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Neurophysiological mechanisms of quiet vigilance in neurodegenerative diseases: an electroencephalography research program

Ph.D. thesis

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"Without ambition one starts nothing. Without work one finishes nothing. The prize will not be sent to you. You have to win it." (Ralph Waldo Emerson)

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Executive summary

In the field of neurophysiological research, the term vigilance refers to a variety of mental states of monitoring of external world during wakefulness, related to activities in brain circuits (Steriade, 1999). These mental states are modulated by the projections of ascending reticular activating systems (ARASs), namely neural circuits mostly composed of sub-systems formed by nuclei and fiber projections (Lin et al., 2011). The ARASs were described in the 1949 by the neurophysiologists Giuseppe Moruzzi and Horace Magoun who first investigated the neural components regulating the brain's sleep-wake mechanisms in cats; but, they were also defined later, by the neuropsychologist Aleksandr Romanovič Lurija, as the components of the "first block of the brain", regulating arousal and the state of vigilance (Luria, 1973). ARASs are formed by parallel sub-systems running across brainstem, basal forebrain, and diencephalon using dopaminergic, noradrenergic, serotonergic, histaminergic, cholinergic, and glutamatergic neurotransmitters as different contributors to the regulation of general brain arousal and vigilance during wakefulness (Moruzzi and Magoun, 1949).

Experimental studies have shown that high level of the vigilance, associated with a finalized behaviour, is characterized by high activity of ARASs and desynchronization of the cortical electroencephalographic (EEG) signals at frequencies in the alpha (8-12 Hz) and beta (13-30 Hz) bands, associated with the synchronization of frequencies in the theta (4-7 Hz) and gamma (> 30 Hz) bands. On the contrary, when mental activity is at rest, in a quiet vigilance, EEG signals appear characterized by a synchronized activity at alpha rhythms (Moruzzi and Magoun 1949; Buzsaki and Gage 1989).

Buzsaki and colleagueas showed that cholinergic neurons play the main role in the event related variation of vigilance and related changes in on-going EEG activity (Buzsaki et al., 1988). The release of acetilcholine (ACh) from basal forebrain nuclei to the cortex is high during waking as a function of attention load and lowest during sleep. Furthermore, it appears that the activity of brain ACh neurons originating from pons are also involved in *sleep-stage* when dreams arise (Becchetti and Amadeo 2016). In parallel, dopaminergic neurons modulate motivation and cognitive aspects of sensory information processing as well as the control of motor function via mesocortical-mesolimbic and mesostriatal pathway, respectively (Gratewicke et al., 2015).

Malfunctioning of these subcortical cholinergic and dopaminergic neuromodulatory circuits may cause a variety of behavioural and cognitive dysfunctions as those observed in the most common progressive neurodegenerative dementing disorders such as Alzheimer's (AD),

Parkinson's (PD), and Lewy Bodies diseases (DLB; Berridge et al., 2003; Gratwicke et al., 2015).

AD is the most prevalent type of neurodegenerative dementia, representing 60-80% of cases, and is characterized by accumulation of Aβ1-42 and phospho-tau in the brain, associated with severe deficits in episodic memory in its typical clinical manifestation (Alzheimer's Association 2016; Alzheimer's society 2017). A certain level of those cognitive deficits is detectable even before dementia in AD patients, the so-called prodromal stage of amnesic mild cognitive impairment (MCI) where objective disorders of episodic memory (i.e., times, places, associated emotions, contextual knowledge) can be measured by neuropsychological scales. The identification of this prodromal phase of AD lead clinicians and researchers to start immediately interventions to delay the progression of the disease.

PD and DLB represent the 10-15% of the cases of dementia in seniors and are characterized by both frontal executive deficits and motor symptoms (McKeith et al., 2004). PD is mainly characterized by motor symptoms (the three core features are tremor, bradykinesia and rigidity) but recently, cognitive symptoms have caught the attention of the researchers due to the strength by which they manifest in the time (humour disturbance, frontal executive dysfunctions and dementia) (Schneider et al., 2017). Some evidence correlated with motor and cognitive symptoms to the distribution of neuropathological markers of PD (alpha-synuclein intra-cellular inclusions forming the so-called Lewy bodies) in substantia nigra at earlier stages and then in other brain regions including those of cerebral cortex (Braak et al., 2003; Caviness et al., 2016). Unfortunately, there is not an intervention plan to prevent neurodegeneration. DLB is clinically characterized by progressive dementia that is frequently accompanied by parkinsonism and visual hallucinations.

Compared with AD and PD patients, DLB patients have more frequent neuropsychiatric symptoms such as psychosis, depression and apathy, as well as disabling cognitive deficits (i.e. dementia) and abnormalities in sleep behavior (Aarsland et al., 2005; Bostrom et al., 2007a, 2007b; Ricci et al., 2009; Rongve et al., 2010a, 2010b, 2010c). Unfortunately, there is limited information regarding the prodromal DLB state compared with that of AD and PD. The reason of this limitation could be due to the missing definitions of clinical conditions of prodromal DLB.

Due to the fast diffusion of these diseases across aging and the lack of *disease-modifying* therapies, costs related to the management of AD, PD and DLB patients with dementia are expected to rise near future. Therefore, there is much interest in a better neurobiological and neurophysiological understanding of the prodromal stages of those diseases. This understanding

may trigger the validation of instrumental biomarkers of AD, PD and DLB that may probe the function of brain circuits underpinning cognitive functions. These biomarkers may also support decision-making processes underlying clinical management of AD, PD and DLB patients.
For the diagnosis of AD in research context, cerebrospinal fluid (CSF) and positron emission tomography (PET) biomarkers of Aβ1-42 and phospho-tau are used (Dubois et al., 2014). A useful diagnostic biomarker of PD and DLB probes striatal dopaminergic function by single-photon emission tomography or PET (McKeith et al., 2017). Unfortunately, CSF and PET markers are invasive and relatively expensive for a serial screening of large elderly population at risk of AD, PD and DLB; therefore, they should be better devoted to a second line screening on high-risk subjects intercepted with non-invasive and more cost-effective procedures. The electroencephalography in *resting-state* condition (rsEEG) may be a valid candidate to this respect. Indeed, rsEEG markers can give an index of cortical arousal in quiet wakefulness, as revealed by the effects of the administration of a pharmacological agent enhancing vigilance (i.e., modafinil) and sleep deprivation on the regulation of brain rsEEG rhythms in humans (Del Percio et al., 2019).

The aim of this PhD thesis was to improve our understanding of neurophysiological correlates of the quiet vigilance in patients with the most prevalent neurodegenerative dementing disorders such as AD, PD, and DLB. This aim was pursued by three **retrospective** rsEEG studies developed in the international clinical and EEG databases of High-resolution EEG Laboratory at the Department of Physiology and Pharmacology "V. Erspamer" at Sapienza University of Rome. These studies were developed in cooperation with the Partners of European Consortium of DLB.

In the **first study,** we tested the hypothesis that resting state eyes-closed electroencephalographic (rsEEG) rhythms might reflect cortical arousal in patients with dementia due to AD (ADD), PD (PDD), and Lewy body disease (DLB). Clinical and rsEEG data of 42 ADD, 42 PDD, 34 DLB, and 40 healthy elderly (Nold) subjects were extracted from our international archive. Demography, education, and Mini Mental State Evaluation score were not different between the patient groups. Individual alpha frequency peak (IAF) determined the delta (< 4 Hz), theta (3-5 Hz), alpha1 (5-7 Hz), alpha2 (7-9 Hz), and alpha3 (9-13 Hz) frequency bands. Fixed beta1 (14-20 Hz), beta2 (20-30 Hz), and gamma (30-40 Hz) frequency bands were also considered. The rsEEG cortical sources were estimated by means of the exact low-resolution brain electromagnetic source tomography and were then classified

across individuals, on the basis of the receiver operating characteristic curves. Results were quite interesting at both group and individual levels. At the group level, compared to the Nold subjects, IAF showed marked slowing in the PDD and DLB patients and moderate slowing in the ADD patients. Furthermore, all patient groups over the Nold subjects showed lower posterior alpha 2 source activities. This effect was dramatic in the ADD, marked in the DLB, and moderate in the PDD patients. These groups of patients also showed higher occipital delta source activities, but this effect was dramatic in the PDD, marked in the DLB, and moderate in the ADD patients.

At the individual level, the posterior delta and alpha sources allowed good classification accuracy (approximately 0.85-0.90) between the Nold subjects and patients, and between ADD and PDD patients.

We concluded that in quiet vigilance, delta and alpha sources unveiled different spatial and frequency features of the cortical neural synchronization underpinning brain arousal in ADD, PDD, and DLB patients.

In the **second study,** we hypothesized that PD patients may show peculiar clinical manifestations related to vigilance (i.e., executive cognitive deficits and visual hallucinations), reflected in rsEEG rhythms. Clinical and rsEEG rhythms in age-, sex-, and education-matched PD (N = 93), AD (N= 70), and Nold (N = 60) subjects were available from the same international archive of the first study. The same methodology for EEG sources estimation was applied as well. Results showed that: (1) compared to the Nold subjects, the AD and PD patients showed higher widespread delta source activities (PD > AD) and lower posterior alpha source activities (AD > PD); (2) the PD patients with the most pronounced motor deficits exhibited very low alpha source activities in widespread cortical regions; (3) the PD patients with the strongest cognitive deficits showed higher delta and alpha source activities in widespread cortical regions; and (4) compared to the PD patients without visual hallucinations, those with visual hallucinations were characterized by higher parieto-occipital alpha sources activities. These results suggest that in PD patients resting in quiet vigilance, abnormalities in cortical neural synchronization at delta and alpha frequencies are differently related to cognitive, motor, and visual hallucinations. Interestingly, parallel PD neuropathological processes may have opposite effects on cortical neural synchronization mechanisms generating cortical alpha rhythms in quiet vigilance, while cortical delta rhythms may be mainly related to neuropathological processes affecting cerebral cognitive systems.

The **third study** tested if cortical sources of rsEEG rhythms may differ as a function of different clinical symptoms in sub-groups of patients with dementia with DLB. Clinical and rsEEG rhythms in age-, sex-, and education-were matched in DLB (N=46), AD (N=60), and Nold (N=20) subjects. Results showed that compared with the Nold subjects, the DLB and AD patients exhibited greater spatially distributed delta source activities (DLB > AD) and lower alpha source activities posteriorly (AD > DLB). In relation to the DLB controls, the DLB patients with (1) rapid eye movement (REM) sleep behavior disorders showed lower delta and alpha source activities in widespread posterior cortical regions; (2) greater cognitive deficits exhibited higher delta source activities posteriorly; (3) visual hallucinations pointed to greater parieto-frontal delta and parietal alpha source activities; (4) cognitive fluctuations manifested higher parietal alpha source activities. These rsEEG results suggest that when prominent, any clinical feature was associated with a different topography of delta and alpha source activities in the DLB patients.

In conclusion, the three studies unveiled specific abnormalities in rsEEG rhythms at delta and alpha frequencies in AD, PD, and DLB patients experiencing quiet vigilance. Interestingly, DLB patients with visual hallucinations showed different abnormalities in cortical delta and alpha rhythms when compared to abnormalities revealed in PD patients with visual hallucinations (second study), thus unveiling different neural substrate and possibly different clinical features of this significant symptom. In the same line, DLB and PD patients with greatest cognitive deficits showed different abnormalities in cortical delta and alpha rhythms. Overall, these effects may represent the neurophysiological correlates of abnormalities in ARASs, cortical arousal, and cholinergic and dopaminergic systems probed by EEG techniques in AD, PD, and DLB patients with indications that the cholinergic systems may mainly affect posterior cortical alpha rhythms of rsEEG activity in AD patients, while dopaminergic systems may mainly impinge on diffuse cortical delta rhythms in DLB and PD patients. These effects were strictly related to clinical manifestations of the mentioned diseases.
Future studies may cross-validate those results in prospective, harmonized rsEEG studies in AD, PD, and DLB patients followed from prodromal to dementia stages of the diseases.

Introductory Part

Cortical arousal system: the role of ascending reticular activating systems (ARASs)

The first observation of a wake-related structure was that intact brain-stem structures were critical to maintaining arousal as evidenced by EEG recording in cats (Moruzzi and Magoun, 1949). The definition of the ascending reticular activation system (ARASs) was given to indicate the arousal system. It reaches the cortex through: (a) a ventral pathway (basal forebrain cholinergic nuclei and histaminergic neurons of posterior hypothalamus); (b) the aminergic nuclei (the noradrenergic neurons of the locus coeruleus, the serotoninergic neurons of the raphe nuclei); (c) and a dorsal pathway, the thalamic relay (Steriade and McCarley, 1990).

Most recently, a descending pathway to the spinal cord has been discovered to be important for maintaining muscle tone (it also plays a role in the support of the vigilance) (Holstege and Kuypers, 1987).

This introductive chapter about the ARASs (figure 1) aims to show the basic mechanisms involved in the regulation of cortical arousal of quiet a vigilance.

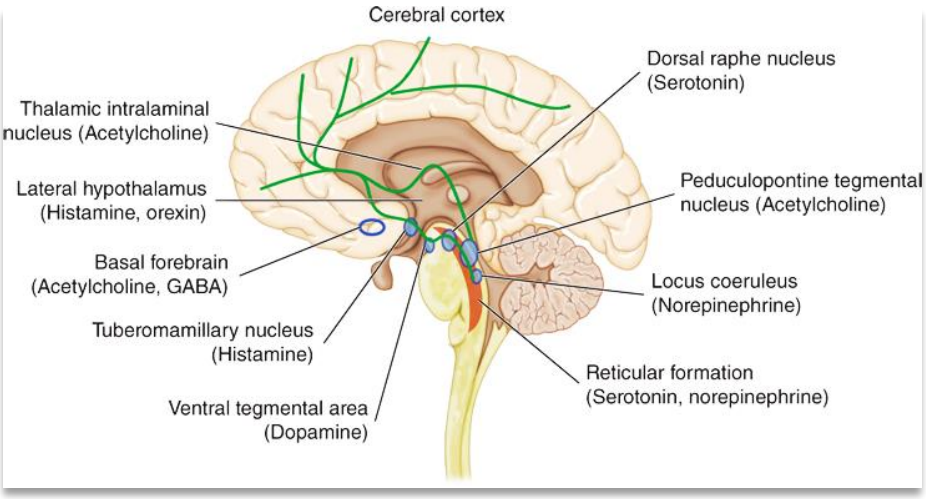

Figure 1. *The Image Shows The Main Components Of Reticular Ascending Activating System (Aras) With The Projections (Green Line) To Cerebral Cortex. (Edited And Revised From The Source Www.Accessmedicine.Com).*

Ventral pathway

The ventral pathway of ARASs is composed by basal forebrain and posterior hypothalamus. The first is a set of structures important in the production of acetylcholine, which is then distributed widely throughout the brain. The cholinergic neurons tonically discharge during wakefulness (Buzsaki et al., 1988). They can act directly on the cerebral cortex or thalamic reticular neurons suppressing them and generating the spindles of the sleep. The release of acetylcholine from the nuclei of the basal forebrain induces cortical desynchronization and fast EEG rhythms, while deactivation of this area induces cortical synchronization with slow waves activity of EEG rhythms (Casamenti et al., 1986). The activity of the basal forebrain is modulated by the neurons of the lower brain reticular structure (i.e., glutamatergic, noradrenergic, histaminergic and GABAergic). In particular, GABAergic ascending neurons also project to the cortex and play a synergic activity with cholinergic neurons in modulating cortical activation (Freund and Meskenaite, 1992; Jones and Muhlethaler, 1999).

The second structure of the ventral pathway of ARASs is the posterior hypothalamus that has widespread projection connecting with a lot of brain regions involved in the control of the wakefulness (cortex, thalamus, basal forebrain, anterior hypothalamus and brain stem cholinergic and noradrenergic nuclei) (Ford, 1995). It contains different neurotransmitters (dopamine, glutamate, GABA, histamine) and neuropeptides. Most recently, it has gained more importance due to its involvement in neocortical activation (Steininger et al., 1999). Muscimol (GABA-receptor agonist) injections induce sleep in cats (Lin et al., 1992). Furthermore, experimental data have shown the importance of another neurotransmitter that is the histamine. First discovered as a neuromodulator of an immune response, then it has been recognized as a transmitter inducing drowsiness if blocked (Monnier et al., 1967).

Aminergic system

The location and projections of diffuse ascending reticular monoaminergic system, that includes the dopaminergic (DA), noradrenergic (NA), serotonergic (5-HT), and histaminergic (HA) circuitries, were discovered in the 1960s for its important role in psychiatric disorders.

Figure 2 shows the main locations of cholinergic and aminergic nuclei with their projections to the cerebral cortex. Inhibition of catecholamine (dopamine and noradrenaline) synthesis induces waking disturbances, on the contrary, an accumulation of them is responsible for waking state and behavioural excitation (Fuxe et al., 2007).

The tonic activity of noradrenergic, dopaminergic and serotoninergic neurons that is observed during the wake, decreases during the sleep. Noradrenergic neurons are also involved in the activation of wake onset as revealed by experiment in noradrenergic neurons of the locus coeruleus in mice (Carter et al., 2009). Some of brainstem noradrenergic neurons are also involved in paradoxical sleep and they modulate cortical arousal as well as cognitive aspects of the waking, such as perception (Cirelli et al., 1996). Dopaminergic neurons play an important role in the control of motor function via mesostriatal pathway as well as motivation and cognitive aspects via mesocortical and mesolimbic pathways that can modulate cortical arousal (Gratewicke et al., 2015). A lesion of dopaminergic cells of periaqueductal grey matter results in increased sleep (Lu et al., 2006). Furthermore, the drug "modafinil" that promotes wake, acts through dopamine D2 receptors in the ventral tegmental area (VTA) (Korotkova et al., 2007).

Finally, the serotonin induces inhibition through the action on 5-HT 1 A receptors at postsynaptic level (Jones, 2005) but its synergic activity with acetylcholine may play a role in cortical activation (Dringenberg and Vanderwolf, 1998).

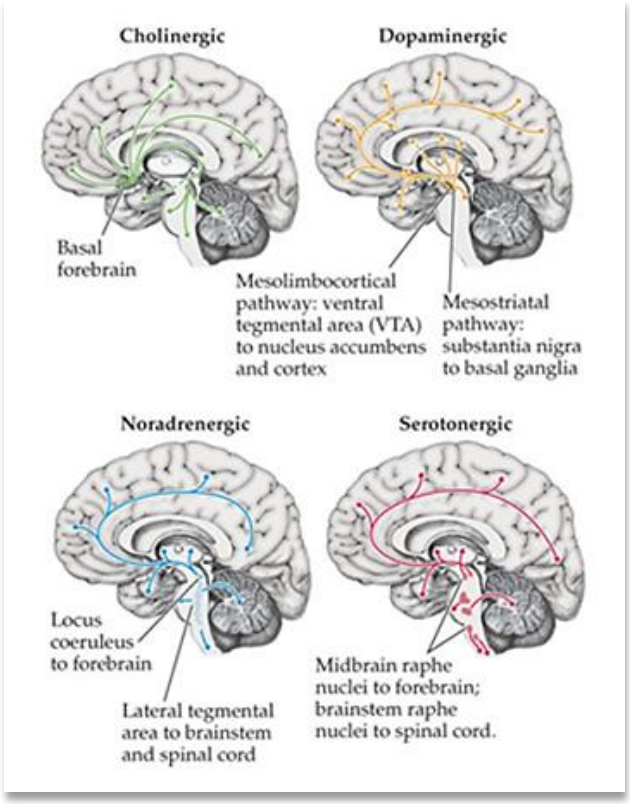

Figure 2. *Single components of ARASs (i.e. cholinergic and aminergic networks) regulating wakefulness (revised from Watson and Breedlove 2016).*

Dorsal pathway

The critical constituent of the ascending reticular activating system is the thalamus. First discovered by Galen in the first century, from the 18th century it is considered the gateway of sensory inputs that receives and sends inputs to the cortex (Bickford et al., 1994; Sherman, 2005) playing an important role in the neuromodulation of the brain. A perithalamic region of reticular nuclei surrounds the thalamus. This region takes the name of reticular thalamus and it is rich in GABAergic neurons. It receives inputs from the fifth and sixth layers of the cortex and from relay thalamus (so defined as they receive excitatory glutamatergic input from peripheral sensory pathways and projects to one or few well-defined cortical areas). The reticular nucleus is important in the control of thalamocortical and corticothalamic connections through the modulation of GABAergic input on the relay thalamus (figure 3). It can be divided into different sections that have connections with thalamus and cortex and different functions (sight, hearing, touch, movement or limbic functions).

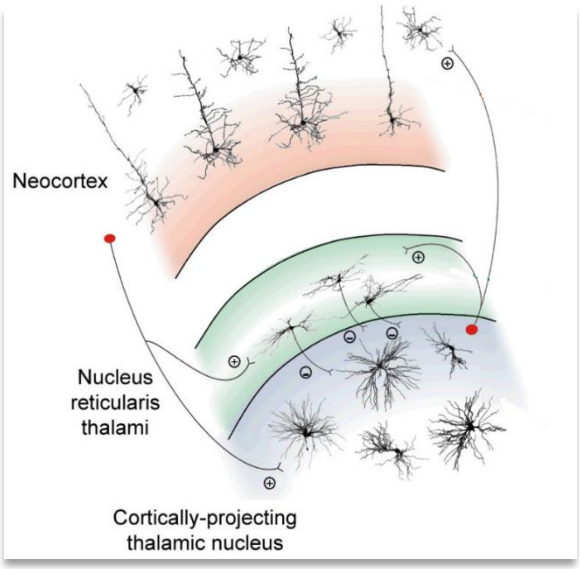

Figure 3. *Schematic diagram of a cortico-thalamo-cortical module with its most relevant cellular components and synaptic connections (thalamic interneurons and neocortical neurons other than those in layer 4 and 5/6 have been omitted for clarity). (+) and (−) indicate excitatory and inhibitory synapses, respectively. (Revised from Crunelli and Hughes 2010).*

Located in the diencephalon, the thalamus is formed by four components (hypothalamus, epithalamus, ventral thalamus and dorsal-relay thalamus). The most important region is *dorsal thalamus*, composed by allothalamic and the isothalamic region. The allothalamic region can be divided in: (a) paraventricular region (receiving afferents from the amygdala); (b) the centre-median-parafascicular complex which appears to be a major element in the basal ganglia system

that is involved in motor control (having projections to the striatum); (c) and the intralaminar region that receives inputs from ascending reticular activating system and plays a modulatory role in regulation of cortical arousal.

The isothalamic constitutes 90% or more of the dorsal thalamus and contains the major projections to the cortex. Lesions of these areas could affect cognition. The internal and superior laminae divide the isothalamus into several subregions (regio superior, superregio medio-posterior, superregio basalis and regio inferolateral).

