks, such as the inhibition-deficit account of both brain aging and age-related pathology (Hasher & Zacks, 1988). Compensatory adjustments in activation have also been reported in frontal regions in the absence of clear pathology or grey matter atrophy (PASA: posterior anterior shift in aging; Davis et al., 2008) and in contralateral homologues (HAROLD: hemispheric asymmetry reduction in older adults; Cabeza et al., 2002). These changes in activation have been associated with the relative preservation of cognitive performance. Conversely, maladaptive activations have been associated with cognitive decline and pathological aging, such as increased functional connectivity between cortical and subcortical regions (e.g., Joo et al., 2016). Age-related changes in cognitive strategy use have also been observed (Hinault & Lemaire, 2020). The ELSA model (Early to Late Shift in Aging; Dew et al., 2011) was proposed to describe the age-related shift from a proactive (i.e., mediated by the instructional cue) to a reactive (i.e., mediated by the test probe) cognitive control strategy. These changes in strategy may indicate deliberate compensatory efforts or an inability to deploy proactive cognitive resources.

The concepts of reserve, maintenance, and disconnection have been applied both in the context of healthy aging and in the context of age-related pathology. The disconnection framework was originally introduced by Geschwind (1965) to account for pathologies involving a cognitive dysfunction related to an event (e.g., a stroke) that might “disconnect” brain regions. This framework has been widely used to account for neuroimaging findings in both healthy and pathological aging (Delbeuck et al., 2003; Bennett & Madden, 2014; Madden et al., 2017). Without a clear injury or event such as a stroke, however, a “disconnection” is

generally not a simple and complete bisection, and there is considerable inter-individual variability in cognitive performance in older adults that cannot be explained entirely by the white-matter structural or fMRI connectivity differences that have been observed so far (e.g., Hedden & Gabrieli, 2004; Hultsch et al., 2008). The concept of cognitive reserve (Stern, 2009) was proposed to provide an explanation for differential susceptibilities to brain aging and pathology between individuals. Cognitive reserve refers to the moderating effect of intellectual, social and physical activities on cognitive performance changes related to age and/or pathology (e.g. Stern et al., 2018). The concept of maintenance is strongly associated with cognitive reserve but refers to mechanisms preventing the development of brain lesions or other pathological processes before their occurrence, thus limiting alterations of brain structure and function (Cabeza et al., 2018; Stern et al., 2018). Research into the biological bases of maintenance, reserve, and disconnection is ongoing. How changes in neural system dynamics may be related to age-related functional disconnection is a focus of the current review.

Neuroimaging investigations of healthy aging and dementia have been done with structural imaging (e.g., anatomical MRI, DTI), and with functional methods benefiting from high spatial (e.g., PET, fMRI) or temporal (i.e., EEG, MEG) resolution. Functional measurements can be done at rest or during the performance of tasks targeting specific cognitive processes. These methods provide complementary findings and helped to further our understanding of changes typically occurring with age, together with the progression of neurodegenerative disease (see Damoiseaux, 2017, for a review). Despite the large number of neuroimaging studies completed, however, age-related changes in temporal dynamics of brain activity and brain networks have been relatively understudied. Temporal dynamics may be essential to understanding age-related cognitive changes, as older adults are particularly impaired in speeded cognitive control tasks (e.g. Li & Zhao, 2015, Staffaroni et al, 2018, Hinault et al., 2019a) and age-related changes in “processing speed” have been proposed to be key to reduced performance on many different cognitive tasks (Salthouse, 1996).

fMRI has been the most widely used neuroimaging method to study age-related changes in neural activity. Despite its limited temporal resolution, fMRI has been used in a few studies examining the age-

related changes in activity patterns over time (e.g., Cabral et al., 2017a; Fu et al., 2019). However, increased magnitude of BOLD activation is not sensitive to neural synchrony and cannot distinguish between alternative interpretations at the cellular level, such as increased firing rates, increased time on task, or increased coupling of oscillatory activity between distinct cell populations. In addition, both cognitive and motor processes slow with aging, so factoring out differences of reaction time (e.g., Gold et al., 2010) cannot entirely account for the potential confound of time on task, nor determine why specific cognitive processes are more delayed than others. M/EEG methods, however, can directly measure neural activity at the millisecond level, and thus they are uniquely able to specify brain networks' temporal dynamics and short-scale variability, both at rest and during task performance at a temporal resolution that is relevant for the types of changes in cognition observed in aging (e.g., Salthouse, 2010). Both methods possess excellent temporal resolution, but MEG activity provides a more accurate estimation of the neuroanatomical location of the source of brain activity (see Baillet et al., 2017, for a review).

The importance of temporally specific activity and synchrony between brain regions was revealed by cellular recording in animals (e.g. Fries, 2015; Miller et al., 2018). Synaptic changes between sparse bursts of spiking during working memory maintenance were found to underlie working memory performance. Moreover, synchrony acts to dynamically shape the task-relevant network out of larger overlapping circuits, and ensures that a presynaptic activation pattern arrives at postsynaptic neurons in a temporally coordinated manner (Buschman et al., 2012). Inhibition is temporally focused, which allows excitation in between periods of inhibition, leading to synchronized excitatory output to optimally drive postsynaptic neurons (e.g. Fries, 2015). Measuring this type of temporal precision in human neural activity, however, is generally not possible. In humans, M/EEG studies have mainly contrasted amplitudes of event-related responses or oscillatory power between groups over averaged time periods (see Box 2 for M/EEG methods for characterizing brain dynamics). These methods have the potential to investigate changes of temporal dynamics, although few studies have been conducted to investigate the potential presence of delays in brain activations, differences in the time course of the organization of functional networks, or impaired maintenance of neural synchrony over time (e.g., Ariza et al., 2015; Deiber et al., 2013; Proskovec et al., 2016).

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Box 2. Methods for characterizing brain dynamics

To investigate normal and pathological aging effects on the temporal dynamics of neural activity in humans, several techniques have been considered. Age-related changes in brain dynamics have been observed using fMRI time courses during both task performance (e.g. Clapp et al., 2011) and rest (e.g. Cabral et al., 2017; see also Hansen et al., 2015). Intrinsic functional connectivity measured with fMRI is highly similar to that measured at a much finer temporal scale using methods such as M/EEG (review in Sadaghiani & Wirsich, 2019). The higher temporal resolution of these methods, however, provides the opportunity to measure much more subtle changes in the dynamics of neural activity, which may be important, for example, for identifying early signs of vulnerability to age-related cognitive decline, or for understanding the neural mechanisms underlying age-related changes in fMRI activation as discussed in Box 1. Brain activity at a given sensor or source has been assessed through event-related responses and oscillatory activity. Event-related responses (event-related potentials for EEG, event-related fields for MEG) refer to electrophysiological activity time-locked to a stimulus onset or a behavioral response (Luck, 2014). Event-related responses are labeled as a function of their polarity and their canonical time of occurrence (e.g., P300 for a positive deflection occurring about 300ms following stimulus presentation), and have been associated with specific cognitive processes. Time-frequency decomposition generally considers oscillatory activity in the canonical delta (1-4 Hz), theta (4-8 Hz), alpha (8-13Hz), beta (14-30Hz), and gamma bands (30-100+ Hz; e.g., Klimesch, 1999). Temporal differences can be observed in the latency of event-related responses or time-frequency modulations, or in the power spectrum of brain activations. Oscillatory activities are recorded across both time (i.e., variations over time) and frequency (i.e., amplitude and phase variations over frequency) domains. They are therefore complex measures of brain dynamics (e.g., Jensen, 2019). Variations of oscillatory characteristics such as the alpha peak frequency (e.g., Haegens et al., 2014) can lead to changes of the overall organization of communication dynamics with a reduction of fast high frequency activities and increase in slower low frequencies. These measures and their relationship to cognitive performance may also be modulated by task and sex (e.g. Ghazi et al., 2021).

Using M/EEG, brain connectivity has mainly been assessed through phase synchrony analyses and correlations between the time courses of signals from two sensors, or between the localized signals of two brain regions (e.g., Palva & Palva, 2018). Oscillatory coupling refers to the association of the oscillatory activities between two brain regions, while cross-frequency coupling refers to the relationship between oscillatory activities in two different frequency bands. One way to quantify oscillatory coupling is through coherence, which refers to the cross-correlation of activity of two brain regions in a given frequency band. Another common method is phase synchrony analysis, in which the phase represents the position on the waveform (e.g. peak or trough of the oscillation) at a given time. If the mean phase difference of two signals is consistent across time, the signals are described as synchronized or “locked”. Phase locking value (PLV) between brain regions has been associated with neural communications (e.g., Fries, 2015). The most common form of cross-frequency coupling is phase-amplitude coupling (PAC), in which the power of the higher frequency is modulated according to the phase of the lower frequency (e.g., Tort et al., 2010). One limitation of phase- and coherence-based analyses of connectivity is that they are undirected, which means it is not possible to determine whether information is travelling in one direction versus the other. Effective connectivity measures (e.g., dynamic causal modeling, transfer entropy, Granger causality) have been proposed to investigate directed brain connectivity (e.g., Sakkalis, 2011; Vicente et al., 2011). Multiscale entropy also provides important information about the variability of brain couplings (Costa et al., 2002) at both local and global levels.