Among the above mentioned subregions: the nucleus medialis receives a large projection from the dorsolateral prefrontal cortex, amygdala, ventral globus pallidus and nigral projections. It projects to prefrontal cortex and it is involved in cognition, sleep-wake cycle and executive function; The pulvinar-lateral posterior complex, which has a lot of reciprocal connections with the associated parieto-occipito-temporal cortical areas, is involved in attention and it is correlated to visual hallucination; the motor thalamus in the infolateral regio transfers information from the substantia nigra (sub-regio dorsalis), the globus pallidus (subregio oralis) and the cerebellum (subregio intermedia) to the prefrontal, supplementary, premotor, motor and somatosensory areas of the cerebral cortex. The motor thalamus receives projections from the nucleus perithalamicus in a specific diffuse manner, which can also contribute to the transfer of motor information (Herrero et al., 2002).

Electrical experiments on brain slices have suggested that thalamic activity is sufficient to alter the cortical state. Thalamocortical neurons are directly excited by stimulation of the brain stem reticular nuclei. During wakefulness, brief activation of the thalamic reticular nucleus is sufficient to evoke thalamic bursts and cortical spindles (Halassa et al., 2011). They receive cholinergic input from the cholinergic reticular nuclei at midbrain pontine junction and aminergic input from locus ceruleus and raphe nuclei as shown by some experiments in rats (Lindvall and Björklund, 1974) but the monominergic neurons seem not be involved in tonic activation processes of thalamocortical systems (Jones and Moore, 1977). On the contrary, the result of local application of a cholinergic agonist is a loss of hyperpolarizing oscillation, the increase of metabolic activity of the thalamic neurons and an EEG desynchronized (Buzsaki et al., 1988).

Three major dementia types (ADD, PDD, DLB)

Alzheimer's, Parkinson's and Lewy Body diseases (AD, PD, DLB) are the major neurodegenerative disorders that can progress to dementia (ADD, PDD, DLB).

The ADD represents approximately 60-80%, while PDD and DLB the 10%-15% of all dementia cases in aged people over 65 (Alzheimer's Association, 2016; Alzheimer's society 2017). Demented people suffer from a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities (Diagnostic and Statistical Manual of Mental Disorders -DSM).

"Dementia" tends to increase with age (Graves and Kukull, 1994), the reason why, with the rise of expectancy life, dementia is a growing socioeconomic and medical problem.

In 1906 the psychiatrist and neuropathologist Alois Alzheimer gave the name at the most prevalent form of neurodegenerative and age-related dementia in the modern society, the Alzheimer's disease (AD). In the 2016 Alzheimer's Disease International's "World Alzheimer Report" estimated 44 million people worldwide and this number is expected to double in the next years. At the basis of the Alzheimer's disease there are neurological dis-functions due to the neuron's death triggered by neuropathological pathway. AD affects patients in different ways, changing the rate of progression for each subject (Weiner et al., 2015).

The most common symptoms of the AD disease are memory loss that disrupts daily life and challenges in planning or solving problems.

In 1984 Kosaka and colleagues described the cytoplasmic inclusions of α-synuclein in the brain-stems of patients affected by Parkinson's disease. These inclusions were firstly noticed in 1910 by the neurologist Fritz Heinrich Lewy (Lewy et al., 1912) who studied the brain of people showing dementia. In its memory, these cytoplasmic inclusions took the name of Lewy Bodies (LB). The clinical constellations of DLB and PDD include progressive cognitive impairment associated with extrapyramidal motor impairments (parkinsonism), visual hallucinations, and fluctuations of attention and wakefulness. The cognitive domains that are impacted in DLB and PDD overlap substantially, with prominent executive dysfunctions and visual-spatial abnormalities and variable impairment in memory capacities. In DLB, dementia often heralds the onset of illness in advance of parkinsonian motor signs, but by consensus may follow their development up to 1 year from their onset. In contrast, a diagnosis of PDD is made when cognitive impairments develop in the setting of well-established PD (Gomperts, 2016).

Neuropathology

In AD, the symptoms are caused by a progressive loss of cholinergic functions due to neuronal cell death firstly in the hippocampus and then in the cerebral cortex, brain regions involved in thought processing and memory (Selkoe, 1991; Blennow et al., 2006; Mucke, 2009). The neuropathological process that affects the neurons of AD patients, depends on two kinds of protein aggregates: amyloid plaques, also called senile plaques, and tangles of hyper-phosphorylated tau-protein, also called neurofibrillary tangles (Figure 1).

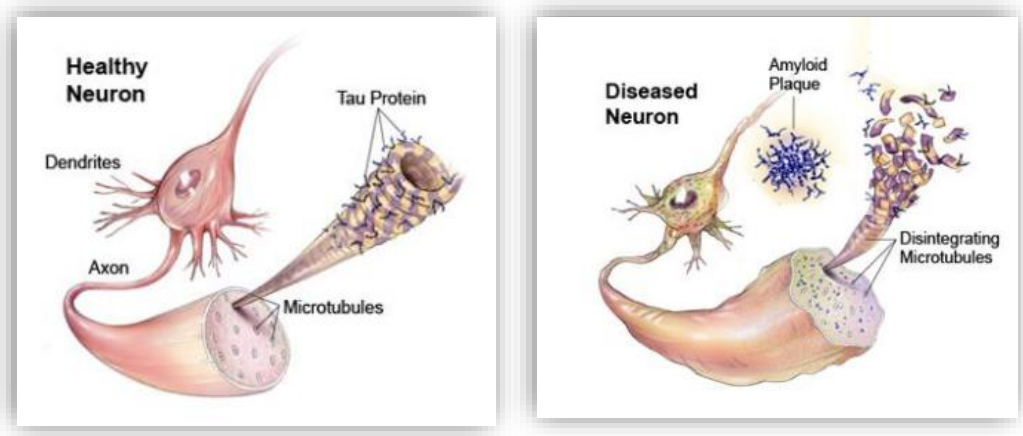

Figure 1. *A healthy neuron (left) compared to diseased neuron (right) with the amyloid plaque and phosphorylated tau (revised illustration Bob Morreale for American Health Assistance Foundation).*

Amyloid precursor protein (APP) is a transmembrane protein without known function that is constitutively cleaved into peptides during cell's metabolism (Haas et al.,1992). The two amyloidogenic forms of amyloid protein (40 or 42 amino acid Aβ peptide) are released after cleavage by β-secretase and γ- secretase enzymes and are usually quickly removed from the brain. However, in the case of overproduction or impaired clearance, Aβ aggregates into extracellular oligomers, fibrillary and, eventually, plaques (Masters et al., 1985). Tau is an intracellular microtubule binding protein that, when hyper-phosphorylated, will cause disassembly of microtubules and thus will impair axonal transport and compromise neuronal and synaptic function (Braak et al., 2003; Iqbal et al., 2005). Weather tangle formation is a cause or a consequence of the disease is still under debate. The dominating hypothesis for the cause of AD is the cascade Aβ hypothesis (Hardy and Selkoe, 2002). According to this hypothesis, abnormal metabolism of the amyloid precursor protein (APP) and the subsequent accumulation of toxic Aβ peptides interferes with the neuron-to-neuron communication at synapses and contributes to cell death. After the cell's death, the aggregates spread out in the

extracellular space. Tau tangles block the transport of nutrients and other essential molecules inside neurons and are also believed to contribute to cell death.

Apart from the damage to ascending cholinergic projections in Alzheimer's disease, biochemical studies on human brain post mortem have revealed several other neurochemical abnormalities. These include reductions in 5-hydroxytryptamine (5-HT) and 5-HT receptors, and in noradrenaline. Some regions of cerebral cortex show reduced concentrations of GABA (Rossor and Iversen, 1986). Furthermore, evidence exists for both cholinergic and glutamatergic involvement in the aetiology of Alzheimer's disease. The glutamatergic hypothesis links the cognitive decline in patients with Alzheimer's to neuronal damage resulting from overactivation of N-methyl-d-aspartate (NMDA) receptors by glutamate. The sustained low-level activation of NMDA receptors, which are pivotal in learning and memory, may result from deficiencies in glutamate reuptake by astroglial cells in the synaptic cleft (Francis, 2005).

Parkinson's and Lewy Body disease are well characterized by α-synuclein deposition (Jellinger et al., 2009). α-synuclein is a human protein encoded by the gene *SNCA.* It is predominantly expressed in the neocortex, hippocampus, substantia nigra, thalamus, and cerebellum. In the brain, it is localized in presynaptic terminals where it is involved in neurotransmitters released from synaptic vesicles. If the gene is mutated, the protein forms a stably folded tetramer (aggregates) (Figure 2) (Bartels et al., 2011).

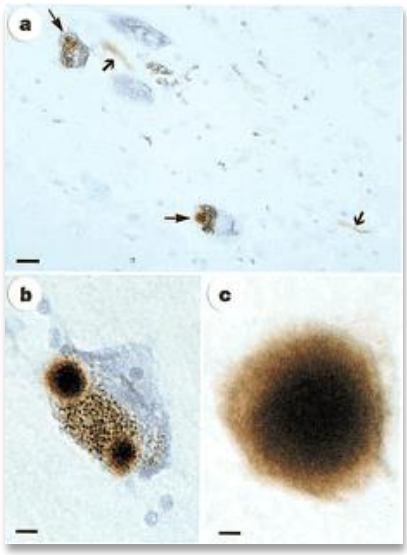

Figure 2. *Lewy body in substantia nigra from patients with Parkinson's disease (from the MRC Cambridge Brain Bank) immunostained for α-synuclein (from Spillantini et al., 1997).*

However, PDD and DLB patients also show AD-type pathology (i.e. cerebral neurofibrillary tangle and Aβ plaques) (Hansen et al., 1998). The pathological substrate seems to follow the Braak stages (a method describing the progressive formation of aggregates from the lower brainstem to the neocortex) (Braak et al., 2003). In PDD, LB are primarily diffuse in the subcortical regions of the brain, predominantly in the midbrain substantia nigra and locus coeruleus (Nussbaum and Ellis, 2003) whereas, DLB is characterized by the presence of Lewy bodies in the subcortical (midbrain) and cortical (frontotemporal) regions of the brain, as well as amyloid plaques. Neurofibrillary tangles are less common in dementia with Lewy bodies (McKeith, 2004).

In PDD and DLB different sub-cortical and cortical networks are compromised. In DLB, dopamine via nigral degeneration and acetylcholine via basal forebrain degeneration are the neurochemical systems most consistently affected (Tiraboschi et al., 2000). The neurophysiological model of the interrelation among neurotransmitters and their effects on the functionality of the brain cortex, proposed by Gratwicke et al., 2015 is shown in figure 3.

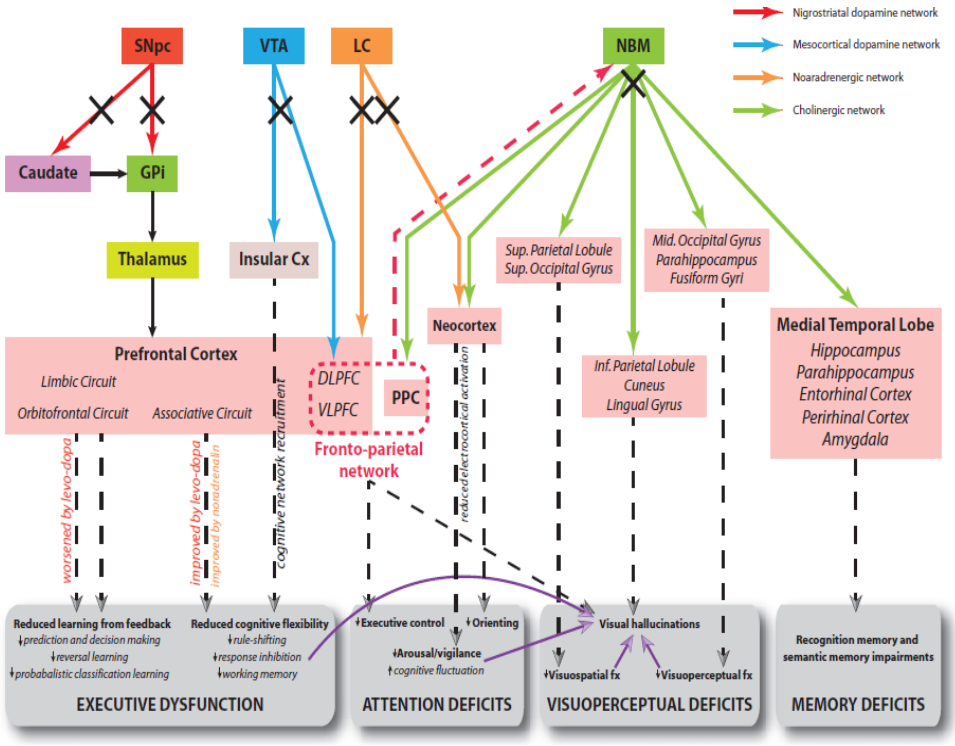

Figure 3. *Hypothetical model of neural circuits malfunctioning in PDD and the corresponding cognitive deficits. Legend: Cx = cortex; DLPFC = dorsolateral prefrontal cortex; GPi = globus pallidus (internus); PPC = posterior parietal cortex; SNpc = substantia nigra pars compacta; VLPFC = ventrolateral prefrontal cortex; VTA = ventral tegmental area (Gratewike et al., 2015).*

In PDD there are evidences about the deficits occurring in dopaminergic nigro-striatal pathway, responsible of motor impairment, as well as cortically projecting dopaminergic neurons in the mesocortical limbic system (Scatton et al., 1983), fronto-striatal network responsible of executive dysfunctions (Middleton and Strick, 2000), loss of neurons in the nucleus basalis of Meynert leading to cortical cholinergic denervation (Whitehouse et al., 1983) and cholinergic cell loss in pedunculopontine in PDD with hallucinations (Hepp et al., 2013). The noradrenergic network, involved in control of the vigilance with its projections from the locus coeruleus to the thalamus, amygdala and cortex is also compromised in Parkinson's disease (Bertrand et al., 1997).

The altered neurophysiology of motor dysfunctions in PD and DLB, called parkinsonism (a clinical syndrome characterized by tremor, bradykinesia, rigidity, and postural instability), have been clarified.

The motor circuit originates from the precentral and postcentral sensorimotor fields, engages specific portions of the basal ganglia (corpus striatum-caudate nucleus and putamen-, the globus pallidus, the subthalamic nucleus, and the two parts -pars compacta and pars reticularis- of the substantia nigra) and ends back in the precentral motor fields of the frontal lobe.

In healthy subjects there are two pathways involving basal ganglia and the activation of two types of dopamine receptors (D1 and D2) on the striatum by dopaminergic inputs from substantia nigra (pars compacta) (figure 4):

a direct pathway (activation of D1 receptors) involving the neurons projecting from the putamen to the inner part of the Globus Pallidus (GPi) and to the pars reticulata of the Substantia Nigra (SNr), the output nuclei of the BGs. This pathway has an inhibitory effect - GABAergic - directed on the GPi / SNr neurons, thus reducing the excitatory effect of these nuclei on the thalamus, consequently going to promote the movement;

-an indirect pathway (activation of D2 receptors) that connects the putamen with the output nuclei through the external Globus Pallidus (GPe) and the subthalamic nucleus (STN).

The stimulation of this indirect path leads to the inhibition of the GPe, the disinhibition of the STN and the excitement of GPi / SNr. The inhibitory effect on the thalamus is thus improved. The result is a reduction on excitatory glutamatergic input on the cortex and "inhibition" of the movement.

In healthy subjects, the balance between the two pathways allows good motor control. In PD patients, the degeneration of dopaminergic nuclei of the substantia nigra is responsible for unbalance of glutamatergic inputs on motor cortex (Maiti et al., 2017)

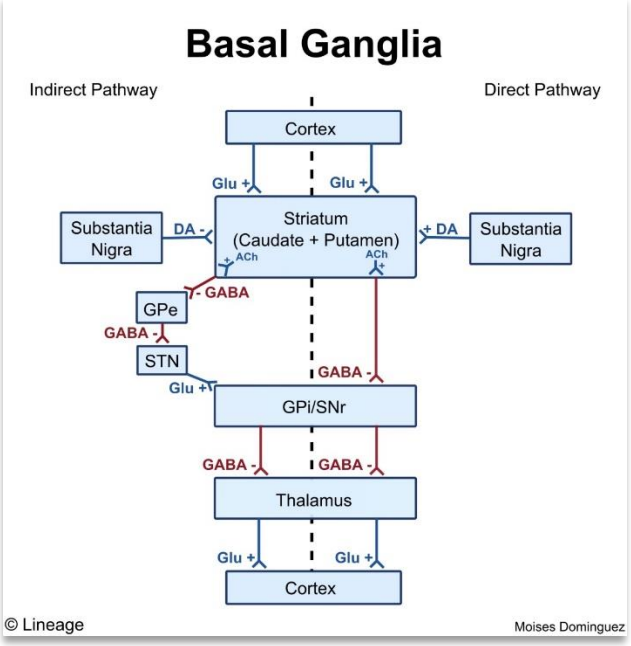

Figure 4*. The image shows the direct and indirect pathways involved in motor control in healthy subjects. Legend: Glu=glutamate, DA=dopamine, STN=subthalamic nucleus, SNr=substantia nigra pars reticulate, GPe= globus pallidus externus, GPi= globus pallidus internus (from https://step1.medbullets.com/neurology/113008/basal-ganglia).*

Clinical features

Alzheimer's, Parkinson's and Lewy Bodies diseases are three complex neurocognitive syndromes influenced by deficits of interrelated cortical (AD, PD, DLB) and subcortical (PD and DLB) networks.

The main clinical symptoms of AD are loss memory and challenges in planning or solving problems probably due to the loss of cholinergic nuclei. However, other many symptoms are very common: difficulty completing familiar tasks at home, at work or at leisure; confusion with time or place; trouble understanding visual images and spatial relationships; new problems with words in speaking or writing; misplacing things and losing the ability to retrace steps; decreased or poor judgment; withdrawal from work or social activities; changes in mood and personality, including apathy and depression (Alzheimer's Association, 2014). However, the content of these symptoms will vary dramatically from patient to patient, depending upon their premorbid personality, life experiences, and social as well as cultural influences. In this contest, the caregiver plays an important role in the management of the disease even if this role pays high costs in terms of money and quality of life.

PDD and DLB are affected by attentional, executive, memory dysfunctions, mood disturbances and parkinsonism (defined as bradykinesia in combination with rest tremor, rigidity, or both). Most prominent are the executive dysfunctions which term indicates several cognitive abilities, including problem-solving, planning/sequencing, rule-shifting/maintenance, task-switching, manipulation in working memory and response inhibition already present at the onset of Parkinson's disease (Dubois and Pillon, 1997). The main hypothesis is that these dysfunctions are due to degeneration of fronto-striatal network but, the new evidence, *post mortem*, have shown a degeneration of the projections of ventral tegmental area (VTA) in the mid brain to the limbic region (mesocortical dopamine network) (Scatton et al., 1983). Executive functions are probably more impaired in PDD than in DLB. Visual symptoms, common in PDD likely due to a reduced metabolism in both dorsal and ventral visual pathway, include visual hallucinations, although they are less common than in DLB. Other non-motor features, including autonomic dysfunctions and sleep disorders may occur according to the severity of dementia, while mood disturbances have a similar frequency as in DLB (Jellinger and Korczyn, 2018). Even if PDD and DLB have many similar clinical aspects, there are differences in timing and in the profile that allow to identify two different clinical syndromes and apply separate diagnostic criteria. Table 1 sums up in the detail, the overlap and the differences between them. Furthermore, before the stage of dementia, there are more evidence clinical features. In Parkinson's disease, patients primarily suffer from extrapyramidal symptoms that can be followed by slow cognitive impairment, not always progressing in dementia.

In patients with Lewy bodies disease have been identified core clinical features, present already in the first stages of the disease. The core clinical features of DLB have been well described by the DLB Consortium (McKeith et al., 2017) and are summed up in the following: (a) fluctuation: DLB fluctuations occurring as spontaneous alterations in cognition, attention, and arousal. They include incoherent speech, variable attention, or altered consciousness. At least one measure of fluctuation should be documented when applying DLB diagnostic criteria. Fluctuations may also occur in advanced stages of other dementias, so they best predict DLB when they are present early; (b) visual hallucinations: recurrent, complex visual hallucinations occur in up to 80% of patients with DLB and are a frequent clinical sign post to diagnosis. They are typically well-formed, featuring people, children, or animals, sometimes accompanied by related phenomena including passage hallucinations, sense of presence, and visual illusions; (c) parkinsonism: spontaneous parkinsonian features, such as bradykinesia and rigidity, are common in DLB, eventually occurring in over 85%, while rest tremor is less frequent (Fritz et al., 2016). Many DLB patients' parkinsonism falls short of this, so documentation of only one

of these cardinal features is required; (d) REM sleep behavior disorder: RBD is a parasomnia manifested by recurrent dream enactment behavior that includes movements mimicking dream content and associated with an absence of normal REM sleep atonia. RBD is now included as a core clinical feature because it occurs frequently in autopsy-confirmed cases compared with none-DLB (76% vs 4%). Conditions mimicking RBD are common in people with dementia, e. g., confusional awakenings, severe obstructive sleep apnea, and periodic limb movements, all of which must be excluded by careful supplementary questioning to avoid a false-positive diagnosis.

Table 1 Clinical overlap and dissimilarities between dementia with Lewy bodies (DLB) and Parkinson disease with dementia (PDD)

Overlap	Dissimilarities
Rigidity, akinesia	Some cognitive dysfunctions: deficiencies of attention greater, episodic verbal memory tasks lower in DLB
Cognitive impairments	Tremor less frequent in DLB
Frontal executive dysfunction	Motor performance: slower walk and poorer balance in DLB
Visual-constructive impairment	Hallucinations (visual) more frequent in DLB
Mild language impairment	Relative timing of dementia and parkinsonism (one year rule)
Mood disturbances (depression, anxiety)	Onset of dementia earlier in PDD
REM sleep behavior disorder (RBD)	Orthostatic hypotension more frequent in DLB
Neuroleptic sensitivity	Frontal/temporal-associated cognitive subsets more severe in DLB, cognitive decline is faster in DLB/DLB+AD
	Delusions, visual hallucinations, and attentional fluctuation more frequent in DLB
	Visual hallucinations: spontaneous in DLB; after L-dopa therapy in PDD, but also in drug-naive cases

AD Alzheimer disease

Table 1 *shows the clinical overlap and dissimilarities between dementia with Lewy bodies and Parkinson's disease with dementia (PDD) (Jellinger and Korczyn, 2018).*

Risk factors

The identification of the risk factors could help to improve the monitoring of those patients with higher probability to get ill. However, the AD, PD and DLB are multifactorial diseases with both familiar/genetic risk factors for AD and sporadic factors for PD and DLB, both sporadic genetic risk due to co-morbidity of aging-diseases and lifestyle quality. The occurrence of the AD due to familial/genetic risk factors came in the early aging, before 65 years, while the AD due to sporadic (not from the birth) genetic mutation has a late-onset occurrence, later 65 years. In less of 1%, the cases of the AD depend on three genes mutation (Bekris et al., 2010). More specifically, these three genes are those encoding for the amyloid precursor protein (APP) and the genes for the presenilin 1 and presenilin 2 proteins (regulating the action of the enzyme γ-

secretase, seen in the above paragraph). The transmission of these genes is autosomal dominant that means the presence of almost one copy (allele) of these three genes mutated from the birth (inherited from a parent) will be responsible for the early onset of the AD. The mutation of presenilin 2 induces the development of the AD with 95% of probability (Goldman et al., 2011). Concerning the PD and DLB, different sporadic genetic factors may be involved in the etiopathology of PDD and DLB: mutations in *SNCA*, the gene of α-synuclein as well as mutations in GBA (glucocerebrosidase), and MAPT (microtubule-associated protein tau) may be responsible on the onset of the two diseases (McKheit et al., 2017) even if the pathological mechanisms are not yet clarified. Other risk factors to consider for all three diseases are: (a) aging; (b) APOE-ε4 Gene: the APOE gene provides the blueprint for a protein that transports cholesterol in the bloodstream. Everyone inherits one of three forms of the APOE gene (ε2, ε3 or ε4) from each parent. The ε3 form is the most common, and the ε2 form the least common. Those who inherit one copy of the ε4 form have a three-fold higher risk of developing AD than those without the ε4 form, while those who inherit two copies of the ε4 form have an 8- to 12-fold higher risk (Alzheimer's Drug Discovery Foundation, 2015; Loy et al., 2014). In addition, those with the ε4 form are more likely to develop AD at a younger age (Spinney, 2014). Having the ε2 form may decrease one's risk compared with having the ε3 form. While the above-mentioned risk-factors are inevitable, other risk factors can be modified to reduce risk of cognitive decline and dementia; (c) Cardiovascular Disease Risk Factors: the factors that increase the risk of cardiovascular disease are also associated with a higher risk of dementia such as smoking (Beydoun et al., 2014), obesity in midlife (Rönnemaa et al., 2001) and diabetes (Gudala et al., 2013). Midlife hypertension (Rönnemaa et al., 2001) and midlife high cholesterol are also implicated as risk factors for dementia; (d) education: According to the "cognitive reserves" hypothesis, having more years of education builds a "cognitive reserve" that enables individuals to better compensate for changes in the brain that could result in symptoms of AD or PD or DLB (Stern Y., 2012); (e) traumatic Brain Injury (TBI): compared with no TBI, moderate TBI is associated with twice the risk of developing Ad, PD or DLB, and severe TBI with 4.5 times the risk (Plassman et al., 2000).

A precursor to dementia: Mild cognitive impairment (MCI)

Mild cognitive impairment (MCI) is considered a clinical state showing objective impairment on neuropsychological tests, but not fulfil the clinical criteria for dementia (Flicker et al., 1991; Petersen et al., 2001). Individuals with MCI convert to dementia at a rate of approximately 5-

10% per year in contrast to 1-2% in healthy controls (Petersen, 2011), and it is under debate if MCI may represent a prodromal stage of AD or other forms of dementia (Petersen et al., 2014). As such, MCI represents an important group for the early identification of those at risk of developing dementia, as well as for implementing early treatment options. The revised National Institute on Aging-Alzheimer's Association (NIA-AA) diagnostic criteria (Albert et al., 2011) defined two main subtypes of MCI: (1) amnestic MCI (aMCI), defined by the presence of episodic memory impairment, and (2) non-amnestic MCI (naMCI), defined by impairment in one or more non-memory cognitive domains. The impairment can further be classified as single domain (impairment restricted on one cognitive domain), or multiple domains (impairment in two or more cognitive domains). For example, 70-90% of aMCI patients who progress to dementia show clinical signs of AD (Petersen et al., 2009; 2001), and naMCI patients may progress to others dementing conditions such as Lewy body dementia, frontotemporal dementia, or vascular dementia (Jack et al., 2009; Petersen et al., 2009). The current consensus is that most MCI patients who convert in AD mostly exhibit an impairment in episodic memory, but other cognitive domains may also be impaired (Albert et al., 2011). The neuropathological features of aMCI include the presence of neurofibrillary tangles in the medial temporal lobes, diffuse cortical amyloid deposition, synaptic loss, and degeneration of the cholinergic system (Drago et al., 2011; Mufson et al., 2012; Stephan et al., 2012). Furthermore, MCI patients show a significant neuronal loss in the entorhinal cortex and hippocampus (Mufson et al., 2012; Stephan et al., 2012). There is some evidence that levels of amyloid deposition may be related to cognitive function in healthy older adults without cognitive impairment and in MCI patients, but not in AD patients (Villemagne et al., 2008), which may be related to the rapid accumulation of amyloid in the early and preclinical phases of the disease followed by a plateau in the later stages (Masdeu et al., 2012). Therefore, the correlation between the amyloid deposition and cognitive impairment remains unclear but emerging evidence is suggestive of a greater relationship as described in the following paragraphs.

Diagnostic criteria for AD

The diagnostic criteria of Alzheimer's disease are still under debate. Only the brain autopsy, after death, can confirm the diagnosis due to the abnormal accumulation of neurofibrillary tangle and Aβ protein in the whole brain. However, mental and behavioral tests and physical examinations allow physicians to make an accurate diagnosis of AD in 90 percent of cases (American Health Assistance Foundation, AHAF, 2010). Neuropsychological examinations

may be used to identify cognitive symptoms. The most commonly administered tests are the Mini-Mental State Exam (MMSE) (the score from 0 to 30, where a score under 12 indicates severe dementia) and some cognitive scales of Alzheimer's Disease Assessment (ADAS cog; Skinner et al., 2013). AD patient's scores typically decrease 2 to 4 points every year (Alzheimer's Association, 2014). The actually challenge is to define diagnostic criteria able to identify the disease in the early stage, before the manifestation of clinical symptoms for a quick intervention and preventing the fast neurodegenerative process. MMSE offers only a marginal assessment of some cognitive abilities which are considered important both for AD and other types of dementia and, furthermore, it doesn't result sensitive to the cases of very mild cognitive impairment. The ADAS results deficient in test-retest reliability and the performance of the patients seems to be influenced by other factors, such as their mood at the time of the task. Such neuropsychological assessment, therefore, seems to be not able to discriminate AD risk in a preclinical phase (in cognitively healthy elderly subjects) and the potential conversion from a preclinical form to AD or from MCI to AD (Lin et al., 2011). Thus, an accurate diagnosis of AD results to be very complex, also because of the presence, in elderly subjects, of comorbidities that might contribute to the cognitive impairment. Besides the diagnostic criteria of the Diagnostical and Statistical Manual of Mental Disorders (DSM-V), the diagnosis of AD patients is also based on the parameters of National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association (NINCDS_ADRDA- Mc Khan et al., 1984). According to these criteria, AD can be classified as "well-defined AD" (clinical diagnosis with histological confirm), "probable AD" (typical clinical syndrome without histological confirm) and "possible AD" (atypical clinical characteristics that seem not to have an alternative diagnosis without histological confirm). Although the great sensitivity and specificity of the NINCDS-ADRDA criteria, AD cases are very often diagnosed in an advanced stage of cognitive impairment (Knopman et al., 2001). Dubois et al. (2007) proposed the concept of "prodromal AD" and exhibited new additional criteria for the detection of the different phases of the disease: the main core of this assumption is based on the presence of several impairments of episodic memory which, together with a possible presence of diagnostic biomarkers, identify AD in the entire course of the clinical disease's spectrum. The first criterion, the criterion A, specifies that a deficit of episodic memory, assessed with specific tests, must be present. The presence of a biological mark is established by the criterion B (structural image), the criterion C (cerebrospinal fluid), the criterion D (molecular image), or the criterion E (dominant mutation in the family). The new criteria highlight the importance of neuroimaging techniques in the diagnostic procedures of

AD and consider also preclinical and early phases of the disease. In 2011, the National Institute on Aging (NIA) and the Alzheimer's Association proposed revised criteria and guidelines for diagnosing Alzheimer's disease (Sperling et al., 2011; Albert et al., 2011). These criteria and guidelines update diagnostic criteria and guidelines published in 1984 by the ADRDA (McKhann et al., 1984) and incorporate three notable changes: (1) they identify two stages of Alzheimer's disease: mild cognitive impairment (MCI) due to Alzheimer's disease and dementia due to Alzheimer's disease; (2) they propose criteria for a preclinical phase of Alzheimer's disease, occurring before symptoms such as memory loss develop; (3) they incorporate biomarker tests.

In 2014, Dubois and colleagues from the International Working group (IWG) proposed a method to simplify the diagnosis for AD. They indicated an appropriate clinical AD phenotype (typical such as with evidence of a specific episodic memory profile characterized by a low free recall and reduction of hippocampal volume; or atypical, less frequent but well defined clinical phenotypic variants of non-amnestic focal cortical syndromes, including logopenic aphasia, posterior cortical atrophy, and frontal variant AD) and a pathophysiological biomarker. They proposed topographical biomarkers of the disease, such as volumetric MRI to identify hippocampal atrophy and fluorodeoxyglucose PET for the accumulation of Aβ-amyloid in the brain to better monitor the course of the disease. Furthermore, they proposed a revision for typical AD: "*A research diagnosis of typical AD can be made in the presence of an amnestic syndrome of the hippocampal type that can be associated with various cognitive or behavioral changes, and at least one of the following changes indicative of in-vivo Alzheimer's pathology: a CSF profile consisting of decreased Aβ1–42 levels together with increased T-tau or P-tau concentrations, or an increased retention on amyloid tracer PET*". The most innovative aspect of the 2007 criteria was the first introduction of biomarkers into the core diagnostic framework. Finally, the last diagnostic criteria have been proposed by Jack and colleagues in 2018 of the National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework.

Alzheimer's disease is defined based on specific pathological processes, deviating from the approach based on the observation of clinical symptoms and the deterioration of cognitive and functional functions. This new theoretical framework defines the disease based on the in vivo presence of specific toxic proteins, by biochemical analysis or neuroimaging methods. According to the authors, the biological definition of AD is independent of the clinical phenotype (typically the presence of memory deficits) but based on the A / T / N scheme, where "A +" and "T +" denote the pathological state of beta-amyloid protein (Aβ) and phosphorylated

tau, respectively, while "N +" refers to the presence of neurodegeneration (e.g. hypometabolism or cortical atrophy). According to this new definition, AD is referred to in a continuum, in which the alterations of the different proteins define the state of disease. An "A-" individual will be considered not affected by AD (or with non-AD type pathological changes, if "T +" and / or "N +"), while an individual with a pathological state limited to the Aβ protein ("A +", "T-" and "N-") will be in a condition that the authors define as AD pathological change, i.e. at an early stage of illness. The diagnosis of AD can instead be applied together with the presence of a pathological state of "A +" and "T +". An "N +" state (evidence of neurodegeneration) does not support the diagnosis but is an indicator of the disease stage.

Diagnostic criteria for PD

According to the guideline described by Movement Disorder Society (MDS) Task Force (Emre et al., 2007), the diagnosis of dementia associated with Parkinson's disease is possible if the patient shows the following core and associate cognitive/behavioral features:

Core features: (a) diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria (for parkinsonism evaluation); (b) dementia syndrome defined as: impairment in more than one cognitive domain; representing a decline from premorbid level; deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms.

Associated clinical features: (a) cognitive features impaired (attention, executive functions, visuo-spatial functions, memory and language); (b) behavioral features (apathy, depression, hallucinations, delusions, excessive daytime sleepiness).

The diagnosis is uncertain if the following points are verified: (a) co-existence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g. presence of relevant vascular disease in imaging; (b) time interval between the development of motor and cognitive symptoms not known.

The diagnosis of probable PDD is made if there are both core features and the following associate clinical features: (a) typical profile of cognitive deficits including impairment in at least two of the four core cognitive domains (impaired attention which may fluctuate, impaired executive functions, impairment in visuo-spatial functions, and impaired free recall memory which usually improves with cueing); (b) the presence of at least one behavioral symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness)

supports the diagnosis of Probable PDD, lack of behavioral symptoms, however, does not exclude the diagnosis.

The diagnosis of possible PDD is made if there are both core features and the following associate clinical features: (a) atypical profile of cognitive impairment in one or more domains, such as prominent or receptive-type (fluent) aphasia, or pure storage-failure type amnesia (memory does not improve with cueing or in recognition tasks) with preserved attention; (b) behavioral symptoms may or may not be present.

The MDS task Force has also described the guideline for the identification of Parkinson's disease with mild cognitive impairment (PDMCI). The criteria described are in the following: (a) diagnosis of Parkinson disease (PD) is based on the UK PD Brain Bank Criteria; (b) gradual decline in cognitive ability in the context of established PD, reported by either the patient or informant or observed by the clinician; (c) cognitive deficits on either formal neuropsychological testing or a scale of global cognitive abilities; (d) cognitive deficits are not sufficient to interfere significantly with functional independence, although subtle difficulties on complex functional tasks may be present.

Furthermore, there are two subtypes classification:

PD-MCI single-domain: abnormalities on two tests within a single cognitive domain (specify the domain), with other domains unimpaired;

PD-MCI multiple-domain: abnormalities on at least one test in two or more cognitive domains (specify the domains).

Diagnostic criteria for DLB

According to the guideline of DLB Consortium (McKeith et al., 2017), the diagnosis of DLB is made if the patient shows the following *core clinical features* (the first 3 typically occur early and may persist throughout the course): fluctuating cognition with pronounced variations in attention and alertness; recurrent visual hallucinations that are typically well formed and detailed; REM sleep behavior disorder, which may precede cognitive decline; one or more spontaneous cardinal features of parkinsonism: these are bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity.

Other *supportive clinical features* that could help for the diagnosis are: severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction, e.g., constipation, orthostatic hypotension,

urinary incontinence; hypersomnia; hyposmia; hallucinations in other modalities; systematized delusions; apathy, anxiety, and depression.

Furthermore, the recent scientific advances have discovered *indicative biomarkers* as: reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET; abnormal (low uptake) 123iodine-MIBG myocardial scintigraphy; polysomnographic confirmation of REM sleep without atonia.

Other *supportive biomarkers* are: relative preservation of medial temporal lobe structures on CT/MRI scan; generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity the cingulate island sign on FDG-PET imaging; prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range.

Probable DLB can be diagnosed if: (a) two or more core clinical features of DLB are present, with or without the presence of indicative biomarkers; or (b) only one core clinical feature is present but with one or more indicative biomarkers.

Possible DLB can be diagnosed if: (a) only one core clinical feature of DLB is present, with no indicative biomarker evidence; or (b) one or more indicative biomarkers is present but there are no core clinical features.

DLB is diagnosed when dementia precedes or is concurrent with parkinsonism. Parkinson disease dementia should be used to describe dementia that occurs in the context of well-established Parkinson disease. For research studies that distinguish between DLB and Parkinson disease dementia, a 1-year rule is recommended for a diagnosis of DLB, such that dementia should begin no later than 1 year after the onset of parkinsonism.

Finally, the scientific community is trying to identify clinical features of patients who will develop DLB with dementia. Today, the criteria are limited but some studies reported disturbances of REM sleep, mild deficits in attentional and executive functions and subtle parkinsonism in patients that have developed probable DLB (Ferman et al., 2013).

Pre-clinical biomarkers

Neuroimaging and fluid biomarkers are a promising area of research for detecting AD, PD and DLB (Saeed et al., 2017). Multiple brain imaging procedures can be used to identify abnormalities in the brain, including Positron Emission Tomography (PET), Magnetic Resonance Imaging (MRI), and Computed Tomography (CT) scans. The high spatial resolution, sensitivity and specificity of MRI are the reason why this technique is considered the most powerful instrument to identify structural alterations and cerebral atrophy using

volumetric measures of the entire brain (Kochunov et al., 2005). The most consistent evidence showed by MRI studies in AD patients greater atrophy of medial temporal lobe (MTL, hippocampus, amygdala, entorhinal cortex and parahippocampal gyrus) structures than patients with DLB, particularly the hippocampus, which is strongly correlated at autopsy with tangle rather than plaque or LB-related pathology (Burton et al., 2009). Furthermore, MRI in AD shows the ventricular dilatation and a reduced total volume in the brain (Busatto et al., 2008). In AD, this atrophy is localized at medial temporal limbic cortex level during the initial phases of the disease. Later, the atrophy progresses and expands to paralimbic cortical regions and to the neocortex (Braak et al., 2003). The temporal limbic cortex has a fundamental role in episodic memory and, given that memory deficit is the first symptom in AD, it results to be the main target in neuroimaging studies (Xu et al., 2000; De Santi et al., 2001).

Several longitudinal MRI studies provided valid information about preclinical stages of the disease: the grey matter atrophy is also seen in MCI subjects and the medial temporal lobe atrophy might be considered as a neurostructural biomarker of MCI-AD conversion (Schroeter et al., 2009). Some authors revealed that reduced hippocampal volume might be seen even six years before the onset of the disease (den Heijer et al., 2006; Csernansky et al., 2005). Ulterior sub-regional analysis has shown that in subjects with normal cognition, the volume of some restricted parts of hippocampus (CA1 and subiculum) is more closely associated to the conversion to MCI compared to the hippocampus total volume. Volume loss in these regions precedes cognitive impairment and conversion to MCI by several years and it's able to discriminate cognitive stable individuals from MCI individuals with an accuracy of more than 93% (Apostolova et al., 2010). The volume of the entorhinal cortex also seems to predict cognitive impairment in elderly subjects with normal cognition with an accuracy of 90% (Martin et al., 2010).

FDG-PET and SPECT, provide information about glucose regional metabolism and cerebral perfusion, respectively. The characteristic pattern in AD patients is that of hypometabolism/hypoperfusion of parietal-temporal cortex (Herholtz et al., 2002).

PET images of amyloid-binding agent Pittsburgh compound B tracer (PET-PiB), hypometabolism in temporoparietal regions, established by FDG-PET and structural abnormalities observed with MRI, are the first markers of Alzheimer's disease to be described (Ikonomovic et al., 2008; Small et al., 2000).

PET images allow in vivo analysis of Aβ42 presence in the brain and their spatial distribution. PiB results to be closely related to amyloid plaques burden revealed in the autopsy.

Hypometabolism in temporoparietal regions reflect also changes in cerebral structure and result evident before the onset of cognitive symptoms in AD.

Dubois and colleagues in 2007 have described the important role of cerebrospinal fluid's marker (CSF) in preclinical stages of Alzheimer's disease. It deals with the concentration of Aβ42, total tau (t-tau) and phosphorylated tau (p-tau) in the CSF reflecting the abnormal accumulation in the brain. They have defined "topographical biomarker" if they identify downstream brain changes indicative of the regional distribution of Alzheimer's pathology (Dubois et al., 2007). Generally, healthy elderly people show a higher level of amyloid protein compared to healthy younger people, but the neurophysiological process allows to excreted in the CSF the abnormal proteins that are toxic for the health. Since in the AD patients there is a higher accumulation of amyloid plaques in the brain, it means that it is not correctly excreted in the CSF. On the contrary, high levels of tau protein in the CSF reflect the progression of the disease associated to the presence of tau protein in the cerebral cortex (Seppala et al., 2012). Thus, low levels of Aβ42 together with increased levels of p-tau and t-tau in the CSF are able to identify AD with good accuracy. However, even if low levels of Aβ42 in the CSF appear early in AD course and seem to predict the conversion from MCI to AD (Buchhave et al., 2012), in some cases, they appear earlier in subjects with a normal cognition, during a phase that precedes MCI condition (Fagan et al., 2009). It is not already clear if a decrease in CSF Aβ42 concentration levels precedes the increase of tau levels or vice-versa (Fagan et al., 2009).

It was shown that the reduction of CSF Aβ42 levels precedes the cognitive impairment in non-demented subjects by about 8 years and a combination of this index with p-tau levels increases its sensitivity and specificity in predicting dementia (Stomrud et al., 2007). In independent AD familiar studies, the decrease in Aβ42 levels and the increased levels of tau in the CSF of asymptomatic individuals who were pathogenic mutations PSEN1 and APP carriers were found more than 10 years before the onset of the cognitive symptoms (Ringman et al., 2012; Moonis et al., 2005). Dubois et al. (2014) assert that the information about low Aβ42 and high p-tau and t-tau concentrations in CSF, significantly increases the accuracy of AD diagnosis even at a prodromal stage. However, CSF biomarkers cannot be used as standalone tests, and should be interpreted in a larger clinical context with confounding factors taken into account. In conclusion, pathophysiological biomarkers of AD, allows to identify asymptomatic patients at risk for AD (Morris et al., 2009). Thus, the combination of a specific cognitive profile, consistent with typical or atypical AD, and a positive pathophysiological marker moves the patient from an underestimated status of MCI to that of prodromal AD (Dubois et al., 2014).

In contrast, the development of broadly applicable CSF, blood, peripheral tissue, or genotypic biomarkers for DLB remains elusive. CSF a-synuclein is not yet proven as a biomarker. In DLB, the (DaTScan) SPECT or 18Fluorodopa PET show a higher reduction of dopamine transport binding in caudate and posterior putamen compared to AD, but no differences DLB and PDD (Marquie et al., 2014; Gomperts et al., 2016). Voxel-based morphometric MRI studies revealed greater grey matter loss in frontotemporal, occipital, and parietal areas in DLB compared to PDD (Beyer et al.,2007). 11C PIB-PET imaging showed increased Aβ brain deposition in more than 50% of DLB cases, with more modest and less frequent Aβ accumulation in PDD (Gomperts et al., 2016).

On the contrary, PDD, compared to DLB, have a lower dopamine uptake in striatum, proportional with dopaminergic cell loss in substantia nigra pars compacta and the severity of parkinsonism (Colloby et al., 2012). White matter hyperintensities (WMH) on T2- weighted MRI have been observed in parieto-occipital areas in PDD cases with low CSF Aβ levels (Compta et al., 2016), without significant difference of progression between PDD and DLB (Burton et al., 2006), but more severe WMHs have been observed in the temporal lobe in DLB (Sarro et al., 2017). With the support of MRI, WMH may be a powerful diagnostic tool to investigate the progression of AD-related pathology in DLB and perhaps to distinguish DLB from PDD (Burton et al., 2006). Preliminary tau-PET studies suggest a gradient of tau binding from PD/non-demented (minimal) to PDD (low), DLB (intermediate), and AD (highest) (Bohnen et al., 2017). 123Iodine-MIBG myocardial scintigraphy quantifies postganglionic sympathetic cardiac innervation, which is reduced in LB disease (McKeith et al., 2017). Evidence is building to support quantitative EEG as a DLB biomarker, characterized by specific abnormalities in posterior derivations. These include a pre-alpha-dominant frequency, either stable or intermixed with alpha/theta/delta activities in pseudoperiodic patterns (Bonanni et al., 2008).