Dynamic neural activity can be investigated, not just in individual brain areas or couplings, but also across entire networks. In order to evaluate brain networks’ characteristics over time, Hidden Markov Models represent brain activity as a succession of discrete states (i.e., characterized by matrices of specific couplings between brain regions), with each state in the finite set of states being dominant at certain time points and not at others (e.g., Tal et al., 2020). Graph theory analyses have also been conducted to examine changes with aging (e.g., Van Straaten & Stam, 2013; Hinault et al., 2021). Brain networks are described as an architecture composed of nodes (i.e., brain regions) and edges between each pair of nodes (i.e., functional or effective connectivity). Graph analyses can provide useful information about the segregation (i.e., functional

specialization between distinct subnetworks) and integration (i.e., interconnectedness between subnetworks) of functional networks (e.g., Wig, 2017).

Investigating specific temporal differences in both local activity and connectivity between brain regions with age could reveal highly sensitive elements associated with healthy and pathological aging effects on brain activations, with a potential for clinical applications and new theoretical considerations. Disruptions of dynamic network communication could lead to the neurocognitive changes observed during aging, as well as in neurological disorders (Voytek & Knight, 2015). Here, we review EEG and MEG studies that included the temporal dimension in their investigation of healthy and pathological aging effects on brain activity and brain networks. The temporal dimension is understood to include many possible aspects of neural activity. Here we focus on two main areas: 1) differences in the time of onset of task-related modulations, 2) conversely, maintenance of sustained communications, which requires resistance to induced changes or spontaneous variability over time. While some of these characteristics could be, and have been, identified with fMRI, M/EEG methods can provide unique and possibly critical elements. For example, M/EEG can detect sub-second age-related changes in the time of onset of task-related modulations, which may have significant functional consequences years before such changes become substantial enough to be detectable with fMRI. A different perspective on the importance of the temporal dimension comes from the example of sustained communication, during which M/EEG can measure the consistency and coordination of the temporal phases of oscillatory activity over time between brain regions or the interactions between frequency bands. Changes in such coordination within or between frequency bands can have substantial impact on the effectiveness of neural communication but might not show any difference in fMRI connectivity measures. Thus, in addition to measures that are explicitly time-related, such as the latency of an event-related component, in this review we argue that there are other aspects of neural activity that also depend on temporal precision in neural signaling and are highly appropriate for the investigation of healthy and pathological aging effects on brain activity (Figure 1).

We present evidence that intraregional activity and interregional communication could rely upon temporally specific, stable and synchronous activity over time, together with fast and robust changes of activity to adjust to dynamic situations. With aging, the preservation of dynamic network communications similar to young adults, or compensatory implementation of earlier task-related modulations and increased synchrony, could be a major determinant of the preservation of cognitive performance. Conversely, delayed (Figure 1) or noisy and variable communications could impair the effectiveness of the whole network and be associated with the cognitive decline observed with age and pathology. Considering the temporal dimension of brain activity can, therefore, reveal critical changes associated with both healthy aging and neurodegenerative disorders, and could further our understanding of i) processes underlying normal and pathological aging and their variability between individuals, ii) the association between M/EEG temporal dynamics and other modalities of brain imaging, and iii) theoretical concepts of brain aging and dementia, such as the disconnection syndrome or cognitive reserve. We hypothesize that future studies that involve more direct investigations of these temporal dimensions of neural activity will find them to be powerful indicators elucidating the causes of individual differences in cognition during healthy aging and during the early stages of pathological aging.

Figure 1: Illustration of age-related changes in the dynamics of fronto-parietal phase synchrony. A) the left arrow indicates a transient task-related effect that disrupts the ongoing phase synchrony between two brain regions. The right arrow indicates the length of time to restore the original phase synchrony when this task period ends. In older adults, the length of time needed to change connectivity has increased and the time to establish or re-establish phase synchrony is delayed. B) During conditions such as sustained attention or working memory maintenance, synchrony between two regions can be sustained over time in both groups. Relative to young adults, where phase synchrony is maintained over the whole period, even a small difference

in the frequencies of local activity in the two regions in older adults can lead to an earlier decay of such synchrony.

Brain activations and communications are complex phenomena unfolding over time, and specific temporal dynamics can provide highly sensitive elements associated with cognitive performance, variability between individuals and the progression of neurodegenerative disease. The term “time” refers here to “rapid dynamics of electrophysiological signals that are often but not necessarily oscillatory” (Cohen, 2011). In this review, we chose to selectively describe and discuss previous M/EEG work that explicitly considered brain dynamics (and its converse, stability) through interactions involving time windows, temporal variability or sustained connectivity patterns across time. We first describe locally coherent changes in the temporal dynamics of brain activity with normal and pathological aging (part 2). Healthy aging is typically investigated in individuals above 60 or 65 years of age with no current indication of cognitive problems, while patients ranging from subjective complaints to diagnoses of probable dementia are included to investigate pathological aging. Changes of temporal dynamics of whole-brain network activity are then discussed (part 3). We also discuss how the integration of M/EEG with other biological or neuroimaging methods can provide a better understanding of changes occurring during normal and pathological aging (part 4). Finally, the theoretical contribution of these findings is discussed with regards to existing frameworks of normal and pathological aging (part 5). We also provide concluding remarks and recommendations for future studies (part 6).

2. Locally coherent changes of temporal dynamics with aging

2.1. Brain activity slows with aging

2.1.1. Healthy aging

The most frequently reported finding in studies that investigated age-related changes of brain activity is a global slowing of brain activations (see Celesia, 1986). This global slowing was interpreted as reflecting changes in neurotransmission and conduction velocity (e.g., Dustman et al., 1993). Kropotov et al. (2016) reported that the peak latency (i.e., time when the peak voltage of the component is observed) of both early and late components (e.g., N2, P3, contingent negative variation) increased with age (subjects aged between 18 and 84 years; see also Friedman, 2003). The amplitudes of each component did not show a consistent

decrease with age, suggesting a specific alteration of the timing of brain activity rather than reduced activations. This general slowing of components' latency is in line with the slowing of reaction time and task completion during aging (e.g., Salthouse et al., 1996; Anderson & Craik, 2017) and suggests a neural mechanism underlying this finding.

A global slowing of neural activity has also been indicated by observations of oscillatory activity using M/EEG, and a relative preservation of the frequency distribution of oscillatory brain activity appears to be associated with the preservation of cognitive performance relative to a general slowing of brain activity (see Murty et al., 2020, for a review). There is a shift in the frequency spectrum (see Box 3 for an overview of the different frequency bands and their putative cognitive roles) during healthy aging, with relatively increased power in the lower frequency bands (i.e., delta, theta) and decreased higher-frequency power (i.e., alpha, beta, gamma; Celesia, 1986; Vlahou et al., 2014). One element consistently observed across studies and associated with this shift in the power frequency distribution, is the slowing of the alpha peak frequency with age (Finnigan & Robertson, 2011; Scally et al., 2018). The alpha peak frequency is the frequency within the alpha band showing the highest power. While it is generally observed at 10Hz in a younger population (e.g., Uhlhaas & Singer, 2006), the alpha peak frequency typically shows a slowing with aging (8-9Hz) or even a transition from alpha to the canonical theta band range (Finnigan & Robertson, 2011; Figure 2). Modulations of alpha peak-frequency in response to task demands seem to be more different across brain regions in young adults than in older adults, suggesting reduced top-down control of sensory processing with aging (e.g., ElShafei et al., 2020). Interestingly, slower dynamics of oscillatory activity have been correlated with cognitive changes in healthy older adults (e.g., Rossiter et al., 2014; Gola et al., 2012). However, slower dynamics are not the only age-related change of oscillatory activity. Lower signal-to-noise ratio was also observed in older adults, with larger noise at higher relative to lower frequencies (e.g., Voytek et al., 2015). This difference was found to mediate age-related decline and could also explain changes in couplings between brain regions with aging (see 3.1).