Clinical management of dementia

Currently, there aren't a disease-modifying therapies for AD, PD and DLB but many drugs are used to treat the clinical symptoms. The use of cholinesterase inhibitors (ChEIs) (Wang et al., 2015; Galasko, 2017) is common as pharmacological therapy as the reduction of cholinergic markers has been demonstrated in ADD, PDD and DLB (Klein et al., 2010; Shimada et al., 2009). Donepezil and rivastigmine have beneficial effects on both cognitive and psychiatric symptoms as they may reduce apathy, visual hallucinations, and delusions (Tsuno et al., 2015;

Sobow et al., 2007). The use of antipsychotics should be avoided for their negative effects on motor symptoms (Burghaus et al., 2012). Low-dose quetiapine may be relatively safer than other antipsychotics and is widely used, but a small placebo-controlled clinical trial in DLB was negative (Connolly et al., 2012). Levodopa, a precursor of dopamine, is administered for the treatment of the parkinsonism and it is generally well tolerated but produces significantly less motor response in DLB than in PD and may be associated with an increased risk of psychosis (Galasko, 2017; Goldman et al., 2008). Additionally, strategies to decrease the level of αSyn, to prevent cell-to-cell transmission of misfolded αSyn, and deep brain stimulation of the cholinergic nucleus basalis of Meynert have been discussed (Zhang et al., 2015). A recent review of non-pharmacological interactions for DLB gave no definite results (Connors et al., 2017), while bilateral deep brain stimulation of the NBM for PDD showed potential improvement of neuropsychiatric symptoms (Gratwicke et al., 2018).

Methodological Part

The electroencephalography (EEG)

The electroencephalography (EEG) is a non-invasive method to record the electrical activity of the brain along the scalp. It presents a high temporal resolution, on the milliseconds scale, adequate to follow brain activity, but a relatively modest spatial resolution (over the centimetre), fundamentally limited by the inter-sensors distances and by the fundamental law of electromagnetism. Hans Berger, in 1929, discovered a difference in electrical potential between the needles inserted into the scalp or between two small metal plates (electrodes) when they were placed in contact with the skin. Later, the EEG technique was perfected by Herbert Jasper: he found the potential difference between an active electrode (which records the neuronal activity), and a reference electrode. The EEG is mainly a result of the summation of postsynaptic potentials occurring at the cortical level, involving the synchronous activity of about a hundred thousand neurons. If the cells do not have similar spatial orientation, their ions do not line up and create waves to be detected. Pyramidal neurons of the cortex are thought to produce the most EEG signal because they are well-aligned and fire together.

Electrodes are placed on specific sites on the scalp to detect and record the electrical impulses within the brain. EEG activity shows oscillations with several characteristics (e.g. frequency ranges, spatial distributions, etc…) associated with different states of brain functioning (e.g., waking and the various sleep stages). A frequency is the number of times a wave repeats itself within a second. If any of these frequencies are deficient, excessive, or difficult to access, our mental performance can suffer. Amplitude represents the power of electrical impulses generated by the brain. Volume or intensity of brain wave activity is measured in microvolts. The electroencephalography is typically described in terms of rhythmic activity and transients. The rhythmic activity is divided into frequency bands: gamma greater than 30Hz, beta (13-30Hz), alpha (8-12 Hz), theta (4-8 Hz), and delta (less than 4 Hz). To some degree, these frequency bands are a matter of nomenclature, but these designations arose because rhythmic activity within a certain frequency range was noted to have a certain distribution over the scalp or a certain biological significance.

Frequency bands

The range of the clinically relevant EEG frequency components lies between 0.1 and 100 Hz and commonly in routine clinical settings it may be more restricted (i.e., between 0.1 and 70 Hz) (Amzica and Lopes da Silva, 2017). The main frequency bands are shown in Figure 1 and described below:

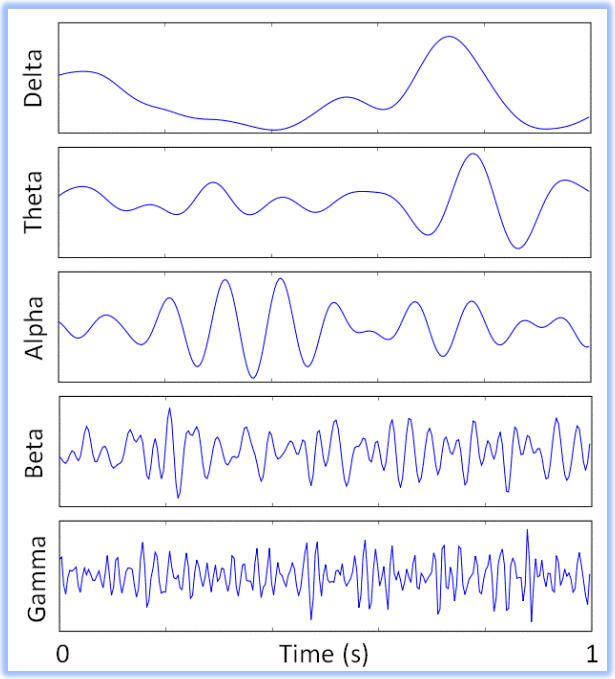

Figure 1. *Normal adult brain waves (they are referred to 1 s of duration): delta (< 4 Hz), theta (4-7 Hz), alpha (8-13 Hz), beta (14-30 Hz), and gamma (30-100 Hz).*

Delta is the lowest frequency (range up to 4 Hz). It is the physiological rhythm of the third and fourth stage of human sleep and anaesthesia. It may also occur in the presence of subcortical lesions. It is usually most prominent frontally in adults (i.e. FIRDA - Frontal Intermittent Rhythmic Delta) and posteriorly in children (i.e. OIRDA - Occipital Intermittent Rhythmic Delta). The delta band is characterized by high amplitude and slow waves. At the neurophysiological level, the presence of delta rhythm can be explained by the interplay between two membrane currents:

the transient calcium current (I_t) underlying the low-threshold spike (LTS) and a hyperpolarization-activated cation current (I_h) in thalamocortical cells.

The activation of lowthreshold calcium current induces the depolarization of membrane toward threshold for a burst of sodium-dependent fast action potentials. Then, the depolarization inactivates the portion of I_h that was active immediately before the calcium spike. Repolarization of the membrane due to I_t inactivation is followed by a hyperpolarizing overshoot due to the reduced depolarizing effect of I_h. The hyperpolarization in turn de-

inactivates I_h and activates I_t, which depolarizes the membrane toward threshold for another calcium spike (Amzica and Lopes da Silva, 2017).

Theta is the frequency range from 4 Hz to 7 Hz. Theta is seen normally in young children. It may be seen in drowsiness or arousal in older children and adults; excess theta for age represents abnormal activity. It can be seen as a focal disturbance in focal sub-cortical lesions; Theta rhythm should not be confused with a slowing down of alpha activity seen in metabolic encephalopathy or deep midline disorders or some instances of hydrocephalus (Ingvar et al., 1976; Saunders and Westmoreland, 1979). Theta is believed to reflect activity from the limbic system and hippocampal regions. Theta is observed in anxiety, behavioral activation and behavioral inhibition. When the theta rhythm appears to function normally it mediates and/or promotes adaptive, complex behaviors such as learning and memory. About the generation of the theta rhythm there isn't a clear mechanism. The main hypothesis points the focus on the activity of the achethylcoline on the hippocampal interneurons, which activation give impulses of theta rhythm toward the pyramidal cells of the cortex. The main network involved in this connection is the supramammillary nucleus of the hypothalamus to the medial septum with the extention to the brainstem and diencephalon. However, it seems that also glutamatergic inputs could play a role in the generation of theta rhythm (Amzica and Lopes da Silva, 2017).

Alpha is the frequency range from 7 Hz to 13 Hz, generally with a predominant peak at 10 Hz. Alpha is a common state for the brain and occurs whenever a person is alert (it is a marker for alertness and sleep), but not actively processing information. It emerges with closing of the eyes and with relaxation, and attenuates with eye opening or mental exertion. Alpha rhythm is more evident in the occipital cortex.The posterior basic rhythm is actually slower than 8 Hz in young children (therefore technically in the theta range). Besides the classic alpha rhythm of the visual cortex, there are rhythmic activities in the same frequency range that can be recorded from the somatosensory cortex (called the mu rhythm) and the temporal cortex (called the tau rhythm). Experimental studies in vivo and in vitro have tried to explained the mechanism of the generation of the alpha rhythm. With the application of fine microelectrode arrays in monkeys (across the visual cortex and inferior temporal cortex), alpha current generators were found in all layers, with the infragranular neurons (layer V) acting as primary local generator in the visual cortex, in contrast, in the inferior temporal cortex, alpha current generators were found in supragranular (layers I-III) and infragranular layers (layers V-VI), with the supragranular generator acting as the primary local generator. However, the alpha activity recorded in the

cortex should be driven by the activion of thalamic cells (Amzica and Lopes da Silva, 2017). In vitro experiments in the nucleus geniculate of cats have shown the generation of the alpha rhythm after the activation of metabotropic receptor of glutamate (mGLUR1a) localized on postsynaptic level of the corticothalamic fibers (Hughes and Crunelli, 2005).

Beta is the frequency range from 14 Hz to about 30 Hz. It is fast activity and it reflects desynchronized brain tissue as it is a proper rhythm of the wakefulness. It is seen usually on both sides in symmetrical distribution and is most evident frontally. Beta activity is closely linked to motor behavior and is generally attenuated during active movements. Low amplitude beta with multiple and varying frequencies is often associated with active, busy or anxious thinking and active concentration. Rhythmic beta with a dominant set of frequencies is associated with various pathologies and drug effects, especially benzodiazepines. It may be absent or reduced in areas of cortical damage. It is the dominant rhythm in patients who are alert or anxious or who have their eyes open. Beta rhythm is generated by the combination of achethylcoline, serotonin and noradrenaline on nucleus reticularis of thamalus that activate thalamic cells and prevent the slow waves activity on the cortical cells.

Gamma is the frequency range of approximately 30–100 Hz. Gamma rhythms are thought to represent binding of different populations of neurons together into a network to carry out a certain cognitive or motor function. When the brain needs to simultaneously process information from different areas, its hypothesized that the 40Hz activity consolidates the required areas for simultaneous processing. A good memory is associated with well-regulated and efficient 40Hz activity, whereas a 40Hz deficiency creates learning disabilities. Synchronized gamma frequency oscillations are generated by the activation of acetylcholine muscarinic receptors, enhanced with arousal and attention, and also by electrical stimulation of the mesencephalic reticular formation.

EEG data acquisition

The *International Federation of Clinical Neurophysiology* (IFCN) has described the parameters to record brain activity in resting state condition. In clinical research, resting state electroencephalographic (rsEEG) rhythms are often recorded from the patient's scalp during short (i.e., minutes) eyes-closed and -open conditions. This research mainly focuses on abnormalities in the frequency and topographical features of rsEEG rhythms to unveil neural

dysfunctions in the regulation of quiet wakefulness in psychiatric and neurological diseases. Vigilance dysregulations may affect the selectivity and efficiency of several higher cognitive functions such as attention (i.e., focused, sustained, selective or reflexive), episodic memory (i.e., encoding and retrieval of autobiographical events), and executive frontal functions (i.e., working memory and inhibitory control). Firstly, a few days prior to the recording of rsEEG rhythms, subjects should be instructed to have regular sleep on the night before that recording. Subjects should also be instructed not to use psychoactive substances and medications (i.e., foods and drinks including nicotine, caffeine, alcohol, and other stimulants in any form in the morning of the experiment). Subjects may take their psychoactive medication (i.e., benzodiazepines, antidepressant, etc.) normally the day before the EEG recording but not in the morning of that recording (the decision for this act should be agreed after proper clinical consultation). It is assumed that such a short withdrawal of medications should be insufficient to cause discontinuation problems and should allow harmonizing the assumption of the therapeutic regimen in all subjects enrolled. Secondly, the preferred time for the recording of rsEEG rhythms is the morning after a satisfying light breakfast. Thirdly, a brief interview of the subjects should confirm the standard subjects' quality of sleep during the night preceding the recording and the above conditions. If negative, the recording should be postponed to another date.

Recording of rsEEG rhythms is an experiment in the Clinical Neurophysiology of vigilance and should meet the following conditions: a quiet and dimly lighted room, acoustic noise should be negligible in the recording chamber, the subject should rest on a comfortable half reclined armchair or bed, the wall in front of him/her should be painted with a uniform light colour (e.g., white, very pale yellow or green) with only a central fixation target at the height of his/her eyes. Three resting state conditions are typically used: the first condition tests the neurophysiological mechanisms keeping the state of low vigilance with eyes-closed for several minutes (i.e., 5-15 min). It also probes the transition to drowsiness and sleep, hence the experimenter (or trained technologist) should not alert the subject in case of sleep. The instructions invite the subject to sit quietly, stay relaxed in a state of mind wandering (i.e., no goal-oriented mental activity), and keep the eyes closed. The second condition tests the neurophysiological mechanisms regulating the increase and decrease in the vigilance level while opening and closing the eyes sequentially (i.e., 5-10 min). The periods of eyes-open and -closed in response to experimenter's cue are short (i.e., 1 min), and the sequence of eyes-open and –closed is repeated (i.e., 2-4 times). The instructions to the subject are like those of the first condition. The experimenter will have to

alert the subject in case of sleep to have enough EEG data related to the proper mental set. If the subject does not follow the instruction, the experimenter will repeat them.

The third condition tests the neurophysiological mechanisms underlying the steady maintenance of low vigilance at eyes closed (i.e., 3-5 min) and moderate vigilance at eyes open (i.e., 3-5 min). The instructions to the subject are like those of the second condition.

The recording of the EEG is obtained by placing electrodes on the scalp with a conductive gel or paste, according the preferred method (applying single electrodes or a cup). The use of the cup could be the best solution when high-density arrays of electrodes are needed. Before the application of the electrodes is very important to prepare the scalp area to reduce impedance due to dead skin cells.

The International 10–20 system is an internationally recognized method to describe and apply the location of scalp electrodes in the context of an EEG test or experiment. This method was developed to ensure standardized reproducibility so that a subject's studies could be compared over time and subjects could be compared to each other. This system is based on the relationship between the location of an electrode and the underlying area of cerebral cortex. The "10" and "20" refers to the fact that the actual distances between adjacent electrodes are either 10% or 20% of the total front–back or right–left distance of the skull.

Each site has a letter to identify the lobe and a number to identify the hemisphere location. The letters F, T, C, P and O stand for frontal, temporal, central, parietal, and occipital lobes, respectively. The "C" letter is used only for identification purposes because there exists no central lobe. A "z" (zero) refers to an electrode placed on the midline. Even numbers (2,4,6,8) refer to electrode positions on the right hemisphere, whereas odd numbers (1,3,5,7) refer to those on the left hemisphere. In addition, the letter codes A, Pg and Fp identify the earlobes, nasopharyngeal and frontal polar sites respectively.

Two anatomical landmarks are used for the essential positioning of the EEG electrodes: first, the nasion which is the distinctly depressed area between the eyes, just above the bridge of the nose; second, the inion, which is the lowest point of the skull from the back of the head and is normally indicated by a prominent bump (Figure 2). Furthermore, to record the signal of the brain activity, the EEG system requires the application of a reference electrode wich voltage is noted, generally placed in an electrical neutral area (this area could have a background electrical activity and could introduce "noise" which is a source of artefact).

The EEG activity, recorded on the scalp, is a result of a summation of ions currents wich generators have different locations. The generator is the source of the current, and the surrounding tissue and fluids are the volume through which it is conducted. Because of the distance between the skull and brain and their different resistivities, EEG data collected from any point on the human scalp includes activity generated within a large brain area. This volume conduction provokes the spatial smearing of EEG data and is not possible to have an exact topographic exstimation of the electrical source. This is called the "linear inverse problem".

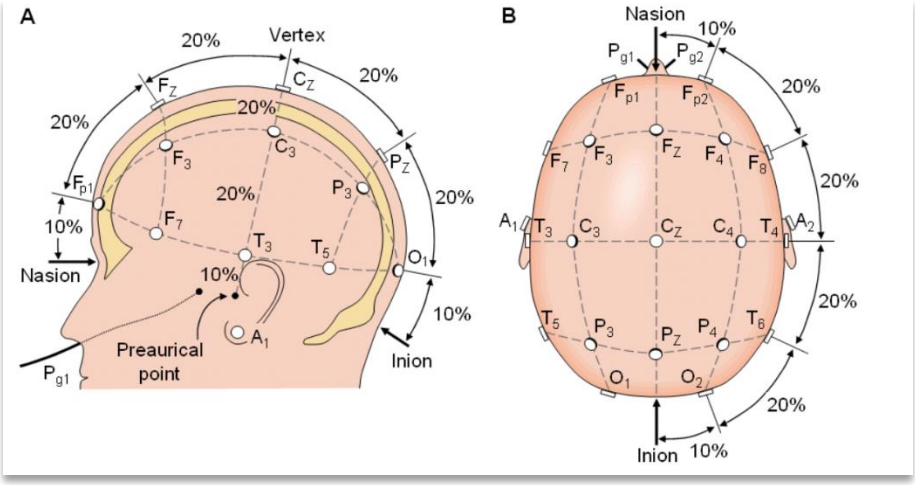

Figure 2. *Diagram of the international 10/20 system seen from the (A) left and (B) above the head. Each electrode is assigned a nomenclature with a letter and a number. The letters indicate the areas of the scalp: F (Frontal), C (Central), T (Temporal), P (Parietal) and O (Occipital); numbers are odd for the left side and even for the right side.*

Inverse solution method

Methods for localization are termed "inverse solutions methods". A good method for a true functional tomography allows to minimize the error of the estimation of the source current. However, a perfect tomography cannot exist. From a more optimistic point of view, one might expect that whatever little information is contained in EEG measurements, it should suffice to allow for at least an "approximate" tomography. For this work the freeware eLoreta (exact low resolution brain electromagnetic tomography) has been used to solve the linear inverse problem (Pascual-Marqui, 2007).

The eLORETA method is a discrete, three-dimensional (3D) distributed, linear, weighted minimum norm inverse solution. In the current implementation of eLORETA, computations were made in a realistic head model, using the MNI152 template, with the three-dimensional solution space restricted to cortical grey matter, as determined by the probabilistic Talairach

atlas. The standard electrode positions on the MNI152 scalp were taken from (Jurcak et al., 2007; Oostenveld and Praamstra, 2001). The intracerebral volume is partitioned in 6239 voxels at 5 mm spatial resolution. Thus, eLORETA images represent the electric activity at each voxel in neuroanatomic Montreal Neurological Institute (MNI) space as the exact magnitude of the estimated current density. Anatomical labels as Brodmann areas are also reported using MNI space, with correction to Talairach space (Brett et al., 2002).

Experimental Part

General aim and objectives of the PhD thesis

Previous studies have shown abnormalities of rsEEG rhythms in patients with AD, PD, and DLB (Dierks et al., 1993, 2000; Huang et al. 2000; Serizawa et al., 2008; Kamei et al., 2010; Andersson et al. 2008; Bonanni et al., 2008). These abnormalities may qualify rsEEG markers probing patients' cortical arousal in quiet wakefulness. Indeed, previous evidence has shown that in healthy adults, rsEEG rhythms change in relation to the administration of a pharmacological agent enhancing vigilance (i.e., modafinil) and the sleep deprivation (Del Percio et al., 2019). Furthermore, experimental studies have disclosed that the high level of vigilance, associated with a finalized behaviour, is characterized by high activity of the ARASs and desynchronization of the cortical EEG signals at high frequencies in the alpha (8-12 Hz) and beta (13-30 Hz) bands. On the contrary, when mental activity is at rest, in a quiet wake, the EEG signal appears characterized by a synchronized activity at alpha rhythms (Moruzzi and Magoun 1949; Buzsaki and Gage 1989). An alteration of these rhythms suggests dysfuntions of neurophysiological mechanisms regulating quiet vigilance. At the basis of the functioning of these mechanisms are the components of the ascending reticular activating system (i.e. cholinergic, dopaminergic, noradrenergic, serotoninergic and noradrenergic systems), mostly impaired in dementing disorders (Berridge et al., 2003; Gratwicke et al., 2015).

This PhD thesis has been developed applying advanced procedures estimating cortical sources of rsEEG rhythms at individual frequency bands in AD patients (Moretti et al., 2004; Babiloni et al., 2016). The use of those procedures aimed at unveiling abnormalities in cortical neural synchronization mechanisms related to the manteinance of quiet vigilance in AD, PD, and DLB patients to better understand the clinical neurophysiology of those diseases and provide a proof of concept of rsEEG source variables as candidate cost-effective and easily available biomarkers for monitoring brain functions in these diseases. This aim was pursued with the following objectives:

1) to unveil differences in the spatial and frequency features of the cortical sources of rsEEG rhythms in patients with ADD, PDD, and DLB at the group and individual levels;
2) to unveil modulation of cortical sources of rsEEG rhythms at delta and alpha frequencies as a function of relevant clinical features in PD patients such as the severity of cognitive, motor, and visual hallucinations;

3) to unveil modulation of cortical sources of rsEEG rhythms at delta and alpha frequencies as a function of relevant clinical features in DLB patients such as the severity and fluctuation of cognitive deficits, REM behavioral disorders, and visual hallucinations.

I study

Abnormalities of cortical neural synchronization mechanisms in patients with dementia due to Alzheimer's and Lewy body diseases: an EEG study

Introduction

Major neurocognitive disorder, also known as dementia, is a significant cognitive decline from a previous level, with the loss of independence in everyday activities and often emotional, motivational, and behavioral symptoms (American Psychiatric Association, 2013). Patients with dementia are 46 million worldwide (World Alzheimer Report 2015). During aging, the most frequent form of dementia is Alzheimer's disease dementia (ADD), accounting for >50% of patients, while dementia due to Parkinson's disease and Lewy body (PDD and DLB) affect approximately 10-20% of the cases.

ADD, PDD, and DLB are due to progressive neurodegenerative processes associated with an abnormal accumulation of proteins in the brain (i.e. Aβ1-42 extracellularly and intracellular phosphorylated tau protein or α-synuclein), causing axonal dysfunction, neuronal loss, and brain atrophy (Bhat et al., 2015). ADD can be detected even in the prodromal stage of mild cognitive impairment (MCI) using cerebrospinal fluid (CSF) and positron emission tomography (PET) diagnostic biomarkers of Aβ1-42 and phospho-tau (McKhan et al., 2011; Dubois et al., 2014). Compared to ADD, PDD and DLB are characterized by prominent intracellular Lewy bodies in subcortical (mostly in PDD) and cortical (primarily in DLB) regions.

From the clinical point of view, ADD typically shows a prominent hippocampal amnesic syndrome with minor linguistic, visuospatial, and visual variants (Dubois et al., 2014). PDD and DLB present executive, attentional, and verbal cognitive dysfunctions in addition to the classical motor symptoms including akinesia, rigidity, tremor, and postural instability (Huber et al., 1989; Dubois and Pillon, 1997; Hughes et al., 2000; Levy et al., 2000; Wolters, 2001; Aarsland et al., 2003; Walker et al., 2015; Emre et al., 2007; Buter et al., 2008). Depression and apathy are also often detected in PDD and DLB. Typically, motor simptoms are the primary and early manifestation of PD, followed by dementia. In contrast, DLB is primarily characterized by visual hallucinations, marked diurnal cognitive (attention, alertness, memory,

planning, and abstract thinking) fluctuation, and presence of rapid eye movement sleep behavior disorders (McKeith et al., 2005).

Differential diagnosis and disease monitoring of ADD, PDD, and DLB are crucial since they have specific pathological processes and lesions and consequently require different treatments. At the same time, the extraction of new valid clinical indexes and biomarkers is tricky and requires advanced procedures (Karantzoulis and Galvin, 2013). Among other biomarkers, resting-state eyes-closed electroencephalographic (rsEEG) rhythms have extensively been studied as a possible tool to assess the neurophysiological correlates of dementia (Giaquinto and Nolfe, 1986; Breslau et al., 1989; Briel et al., 1999). This technique is cost-effective, non-invasive, and repeatable over time after a relatively short period (a few weeks) in healthy subjects if general conditions are comparable (quality of sleep, brain health, psychoactive substances, and drugs, etc.). During wakefulness, patients are instructed to be quiet (eyes closed) with mind wandering freely, without any oriented mental operation including focused attention, memory recall, planning, etc. They are also asked to avoid drowsiness and falling asleep. Although rsEEG rhythms are promising markers for a neurophysiological evaluation of the disease status and progression, they may not have an accurate diagnostic value. Indeed, rsEEG rhythms do not directly reflect the peculiar pathophysiological markers of ADD, PDD, and DLB. Rather, they may be part of the "topographic markers", according to the definition given by Dubois and colleagues (2014). The topographic markers are not necessarily specific for ADD, PDD or DLB, but they can provide an index of the extent to which ADD, PDD, and DLB patients show abnormalities in the structure and function of the brain across the disease progression and therapeutic intervention.

A bulk of previous studies has investigated rsEEG rhythms in groups of ADD, PDD, and DLB patients compared to normal elderly (Nold) subjects. rsEEG of AD patients is characterized by high power in widespread delta (<4 Hz) and theta (4-7 Hz) rhythms, as well as low power in posterior alpha (8-12 Hz) and/or beta (13-20 Hz) rhythms (Dierks et al., 1993, 2000; Huang et al. 2000; Jelic et al., 2000; Ponomareva et al., 2003; Jeong, 2004; Babiloni et al., 2006a). In temporal areas, delta power is also abnormally high in ADD patients in relation to regional hypometabolism and memory deficits (Valladares-Neto et al., 1995). Furthermore, a short-term cholinergic regimen with Acetylcholinesterase inhibitors partially normalizes theta (4–7 Hz; Brassen and Adler, 2003), alpha (8–12 Hz; Onofrj et al., 2003), and delta (0–3 Hz; Reeves et al., 2002) rhythms. In the same line, long-term administration of the regimen shows beneficial effects on theta and alpha/theta ratio, especially over the frontal areas (Kogan et al., 2001; Rodriguez et al., 2002).

In PDD patients, an emerging feature is a topographically widespread slowing of rsEEG rhythms, with prominently high power in delta and/or theta rhythms (Neufeld et al., 1988, 1994; Fünfgeld, 1995; Bonanni et al., 2008; Serizawa et al., 2008; Kamei et al., 2010; Pugnetti et al., 2010; Soikkeli et al., 1991). In these patients, dopaminergic therapy has been reported to normalize partially both the abnormal increment of the theta power and the reduction of the alpha power (Melgari et al., 2014). Similar results were obtained in ADD and PDD patients using magnetoencephalographic (MEG) techniques (Stam et al., 2006; Bosboom et al., 2006, 2009). In PD patients with cognitive deficits, a significant correlation was reported between rsEEG rhythms and total phosphorylated α-synuclein but not total α-synuclein, phosphorylated tau protein, amyloid beta peptide or synaptic proteins (Caviness et al., 2016). Finally, wavelet rsEEG coherence between electrode pairs but not relative wavelet rsEEG energy allowed differentiating between PDD and ADD individuals (Jeong et al., 2016).

Noteworthy, DLB patients exhibit rsEEG features distinct from those of ADD and PDD, so these features are considered to be "supportive" in authoritative international diagnostic guidelines (McKeith et al., 2005). Specifically, widespread delta and theta power over the scalp were higher in DLB than ADD patients (Andersson et al., 2008; Kai et al., 2005). Furthermore, posterior beta power is greater in DLB than ADD patients (Andersson et al., 2008; Kai et al., 2005). In DLB patients, another characterizing feature is the fluctuation of global delta power over a few minutes (Walker et al., 2000a, b; Andersson et al. 2008; Bonanni et al., 2008). This fluctuation was observed in the vast majority of DLB patients, only half of PDD patients, and very few ADD patients (Bonanni et al., 2008). It was also evident at the MCI stage of DLB, with a maximum representation over the occipital electrodes (Bonanni et al., 2015). Furthermore, the fluctuation of the dominant rsEEG frequency and the power of the alpha and slow rsEEG frequencies are partially normalized by a short-term administration of Acetylcholinesterase inhibitors in DLB patients (Onofrj et al., 2003). DLB and ADD patients differ for rsEEG dominant frequency and power variability and prevalence over the posterior electrodes (Bonanni et al., 2016). Finally, compared to controls, DLB patients show a disrupted alpha posterior-to-anterior directed information flow, whereas ADD patients unveil a disrupted beta posterior-to-anterior directed information flow (Dauwan et al., 2016). The disruption of alpha directed connectivity was suggested to characterize the clinical syndrome of DLB in comparison with ADD (Dauwan et al., 2016).

A first methodological limitation of most of the previous rsEEG studies in ADD, PDD, and DLB patients regards the spatial analysis of the rsEEG rhythms. The analysis of the rsEEG rhythms was typically performed at scalp electrodes and may be affected by reference electrode

and head volume conduction effects, which blur spatial analysis of the distribution of rsEEG potentials (Nunez, 1995). To enhance such a spatial analysis, one can use analytical procedures for the estimation of cortical sources of eyes-closed rsEEG rhythms. For example, a popular approach for the rsEEG cortical source estimation is called low-resolution brain electromagnetic tomography (LORETA; Pascual-Marqui et al., 1994). LORETA uses a brain source space coregistered to the Talairach brain atlas often adopted in neuroimaging studies, performed in AD patients to probe brain atrophy and hypometabolism. Furthermore, the LORETA software is freely available and has been successfully used in cognitively impaired elderly subjects (Caso et al., 2012; Nishida et al., 2011). With LORETA, we have demonstrated a positive correlation between the posterior cortical sources of low-frequency alpha rhythms (8–10.5 Hz) and the global cognitive status in Nold, amnesic MCI, and mild AD subjects as a whole group; in contrast, the correlation was negative for occipital cortical sources of the delta rhythms (Babiloni et al., 2006a,b,c; 2013). Compared to the groups of Nold and ADD subjects, the PDD group exhibited higher values of central delta and parietal-occipital-temporal theta sources, in contrast to lower values of parietal-occipital-temporal beta 1 (12-20 Hz) sources (Babiloni et al., 2011). Finally, the parieto-occipital alpha 1 source activity was lower in ADD than the PDD and Nold groups (Babiloni et al., 2011). For the present study, we used the exact LORETA (eLORETA; Pascual-Marqui, 2007), which represents the improved version of LORETA and standardized LORETA (Pascual-Marqui et al., 1994, 2002). Compared to LORETA and standardized LORETA, eLORETA exhibited a better source localization in some control parameters (Canuet et al., 2011).

A second methodological limitation of previous rsEEG studies in ADD, PDD, and DLB patients refers to the frequency analysis of rsEEG rhythms. In the majority of the previous studies, the analysis of rsEEG rhythms was performed using standard (fixed) frequency bands in all subjects despite their remarkable inter-individual variability. For example, the choice of fixed EEG bands did not take into account the “slowing” of the EEG rhythms in demented subjects (Moretti et al., 2004; Cozac et al., 2016; Bonanni et al., 2016). To improve the frequency analysis, we have identified the two frequency landmarks in each individual, namely the transition frequency (TF) and the individual alpha frequency peak (IAF; Klimesch, 1996, 1999; Klimesch et al., 1998). TF marks the transition frequency between the theta and the alpha bands, whereas the IAF is defined as the maximum power density peak in the alpha range (6-13 Hz). Based on the TF and IAF, we determined the delta, theta, and alpha frequency band ranges on an individual basis.

Keeping in mind the above data and methodological remarks, the hypothesis of this retrospective exploratory study was that our rsEEG source estimation approach might be able to unveil differences in the spatial and frequency features of the cortical rsEEG rhythms in patients with ADD, PDD, and DLB at the group and individual levels. For this reason, the PDD, ADD, and DLB groups were carefully matched for demographic variables and global cognitive status (i.e. Mini Mental State Examination, MMSE, score). A group of Nold subjects served as a control population. The statistical analysis tested the hypothesis that, compared to PDD and DLB patients, subjects with ADD might present differences in the spatial and individual frequency features of the rsEEG sources, thus reflecting a possible different impact of the respective diseases on cortical neural synchronization mechanisms underpinning brain arousal in quiet wakefulness.

Materials and Methods

Subjects

For this retrospective exploratory study, we used the rsEEG data of an international archive, formed by clinical, neuropsychological, and electrophysiological data in 40 Nold, 42 ADD, 42 PDD, and 34 DLB subjects matched. These subjects were recruited by the following qualified clinical units of the informal European E-DLB and PDWAIVE Consortia: University of Rome "La Sapienza" (Italy), IRCCS Fatebenefratelli of Brescia (Italy); IRCCS SDN of Naples (Italy); IRCCS Oasi Maria SS of Troina (Italy); University of Genova (Italy); Hospital San Raffaele of Cassino (Italy); IRCCS Hospital San Raffaele Pisana of Rome (Italy); University "G. d'Annunzio" of Chieti and Pescara (Italy); General Hospital of Linz (Austria); Istanbul University (Turkey), and University of Basel (Switzerland).

The four subject groups (PDD, ADD, DLB, and Nold) were carefully matched for age, gender, and education (i.e. the mean values of age, gender and education were not different in these groups). The three groups of patients with dementia were also carefully matched for their Mini Mental State Examination score (MMSE; Folstein et al. 1975).

Table 1 summarizes the relevant demographic and clinical (MMSE score) data of the four groups, together with the statistical comparison between the groups for age (ANOVA), gender (Kruskal-Wallis test), education (ANOVA), and MMSE score (Kruskal-Wallis test). As expected, a statistically significant difference was found between the Nold group and the other three groups only for MMSE score. Specifically, there was a higher MMSE score in the Nold

than the ADD, PDD, and DLB groups ($p < 0.00001$). On the contrary, no statistically significant difference between the groups was found for age, gender, and education ($p > 0.05$).

The Local institutional Ethical Committees approved the study. All experiments were performed with the informed and overt consent of each participant or caregiver, in line with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the local Institutional Review Board.

MEAN VALUES (± SE) OF DEMOGRAPHIC DATA AND GLOBAL COGNITIVE STATUS (MMSE score)					
	Nold	ADD	PDD	DLB	Statistical analysis
N	40	42	42	34	
Age	72.9 (± 1.1 SE)	73.3 (± 1.0 SE)	74.1 (± 1.1 SE)	75.1 (± 1.1 SE)	ANOVA: n.s.
Gender (M/F)	16/24	17/25	18/24	11/23	Kruskal-Wallis: n.s.
Education	8.5 (± 0.6 SE)	8.1 (± 0.8 SE)	7.0 (± 0.6 SE)	7.4 (± 0.8 SE)	ANOVA: n.s.
MMSE	28.7 (± 0.2 SE)	18.9 (± 0.6 SE)	18.8 (± 0.7 SE)	18.6 (± 0.8 SE)	Kruskal-Wallis: H=88.7, p<0.00001 (Nold>ADD, PDD, DLB)

***Table 1**. Mean values (± standard error of the mean, SE) of the demographic and clinical data and results of their statistical comparisons ($p < 0.05$) in the groups of normal elderly (Nold) subjects and patients with dementia due to Alzheimer's disease (ADD), Parkinson's disease (PDD) and Dementia with Lewy Bodies (DLB). Legend: MMSE = Mini Mental State Evaluation; M/F = males/females; n.s. = not significant ($p > 0.05$).*

Diagnostic criteria

Probable ADD was diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR; American Psychiatric Association) and the National Institute of Neurological Disorders and Stroke–Alzheimer Disease and Related Disorders (NINCDS–ADRDA) working group (McKhann et al., 1984). These accepted criteria are fulfilled in a two-step diagnostic process where there is an initial identification of a dementia syndrome and, then, the application of criteria based on the clinical features of the AD phenotype. The DSM-IV-TR criteria require the presence of both a progressive memory

disorder and impairment in at least one additional cognitive domain, both of which interfere with social function or activities of daily living (ADL).

The ADD patients underwent general medical, neurological, and psychiatric assessments. They were also rated on some standardized clinical scales that included MMSE (Folstein et al., 1975), clinical deterioration rate (CDR; Hughes et al., 1982), 15-item geriatric depression scale (GDS; Yesavage et al., 1983), Hachinski Ischemic Score (HIS; Rosen et al., 1980), and Instrumental Activities of Daily Living scale (IADL; Lawton and Brodie, 1969). Neuroimaging diagnostic procedures (MRI) and complete laboratory analyses were carried out to exclude other causes of progressive or reversible dementias and to have a clinically homogenous ADD patient group. Inclusion criteria were as follows: (1) objective impairment at neuropsychological evaluation, as defined by performance below 1.5 standard deviations (SD) from the mean value for age- and education-matched controls; (2) clinical dementia rating score higher than 0.5; and (3) abnormal activities of daily living as reflected by clinical history and evidence of independent living.

Exclusion criteria included any evidence of (1) frontotemporal dementia, diagnosed according to the criteria by the Lund and Manchester Groups (1994), (2) vascular dementia, diagnosed according to the NINDS-AIREN criteria (Roman et al., 1993), (3) extrapyramidal syndromes, (4) reversible dementias (including pseudodementia of depression), and (5) Lewy body dementia. When given, benzodiazepines, antidepressant and/or antihypertensive agents were suspended for about 24 h before EEG recordings. This procedure did not ensure a complete washout of the drug –longer periods would not have been applicable for obvious ethical reasons- but it made it possible to compare the drug condition across the patients.

A battery of neuropsychological tests assessed general cognitive performance in the domains of memory, language, executive function/attention, and visuoconstruction abilities (some of the patients received the CERAD-plus battery). The tests assessing memory included the delayed recall of Rey figures (Rey, 1968), and/or the delayed recall of a story (Spinnler and Tognoni, 1987). The tests assessing language included the 1-minute verbal fluency for letters, fruits, animals or car trades (Novelli, 1986), and/or the Token test (Spinnler and Tognoni, 1987). The tests assessing executive function and attention included the Trail Making Test Part A and B (Reitan, 1958). Finally, the tests assessing visuoconstruction included the copy of Rey figures.

The diagnosis of PD was based on a standard clinical assessment of tremor, rigidity, and bradykinesia and the clinical UK Brain Bank Criteria of PD (Gelb et al., 1999). As measures of severity of motor disability, the Hoehn and Yahr stage (Hoehn and Yahr, 1967), and the Unified

Parkinson Disease Rating Scale-III (UPDRS-III; Fahn and Elton, 1987) for extrapyramidal symptoms, were used. A diagnosis of PDD was given to the patients with a history of dementia (inclusion criteria as for ADD) preceded by a diagnosis of PD for at least 12 months.
On the basis of the clinical features and neuroradiological findings, exclusion criteria for PDD included the following forms of parkinsonism: (1) DLB (McKeith et al., 1996), (2) drug-induced parkinsonism, (3) cerebrovascular parkinsonism, and (4) atypical parkinsonism with absent or minimal responses to antiparkinsonian drugs.
All PDD patients underwent a battery of clinical scales including the Neuropsychiatric Inventory (NPI; Cummings et al., 1994), the scale for the assessment of Behavioral and Psychological Symptoms of Dementia (BPSD), the MMSE, the Dementia Rating Scale-2 (DRS-2; Jurica et al., 2001), the Epworth Sleepiness Scale (ESS), and the Alzheimer's Disease Cooperative Study for the Activities of Daily Living (ADCS-ADL). All PDD subjects also underwent a battery of neuropsychological tests. This battery included neuropsychological tests assessing the general cognitive performance in the domains of memory, language, executive function/attention, and visuoconstruction abilities (some of the patients received the CERAD-plus battery).

Dementia was diagnosed in the DLB patients as for the ADD and PDD patients (see above inclusion and exclusion criteria). The diagnosis of the probable DLB was carried out in agreement with the consensus guidelines (McKeith et al., 2005). Concerning the detection of the core and suggestive features of DLB, the NPI item-2 investigated the occurrence frequency and the severity of hallucinations (Cummings et al., 1994). The Frontal Assessment Battery (FAB; Dubois et al., 2000) and the Clinician Assessment of Fluctuations (Walker et al., 2000) were included to investigate, respectively, the severity of the frontal dysfunction and the presence and severity of the cognitive fluctuations. UPDRS-III (Fahn and Elton, 1987) assessed the presence and severity of extrapyramidal signs. The presence and/or absence of rapid eye movement (REM) sleep behavior disorder (RBD) was determined according to minimal International Classification of Sleep Disorders criteria (American Academy of Sleep Medicine, 2014). All DLB subjects also underwent a battery of neuropsychological tests. This battery included neuropsychological tests assessing the general cognitive performance in the domains of memory, language, executive function/attention, and visuoconstruction abilities (some of the patients received the CERAD-plus battery).

All Nold subjects underwent a cognitive screening (including MMSE and GDS) as well as physical and neurological examinations to exclude any dementia or major cognitive deficit. Subjects affected by chronic systemic illnesses (diabetes mellitus, as an example) were excluded, as well as subjects receiving chronic psychoactive drugs. Subjects with a history of previous or present neurological or psychiatric disease were also excluded. All Nold subjects had a GDS score lower than the threshold of 5 (no depression) or no depression after an interview with a physician or clinical psychologist.

EEG recordings and data analysis

EEG data were recorded while subjects were set with eyes closed in a standard resting state condition (rsEEG). At least 5 minutes of rsEEG data were recorded (128 Hz or higher sampling rate, with a bandpass between 0.01 Hz and 100 Hz) from a minimum number of 19 exploring scalp placed according to the 10–20 System (i.e. Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2; see Figure 1). Linked earlobe reference electrode was preferred, but not mandatory to respect the methodological facilities and standard internal protocols of the clinical recording units. A ground electrode was typically located between the AFz and Fz electrodes, and electrodes impedances were kept below 5 Kohm. Horizontal and vertical electro-oculographic activities (0.3-70 Hz bandpass) were also recorded to monitor blinking and eye movements. EEG recordings were performed, in all subjects, in the late morning to minimize drowsiness. Furthermore, an operator controlled on-line the subject and the EEG traces to keep the level of vigilance constant.

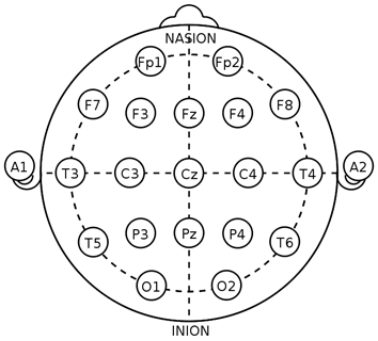

Figure 1*. Recording sites of the 19 scalp electrodes positioned according to the International 10–20 System (i.e. Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2). These electrodes were used for the recording of the resting state eyes-closed electroencephalographic (rsEEG) rhythms. The artifact-free rsEEG data were used as an input for the freeware used for the rsEEG source estimation, namely the exact low-resolution brain electromagnetic source tomography (eLORETA).*

The recorded rsEEG data were band-passed to avoid aliasing, down-sampled to 128 Hz (when recorded with higher sampling frequency), segmented in consecutive 2-s rsEEG epochs, and analyzed off-line. We rejected the rsEEG epochs associated with operator's markers indicating drowsiness, verbal warnings, eyes opening, arm/hand movements or other events (e.g. sweat, sway, head movements, etc.) disturbing the rsEEG recordings. Furthermore, the rsEEG epochs with ocular (e.g. rapid eye opening despite the request to maintain the eyes closed), muscular, and other types of artifacts were preliminarily identified by an automatic computerized procedure. The rsEEG epochs with sporadic and well-shaped blinking artifacts were corrected from the EOG activity by an autoregressive method (Moretti et al., 2003). Two independent experimenters –blind to the diagnosis at the time of the rsEEG analysis– manually revised the rsEEG epochs accepted for further analysis. The rsEEG epochs with signs of a sleep intrusion (an on-going increase of theta, K complex, spindles, etc.) were rejected. To harmonize the rsEEG data collected with different reference electrodes, all artifact-free rsEEG epochs were re-referenced to the common average for further analysis.

A standard digital FFT-based power spectrum analysis (Welch technique, Hanning windowing function, no phase shift) computed the power density of the EEG rhythms with 0.5 Hz of frequency resolution. This standard FFT procedure was implemented by a home-made software developed under Matlab 6.5 (Mathworks Inc., Natick, MA).

According to a previous study of our group (Moretti et al., 2004), the frequency bands of interest were individually identified based on the following frequency landmarks: the transition frequency (TF) and the individual alpha frequency peak (IAF). In the EEG power density spectrum, the TF marks the transition frequency between the theta and alpha bands, defined as the minimum of the rsEEG power density between 3 and 8 Hz (between the delta and the alpha power peak). IAF is defined as the maximum power density peak between 6 and 14 Hz. These frequency landmarks were previously well described by Dr. Wolfgang Klimesch (Klimesch, 1996, Klimesch, 1999 and Klimesch et al., 1998).

TF and IAF were individually computed for each subject involved in the study. Based on TF and IAF, we estimated the frequency band range for each subject as follows: delta from TF -4 Hz to TF -2 Hz, theta from TF -2 Hz to TF, low-frequency alpha band (alpha 1 and alpha 2) from TF to IAF, and high-frequency alpha band (or alpha 3) from IAF to IAF+2 Hz. The other bands were defined based on standard fixed frequency ranges: beta 1 from 14 to 20 Hz, beta 2 from 20 to 30 Hz, and gamma from 30 to 40 Hz. The alpha 1 and alpha 2 bands were computed

for each subject as follows: alpha 1 from TF to the midpoint of the TF-IAF range and alpha 2 from this midpoint to IAF.

We used the freeware called "exact LORETA" (eLORETA) for the linear estimation of the cortical source activity of rsEEG rhythms (Pascual-Marqui, 2007). It represents the improved version of the previous pieces of software called LORETA (Pascual-Marqui et al., 1994) and standardized LORETA (Pascual-Marqui et al., 2002). Both standardized LORETA and eLORETA show the same low spatial resolution, with zero localization error in the presence of measurement and biological noise (Pascual-Marqui, 2007; Pascual-Marqui et al., 2002). However, eLORETA exhibits a better source localization in some control parameters (Canuet et al., 2011).