Figure 2. Slowing in alpha peak frequency in older adults relative to young adults. EEG power spectral density from the occipital electrode Oz. Adapted from Scally et al., 2018.

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Box 3. Rhythms of the brain: the putative cognitive roles of the different frequency bands

Recordings of electrical and magnetic cortical activity revealed that the power spectrum of oscillatory activity shows peaks within specific frequency bands (e.g., Mazaheri et al., 2018). Although there are no one-to-one mappings between oscillatory activity in a given frequency band and a cognitive process, different frequencies have nevertheless been associated with distinct processes and cognitive activities (e.g., Hinault & Lemaire, 2016; Jensen et al., 2019). Oscillatory brain activity thus constitutes a major part of the physiological basis of cognition (e.g., Buzsàki, 2006, 2019). In human recordings using M/EEG methods, oscillatory activity has mainly been investigated between 1Hz and 100Hz. The slowest frequency band is the delta band (1-4Hz), the phase of which has been associated with network excitability and activation. This overall modulatory role could then be involved in facilitating or impeding information processing (e.g., Lakatos et al., 2005, 2008). The theta frequency band (4-8Hz) is a prominent oscillatory activity, whose putative role depends in part on the neuroanatomical source of the activity (e.g, Töllner et al., 2017). Theta arising from medial frontal regions has mainly been associated with working memory maintenance and updating (e.g., Scheeringa et al., 2009), together with error processing, which could reflect the updating and

reconfiguration of mental task sets (e.g., Cohen & van Gaal, 2013). Theta activity arising from sources in the medial temporal lobe has been associated with episodic memory (Herweg et al., 2019).

The alpha band (8-13Hz) has been intensively studied and was the first described oscillatory activity (Berger, 1938), although its functional significance is still a matter of debate (e.g., Jensen & Mazaheri, 2010; Klimesch, 2012; Palva & Palva, 2007; Sadaghiani & Kleinschmidt, 2016; Van Diepen, 2019). It has been proposed that alpha activity reflects the active inhibition of irrelevant sensory processing (Jensen & Mazaheri, 2010; Klimesch, 2012). In addition to the regulation of the processing of potentially interfering information, alpha activity is also associated with attention allocation and the active maintenance of working memory representations (Palva & Palva, 2007). Beta oscillations (14-30Hz) appear to be strongly associated with motor preparation and sensorimotor processing (e.g., Van Ede et al., 2017). Similarly to the alpha band, beta rhythms were also associated with the top-down control of information processing (e.g., Jensen et al., 2015). Oscillations in the gamma band (30-100+Hz) have been intensively studied and could constitute the main physiological basis of bottom-up information processing and integration of perceptual information (e.g., Jensen et al., 2014).

Important interactions also exist across frequency bands. These interactions could serve in the integration, coordination and regulation of neuronal activity (e.g., Palva & Palva, 2018). Indeed, the power in the gamma band is nested within the phase of both theta and alpha oscillations (e.g., Bonnefond et al., 2017). Both theta and alpha thus play a role in coordinating neural activity in higher frequency bands. The association between gamma power and alpha phase has been associated with a gating of the information flow between regions and the active inhibition of couplings that are not required for the task (e.g., Bonnefond et al., 2017). Conversely, theta-gamma coupling could reflect integration and coordination of working memory processes and attention allocation (e.g., Axmacher et al., 2010; Sauseng et al., 2008).

Thus, both activity within each of the frequency bands and the coordination of activity across frequency bands are important to information processing and cognitive functions. Both the phase and frequency of these oscillations depend on the time constants of the neural circuits and systems from which they arise. Even small changes in these time constants, due to age, injury or disease, could potentially have large effects on cognition.

2.1.2. *Pathological Aging*

The slowing of brain activity could also serve as indicator of tissue integrity and progression of neurodegenerative processes. The global shift in power frequency distribution of brain activity has been reported to be larger in AD patients relative to healthy controls, and was associated with extracellular deposits of amyloid beta and aggregates of hyperphosphorylated tau protein associated with AD progression (Müller & Schwartz, 1978). After a seven-year follow-up, Prichep et al., (2006) evaluated the resting-state EEG of healthy elderly with subjective complaints during the initial study phase. Although the alpha peak was not directly investigated to assess oscillatory slowing, they observed that individuals with cognitive decline and/or conversion to dementia showed increased activity in the canonical theta range and decreased activity in the canonical alpha range in comparison to individuals with stable cognitive performance. This effect is consistent with an alpha peak transition to the theta band. It is possible that some of the changes associated with cognitive decline in presumably healthy older adults might reflect preclinical changes related to neurodegenerative disease. This change in oscillatory activity enabled an overall prediction accuracy of 90% for conversion of MCI to AD. Source reconstruction revealed that the slowing of the parieto-temporal regions was stronger in individuals who converted to AD than for individuals who remained stable or declined only to the MCI stage (Prichep et al., 2007). The general slowing of oscillatory activity, therefore, shows a strong predictive value for subsequent cognitive decline and development of pathological aging, and suggests that some aspects of brain activity dynamics may be a central indicator of brain and cognitive health, not just aging *per se*.

2.2. *Slowing of specific task-related oscillatory activity and event-related responses*

2.2.1. *Healthy aging*

In addition to the global slowing of brain activity with age, specific event-related responses and oscillatory activities were found to be altered relative to other components or in other frequency bands, suggesting the age-related slowing of neural activity might be more pronounced in some brain areas or for some cognitive processes relative to others. In a visuospatial attention task, differences in the latency of P1/N1 components (associated with sensory processing) have been reported in healthy older adults relative to

younger participants while some later components such as P2 were similar between groups (Curran et al., 2001; see also Finnigan et al., 2011; Missonnier et al., 2004). The increased latency of P1/N1 and the slower reaction times were observed without differences in event-related responses' amplitude, suggesting a specific effect on the temporal dynamics of information processing. Conversely, Gao et al. (2009) observed differences in amplitude but not in the latency of the N170 component (associated with object and face processing and prediction errors). Cognitive performance was similar between young and healthy older participants. This suggests that the preservation or the alteration of the time course of early sensory components might be critical to the preservation or the alteration of cognitive performance with aging.

Specific age-related changes have also been observed for the P3 component (i.e., positive deflection observed about 300ms following stimulus onset; P3a is observed over frontal-central electrodes and P3b is higher over parietal electrodes). P3a has been associated with the processing of novelty and attention allocation, while P3b is observed following improbable events and in dual-task paradigms with high workload (Polich, 2007). Consistently across studies (Coben et al., 1983; Celesia et al., 1986; Curran et al., 2001; Deiber et al., 2013), the latencies of the P3 components have been found to be delayed in healthy older adults relative to younger participants. Importantly, the P3 slowing in attention tasks has been reported even when other components such as N1 or P1 remained unchanged (Polich et al., 1997). Such specific delay relative to other components may suggest that the initial processing of stimuli is not impacted, but the fast determination that an event is new and the goal-directed allocation of attention is critically altered during both healthy and pathological aging. Changes of P3a latency appear to follow a lifespan trajectory and to show a curvilinear slowing with age (Figure 3A; Celesia, 1986; Polich et al., 1996; Van Dinteren et al., 2014).

Regarding oscillatory activity, Deiber et al. (2013) reported delayed cue-related alpha and beta modulations in older participants relative to young adults (see also Dustman et al., 1993) and other frequency bands. Age mainly delayed activity rather than reducing its amplitude. Therefore, aging effects on attention orienting and cognition appear to be strongly determined by the ability to engage the relevant processes at the right time. Gola et al. (2012) specifically investigated beta oscillatory activity in a visual attention task (i.e., participants had to determine, after a preparation cue, which of two targets appeared first). They observed that

a subgroup of healthy older participants showed later posterior beta modulations than others, did not maintain beta activity during the inter-stimulus interval, and had lower behavioral performance. Subgroups had similar MMSE score, age and education level, which suggests a specific difference in the efficiency of attentional processes. Unfortunately, other than this work, oscillatory activity is mostly assessed on averaged time periods, and few studies are available regarding age-related delayed latencies of task-related modulations of oscillatory activity in specific frequency bands.

2.2.2. Pathological aging

In contrast with P3b (e.g., O’Connell et al., 2012), the latency of P3a has also been found to be delayed in AD patients relative to healthy controls (Jackson & Snyder, 2008; Pokryszko-Dragan et al., 2003), and has been found to be a useful predictor of conversion to AD after a 24-month follow-up (Gironell et al., 2005). The frontal P3a latency appears to be more influenced by age and pathology, while the posterior component is less influenced (e.g., O’Connell et al., 2012). Although this association was not directly assessed, this phenomenon could be associated with frontal structural changes (Spreng & Turner, 2019), and help predict neurodegenerative progression.

2.3. Earlier latencies in older participants

Although brain activity is mostly found to be delayed and/or slower in older adults, earlier latencies have also been reported in the context of similar behavioral performance between young and healthy older adults. Indeed, Proskovec et al (2016) recorded MEG activity while young and healthy older participants performed a working memory task. They observed that, while both groups showed similar behavioral performance, older adults showed larger and earlier alpha activity over occipital regions than young adults (see also Babiloni et al., 2004). Such earlier alpha modulation was interpreted as reflecting a compensatory mechanism to maintain working memory performance in healthy older participants. Parieto-occipital alpha activity could reflect the top-down inhibition of the dorsal visual stream to protect items retained in working memory from the potential interference of incoming visual information. Likewise, in a study of event-related responses during the resolution of arithmetic interference, Hinault et al. (2016) investigated the time course of brain activity in young and healthy older adults. Both groups showed similar behavioral performance, but

early (N2) and late (conflict slow potential) components associated with adjustment of cognitive control during strategy execution were observed earlier in older adults than in young adults. As the arithmetic strategy was cued on each problem, age-related differences were interpreted as reflecting larger top-down preparatory adjustments in older adults to reach behavioral performance similar to young adults. Staub et al. (2014) also observed a shorter P2 latency and a marginally significant shorter N2 latency in healthy older adults relative to young adults in a Go/Nogo task (Figure 3B). Older adults were faster than young adults and had similar accuracy levels, suggesting the shorter latencies reflected compensatory adjustments of conflict monitoring processes to maintain behavioral performance.

Figure 3. A) Developmental trajectories of the frontal (Fz) and parietal (Pz) P300 latency across the lifespan. The latencies of the P3 components have been found to be delayed in healthy older adults relative to younger participants and have been associated with cognitive decline. Adapted from van Dinteren et al. (2014). B) Event-related responses from the Fz electrode as a function of age (young, old). In this study, the decreased latency of the event-related responses in older adults relative to young adults was associated with sustained behavioral performance and therefore suggests a compensatory mechanism. Adapted from Staub et al., (2014).

As a summary, results revealed an overall slowing of brain activity during both normal and pathological aging that has been associated with structural changes and the progression of neurodegenerative processes. The overall oscillatory structure is not radically modified, but relatively more power at low-frequencies and less at high-frequencies has been observed, and could reflect either power changes or a

frequency shift. Slowed neural activity seems to have a specific effect on processing steps and modulations of oscillatory activity associated with cognitive control and attention orienting, which is consistent with the main cognitive changes observed in during healthy and pathological aging (Salthouse, 2010). This finding is also greater in pathological aging relative to healthy aging. However, in line with the increased inter-individual variability with age (e.g., Hedden & Gabrieli, 2004; Hultsch et al., 2008), important changes have been observed as a function of the investigated population. On one hand, greater slowing is associated with larger cognitive alteration and conversion to dementia. On the other hand, individuals with preserved cognitive performance show no difference in the time course of brain activity relative to young adults, or can even show earlier, possibly compensatory, activations. While these locally coherent activations suggest a functional reorganization of the engaged network, connectivity analyses are necessary to draw conclusions regarding the effects of normal and pathological aging on the interactions among brain regions over time.

3. Temporal dynamics of connectivity in the aging brain

3.1. Disruption of neural synchrony

3.1.1. Healthy aging

Recent work has enabled the investigation of whole-brain dynamics and their evolution over time, both at rest and during task-completion. Communications between brain regions have mainly been assessed through correlation of the time courses of activity, or phase synchrony over time between brain regions. The decline of sustained task-related synchrony in older adults appears to be critically associated with cognitive changes with age. Indeed, Harris et al., (2017) investigated age-related changes of phase synchrony across time associated with auditory temporal processes. In addition to a lower alpha peak frequency in healthy older participants, decreased theta PLV between frontal and central sites was associated with a higher auditory detection threshold (i.e., reduced detection of noise bursts). The potential interaction between PLV and alpha peak frequency was not assessed, but both were significant predictors of cognitive performance in older adults. Therefore, disrupted fronto-central theta synchrony with age may explain, in part, the observed differences between age groups in perception. Relatedly, Toth et al. (2014, Figure 4) showed specific decrease of theta synchrony between frontal and posterior sites in healthy older adults relative to younger individuals during a

working memory task (see also Li & Zhao, 2015). This decreased theta synchrony was only observed during the maintenance phase and was associated with cognitive performance (see also Pons et al., 2010; Vysata et al., 2014, for similar results in the alpha band).

Figure 4. Left frontal midline theta connectivity with parietal regions in young and healthy older adults during a WM maintenance task. Lower synchrony was observed in older adults relative to young adults and was greater on High relative to Low WM load. Adapted from Toth et al., (2014). Decreased synchrony during working memory maintenance may reflect imprecision in the two temporal frequencies or fluctuation in the frequencies over time.

An altered balance between local oscillatory activity and distant phase synchrony was observed during healthy aging (Hinault et al., 2020). When participants had to update relevant information in working memory, gamma synchrony between the inferior frontal gyrus and occipital lobe was negatively correlated with the occipital lobe alpha-gamma PAC. The reduction of this task-related modulation in synchrony in healthy older

adults relative to young adults was associated with lower cognitive performance. This suggests that fast and effective working memory updating requires low local coupling between faster and slower frequencies so that the phase of the faster frequency related to the newly relevant information can synchronize with that of distant brain regions.

3.1.2. Pathological aging

The alteration of temporally coupled activity appears to be a major prognostic marker of neurodegenerative progression, and of general cognitive functioning in older adults. Independent of age, relative to healthy controls, MCI patients showed reduced alpha and gamma resting-state synchrony (Koenig et al., 2005). This alteration of alpha synchrony may denote an inhibition deficit and is in line with the disrupted synchrony observed in AD patients (Vecchio et al., 2016). Pusil et al. (2019) used dynamic phase coupling of resting-state source MEG to distinguish stable MCI and progressive MCI patients after a three-year follow-up. The best classification performance (94%) was achieved with the gamma band in the default-mode (DMN i.e., set of brain regions including medial and lateral parietal, medial prefrontal, and medial and lateral temporal cortices, and activated during wakeful rest and mind-wandering; e.g., Buckner et al., 2008) and cingulo-opercular (i.e., network composed of insula, dorsal anterior cingulate cortex and thalamus and associated with attentional control; Sadaghiani & D'Esposito, 2015) networks. Specific alterations of communication may also help to distinguish dementia types and further our understanding of the underlying neurodegenerative mechanisms. Dauwan et al. (2016) used phase transfer entropy to investigate dynamic communications between brain regions and were able to distinguish AD patients from patients with Lewy body dementia (i.e., dementia associated with abnormal accumulations of alpha-synuclein proteins in the brain). They revealed that the alpha posterior-to-anterior connectivity was altered in patients with Lewy body dementia while this connectivity was disrupted in the beta band for AD patients (see also Poil et al., 2013).

Poza et al. (2017) investigated the influence of alpha slowing on the frontal and posterior alpha-gamma PAC. Relative to controls, AD patients showed alterations of alpha-gamma PAC that were associated with individual alpha peak frequency in resting-state activity. This points to an important mechanistic finding, as

the slowing of oscillatory activity could lead to a disruption of the inhibitory-gating role of alpha on gamma activity (Mathewson et al., 2011).

3.2. Compensatory vs. maladaptive network changes

3.2.1. Healthy aging

In contrast with the decreased synchrony and communications between brain regions usually associated with cognitive decline, increased synchrony has also been reported. Correlations of resting-state data with external cognitive measures, together with task-related data and performance, are critical to determine the compensatory or maladaptive nature of increased synchrony of functional networks and their association with specific cognitive processes. Increased synchrony and communications can sometimes reflect a need to compensate for neural changes and be effectively associated with maintained cognitive performance similar to that of younger individuals. Ariza et al (2015) used MEG to investigate the functional networks engaged in a task involving the active maintenance of relevant information and the control of external interference. They observed that healthy older adults' network activity consisted in increased fronto-occipital alpha phase synchrony and higher network clustering into subnetworks compared to younger adults. Results were interpreted as older adults requiring higher synchronization between brain regions and network segregation to achieve effective cognitive performance and interference control (e.g., Wang et al., 2017; Nobukama et al., 2019). Likewise, Phillips and Takeda (2010) observed larger gamma synchrony in healthy older adults relative to young adults in association with the preservation of cognitive performance when participants were asked to identify the location of a target item in search displays also containing similar distractors. Results were interpreted as reflecting additional top-down control of attention and increased use of working memory resources to maintain similar performance to that of young adults.