The present implementation of eLORETA uses a head volume conductor model composed of the scalp, skull, and brain. In the scalp compartment, exploring electrodes can be virtually positioned to give EEG data as an input to the source estimation (Jurcak et al., 2007). The brain model is based on a realistic cerebral shape taken from a template typically used in neuroimaging studies, namely that of the Montreal Neurological Institute (MNI152 template; Mazziotta et al., 1995). The electrical brain source space is formed by 6,239 voxels with 5 mm resolution, restricted to cortical gray matter (Fuchs et al., 2002). An equivalent current dipole is located in each voxel. The eLORETA solves the so-called EEG inverse problem in the mentioned head volume conductor model by estimating "neural" current density values, at any cortical voxel, for each frequency bin. Input for this regularized inverse estimation (Pascual-Marqui et al., 2002) is the EEG spectral power density computed at all virtual scalp electrodes. eLORETA cortical source solutions estimate current density values at x, y, and z vectors of any brain voxel able to predict EEG spectral power density at all scalp electrodes. Among the infinite solutions to the EEG inverse problem, a regularization procedure selects the maximally smoothed solution at the cortical source level of the eLORETA head model. Afterward, this solution is normalized by the computation of the eLORETA current density at each voxel (as the mean of the x, y, and z vectors) with current density value averaged across all frequencies (0.5–45 Hz) and 6,239 voxels of the brain volume. For this reason, normalized eLORETA solutions are reported by a unit scale in which "1" means equal to the average value of eLORETA current density computed across all frequencies and voxels. The general procedure typically fits EEG power density in a Gaussian distribution and reduces inter-subject variability (Leuchter et al., 1993).

In line with the general low spatial resolution of the present EEG methodological approach (i.e. 19 scalp electrodes), the eLORETA solutions were averaged across all voxels in a given cortical macroregion of interest (ROI). The ROIs corresponded to frontal, central, parietal, occipital, temporal, and limbic large regions including the Brodmann areas (BAs) listed in Table 2. For the present eLORETA cortical source estimation, a frequency resolution of 0.5 Hz was used, namely, the maximum frequency resolution allowed by the use of 2-s artifact free EEG epochs. The frequency bands of interest (i.e. delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma) were estimated as described above, independently for each subject.

BRODMANN AREAS INTO THE REGIONS OF INTEREST (ROIs)	
Frontal	8, 9, 10, 11, 44, 45, 46, 47
Central	1, 2, 3, 4, 6
Parietal	5, 7, 30, 39, 40, 43
Temporal	20, 21, 22, 37, 38, 41, 42
Occipital	17, 18, 19
Limbic	31, 32, 33, 34, 35, 36

***Table 2**. Regions of interest (ROIs) used for the estimation of the cortical sources of the resting state eyes-closed electroencephalographic (rsEEG) rhythms in the present study. Any ROI is defined by some Brodmann areas of the cerebral source space in the freeware used in this study, namely the exact low-resolution brain electromagnetic source tomography (eLORETA).*

Statistical analysis

The statistical analysis was carried out by means of the commercial tool STATISTICA 10 (StatSoft Inc., www.statsoft.com) in order to test the hypothesis that the rsEEG source activity as revealed by eLORETA solutions would differ between ADD, PDD, and DLB patients using the Nold group as a control reference. With this purpose, an ANOVA was computed using the regional normalized eLORETA solutions (normalized current density at all voxels of a given ROI) as a dependent variable ($p < 0.05$). The ANOVA factors were Group (Nold, ADD, PDD, DLB), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal, and limbic). Individual TF and the IAF were used as covariates. The sphericity assumption was evaluated with the Mauchly's test. The degrees of

freedom were corrected by the means of Greenhouse-Geisser procedure when appropriate. The Duncan test was used for post-hoc comparisons ($p < 0.05$).

The planned post-hoc testing evaluated the prediction of the differences in rsEEG source solutions between the ADD, PDD, and DLB groups using the Nold group as a control reference. Specifically, we expected: (1) a statistical 3-way interaction effect including the factors Group, ROI, and Band ($p < 0.05$); (2) a post-hoc test indicating statistically significant differences of the regional normalized eLORETA solutions with the pattern Nold ≠ ADD ≠ PDD ≠ LBD (Duncan test, $p < 0.05$).

The above statistical analyses were controlled with the Grubbs test ($p < 0.0001$) for the presence of outliers in the distribution of the eLORETA source solutions.

rsEEG sources showing the highest statistically significant differences between the four groups were used as discriminant variables for the classification of Nold and demented individuals of a given group and between the individuals of two groups of dementing disorders. The correct blind classifications of these rsEEG source activities were performed by Matlab 2010b software (Mathworks Inc., Natick, MA, USA) for the production of the receiver operating characteristic (ROC) curves (DeLong et al., 1988). The following indexes measured the performance of the above binary classification: (1) Sensitivity: the rate of positives who were correctly classified as positives (i.e. “true positive rate” in the signal detection theory); (2) Specificity: the rate of negatives (control) who were correctly classified as negatives (i.e. “true negative rate” in the signal detection theory); (3) Accuracy: the mean of the sensitivity and specificity (the amount of subjects in the groups was the same); and (4) Area under the ROC (AUROC) curve. The AUROC curve was a major reference index of the global classification accuracy.

Results

Table 3 reports the mean values of TF and IAF for the four groups (i.e. Nold, ADD, PDD, and DLB), together with the results of the statistical comparisons between the groups (ANOVA). The mean TF was 5.9 Hz (± 0.2 standard error of the mean, SE) in the Nold group, 5.4 Hz (± 0.2 SE) in ADD patients, 4.8 Hz (± 0.1 SE) in PDD patients, and 4.9 Hz (± 0.1 SE) in DLB patients. The mean IAF was 9.0 Hz (± 0.2 SE) in Nold subjects, 8.0 Hz (± 0.3 SE) in ADD patients, 7.3 Hz (± 0.2 SE) in PDD patients, and 7.2 Hz (± 0.2 SE) in DLB patients. The ANOVAs showed the following statistically significant effects: (1) mean TF was greater ($F = 10.4$, $p < 0.0001$) in Nold than in ADD ($p < 0.05$), PDD ($p < 0.00001$), and DLB ($p < 0.00005$)

subjects; it was also higher in ADD group than in PDD ($p < 0.05$) and DLB ($p < 0.05$) groups. (2) the mean IAF was greater ($F = 14.9$, $p < 0.00001$) in the Nold than the ADD ($p < 0.001$), PDD ($p < 0.00001$), and DLB ($p < 0.000005$) patients. It was also higher in ADD than in PDD ($p < 0.05$) and DLB ($p < 0.01$) groups. Of note, 9 ADD, 2 PDD and 5 DLB patients exhibited asymptotic rsEEG power spectra, without any alpha power peak. Therefore, they were not considered for the statistical analysis of IAF. For the analysis of rsEEG cortical sources, the frequency bands from delta to alpha were determined based on the group mean values of IAF.

MEAN VALUES (± SE) OF TRANSITION THETA/ALPHA FREQUENCY (TF) AND INDIVIDUAL ALPHA FREQUENCY PEAK (IAF)					
	Nold	ADD	PDD	DLB	Statistical analysis
TF	5.9 (± 0.2 SE)	5.4 (± 0.2 SE)	4.8 (± 0.1 SE)	4.9 (± 0.1 SE)	ANOVA: F=10.4, p<0.00001 (Nold>ADD>PDD, DLB)
IAF	9.0 (± 0.2 SE)	8.0 (± 0.3 SE)	7.3 (± 0.2 SE)	7.2 (± 0.2 SE)	ANOVA: F=14.9, p<0.00001 (Nold, > ADD > PDD, DLB)

***Table 3**. Mean values (± SE) of transition frequency (TF) and individual alpha frequency peak (IAF) of the rsEEG power density spectra for the groups (i.e. Nold, ADD, PDD, DLB). The table also reports the p values of the statistical comparisons of these values between the groups. See the Methods for a definition of the TF and IAF.*

Figure 2 shows the grand average of the regional eLORETA solutions for the rsEEG source estimation relative to a statistically significant ANOVA interaction effect $F = 8.9$; $p < 0.00001$) among the factors Group (Nold, ADD, PDD, DLB), Band (delta, theta, alpha 1, alpha 2, beta 1, beta 2, gamma), and ROI (frontal, central, parietal, occipital, temporal, limbic). TF and IAF were used as covariates. In the figure, the eLORETA solutions have the shape of typical rsEEG relative power spectra. Notably, the profile and magnitude of the rsEEG source activity spectra in the Nold, ADD, PDD, and DLB groups differs across the ROIs, supporting the idea that the scalp EEG rhythms are generated by a distinct pattern of cortical source activity in these groups. The Duncan planned post-hoc testing showed that the discriminant source pattern ADD < DLB < PDD < Nold is fitted by the parietal, occipital, limbic alpha 2 and alpha 3 sources and the temporal alpha 2 sources ($p < 0.05$ to $p < 0.000001$). Compared to the Nold group, the posterior alpha source activity showed a very marked reduction in the AD group ($p < 0.00001$ to $p <$

0.000001), a marked reduction in the DLB group ($p < 0.00005$ to $p < 0.000001$), and a moderate reduction in the PDD group ($p < 0.005$ to $p < 0.000005$). On the contrary, the pattern PDD > DLB > ADD > Nold was fitted by occipital delta sources ($p < 0.05$ to $p < 0.000001$). Compared to the Nold group, the occipital delta source activity showed a very marked pathological increase in the PDD group ($p < 0.000001$), a marked increase in the DLB group ($p < 0.000005$), and a moderate increase in the ADD group ($p < 0.05$).

A control statistical analysis was performed to verify that the above inter-group differences in rsEEG source activity were not merely due to the presence of few outliers in the individual eLORETA solutions. Specifically, the Grubbs' test ($p < 0.005$) was used to detect the possible outliers from the eight rsEEG sources (i.e. occipital delta; parietal, occipital, temporal, and limbic alpha 2; parietal, occipital, and limbic alpha 3) in the four groups. No outlier was found (see Figure 3), thus confirming the results of the main statistical analysis.

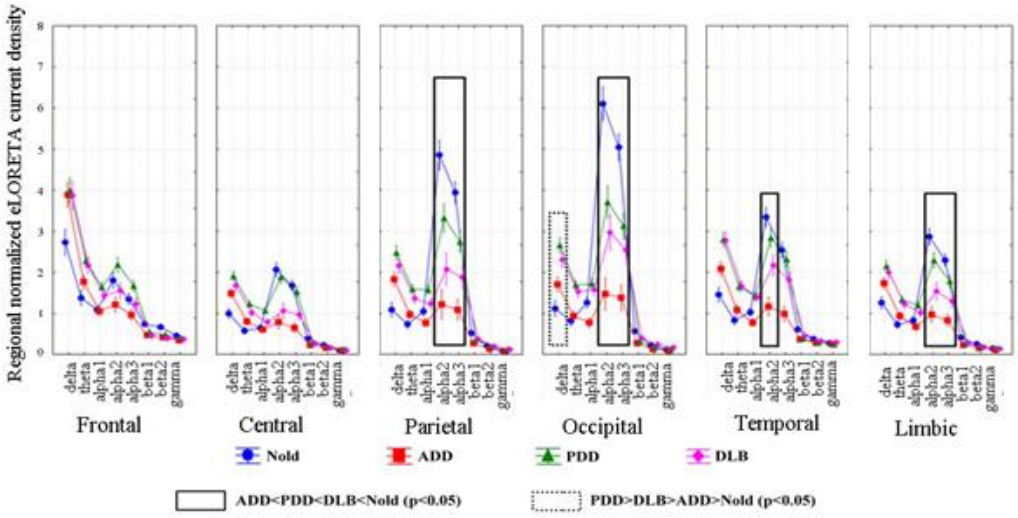

Figure 2. *Regional normalized eLORETA solutions (mean across subjects) of the rsEEG rhythms relative to a statistical ANOVA interaction among the factors Group (Nold, ADD, PDD, DLB), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2 and gamma), and ROI (central, frontal, parietal, occipital, temporal, limbic). This ANOVA design used the regional normalized eLORETA solutions as a dependent variable. Individual transition frequency (TF) and individual alpha frequency peak (IAF) were used as covariates. Regional normalized eLORETA solutions modeled the rsEEG relative power spectra as revealed by a sort of "virtual" intracranial macro-electrodes located on the macro-cortical regions of interest. Legend: the rectangles indicate the cortical regions and frequency bands in which the eLORETA solutions presented statistically significant LORETA patterns: Nold ≠ ADD ≠ PDD ≠ DLB ($p < 0.05$).*

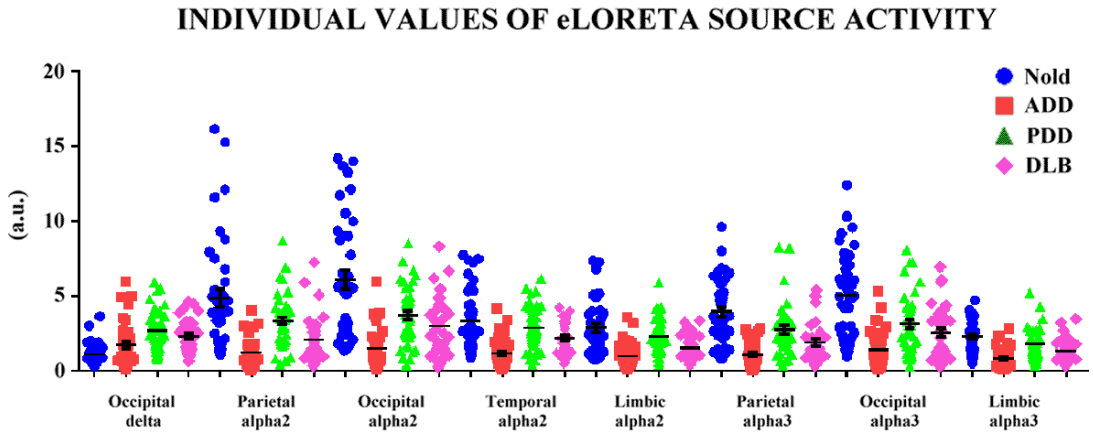

Figure 3. *Individual values of the eLORETA cortical source activity showing statistically significant ($p<0.05$) differences between the Nold, ADD, PDD, and DLB groups (i.e. occipital delta, parietal alpha 2, occipital alpha 2, temporal alpha 2, limbic alpha 2, parietal alpha 3, occipital alpha 3, limbic alpha 3). Noteworthy, the Grubbs' test showed no outliers from those individual values of the eLORETA solutions (arbitrary threshold of $p < 0.0001$).*

Correlation analysis

As a first analysis of the clinical relevance of the main results, the Spearman test was used to evaluate the correlation between the (eLORETA) source activity showing the highest inter-group difference between Nold and patients with dementia (i.e. occipital delta and alpha 2) and the MMSE score, as an index of the global cognition; such a correlation was computed across all Nold, ADD, PDD and DLB individuals as a whole group ($p < 0.05$). A statistically significant negative correlation was found between the activity of the occipital delta source and the MMSE score ($r=-0.25$, $p < 0.002$; Figure 4, top). The higher the occipital delta source activity, the lower the MMSE score. Furthermore, a statistically significant positive correlation was found between the activity of the occipital alpha 2 source ($r = 0.35$, $p < 0.0001$) and the MMSE score (Figure 4, bottom). The higher the occipital alpha 2 source activity, the higher the MMSE score. Finally, the same correlation analysis for any single group separately showed no statistically significant result, possibly because of the very limited range of the MMSE score within the single groups ($p > 0.05$).

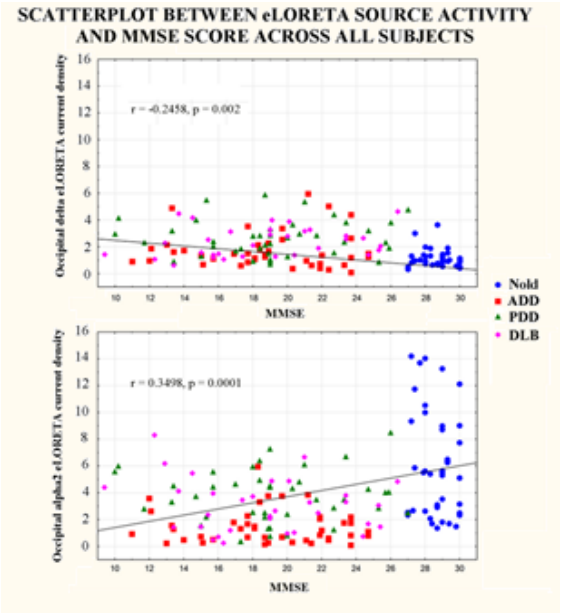

Figure 4. *(Top): Scatterplot showing the correlation between the occipital delta eLORETA source activity of the rsEEG rhythms and the MMSE score in the Nold, ADD PDD, and LDB subjects as a whole group. Spearman test evaluated the hypothesis of a correlation between these two variables ($p<0.05$). The r and p values are reported within the diagram. (Bottom): Scatterplots showing the correlation between alpha 2 (eLORETA) source activity and the MMSE score in the Nold, ADD PDD and LDB subjects as a whole group. The Spearman test evaluated the hypothesis of a correlation these rsEEG and MMSE variables ($p<0.05$). The r and p values are reported within the diagram.*

Classification among Nold, ADD, PDD, and DLB individuals

As a second analysis of the clinical relevance of the main results, the aforementioned occipital delta and alpha 2 rsEEG source activities served as discriminant input variables for the computation of the AUROC curves. These AUROC curves aimed at indexing the classification accuracy in the discrimination between Nold, ADD, PDD, and DLB individuals. An additional discriminant variable was obtained by computing the ratio between the occipital delta and alpha 2 source activities. The results of this analysis are reported in detail in Table 4 and Figure 5. In general, the best classification accuracies between Nold vs. patients with dementia were obtained using the composite marker based on the ratio between occipital delta and alpha 2 source activity. AUROC values was of 0.94 for the Nold vs. ADD individuals, 0.89 for Nold vs. PDD individuals, and 0.92 for Nold vs. DLB individuals (Figure 5). In all these contrasts, the sensitivity and specificity were higher than 85%. Concerning the occipital delta and alpha 2 rsEEG source activities considered separately, the former showed the best classification results in the discrimination between Nold compared to PDD and DLB individuals. For the contrast between the Nold and PDD individuals, the AUROC values reached 0.87 while sensitivity, specificity, and accuracy were 81%, 85%, and 82.9%, respectively (Table 4). In the same line, the contrast between Nold and DLB individuals showed AUROC values of 0.86 while sensitivity, specificity, and accuracy were 79.4%, 80%, and 79.7%, respectively (Table 4). Finally, the occipital alpha 2 source activity exhibited the best classification results in the discrimination between Nold and ADD individuals. The AUROC values reached 0.91 while sensitivity, specificity, and accuracy were 88.1%, 85%, and 86.6%, respectively (Table 4).

Interesting results were also obtained using the above source activities for the classification of the patients with different dementing disorders. The best classification accuracies were obtained using the occipital alpha 2 source activity. For the contrast between ADD and PDD individuals, the AUROC values reached 0.84 while sensitivity, specificity, and accuracy were 81%, 81%, and 81%, respectively (Table 4). With lower classification accuracy, the contrast between the ADD and DLB individuals showed AUROC values of 0.75 while sensitivity, specificity, and accuracy 64.7%, 73.8%, and 69.7%, respectively (Table 4). Of note, classification accuracy was low (< 0.75 of the AUROC curve) using the above source activities for the contrast between DLB and PPD subjects.

CLASSIFICATION OF Nold, ADD, PDD, AND DLB INDIVIDUALS BASED ON rsEEG SOURCE ACTIVITY					
	eLORETA sources	Sensitivity	Specificity	Accuracy	AUROC (>0.75)
Nold vs. ADD	Occipital delta	-	-	-	-
	Occipital alpha 2	83.3%	85.0%	84.1%	0.91
	Occipital delta/alpha2	88.1%	85.0%	86.6%	0.94
Nold vs. PDD	Occipital delta	81.0%	85.0%	82.9%	0.87
	Occipital alpha 2	-	-	-	-
	Occipital delta/alpha2	85.7%	85.0%	85.4%	0.89
Nold vs. DLB	Occipital delta	79.4%	80.0%	79.7%	0.86
	Occipital alpha 2	-	-	-	-
	Occipital delta/alpha2	85.3%	85.0%	85.1%	0.92
ADD vs. PDD	Occipital delta	-	-	-	-
	Occipital alpha 2	81.0%	81.0%	81.0%	0.84
	Occipital delta/alpha2	-	-	-	-

ADD vs. DLB	Occipital delta	-	-	-	-
	Occipital alpha 2	64.7%	73.8%	69.7%	0.75
	Occipital delta/alpha2	-	-	-	-
PDD vs. DLB	Occipital delta	-	-	-	-
	Occipital alpha 2	-	-	-	-
	Occipital delta/alpha2	-	-	-	-

***Table 4**. Results of the classification among Nold, ADD, PDD, and DLB individuals based on the rsEEG source activities. These source activities were those showing statistically significant differences between the three groups in the main statistical analysis (i.e. Nold, ADD, PDD, DLB). The classification rate is computed by the analysis of the area under the receiver operating characteristic (AUROC) curve. The table reports the classification indexes (Sensitivity, Specificity, Accuracy) for all the rsEEG source activities having a value higher than 0.75 in the AUROC curves. Highlighted in red type are the best classification results for each rsEEG source of interest.*

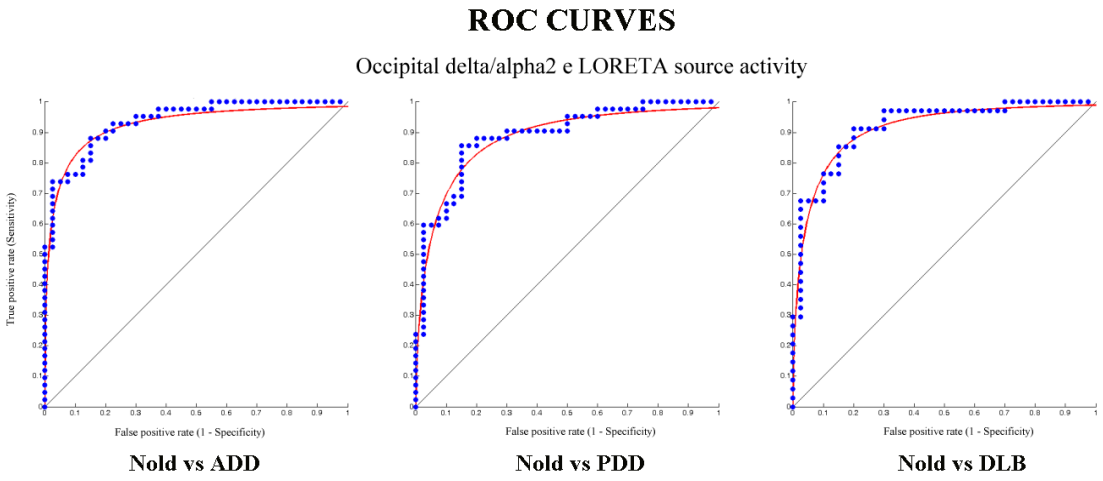

***Figure 5.** Receiver operating characteristic (ROC) curves illustrating the classification of the patients with dementia (ADD, PDD and DLB) and Nold individuals based on the occipital delta/alpha 2 (eLORETA) source activity. The area under the ROC (AUROC) curve was 0.94 in the classification of the Nold and ADD individuals; 0.89 in the classification of the Nold and PDD individuals; and 0.92 in the classification of the Nold and DLB individuals. These results indicate a good classification performance. The true positive rate indicates the probability of the correct classification of the patients with dementia (sensitivity), whereas the false positive rate indicates the probability of the incorrect classification of the Nold individuals (1-specificity).*

Discussion

This retrospective and exploratory study on archived data tested the hypothesis that rsEEG source mapping is able to unveil different spatial and frequency features of the cortical neural

synchronization in three relevant neurodegenerative dementing disorders such as ADD, PDD, and DLB. To test this exploratory hypothesis, cortical rsEEG sources were compared in ADD, PDD, and DLB patients, at the group and the individual levels. As a main methodological novelty, we defined the frequency bands from delta to alpha on an individual basis using TF and IAF as landmarks (Klimesch, 1996, Klimesch, 1999 and Klimesch et al., 1998; Moretti et al., 2004). The choice of this procedure was motivated by the fact that the mean IAF was lower in the ADD (8.1 Hz), PDD (7.3 Hz), and DLB (7.1 Hz) groups than the Nold (9.0 Hz) group. Furthermore, the mean IAF was lower in the PDD and DLB groups than the ADD group. In this case, the use of the standard alpha 1 (8-10/10.5 Hz) and alpha 2 (10-12/13 Hz) sub-bands would have produced differences in the source activity between the AD and PDD/DLB groups merely due to the slowing of the IAF in the latter groups.