Increased synchrony could reflect cognitive reserve and the protection against age-related changes. De Frutos-Lucas et al. (2020) investigated network resting-state synchrony in bilingual healthy older adults and observed larger parieto-occipital theta and beta synchrony compared to monolingual older adults. It was proposed that being bilingual (i.e., considered as larger cognitive reserve) could protect from neurodegenerative alterations by contributing to the preservation of the dynamic synchrony between brain

regions. In other regions and frequency bands, increased synchrony could also reflect a larger need to compensate when such reserve is lower. López et al (2014a) revealed that individuals with lower cognitive reserve (i.e., based on educational level and professional activity) showed larger fronto-posterior theta and alpha synchrony than older adults with higher cognitive reserve during working memory task performance. These results suggest that increased synchrony can reflect reduced network efficiency in individuals with lower cognitive reserve and a larger need to compensate for age-related changes. The reduction of network efficiency would thus require more activity and synchrony to perform the same processing as effectively as an individual with higher reserve, and would be more strongly affected by increased task demand (Reuter-Lorenz & Park, 2014).

3.2.2. Pathological aging

Conversely, the reported hypersynchrony can also sometimes be ineffective in preserving cognitive performance, or even reflect the progression of neurodegenerative alterations (e.g., de Hemptinne et al., 2015). Pons et al. (2010) observed an increase of resting-state lower alpha (7-9 Hz) fronto-occipital synchrony in healthy older participants relative to younger participants, and in MCI patients relative to healthy controls (see also López et al., 2014b; López et al., 2017). Although the association with cognition was not directly assessed, these results importantly suggest that increased long-range connectivity at rest can reflect a failed attempt at compensating modifications of brain networks associated with structural alterations and/or neurodegenerative processes, leading to reduced network efficiency. Koelewijn et al. (2019) investigated a large sample of healthy APOE- ϵ 4 carriers relative to controls and revealed important alpha and beta hyperactivity in parietal regions and hyperconnectivity between parietal regions and the rest of the brain. The ϵ 4 allele of the APOE gene is considered as a risk factor for AD, and has been associated with impaired cognitive functions and reduced hippocampal volume (e.g., Strittmatter et al., 1993). Results suggested that hyperconnectivity may precede the previously reported disconnection in AD by several years. Knyazeva et al., (2013) revealed that AD patients showed both altered resting-state synchrony relative to healthy controls in medial frontal and temporal regions, and hyper synchrony among bilateral temporo-parieto-occipital regions. Such synchrony alteration appears to follow the AD progression sites, and hypersynchrony may reflect a maladaptive increase

in these regions. Further analyses after a one-year follow-up revealed that rapidly progressing AD patients showed significant reductions of synchrony over time among left fronto-temporal regions than slow-progressing patients, and that hypersynchrony during the initial measurement was larger in this subgroup. Therefore, the presence of increased synchrony could be considered as a prognostic marker for disease progression and help to identify individuals at risk of cognitive decline. Findings are in line with Pasquini et al. (2019)'s work linking amyloid- β to a disconnection between prefrontal and medial temporal regions and local medial temporal hyperexcitability (see also Kazim et al., 2017; Ping et al., 2015). According to this account, medial temporal hyperexcitability is the driving force accelerating age-related tau accumulation and brain atrophy (e.g., Corriveau-Lecavalier et al., 2021). Future work on task-related activity is necessary to more clearly disentangle the failed compensation attempt from the neurotoxic activity (e.g., Cabeza et al., 2018) and to develop adapted therapeutic interventions (e.g., Bakker et al., 2015; Haberman et al., 2017).

Changes in the alpha band may also lead to hypersynchrony in other frequency bands in association with alterations of interference suppression and disease progression. When investigating task-related activity, López et al (2014b) observed task-related hypersynchrony in delta, theta, and gamma networks in MCI patients relative to healthy controls, while synchrony in alpha and beta networks was impaired (see also Lopez-Sanz et al., 2017). In line with findings in healthy aging, such hypersynchrony could reflect a lower task-related network efficiency and the need for increased communications to maintain performance. This effect was observed during the completion of an arithmetic subtraction task relative to resting-state activity, consistent with a larger effect of task demands relative to controls. These results may suggest that reduced alpha synchrony leads to disinhibition of irrelevant neural activity, which could be reflected in hypersynchrony (e.g., Jensen & Mazaheri, 2010). Such reduced alpha synchrony could result from either less activity in the alpha band or from the slowing of oscillatory activity and the alpha peak frequency shift. Interestingly, no modulation of the engaged functional network by task load was observed in MCI patients, relative to controls, suggesting an alteration of the network's usually quick and efficient reorganization to match task demands.

3.3. Towards more random network dynamics

3.3.1. Healthy aging

As brain networks tend to show changes of functional communications during both healthy and pathological aging, changes in the stability of neural synchrony have also been reported. Indeed, Ariza et al., (2015) observed fluctuations of the alpha network's synchrony over time that were larger in healthy older adults than in young adults during interference resolution, in line with a decreased ability to engage and maintain functional control networks. McIntosh and al. (2014) applied multiscale entropy on both EEG and MEG datasets and revealed increased local variability over time with aging together with lower between-hemisphere communications. Such increased local variability was mainly observed in the alpha band (e.g., Nobukama et al., 2019). During resting state, however, Coquelet et al., (2017) found no difference between young and healthy older individuals in the standard deviation of resting-state functional connectivity time series based on envelope correlations, and only marginally larger alpha and beta temporal and frontal fluctuations in older adults relative to young adults. This difference between studies may reflect greater age-related changes affecting activity at fast time scales needed for task completion, which are not relevant to resting state connectivity, hence providing a higher sensitivity to detect changes of task-related network stability during healthy aging. This pattern of increased functional network fluctuations with aging appears to reflect a lifespan process and shows a reversed pattern relative to dynamic connectivity changes from childhood to adulthood, in line with an inverted-U evolution (e.g., Smit et al., 2016).

In addition to fluctuations of synchrony over time, changes of whole brain network organization over time have been observed. Results revealed a tendency towards lower network clustering into distinct subnetworks, especially for the alpha network (see Miraglia et al., 2017, for a review). Such tendency suggests an alteration of the balance between integration (i.e., network's communication efficiency across subnetworks) and segregation (i.e., network's tendency to form separate subnetworks) of functional networks. By applying graph theory analyses on EEG sources, Gaál et al. (2010) showed a shift towards a less clustered functional organization of the alpha and beta bands in healthy older relative to younger participants (see also Vecchio et al., 2014). Knyazev et al., (2015) also showed a decreased clustering in the beta and gamma networks in older adults relative to young adults, with a shift to less clustered functional organization (see also Sun et al., 2012). This clustering difference also mediated the association between age and reaction time during the completion of an attention task. The fact that this loss of functional network segregation is observed at

multiple frequency bands suggests that it reflects a general tendency of oscillatory networks with aging, and that the preservation of a segregated structure similar to that seen in younger participants is associated with preserved cognitive performance.

3.3.2. Pathological aging

A tendency toward less segregated network activity was also reported for MCI patients relative to healthy older individuals (Buldú et al., 2011; but see López et al., 2017). Effects were larger in the alpha band between MCI patients and healthy controls, and the alteration of such functional organization has been proposed as a potentially useful marker for the early detection of both MCI and AD (see also Bajo et al., 2010; Miraglia et al., 2016). Differences have also been observed in AD patients relative to healthy controls (Miraglia et al., 2017). Stam et al., (2009) reported that MEG resting-state phase synchrony architecture of alpha and beta bands in AD patients showed a less structured and segregated organization than healthy controls (see also Babiloni, 2016; Chen et al., 2019; De Haan et al., 2009; Tahaei et al., 2012). This effect was associated with lower MMSE scores and seems to be associated with disease progression. The optimally segregated network structure is characterized by direct communications between distant regions and specialized subnetworks. Changes in network clustering with age and pathology led to deviations from this structure toward more random network synchrony in AD patients (see also De Haan et al., 2012). Sitnikova et al. (2018) investigated the transitions over time between MEG connectivity states using Hidden Markov modelling in healthy controls and AD patients. Relative to controls, the state corresponding to the DMN network was observed less often and for shorter periods of time, suggesting that spontaneous synchronization in this network was less stable. These changes were interpreted as potentially underlying impairment of memory retrieval and stimulus independent thoughts with AD.

In sum, both normal and pathological aging strongly influence the dynamic communications between brain regions. The main effect is a loss of synchrony between distant brain regions with age and dementia, which is critical for information transmission and gating of neural activations. As a result of a loss of synchrony in some circuits, older adults may develop, at least temporarily, higher levels of synchrony in other circuits in order to perform the same communications, which influences the effectiveness and speed of

cognitive processes. This overall tendency shows strong individual variability, as some individuals show increased synchrony as a compensatory adjustment to preserve cognitive performance, while hypersynchrony can also reflect failed compensatory attempts or maladaptive adjustments and the progression of neurodegenerative alterations. Finally, when no distractor inhibition or goal updating is required, a lack of stability over time and decreased segregation of the engaged network is critically associated with cognitive decline with age and the progression of neurodegenerative disorders. Changes in temporal dynamics and synchrony with age and pathology can also be combined with other neuroimaging modalities to better understand the association between brain and cognitive changes and the progression of neurodegenerative disorders.

4. Temporally informed multimodal investigation of aging

4.1. M/EEG informed fMRI studies

Several studies aimed at combining the spatial resolution of fMRI activity with the temporal resolution of M/EEG to further our understanding of healthy and pathological aging effects on brain activity. Investigations in young adults revealed distinct associations of alpha and gamma oscillatory variability with BOLD signal variability (e.g., Hinault et al., 2019b; Scheeringa & Fries, 2019) that could further our understanding of brain changes with age and pathology. Balster et al. (2013) reported that simultaneous resting-state EEG and fMRI recording could be more sensitive to age-related changes than fMRI alone. They revealed that the slowing of alpha activity was associated with fMRI changes in the DMN. Moreover, relative to fMRI alone, additional age-related differences in medial frontal and postcentral regions were observed with EEG-informed fMRI (i.e., method investigating covariations between fluctuations of EEG and fMRI signals). M/EEG data are also sometimes more associated with vascular neuropathology, such as decreased blood perfusion, than fMRI data. Kielar et al. (2016) showed that MEG signal transfer entropy across time was associated with hypoperfusion, as measured using arterial spin labeling (i.e., technique enabling the quantification of cerebral blood perfusion). This association was not observed with BOLD signal variability. Time-varying activity can be a sensitive index of perfusion dysfunction and could have clinical implications for the prognosis of cognitive decline and risk of stroke.

Other work combined EEG and fMRI to specifically investigate aging effects on the P3 component. O'Connell et al. (2012) found that aging effects on P3a amplitude and latency were associated with increased activation of the left inferior frontal gyrus and cingulate cortex, and decreased activation of inferior parietal cortex in healthy older adults relative to young adults. Therefore, age-related increased latency of P3a suggests an increased reliance on prefrontal structures during target and distractor processing. This would be in line with less efficient inhibitory processes and the need for additional resources and time to maintain performance. Increased latency of P3b, however, has been reported to be associated with widespread reduction of brain activity (Juckel et al., 2012). Additional multimodal research will be needed to better understand the underlying cognitive and neural mechanisms of these results.

4.2. Temporal dynamics and biomarkers

Although few studies have been conducted to determine the association of blood and CSF biomarkers with M/EEG activity, some results suggest that biological markers of neurodegenerative disease could be associated with brain dynamics and network communications. These studies importantly clarify the association between APOE status and functional connectivity alterations during the progression of neurodegenerative processes. Cuesta et al. (2015) divided groups of healthy controls and MCI patients into carriers and non-carriers of the APOE- ϵ 4 allele. Findings revealed a disruption of delta MEG PLV fronto-posterior synchrony in APOE- ϵ 4 carriers. This finding interacted with whether participants were healthy controls or MCI patients. In healthy controls, frontal-temporal delta and theta synchrony were higher in carriers relative to non-carriers. In contrast, APOE- ϵ 4 carrier MCI patients showed reduced synchrony in the same regions compared to healthy controls or non-carrier MCI patients. This difference might therefore reflect the progression of neurodegenerative alterations: synchrony first increases to maintain cognitive performance, then decreases below normal strength as damage increases (Reuter-Lorenz & Park, 2014). Consideration of such interactions also helps clarify other findings regarding whether age-related changes in neural activity are compensatory, indicative of pathology, maladaptive, or all of these.

Recent studies suggest a strong association between amyloid burden and EEG activity, and point again to a possible initial compensatory mechanism that can no longer be implemented when amyloid load increases.

Following the specification of patients' amyloid and neurodegeneration status (based on ^{18}F -florbetapir PET brain metabolism), Gaubert et al., (2019) investigated EEG resting-state activity between groups of patients (i.e., amyloid positive/negative, neurodegeneration positive/negative). Results revealed that fronto-central theta information transfer over time (i.e., measured through transfer entropy) was higher in neurodegeneration positive subjects than in neurodegeneration negative patients. This association was modulated by the amyloid burden and was not observed in amyloid positive patients. Gouw et al., (2017) investigated the association between EEG activity and amyloid measurements in CSF. They recruited healthy older participants and participants with subjective cognitive impairment. The neurochemical profile of Alzheimer's disease is usually defined by higher Tau and lower A β 42 CSF concentrations (e.g., Galasko et al., 1998; Sunderland et al., 2003). Results revealed that in healthy older adults with normal cognition, the slowing of oscillatory activity was associated with low amyloid concentrations, with both lower alpha peak frequency and greater power in slower relative to faster frequency bands. A one-year follow-up provided converging evidence, as the association between amyloid concentration and EEG changes was larger in participants showing a progression of cognitive decline a year later relative to participants that remained stable (see also Stomrud et al., 2010).

4.3. Structural and functional connectivity

4.3.1. Healthy aging

Functional brain networks are partly constrained by the integrity of underlying white matter tracts connecting brain regions (see Suárez et al., 2020, for a recent review), and microstructural integrity of these tracts tends to be lower in older adults than in younger individuals (e.g., Hinault et al., 2019a; Teipel et al., 2010; Ystad et al., 2011). This integrity reduction with age has been found to be associated with lower resting-state coherence across time between temporal and posterior sites (Teipel et al., 2009).

In addition to inter-hemispheric connections, the influence of longer fronto-posterior tracts has also been assessed, as they show a greater probability of integrity loss than shorter fibers (e.g., Yang et al., 2016). These fronto-posterior tracts are thought to be necessary for working memory and inhibitory control processes. We investigated the association between the microstructural integrity of these tracts, behavioral interference

processing, and EEG source-based time-varying alpha and gamma PLV (Hinault et al., 2020, 2021, Figure 5). Older individuals with better preservation of the inferior fronto-occipital (IFO) fasciculus showed greater and earlier task-related modulations of alpha and gamma long-range PLV between the right inferior frontal gyrus and occipital lobe. Preserved synchrony modulations were associated with better performance. Results reveal that considering the close relationship between structural and time-varying functional connectivity at different frequencies might be critical to understanding individual differences in cognitive functioning even in the absence of distinct neuroanatomical lesions or cognitive decline on standardized neuropsychological tests.

Figure 5. EEG alpha and gamma PLV synchrony was assessed during the completion of an arithmetic verification task including interferences when the proposed solution was the correct answer of another operation type. In older adults, we observed an association between individual levels of structural (right IFO) and functional connectivity, both also being associated with arithmetic interference. Furthermore, mediation analyses also revealed that EEG synchrony was mediating the association between structural integrity and cognitive performance (blue arrow). Individuals with the lowest integrity showed lower functional synchrony between brain regions, which appeared to be the proximal cause of larger behavioral interference. On the other hand, a relative preservation of structural integrity led to larger synchrony and less interference. Data from Hinault et al., 2020, 2021.

4.3.2. Pathological aging

Regarding pathological aging, Teipel et al., (2009) also investigated structural changes and in MCI patients and found that frontal alpha coherence was correlated with white matter volume in the frontal lobe and anterior corpus callosum. Pineda-Pardo et al. (2014) investigated how white matter alterations were correlated with phase synchrony of resting functional MEG networks during both healthy aging and MCI. Network analyses with graph theory revealed a less clustered beta network in MCI patients relative to healthy controls. These reduced and less segregated communications between brain regions were associated with alterations of the IFO and cingulum tracts in MCI patients.

In sum, combining EEG dynamic activity with other modalities can provide a better understanding of normal and pathological aging, and individual differences therein. With age, changes in brain perfusion, the accumulation of neurodegeneration markers, or alterations of white matter integrity will impact the temporal dynamics of brain networks by reducing or delaying brain activations and communications between brain regions. Adopting a multimodal approach can clarify the association between structural integrity and neural communication, the link with biomarkers of pathological aging, or localize changes in time courses to specific brain regions. Multimodal results, together with local activity and connectivity patterns, can inform and extend the main theoretical frameworks of healthy and pathological aging.