Compared to the Nold group, all patient groups (i.e. ADD, DLB, and PDD) exhibited a lower posterior (mostly occipital-parietal) alpha 2 source activity. Its maximum reduction was found in the ADD group while the smallest decrease was observed in the PDD group, with the DLB group showing an intermediate reduction. Differences between the groups were also found in the occipital delta source activity. Compared to the Nold group, the PDD group exhibited its maximum abnormal increase while a moderate increase was seen in the ADD group; again, the DLB group showed an intermediate increase. Noteworthy, a clinically relevant finding was that these source activities exhibited a correlation with the MMSE score (roughly reflecting global cognitive status) across all Nold, ADD, PDD, and DLB subjects as a whole.

The present results extend to source space and individually-determined frequency bands previous MEG and EEG evidence showing differences in the delta, theta, and alpha rhythms in the ADD, PDD, and DLB groups compared to Nold groups (Soikkeli et al., 1991; Primavera and Novello, 1992; Neufeld et al., 1994; Tanaka et al., 2000; Pezard et al., 2001; Babiloni et al., 2004; 2006a, b, 2007, 2009, 2010, 2013, 2015a, b, 2016; Franciotti et al., 2007; Berendse and Stam, 2007; Bonanni et al., 2008, 2015; Stam, 2010). Of interest, the slowing of the posterior rsEEG rhythms has been previously reported in both DLB and PDD groups, compared to the ADD group, as revealed by a greater power of widespread delta and theta rhythms (Kai et al., 2005; Andersson et al., 2008) and the appearance of a “pre-alpha” power peak in the rsEEG spectrum (Bonanni et al., 2008). Furthermore, previous EEG and MEG evidence pointed at a higher power of delta-theta rhythms and a lower power of alpha-beta rhythms in PDD than in non-demented PD patients, at the group level (Soikkeli et al., 1991; Neufeld et al., 1994; Bosboom et al., 2006). Similar results were obtained with a rsEEG source estimation procedure

in ADD and PDD patients, when compared to a group of Nold subjects (Babiloni et al., 2011). In the previous studies, however, the increase in the delta and theta power was observed even in groups of PD patients without dementia so that this rsEEG feature may be nonspecific for the cognitive decline in that disease (Stoffers et al., 2007). Finally, the present results complement previous findings showing a greater fluctuation of these rsEEG rhythms in groups of DLB than in ADD and PDD patients (Walker et al., 2000a, b; Andersson et al. 2008; Bonanni et al., 2008), even at the MCI stage of DLB (Bonanni et al., 2015).

What are the neurophysiological mechanisms underlying these rsEEG abnormalities in the groups of ADD, PDD, and DLB patients? It can be speculated that in quiet wakefulness, the abnormal delta source activity in the posterior cerebral cortex is due to an abnormal interaction between thalamic and cortical pyramidal neural populations, associated with a loss of functional connectivity and a sort of functional isolation of parietal, temporal, and occipital cortical modules (Steriade and Llinas, 1988; Klimesch, 1999; Pfurtscheller and Lopez da Silva, 1999). In patients with dementia, such a functional isolation might be due to a cortical blood hypoperfusion and synaptic dysfunction in the same regions (Stigsby et al., 1981; Brenner et al., 1986; Rae-Grant et al., 1987; Dossi et al., 1992; Kwa et al., 1993; Steriade, 1994; Passero et al., 1995; Valladares-Neto et al., 1995; Niedermeyer et al., 1997; Rodriguez et al., 1999). Another cause of such an isolation might be an impairment of the cortical gray matter especially in the posterior regions (Killiany et al., 1993; Babiloni et al., 2013; Fernandez et al., 2003; Delli Pizzi et al., 2014, 2015, 2016; Babiloni et al., 2015; Graff-Radford et al., 2016; Sarro et al., 2016), as well as a lesion in the brain white matter (Agosta et al., 2012, 2014).
Concerning the abnormalities that we have found in the posterior alpha 2 sources, it can be speculated that they might denote a progressive alteration in the interplay of glutamatergic and cholinergic neurons, thalamocortical high-threshold, GABAergic interneurons, thalamocortical relay-mode, and cortical pyramidal neurons that constitute the complex network regulating the cortical arousal and vigilance in quiet wakefulness (Hughes & Crunelli, 2005; Lörincz et al., 2008, 2009). In physiological conditions, this network produces cycles of excitation and inhibition in thalamic and cortical neurons that might frame perceptual events in discrete snapshots of approximately 70–100 ms during active sensory and motor information processing (Hughes & Crunelli, 2005; Lörincz et al., 2008, 2009). In our groups of patients with dementia, the prominent occipital localization of the alpha 2 abnormalities might be the manifestation of a dysfunction of the gross cholinergic bundle from the basal forebrain to the visual cortex, which is known to be targeted by neurodegenerative processes, especially in ADD and DLB

(Helkala et al., 1996; Holschneider et al., 1999; Mesulam et al., 2004; Ricceri et al., 2004; Teipel et al., 2005; Delli Pizzi et al., 2014; Sarro et al., 2016).

In the present study, another clinically relevant achievement was the good classification accuracy of the individual patients with dementia based on rsEEG sources. Here we obtained an accuracy (i.e. AUROC curve) close to 90% in the classification of Nold subjects vs. patients with dementia, based on the ratio between the occipital delta and alpha 2 source activity. Furthermore, the occipital alpha 2 activity allowed an accuracy around 85% in the classification of ADD vs. PDD patients and around 70-75% for ADD vs. DLB individuals. Such a high discrimination of the Nold vs. ADD individuals is in line with the best accuracies of previous investigations using rsEEG power, or other spectral rsEEG features. In the previous investigations, the discrimination of Nold vs. ADD individuals was 94–45%, that of MCI vs. ADD individuals was 92–78%, and the conversion from MCI to ADD status showed 87–60% of accuracy (Huang et al., 1967, Jelic et al., 2000; Adler et al., 2003; Nuwer, 1997; Claus et al., 1999; Bennys et al., 2001; Brassen et al., 2004; Lehmann et al., 2007; Missonnier et al., 2006; Buscema et al., 2007; Knyazeva et al., 2010; Lizio et al., 2016; Babiloni et al., 2016).
Concerning the classification of ADD vs. PDD individuals, the present discrimination with 76% of success, based on the ratio between the occipital alpha 2 source activity, was intermediate when compared with those reported in previous studies. Using a semiquantitative visual analysis of rsEEG waveforms (i.e. the grand total EEG considering rsEEG slowing and reactivity to eyes opening, Pijnenburg et al., 2008), Roks et al. (2008) discriminated DLB vs. ADD individuals with an accuracy of approximately 78%. In a more recent study, the same type of visual analysis discriminated DLB vs. ADD individuals with an accuracy of about 77% (Lee et al., 2015). Much better classification accuracy was reached by a quantitative analysis of rsEEG features. Snaedal et a. (2012) gave 20 rsEEG features as an input to a series of trained mathematical classifiers (statistical pattern recognition) to discriminate with serial binary classifications patients with ADD, DLB/PDD, and other pathological conditions. The discrimination values were quite good. Specifically, the discrimination of AD vs. DLB/PDD individuals was of 91%. Using the same basic methodology, Engedal et al. (2015) repeated the classification trial for cross-validation purposes and confirmed an accuracy of 86% in the classification of DLB/PDD vs. ADD individuals. In the same line, other rsEEG features allowed the discrimination of ADD vs. DLB individuals with 80-84% of success (Bonanni et al., 2016). To our knowledge, no cross-validated comparisons showed the ability of rsEEG markers in the

discrimination of PDD vs. DLB patients to delineate the bounds between these entities at the individual level.

The clinical neurophysiological model

How can the present neurophysiological (rsEEG source) findings enrich the actual theoretical view of ADD, LBD, and PDD grounded upon neurobiological, neuropathological, and clinical characteristics? Nowadays, neurobiological, neuropathological, and clinical pieces of evidence show puzzling similarities and differences among these dementing disorders. Indeed, these disorders may share some genetic susceptibility risk factors (Meeus et al., 2012), but also interesting differences (Bras et al., 2014). On one hand, some typical genetic mutations increasing the risk of AD (i.e. amyloid precursor protein, presenilin 1, presenilin 2, and APOE genes) can be found in DLB patients. On the other hand, some common genetic mutations increasing the risk of DLB (i.e. α-synuclein and glucocerebrosidase genes) are also observed in PDD.

Concerning the disease neuropathology, DLB and PDD show a similar accumulation of α-synuclein in brain Lewy bodies and neurites, a depletion of tegmental dopamine, and a loss of basal forebrain cholinergic cells (Gomperts, 2016; Barker & William-Gray, 2016; Hall et al., 2014; Hepp et al., 2016). In this context, a pure Lewy body pathology (with a cortical prominence of the Lewy bodies and neurites) is observed only in about 20-40% of DLB patients while the remaining ones show additional AD neuropathological features such as Aβ neuritic plaques and neurofibrillary tangles.

Clinically, both DLB and PDD exhibit a progressive impairment of behavior (i.e. visual hallucinations), fluctuation of wakefulness, vigilance, and attention, as well as REM sleep behavior disorder. However, these symptoms are expected to appear early in the course of DLB and are differentially expressed in PDD, especially the cognitive fluctuation (McKeith et al., 2005). Furthermore, PD motor symptoms are expected to precede dementia at least for one year in PDD but not in DLB (McKeith et al., 2005). Compared to ADD, DLB is thought to show more impairment of visual cognition, but fewer deficits on verbal memory and confrontation naming (Peavy et al., 2016; Scharre et al., 2016; Park et al., 2011; Filoteo et al., 2009).

The above pieces of evidence suggest some neurobiological, neuropathological, and clinical similarities between ADD and DLB and between ADD and PDD. What do the present neurophysiological (rsEEG source) findings add to our understanding of the ADD, LBD, and PDD? On one hand, a reduced activation of the posterior low-frequency alpha sources do

characterize both the ADD and LBD groups. It can be speculated that these diseases might induce a dysfunction of thalamic and cortical interactions with an unselective desynchronizing activity of cholinergic and glutamatergic pathways from the basal forebrain and thalamus to the posterior cerebral cortex. This speculation is grounded upon previous theories on the neurophysiological mechanisms generating physiological on-going cortical alpha rhythms in animal models (Sarter and Bruno, 1997, 1998; Kobayashi and Isa, 2002; Hughes & Crunelli, 2005; Lörincz et al., 2008, 2009).

On the other hand, an increased activation in the posterior delta sources did characterize both the LBD and PDD groups. It can be speculated that these diseases might induce substantial synaptic dysfunction and neurodegeneration of pyramidal neurons in the posterior cerebral cortex. This speculation is grounded upon previous theories on the clinical neurophysiological mechanisms generating abnormal cortical delta rhythms in quiet wakefulness in patients with dementia (Killiany et al., 1993; Passero et al., 1995; Niedermeyer et al., 1997; Rodriguez et al., 1999; Fernandez et al., 2003; Babiloni et al., 2013). Overall, future multi-modal MRI-rsEEG studies should test these hypotheses and unveil whether PDD, DLB, and ADD do belong to a disease continuum of Lewy body and Alzheimer's diseases (Colloby et al., 2016).

II study

Abnormal cortical neural synchronization mechanisms in quiet wakefulness are related to motor deficits, cognitive symptoms, and visual hallucinations in Parkinson's disease patients: an electroencephalographic study

Introduction

It is well known that Parkinson's disease (PD) presents abnormalities in frontal executive and motor functions, due to the progressive neurodegeneration by nigrostriatal dopaminergic neurons in relation to intracellular Lewy bodies and neurofibrillary tangles (Parkkinen et al., 2008). During the PD progression, this core neurodegenerative process of the motor systems impairs related frontostriatal, mesocortical, mesolimbic, and fronto-parietal neural networks, which are modulated by dopaminergic, cholinergic, serotoninergic, and noradrenergic neurotransmitters (Buddhala et al., 2015; Joutsa et al., 2015; Gratwicke et al., 2015; Stahl, 2016). As a result, PD clinical manifestations extend to visual hallucinations, disorders of vigilance and sleep, and fluctuations of cognitive functions (Emre, 2003; Muslimovic et al., 2005; Aarsland et al., 2003; Buter et al., 2008; Hughes et al., 2000; Levy et al., 2000). In particular, visual hallucinations are very frequent (> 50%) in PD patients with dementia (PDD, Fénelon et al., 2000; Nomura et al., 2003; Nishio et al., 2018).

Unfortunately, the mentioned clinical phenotype of the PD partially overlaps with that of other neurodegenerative dementing disorders in seniors such as dementia with Lewy bodies (DLB) and Alzheimer's disease (AD), so the clinical practice in many millions of PD, DLB, and AD patients would benefit of biomarkers that are noninvasive, cost-effective, repeatable over time, and largely accessible worldwide. For an ideal precision medicine, these biomarkers should be sensitive to different brain neural substrates underpinning these neuropathological clinical manifestations.

Among various candidates, biomarkers derived from the spectral analysis of resting state eyes-closed electroencephalographic (rsEEG) rhythms theoretically show all the desired characteristics. For this reason, they were tested in several PD studies as indexes of thalamocortical and corticothalamic neural synchronization mechanisms underpinning the regulation of vigilance in quiet wakefulness (Bonanni et al., 2008; Bosboom et al., 2009, 2006;

Caviness et al., 2016; Fünfgeld, 1995; Kamei et al., 2010; Melgari et al., 2014; Pugnetti et al., 2010; Serizawa et al., 2008). Results of those studies have shown that when compared to normal healthy elderly (Nold) individuals, PD patients with cognitive deficits (PDCD) were characterized by higher rsEEG power at delta (< 4 Hz) and theta (4-7 Hz) rhythms in topographically widespread cortical regions, associated with a reduction of alpha (8-12 Hz) power (Bonanni et al., 2008; Bosboom et al., 2009, 2006; Caviness et al., 2016; Fünfgeld, 1995; Kamei et al., 2010; Melgari et al., 2014; Pugnetti et al., 2010; Serizawa et al., 2008). Compared to PD patients with an intact cognition, PDCD patients exhibited lower frequency in the alpha power peak, greater global theta and delta power over the whole scalp, and lower power at alpha and beta (13-30 Hz) frequency bands (Caviness et al., 2007, 2016a).

To enhance the spatial and frequency details of the above rsEEG results, our Consortim used a methodological approach including (1) the estimation of rsEEG cortical sources by the popular exact low-resolution brain electromagnetic tomography (eLORETA) freeware (Pascual-Marqui, 2007) and (2) the definition of delta, theta, and alpha frequency bands on individual basis using the so-called individual alpha frequency (IAF) peak as a reference in the rsEEG power density spectrum averaged across all electrodes (Babiloni et al., 2018a,b,c; Babiloni et al., 2017a,b). Compared with Nold subjects, PDCD patients showed a reduced activation in occipital, parietal, and temporal cortical sources of alpha rhythms around the IAF, associated with an increase in topographically widespread delta source activities (Babiloni et al., 2018a,b, 2017a,b). Furthermore, such increment in the delta source activities was greater than that observed in control AD and DLB patients. In the same investigations, PDCD patients exhibited less reduction in the alpha source activities than that observed in control AD and DLB patients. As a further step forward, another study using that methodological approach unveiled that in PDCD patients, the acute administration of levodopa reduced both delta and alpha source activities, thus suggesting that the dopamine modulation may increase global cortical excitability in quiet wakefulness (Babiloni et al., 2018c). Indeed, the lower the rsEEG power at the alpha frequencies, the higher the general cortical arousal in both resting state and cognitive-motor events (Pfurtscheller and Lopes da Silva, 1999).

In the present study, we used the mentioned methodological approach to test the hypothesis that cortical sources of rsEEG rhythms at delta and alpha frequencies may differ as a function of relevant clinical features in PD patients such as the severity of cognitive, motor, and visual hallucinations. To test this hypothesis, cortical sources of rsEEG rhythms in age-, sex-, and education-matched PD, AD, and Nold subjects were compared with the focus on statistical

contrasts between matched PD sub-groups with high vs. low motor deficits, high vs. low global cognitive status, and with vs. without visual hallucinations.

Materials and Methods

Subjects

In the present exploratory and observational study, clinical and rsEEG data were taken from an international archive formed by the Clinical Units of the PDWAIVE and E-DLB Consortia. Specifically, the PD group (N = 93) was formed by 22 PDD patients, 48 PD with mild cognitive impairment (PDMCI), and 23 PD with normal global cognition (PDNC). Age-, sex-, and education-matched groups of AD patients (N = 60) and Nold subjects (N = 70) were also taken from the same archive for control purposes. In detail, the AD group was formed by 19 AD patients with dementia (ADD) and 51 AD patients with mild cognitive impairment (ADMCI). Table 1 summarizes the most relevant demographic (i.e., age, gender, and education) and clinical (i.e., mini mental state evaluation, MMSE, score; Unified Parkinson Disease Rating Scale-III, UPDRS III, score; visual hallucinations, VH) features of those Nold, AD, and PD groups. Furthermore, the Table 1 reports the results of the presence or absence of statistically significant differences ($p < 0.05$) among the three groups for the age (ANOVA), gender (Freeman-Halton), education (ANOVA), and MMSE score (Kruskal-Wallis). As expected, there was a higher MMSE score in the Nold than the AD and PD sub-groups ($p < 0.0001$). On the contrary, statistically significant differences were found neither for the MMSE score between the AD and PD sub-groups ($p > 0.05$) nor the age, gender, and education among the Nold, AD, and PD sub-groups ($p > 0.05$). Local institutional Ethics Committee approved the present observational study. All experiments were performed with the informed and overt consent of each participant or caregiver, in line with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the local Institutional Review Board.

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS				
	Nold	AD	PD	Statistical analysis
N	60	70	93	-
Age (years)	70.0	70.4	69.5	ANOVA:

	(± 0.9 SE)	(± 0.7 SE)	(± 0.8 SE)	n.s.
Gender (F/M)	27/33	34/36	33/60	Freeman-Halton: n.s.
Education (years)	9.1 (± 0.1 SE)	9.2 (± 0.4 SE)	8.1 (± 0.4 SE)	ANOVA: n.s.
MMSE score	28.5 (± 0.1 SE)	23.5 (± 0.4 SE)	23.2 (± 0.5 SE)	Kruskal-Wallis: H = 80.4; p < 0.0001 (Nold > AD, PD)
Visual hallucinations	-	-	N= 24	-
UPDRS III Motor	-	-	29.8 (± 1.5 SE)	-

Table 1. *Mean values (± standard error of the mean, SE) of the demographic and clinical data as well as the results of their statistical comparisons (p < 0.05) in the groups of healthy elderly subjects (Nold, N = 70), Alzheimer's disease patients (AD, N = 60), and Parkinson's disease patients (PD, N = 93). Legend: MMSE = Mini Mental State Evaluation; UPDRS III= Unified Parkinson Disease Rating Scale-III ; M/F = males/females; n.s. = not significant (p > 0.05).*

To test the relationship between the rsEEG source activities of interest and the global cognitive status in the PD patients, two sub-groups of PD patients (N = 20) matched for the demographic features and levodopa therapy were considered, namely the PD sub-groups with lowest (MMSE > 26; PD-MMSE-) and highest (MMSE < 25; PD-MMSE+) global cognitive deficits. The confounding influence of motor deficits and visual hallucinations was mitigated matching the PD-MMSE- and PD-MMSE+ sub-groups for the UPDRS III score and using only PD patients without visual hallucinations. Specifically, the PD-MMSE- sub-group was formed by 6 PDMCI and 14 PDNC patients, while the PD-MMSE+ sub-group was formed by 7 PDD, 11 PDMCI, and 2 PDNC patients. Furthermore, the mean time from the clinical diagnosis of PD to the rsEEG recording was quite similar, namely 4.9 years (± 0.9 SE) in the PD-MMSE- sub-group and 4.1 years (± 0.7 SE) in the PD-MMSE+ sub-group. In the same line, no (0%) PD-MMSE- patient and only 2 (1%) PD-MMSE+ patients used psychoactive drugs, while no (0%) PD-MMSE- patient and only 1 (5%) PD-MMSE+ patient used acetylcholinesterase inhibitors. As expected, no statistically significant difference between the PD-MMSE- and PD-MMSE+ sub-groups was found for the time from the clinical diagnosis of PD to the rsEEG recording (T-test:

$p > 0.05$) as well as the use of psychoactive drugs and acetylcholinesterase inhibitors (Fisher test: $p > 0.05$). To test the specificity of the statistical effects, demographic-matched sub-groups of AD patients (N = 20; 14 ADD and 6 ADMCI) and Nold subjects (N = 45) were used as control sub-groups in the statistical analysis. Table 2 summarizes the most relevant demographic and clinical features of the Nold, AD, and PD-MMSE-, and PD-MMSE+ sub-groups. Furthermore, the Table 2 reports the results of the statistical analysis ($p < 0.05$) among the four sub-groups for the age (ANOVA), gender (Freeman-Halton), education (ANOVA), and MMSE score (Kruskal-Wallis). In the same vein, the two PD-sub-groups were compared for the UPDRS III score (t-test). As expected, a statistically significant difference was found for the MMSE score ($H = 73.9$; $p < 0.00001$). Specifically, there was a higher MMSE score in the Nold and PD-MMSE- than the AD and PD-MMSE+ sub-groups ($p < 0.0001$). On the contrary, statistically significant differences were found neither for the UPDRS III score between the PD-MMSE- and PD-MMSE+ sub-groups ($p > 0.05$) nor the age, gender, and education among the Nold, AD, PD-MMSE-, and PD-MMSE+ sub-groups ($p > 0.05$).