5. The theoretical contribution of temporal dynamics in the aging brain

5.1. Alpha activity and the inhibitory deficit account

5.1.1. Healthy aging

Considering alpha oscillatory dynamics can further our understanding of inhibitory alterations during both normal and pathological aging, and the underlying effects on neural dynamics. Although some recent work has led to alternative accounts (Antonov et al., 2020; Foster & Awh, 2019), the findings reviewed here are consistent with a role of alpha oscillatory activity in inhibitory control processes and the regulation of brain activations (e.g., Jensen & Mazaheri, 2010; Klimesch, 2012; Popov et al., 2017; Tang et al., 2013). Indeed, with aging, older adults show significantly reduced abilities to suppress the interference of irrelevant information and to control the tendency to produce automatic responses (e.g., Rey-Mermet & Gade, 2017).

Results demonstrated important changes in alpha oscillatory activity relative to other frequency bands (e.g., Deiber et al., 2013; Vysata et al., 2014), and these changes have been associated with inhibitory decline (Li & Zhao, 2015; Schmiedt-Fehr et al., 2016). Results are consistent with alpha network acting as a functional “backbone” for dynamic brain activity. The preservation of dynamic, segregated alpha network connectivity indeed appears to play a crucial role in the preservation of cognition during healthy aging and its alterations with pathology (e.g., Gaál et al., 2010).

Furthermore, alpha slowing and the alteration of alpha synchrony is strongly associated with changes in other frequency bands (e.g., Celesia, 1986; Finnigan et al., 2011). These findings are consistent with changes in alpha dynamics being associated with a functional reorganization of network dynamics (e.g., Kucyi et al., 2020), and with maladaptive increase in other frequency bands when the alpha network is impaired (e.g., López et al., 2014b). Furthermore, studies investigating PAC highlight that changes in alpha dynamics also impact their cross-frequency interactions with gamma dynamics in healthy older individuals (Hinault et al., 2020). In line with the gating hypothesis, altered alpha oscillatory dynamics and synchrony (e.g., Vysata et al., 2014) would be associated with an altered ability to flexibly control brain activations and associated cognitive processes (Mathewson et al., 2011). Compensatory activations in older adults with preserved cognitive performance are observed and mainly consist in higher alpha synchrony between distant brain regions (e.g., Ariza et al., 2015). Moreover, changes of alpha network dynamics are also associated with the functional reorganization observed in fMRI (Balster et al., 2013) and the alteration of network structure assessed with white-matter microstructural integrity (Teipel et al., 2009; Hinault et al., 2020, 2021).

5.1.2. Pathological Aging

Although cognitive deficits differ between dementia types, and episodic memory remains the hallmark of AD, inhibitory processes are also strongly impaired during pathological aging (e.g., Bélanger et al., 2010). Similarly to healthy aging, alpha alterations are also predominant in MCI and AD patients (e.g., Miraglia et al., 2016; Prichep et al., 2007), and changes of alpha dynamics have been associated with lower cognitive performance (e.g., López et al., 2014b; Prichep et al., 2006), in line with the importance of the control of irrelevant information for cognitive functioning. Alpha network dynamic organization is also critically altered

during pathological aging (e.g., De Haan et al., 2009). Investigations of PAC revealed that alpha changes in AD patients also influence the interaction of this frequency band with faster oscillatory activity (Poza et al., 2017), which could then influence the association between gamma oscillatory activity and cognitive performance (e.g., Pusil et al., 2019). The inhibitory deficit account of normal and pathological aging should, therefore, further emphasize the importance of alpha dynamics in cognitive changes and neurodegenerative processes.

5.2. Dynamic reserve and maintenance

5.2.1. Healthy aging

In order to account for the discrepancy between measures of brain changes associated with age or pathology and cognitive performance, concepts of reserve and maintenance have been proposed (Barulli & Stern, 2013; Cabeza et al., 2018; Stern et al., 2018). Given equivalent ages and levels of brain pathology, cognitive reserve refers to individual variations in the efficiency and effectiveness of engaged cognitive processes and strategies as a function of lifespan intellectual, social and physical activities (e.g., Barulli et al., 2013). High cognitive reserve is therefore associated with a relative preservation of cognitive functioning in the face of changes associated with age or pathology. Cognitive reserve strongly interacts with brain reserve, the structural capital (e.g., grey matter volume, white matter microstructural integrity) that reflects differential developments from childhood to adulthood. In contrast with cognitive reserve, brain reserve is conceptualized as a passive resource during aging and does not involve dynamic adaptations but determines the functional impact of brain changes, because it increases the amount of damage that can accumulate before reaching the threshold where functional impairment is observed. Cognitive reserve also differs from brain maintenance, which refers to the relative absence of brain changes as a determinant of preserved cognition in older age. Brain maintenance therefore involves mechanisms preventing the development of brain lesions and neurodegenerative disorders before they occur.

These concepts provide a framework for understanding the variability of cognitive decline during healthy aging, the risk of pathological aging, and the potential conversion from preclinical stages to dementia. However, the neural and psychological mechanisms underlying these concepts are not well-understood. So

far, they have mainly been discussed in terms of localized differences in activation magnitude and neuroanatomical reorganization through functional MRI (but see Maestú et al., 2014). The findings reviewed here highlight the crucial importance of considering temporal dynamics of brain activations and functional networks. During healthy aging, differences between individuals showing little to no differences in task-related dynamics compared to young adults, relative to others showing slower dynamics and cognitive decline (e.g., Babiloni et al., 2004; Coquelet et al., 2017), could be used as a marker of brain maintenance. Brain maintenance is also expected to be associated with the preservation of phase synchrony between distant brain regions (e.g., López et al 2014a; Hinault et al., 2020, 2021). Earlier activations observed in healthy older individuals (Hinault et al., 2016; Proskovec et al., 2016; Staub et al., 2014) would reflect mechanisms of cognitive reserve to maintain similar cognitive performance to younger individuals. Changes of dynamic connectivity would take place to maintain cognitive performance (e.g., Ariza et al., 2015), while failure to do so would result in cognitive decline. Cognitive reserve is also associated with brain reserve through individual integrity levels of underlying white matter tracts (Hinault et al., 2020, 2021).

5.2.2. *Pathological aging*

Regarding pathological aging, the reduced tendency towards more random network dynamics in some patients than others (e.g., Stam et al., 2009) could be an indicator of slowed disease progression and better maintenance mechanisms. Moreover, as they were associated with amyloid β concentrations (e.g., Gaubert et al., 2019), dynamic communications between brain regions could highlight differences in maintenance adjustments and the variability between patients. The slowing of brain activity and the disruption of neural synchrony has been interpreted as an indicator of disease progression (Prichep et al., 2006; Poza et al., 2017), and the variability of cognitive decline suggests different levels of reserve between individuals. Hypersynchrony between brain regions has been associated with initial preservation, but also with a faster progression of neurodegenerative processes relative to slow-progressing patients (Knyazeva et al., 2013). These results suggest that reserve mechanisms might not be sustainable and thus can become maladaptive. This framework should therefore include specific predictions regarding the time course of brain activities and network dynamics in their specification of individual variations associated with both healthy and pathological

aging. Inclusion of network dynamics will lead to a better understanding of the neural mechanisms underlying reserve and maintenance.

5.3. Interrupted vs. altered communications

5.3.1. Healthy aging

The reviewed findings can further our understanding of the influential disconnection model of healthy and pathological aging (Geschwind, 1965), and help to distinguish severed connections due to discrete areas of damage from more graded impairment or delays in communications. Indeed, the alteration of cortico-cortical tracts and the reduction of the connectivity between the time courses of brain regions have been interpreted as evidence supporting a disconnection (e.g., Madden et al., 2017). In contrast with AD, MCI and healthy aging are both characterized by a lower degree of structural connectivity alterations, which does not necessarily qualify as complete disconnection (e.g., Palesi et al., 2016). Although reduced communications between brain regions have frequently been reported and were in some studies associated with alterations of the integrity of underlying white matter tracts, results mainly consisted in a reduction of phase synchrony (i.e., brains regions would be less “in tune”) than an interruption of signal transmission. The reviewed results (part 4.3 in particular) would suggest that the accumulation of subtle structural alterations lead to delayed communications between brain regions (Figure 1), a loss of synchrony, and a tendency towards random network functional organization (see Figure 6). The structural pathway underlying functional connectivity still allows signal transmission (and no significant brain lesion is observed on anatomical scans), but these small defects could impair the network’s normal functioning, which would then lead to the need for a reorganization of the whole system. The inter-individual variability of these changes can explain the increased variability of functional connectivity and cognitive performance with aging.

Figure 6. Theoretical model on the association between dynamic connectivity time courses and age-related degradation of white-matter integrity (WMI). Upon task cue, older individuals with lower WMI exhibit delayed activation in task relevant network A compared to older-high and younger individuals. Green shading indicates range of variability. After an update cue, older-low exhibit both delayed deactivation of no-longer task-relevant network A, and delayed activation of newly relevant Network B. While maintaining information B, Older-Low show less stability of activation and connectivity. Effect of distraction is also greater in Older-Low, and recovery from it is delayed.

5.3.2. Pathological aging

The disconnection is not always supported in the investigation of pathological aging (e.g., Bajo et al., 2010). However, relative to healthy aging, this pattern is expected to be stronger and to lead to the interruption of network communication in dementia. Given the evolution of network organization and synchrony alterations from healthy aging to MCI and AD, the progressive reduction of synchronized communications could be considered as an early stage between healthy brain functioning and neurodegenerative disconnection. Further direct and longitudinal analyses of the evolution of synchronized communications and of the association between individual functional and structural measures appear to be necessary to better understand such stage progression. In light of the reviewed results, time-varying measures seem to be highly sensitive to these changes and could be critical to identify the risk of cognitive decline and to specify the potential progression of neurodegenerative processes (i.e., the distinction between stable and progressive MCI patients).

Given the theoretical work conducted in healthy young adults (Cabral et al., 2017b; Suárez et al., 2020), the disconnection framework of normal and pathological aging should include specific elements regarding this intermediate stage and of the possibility of altered but not entirely disrupted communications between distant brain regions.

6. Perspectives and guidelines for future research

6.1. Methods for connectivity analyses

Results reviewed here included both sensor and source results. However, sensor results are more susceptible to be influenced by volume conduction effects (e.g., Van den Broek et al., 1998). Volume conduction effects mainly concern EEG data, and refer to the high correlation of signals from different sensors which can bias connectivity estimates by the identification of spurious connectivity patterns (e.g., Brunner et al., 2016; Van de Steen et al., 2016). Connectivity analyses in source space should therefore be favored over analyses in sensor space when possible (i.e., EEG data recorded with a high-density system, individual anatomy and/or spatial positions of fiducials available). The inclusion of structural MRI data in source analyses could also help providing more direct investigations of the association between structural measures (white and grey matter) and brain dynamics. Source-estimation analyses are now available in most signal processing toolboxes (e.g., Gramfort et al., 2014; Oostenveld et al., 2011; Tadel et al., 2011).

Even in source space, connectivity methods vary in their sensitivity to volume conduction effects (e.g., Bruña et al., 2018; Colclough et al., 2016). A specific investigation of the distinct sources of oscillatory activity would help clarifying mixed results regarding aging effects in given frequency bands, as age-related changes of oscillatory could be observed for some sources and not others. In addition to source space analyses, connectivity methods such as transfer entropy or phase synchrony should be favored over coherence and correlation analyses, as they are less sensitive to these effects. Finally, in line with recent work (e.g., Hinault et al., 2020, 2021; Toppi et al., 2018), and considering the previously discussed age-related changes, oscillatory and connectivity investigations of normal and pathological changes should account for individual alpha peak frequency in the definition of individual frequency bands. This reduces the influence of global

slowing on local activity and communications between brain regions and enables distinct conclusions on these phenomena.

6.2. Time as an experimental factor

In comparison to other neuroimaging methods such as fMRI and PET, M/EEG imaging benefits from a high temporal resolution that enables the investigation of brain activations at the millisecond level. Yet, this temporal resolution remains under-utilized. Several M/EEG studies have not been included in this review because analyses have exclusively been focused on comparisons between amplitudes calculated by averaging across time windows covering the whole experimental condition. This provides a similar analysis space to fMRI data but removes major sources of information in the data. Averaging over hundreds of milliseconds improves the signal to noise ratio while still providing a better temporal resolution than fMRI. Although this reduces data complexity, temporal average of functional network connectivity should be avoided as it also reduces the sensitivity to potential between-group differences and prevents the investigation of differences in temporal dynamics (e.g., Ariza et al., 2015, Cohen, 2011). Therefore, the exploitation of the brain dynamics in M/EEG appears to be a major endeavor for future research and could involve a variety of methods ranging from interactions with time windows to advanced modelling methods such as Hidden Markov Models (e.g., Quinn et al., 2018; Shappell et al., 2019) or multiscale entropy (e.g., McIntosh et al., 2014). Importantly, given the potential high correlation between measures over time, appropriate corrections must be applied such as correction for non-independence of data points, cluster-based analyses (e.g., Maris & Oostenveld, 2007) or additional control measures. The specification of temporal dynamics of the brain in healthy and pathological aging could lead to several major empirical and theoretical findings. We recommend, when possible, to include time as an experimental factor and to always investigate interactions between groups and temporal dynamics. This also includes experimental follow-ups to further investigate interactions between neural dynamics at different time scales.

6.3. Task-related brain activity

Although some analyses, such as event-related responses, require task-related data, the majority of reviewed work investigated resting-state activity. This mirrors the tendency observed in fMRI, and reflects

the ease of acquisition together with the generalizability of obtained findings. As cognitive performance involves the fast and efficient engagement of cognitive processes, task-related M/EEG results could potentially be more sensitive to slight signaling delays or disrupted synchrony of communications between brain regions than resting-state activity that can unfold over time without external constraints. Resting-state data does not inform on the speed and efficiency of neural networks associated with specific cognitive processes. This also limits the interpretation of brain activations and connectivity patterns as compensatory versus maladaptive, as this requires larger/smaller or faster/slower activations as a function of better/poorer performance. New investigations of task-related dynamic activation patterns and network organization could further our understanding of the evolution of cognition during healthy aging and dementia.

6.4. Toward a better understanding of between- and within-group variability

Recent neuroimaging works highlighted limitations in group-averaged investigations of brain activity (e.g., Hawco et al., 2020), as they cannot capture the rich variability existing between individuals. As this variability is even larger in the elderly than in the rest of the population (e.g., Hedden & Gabrieli, 2004; Hultsch et al., 2008), future studies should further clarify how brain dynamics are influenced by the variability existing, for example, between genders (e.g., Goldstone et al., 2016), dementia types (e.g., Yu et al., 2016; Filippi et al., 2017), and socio-economic status (e.g., Hurst et al., 2013). The association between brain dynamics observed in middle-aged participants and later cognitive trajectories should also be further specified, as age-related brain changes occur on a lifespan basis, and much of what is reported after age 65 is the outcome of brain changes that occurred years or even decades before. The investigation of individual variability could also benefit from individually defined frequency ranges based on posterior alpha peak frequency (e.g., Toppi et al., 2018). Individual frequency ranges would provide crucial information on individual slowing of oscillatory activity, and would help distinguish power changes from a frequency shift to a different canonical frequency band. Finally, the dynamic connectivity associated with cognitive strategies should be further investigated. A cognitive strategy is a procedure or a set of cognitive processes for achieving a task (Lemaire & Reder, 1999). Relative to younger individuals, older adults have been found to use fewer strategies, to use more demanding strategies less often, to select the most appropriate strategy on each problem less often, and

to be less efficient when executing a given strategy (e.g., Lemaire, 2016; Hinault & Lemaire, 2020). Specifying the neural basis of cognitive strategies and how changes of brain dynamics can affect strategy choice or execution could also provide important elements relative to the concepts of cognitive reserve and resilience (e.g., Barulli et al., 2013).

7. Conclusions

This review aimed to highlight how considering the temporal dynamics of brain activations and networks could provide a better understanding of changes occurring during both healthy and pathological aging. The temporal dimension has been ignored in most previous investigations on the neural correlates of age-related cognitive changes. Findings about local dynamics revealed an overall slowing of brain activity during both normal and pathological aging that more specifically affects neural dynamics associated with cognitive control and attention orienting processes. Normal and pathological aging also strongly influence dynamic communications between brain regions, with a loss of synchrony between distant brain regions and a lower stability over time. It appears that this loss can be mitigated by compensatory adjustments in some individuals, but this compensation may be only a temporary solution which may lead to more rapid subsequent cognitive decline. The combination of M/EEG dynamics with other modalities revealed some associations with changes in brain perfusion, the accumulation of neurodegeneration markers, or alterations of white matter microstructural integrity. As they were not previously considered in the most prevalent frameworks of healthy and pathological aging, findings could provide new and interesting considerations about cognitive decline, the variability between individuals, and mechanistic interactions between structure, function, and behavior. Altogether, further investigations of the brain's temporal dynamics open new fundamental opportunities to specify changes occurring with age and pathology and to develop approaches for prevention and amelioration.

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