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS					
	Nold	AD	PD-MMSE-	PD-MMSE+	Statistical analysis
N	45	20	20	20	-
Age (years)	70.1 (± 1.1 SE)	70.5 (± 1.2 SE)	70.8 (± 2.0 SE)	69.8 (± 1.5 SE)	ANOVA: n.s.
Gender (F/M)	19/26	8/12	8/12	6/14	Freeman-Halton: n.s.
Education (years)	7.8 (± 0.5 SE)	8.0 (± 1.0 SE)	7.2 (± 0.7 SE)	7.0 (± 0.7 SE)	ANOVA: n.s.
MMSE score	28.5 (± 0.1 SE)	20.4 (± 0.8 SE)	28.5 (± 0.3 SE)	20.9 (± 0.8 SE)	Kruskal-Wallis: H = 73.9; p < 0.00001 (Nold, PD-MMSE- > AD, PD-MMSE+)
Visual hallucinations	-	-	N= 0	N= 0	Fisher test: n.s.

UPDRS III Motor	-	-	27.6 (± 3.0 SE)	26.5 (± 2.2SE)	T test: n.s.

Table 2*. Mean values (± SE) of the demographic and clinical data as well as the results of their statistical comparisons (p < 0.05) in the sub-groups of Nold subjects (N = 45), AD patients (N = 20), PD patients with low global cognitive deficits (PD-MMSE-, N = 20), and PD patients with high global cognitive deficits (PD-MMSE+, N = 20). Legend: MMSE = Mini Mental State Evaluation; UPDRS III= Unified Parkinson Disease Rating Scale-III ; M/F = males/females; n.s. = not significant (p > 0.05).*

To test the relationship between the rsEEG source activities of interest and motor deficits in the PD patients, two sub-groups of PD patients (N = 24) matched for the demographic features and levodopa were considered, namely the PD sub-groups with lowest (UPDRS III ≤ 24; PD-UPDRS-) and highest (UPDRS III ≥ 26; PD-UPDRS+) motor deficits. The confounding influence of cognitive deficits and visual hallucinations was mitigated matching the PD-UPDRS- and PD-UPDRS+ sub-groups for the MMSE score and using only PD patients without visual hallucinations. Furthermore, the mean time from the clinical diagnosis of PD to the rsEEG recording was quite similar, namely 5.1 years (± 0.9 SE) in the PD-UPDRS- sub-group and 4.7 years (± 0.8 SE) in the PD-UPDRS+ sub-group. In the same line, no (0%) PD-UPDRS- patient and only 3 (12.5%) PD-UPDRS+ patients used psychoactive drugs, while no (0%) PD-UPDRS- patients and only 2 (8.3%) PD-UPDRS+ patients used acetylcholinesterase inhibitors. As expected, no statistically significant difference between the PD-UPDRS- and PD-UPDRS+ sub-groups was found for the time from the clinical diagnosis of PD to the EEG recording (T-test: $p > 0.05$) as well as the use of psychoactive drugs and acetylcholinesterase inhibitors (Fisher test: $p > 0.05$). Concerning the subjects' cognitive status, the PD-UPDRS- sub-group was formed by 3 PDD, 17 PDMCI, and 4 PDNC patients, while the PD-UPDRS+ sub-group was formed by 3 PDD, 11 PDMCI, and 10 PDNC patients. To test the specificity of the statistical effects, demographic-matched sub-groups of AD patients (N = 25; 7 ADD and 18 ADMCI) and Nold subjects (N = 50) were used as controls in the statistical analysis. Table 3 summarizes the most relevant demographic and clinical features of the Nold, AD, and PD-UPDRS-, and PD-UPDRS+ sub-groups. Furthermore, the Table 3 reports the results of the statistical analysis ($p < 0.05$) among the four sub-groups for the age (ANOVA), gender (Freeman-Halton), education (ANOVA), and MMSE score (Kruskal-Wallis). The MMSE score was higher ($H = 59.1$; $p < 0.00001$) in the Nold than the AD, PD-UPDRS-, and PD-UPDRS+ sub-groups ($p < 0.0001$). On the contrary, statistically significant differences were found neither for the MMSE score among the AD, PD-UPDRS-, and PD-UPDRS+ sub-groups ($p > 0.05$) nor

the age, gender, and education among the Nold, AD, PD-UPDRS-, and PD-UPDRS+ sub-groups ($p > 0.05$). In the same vein, the two PD sub-groups were compared for the UPDRS III score (t-test). As expected, there was a higher UPDRS III score in the PD-UPDRS+ than the PD-UPDRS- sub-group ($p < 0.000001$).

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS					
	Nold	AD	PD-UPDRS-	PD-UPDRS+	Statistical analysis
N	50	25	24	24	-
Age (years)	70.0 (± 1.0 SE)	69.8 (± 1.3 SE)	69.6 (± 1.1 SE)	70.7 (± 1.2 SE)	ANOVA: n.s.
Gender (F/M)	21/29	11/14	7/17	10/14	Freeman-Halton: n.s.
Education (years)	8.2 (± 0.5 SE)	8.4 (± 0.7 SE)	7.8 (± 0.9 SE)	7.3 (± 0.6 SE)	ANOVA: n.s.
MMSE score	28.5 (± 0.1 SE)	24.1 (± 0.5 SE)	24.5 (± 0.7 SE)	24.5 (± 0.9 SE)	Kruskal-Wallis: H = 59.1; p < 0.00001 (Nold > AD, PD-UPDRS-, PD-UPDRS+)
Visual hallucinations	-	-	N = 0	N = 0	Fisher test: n.s.
UPDRS III Motor	-	-	15.2 (± 1.3 SE)	38.4 (± 2.5 SE)	T test: p < 0.000001

***Table 3**. Mean values (± SE) of the demographic and clinical data as well as the results of their statistical comparisons ($p < 0.05$) in the sub-groups of Nold subjects (N = 50), AD patients (N = 25), PD patients with low motor deficits (PD-UPDRS-, N = 24), and PD patients with high motor deficits (PD-UPDRS+, N = 24). Legend: MMSE = Mini Mental State Evaluation; UPDRS III= Unified Parkinson Disease Rating Scale-III ; M/F = males/females; n.s. = not significant ($p > 0.05$).*

To test the relationship between the rsEEG source activities of interest and visual hallucinations in the PD patients, two sub-groups of PD patients (N = 17) matched for the demographic and

levodopa features were considered, namely the PD sub-groups without (PD-VH-) and with (PD-VH+) visual hallucinations. The confounding influence of cognitive and motor deficits was mitigated matching these two PD sub-groups for the MMSE and UPDRS III scores. Specifically, the PD-VH- sub-group was formed by 6 PDD, 10 PDMCI, and 1 PDNC patients, while the PD-VH+ sub-group was formed by 9 PDD, 6 PDMCI, and 2 PDNC patients. Furthermore, the mean time from the clinical diagnosis of PD to the rsEEG recording was quite similar, namely 4.3 years (± 0.8 SE) in the PD-VH- sub-group and 6.5 years (± 1.5 SE) in the PD-VH+ sub-group. In the same line, only 2 (11.8%) PD-VH- patients and 3 (17.6%) PD-VH+ patients used psychoactive drugs, while 2 (11.8%) PD-VH- patients and 7 (41.2%) PD-VH+ patients used acetylcholinesterase inhibitors. No statistically significant difference between the PD-VH- and PD-VH+ sub-groups was found for the time from the clinical diagnosis of PD to the EEG recording (T-test: $p > 0.05$) as well as the use of psychoactive drugs and acetylcholinesterase inhibitors (Fisher test: $p > 0.05$). To test the specificity of the statistical effects, demographic-matched sub-groups of AD patients (N = 20; 13 ADD and 7 ADMCI) and Nold subjects (N = 40) were used as controls in the statistical analysis. Table 4 summarizes the most relevant demographic and clinical features of the Nold, AD, and PD-VH-, and PD-VH+ sub-groups. Furthermore, the Table 4 reports the results of the statistical analysis ($p < 0.05$) among the four sub-groups for the age (ANOVA), gender (Freeman-Halton), education (ANOVA), and MMSE score (Kruskal-Wallis). As expected, the MMSE score was higher in the Nold than the AD, PD-VH-, and PD-VH+ sub-groups ($p < 0.0001$). On the contrary, a statistically significant difference was found neither for the MMSE scores among the AD, PD-VH-, and PD-VH+ sub-groups nor the age, gender, and education among the Nold, AD, PD-VH-, and PD-VH+ sub-groups ($p > 0.05$). Furthermore, there were significant differences neither in the UPDRS III scores between the PD-VH- and PD-VH+ sub-groups ($p > 0.05$) nor the age, gender, and education among the Nold, AD, PD-VH-, and PD-VH+ sub-groups ($p > 0.05$).

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS					
	Nold	AD	PD-VH-	PD-VH+	Statistical analysis
N	40	20	17	17	
Age (years)	70.8 (± 1.1 SE)	71.1 (± 1.1 SE)	70.1 (± 1.5 SE)	70.2 (± 1.6 SE)	ANOVA: n.s.

Gender (F/M)	21/19	10/10	7/10	9/8	Freeman-Halton: n.s.
Education (years)	7.0 (± 0.4 SE)	7.4 (± 1.0 SE)	6.6 (± 0.7 SE)	6.8 (± 0.9 SE)	ANOVA: n.s.
MMSE score	28.5 (± 0.2 SE)	19.7 (± 0.9 SE)	19.8 (± 0.8 SE)	19.7 (± 0.8 SE)	Kruskal-Wallis: H = 68.3; p < 0.000001 (Nold > AD, PDVH-, PDVH+)
Visual hallucinations	-	-	N= 0	N= 17	Fisher test: p < 0.000001
UPDRS III Motor	-	-	33.4 (± 1.5 SE)	37.0 (± 1.5 SE)	T test: n.s.

Table 4*. Mean values (± SE) of the demographic and clinical data as well as the results of their statistical comparisons (p < 0.05) in the sub-groups of Nold subjects (N = 40), AD patients (N = 20), PD patients with absence of visual hallucinations (PD-VH-, N = 17), and PD patients with presence of visual hallucinations (PD-VH+, N = 17). Legend: MMSE = Mini Mental State Evaluation; UPDRS III= Unified Parkinson Disease Rating Scale-III ; M/F = males/females; n.s. = not significant (p > 0.05).*

Diagnostic criteria

The diagnosis of PD was based on a standard clinical assessment of tremor, rigidity, and bradykinesia (Gelb et al., 1999). As measures of severity of motor disability, the Hoehn and Yahr stage (Hoehn and Yahr, 1967) and the Unified Parkinson Disease Rating Scale-III (UPDRS III; Fahn and Elton, 1987) for extrapyramidal symptoms were used.

Diagnosis of PDD was given to the patients with a history of dementia preceded by a diagnosis of PD for at least 12 months. The PDD was diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR; American Psychiatric Association). The inclusion criteria included: (1) a diagnosis of PD as specified above; (2) a gradual decline, in the context of an established PD, in the cognitive status reported by either the patient or a reliable informant, or observed by the clinicians; (3) an abnormally low score to at least one of the neuropsychological tests mentioned in a following section, as defined by performances 1.5 standard deviations (SD) from the mean value for age- and education-matched controls or equivalent scores for abnormality according relative manuals of the tests

used; and (4) moderate to severe impairment in the functional independence in instrumental activities of the daily living.

The status of PDMCI was based on the Diagnostic Criteria for Mild Cognitive Impairment in PD (Litvan et al., 2011). Specifically, the inclusion criteria comprised: (1) a diagnosis of PD as specified above; (2) a gradual decline, in the context of an established PD, in the cognitive status reported by either the patient or informant, or observed by the clinicians; and (3) cognitive deficits not sufficient to interfere significantly with functional independence in the activities of the daily life, although slight difficulties on complex functional tasks may be present.

The exclusion criteria for PD (i.e., PDD, PDMCI, and PDNC) included the following forms of parkinsonism: (1) Lewy Body disease (Geser et al., 2005; McKeith et al., 2005, 1996); (2) drug-induced parkinsonism; (3) cerebrovascular parkinsonism; (4) atypical parkinsonism with absent or minimal responses to antiparkinsonian drugs; and (5) mixed dementing diseases.

All PD (i.e., PDD, PDMCI, and PDNC) patients underwent a battery of neuropsychological tests (for details see Babiloni et al., 2017a, 2017b).

The diagnosis of ADD has been described in the diagnostic criteria of the "I experimental study", meanwhile, the status of the ADMCI was based on the "positivity" to one or more of the following biomarkers: Aβ1-42/ 78 hosphor-tau in the cerebrospinal fluid (CSF), Fluorodeoxyglucose positron emission tomography (FDG-PET) mapping of hippocampus, parietal, temporal, and posterior cingulate regions, and structural magnetic resonance imaging (MRI) of hippocampus, parietal, temporal, and posterior cingulate regions (Albert et al., 2011). The "positivity" was based on the judgment of "abnormality" of the readout given by physicians in charge for the diagnosis of patients, according to the local diagnostic routine of the participating clinical Units. The inclusion criteria for the enrollment of the ADMCI patients were (1) complaints of memory deficits by the patient or a relative; (2) MMSE score ≥ 24, overall Clinical Dementia Rating (CDR; Morris, 1993) score of 0.5; (3) score on the logical memory test (Wechsler, 1987) of 1.5 SD lower than the age-adjusted mean; (4) 15-item Geriatric Depression Scale (GDS; Brown and Schinka, 2005) score ≤ 5; and (5) modified Hachinski ischemia (Rosen et al., 1980) score ≤ 4. The MCI status could be single or multi-domain. Exclusion criteria for the ADMCI patients were other significant neurological, systemic or psychiatric illness, mixed dementing diseases, enrolment in a clinical trial with experimental drugs, the use of antidepressant drugs with anticholinergic side effects, high dose of neuroleptics or chronic sedatives or hypnotics, antiparkinsonian medication and the use of narcotic analgesics.

All AD (i.e., ADD and ADMCI) patients underwent a battery of neuropsychological tests (for details see Babiloni et al., 2017a, 2017b).

All Nold subjects underwent a cognitive screening (including MMSE and GDS) as well as physical and neurological examinations to exclude any dementia or major cognitive deficit or psychiatric disorder. All Nold subjects had a GDS score lower than the threshold of 5 (no depression) or no depression after an interview with a physician or clinical psychologist. Subjects affected by chronic systemic illnesses (diabetes mellitus, as an example) were excluded, as well as subjects receiving chronic psychoactive drugs. Subjects with a history of previous or present neurological or psychiatric disease were also excluded.

Statistical analysis

Four statistical sessions were performed by the commercial tool STATISTICA 10 (StatSoft Inc., www.statsoft.com) to test the control hypothesis and the three working hypotheses. In all the statistical sessions, ANOVA was computed using the rsEEG source activities (i.e., regional normalized eLORETA solutions) as a dependent variable ($p < 0.05$). Mauchly's test evaluated the sphericity assumption and degrees of freedom were corrected by the Greenhouse-Geisser procedure when appropriate ($p < 0.05$). Duncan test was used for post-hoc comparisons ($p < 0.05$). The results of the following statistical analyses were controlled by the Grubbs test ($p < 0.01$) for the presence of outliers in the distribution of the eLORETA source solutions.

The first ANOVA tested the control hypothesis that the rsEEG source activities (i.e., regional normalized eLORETA solutions) differed among Nold, AD, and PD groups. The ANOVA factors were Group (Nold, AD, and PD), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal, and limbic). The confirmation of the control hypothesis may require: (1) a statistically significant ANOVA effect including the factor Group ($p < 0.05$) and (2) a post-hoc Duncan test indicating statistically significant ($p < 0.05$) differences in the rsEEG source activities among Nold, AD, and PD groups (i.e., Nold ≠ AD ≠ PD, $p < 0.05$).

The second ANOVA evaluated the first working hypothesis that the rsEEG source activities (i.e., regional normalized eLORETA solutions) differed as a function of global cognitive deficits (i.e., MMSE) in PD patients (PD-MMSE- vs. PD-MMSE+; Nold and AD as control

groups). The ANOVA factors were Group (Nold, AD, PD-MMSE-, and PD-MMSE+), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal, and limbic). The confirmation of the first working hypothesis may require: (1) a statistically significant ANOVA effect including the factor Group ($p < 0.05$) and (2) a post-hoc Duncan test indicating statistically significant ($p < 0.05$) differences in the rsEEG source activities between PD-MMSE- and PD-MMSE+ groups (i.e., PD-MMSE- ≠ PD-MMSE+, $p < 0.05$).

The third ANOVA evaluated the second working hypothesis that the rsEEG source activities (i.e., regional normalized eLORETA solutions) differed as a function of motor deficits (i.e., UPDRS-III) in PD patients (PD-UPDRS- vs. PD-UPDRS+; Nold and AD as control groups). The ANOVA factors were Group (Nold, AD, PD-UPDRS-, and PD-UPDRS+), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal, and limbic). The confirmation of the second working hypothesis may require: (1) a statistically significant ANOVA effect including the factor Group ($p < 0.05$) and (2) a post-hoc Duncan test indicating statistically significant ($p < 0.05$) differences in the rsEEG source activities between PD-UPDRS- and PD-UPDRS+ groups (i.e., PD-UPDRS- ≠ PD-UPDRS+, $p < 0.05$).

Finally, the fourth ANOVA evaluated the third working hypothesis that the rsEEG source activities (i.e., regional normalized eLORETA solutions) are related to visual hallucinations in PD patients (PD-VH- vs. PD-VH+; Nold and AD as control groups). The ANOVA factors were Group (Nold, AD, PD-VH-, and PD-VH+), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal, and limbic). The confirmation of the third working hypothesis may require: (1) a statistically significant ANOVA effect including the factor Group ($p < 0.05$) and (2) a post-hoc Duncan test indicating statistically significant ($p < 0.05$) differences in the rsEEG source activities between PD-VH- and PD-VH+ groups (i.e., PD-VH- ≠ PD-VH+, $p < 0.05$).

As a first exploratory statistical analysis at the individual level, Spearman test ($p < 0.05$) was used to evaluate the correlation between the MMSE score and rsEEG source activities (i.e., regional normalized eLORETA solutions) showing statistically significant differences ($p < 0.05$) between the PD-MMSE- and PD-MMSE+ groups. In the same line, as a second exploratory statistical analysis at the individual level, Spearman test ($p < 0.05$) was also used

to evaluate the correlation between the UPDRS III score and rsEEG source activities (i.e., regional normalized eLORETA solutions) showing statistically significant differences ($p < 0.05$) between the PD-UPDRS- and PD-UPDRS+ groups.

As a third exploratory statistical analysis at the individual level, the rsEEG source activities (i.e., regional normalized eLORETA solutions) showing statistically significant differences ($p < 0.05$) in the main statistical analyses were used as discriminant variables for the classification between PD individuals with different global cognitive (PD-MMSE- vs. PD-MMSE+), motor (PD-UPDRS- vs. PD-UPDRS+), and psychiatric (visual hallucinations; PD-VH- vs. PD-VH+) status. The correct blind classifications of these rsEEG source activities were performed by Matlab 2010b software (Mathworks Inc., Natick, MA, USA) for the production of the receiver operating characteristic (ROC) curves (DeLong et al., 1988). The following indexes measured the performance of the above binary classification: (1) Sensitivity: the rate of positives who were correctly classified as positives (i.e. "true positive rate" in the signal detection theory); (2) Specificity: the rate of negatives (control) who were correctly classified as negatives (i.e. "true negative rate" in the signal detection theory); (3) Accuracy: the mean of the sensitivity and specificity (the number of subjects in the groups was the same); and (4) Area under the ROC (AUROC) curve. The AUROC curve was used as a major reference index of the global classification accuracy.

Results

Table 5 reports the mean values of TF and IAF for the three groups (i.e., Nold, AD, and PD), together with the results of the statistical comparisons between the groups (ANOVA, $p < 0.05$). The mean TF was 6.0 Hz (± 0.1 SE) in the Nold group, 5.7 Hz (± 0.2 SE) in the AD group, and 5.2 Hz (± 0.1 SE) in the PD group. Furthermore, the mean IAF was 9.3 Hz (± 0.1 SE) in the Nold group, 8.7 Hz (± 0.2 SE) in the AD group, and 7.9 Hz (± 0.2 SE) in the PD group. The ANOVAs using these values as an input showed the following statistically significant findings: (1) the mean TF was greater ($F = 4.4$, $p < 0.0005$) in the Nold and AD than the PD ($p < 0.01$) groups; (2) the mean IAF was greater ($F = 18.1$, $p < 0.00001$) in the Nold than the AD ($p < 0.05$) and PD ($p < 0.00001$) groups as well as in the AD than the PD group ($p < 0.0005$). These findings stress the importance to use the TF and IAF in the determination of the delta to alpha frequency bands in the studies focused on AD and PD patients.

MEAN VALUES (± SE) OF TRANSITION FREQUENCY (TF) AND INDIVIDUAL ALPHA FREQUENCY PEAK (IAF)				
	Nold	AD	PD	Statistical analysis
TF	6.0 (± 0.1 SE)	5.7 (± 0.1 SE)	5.2 (± 0.1 SE)	ANOVA: F = 4.4, p < 0.0005 (Nold, AD > PD)
IAF	9.3 (± 0.1 SE)	8.7 (± 0.2 SE)	7.9 (± 0.1 SE)	ANOVA: F = 18.1, p < 0.00001 (Nold > AD > PD)

Table 5. *Mean values (± SE) of transition frequency (TF) and individual alpha frequency peak (IAF) computed from rsEEG power density spectra in the Nold, AD, and PD groups. The table also reports the p values of the statistical comparisons of these values between the groups (p < 0.05). Legend: Nold = healthy elderly subjects; AD = Alzheimer's disease patients; PD = Parkinson's disease patients.*

Figure 1 shows the grand average of regional rsEEG source activities (i.e., regional normalized eLORETA solutions) relative to a statistically significant ANOVA interaction effect (F = 20.6; p < 0.00001) among the factors Group (Nold, AD, and PD), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal, and limbic). In the figure, rsEEG source activities have the shape of typical rsEEG relative power spectra. Notably, the profile and magnitude of the spectra of the rsEEG source activity in the Nold, AD, and PD groups are different across the ROIs, thus suggesting the concept that scalp-recorded rsEEG rhythms are produced by a distinct pattern of cortical source activity in these groups. In the Nold group as a physiological reference in quiet wakefulness, the dominant values of the eLORETA solutions were observed in occipital (maximum), parietal, temporal, and limbic alpha 2 and alpha 3 sources. Low values of the eLORETA solutions were found in the widespread delta, theta, and alpha 1 sources. The eLORETA solutions in beta 1, beta 2, and gamma sources were very low. Compared to the Nold group, the AD and PD groups showed a substantial decrease of the eLORETA solutions in posterior (i.e., parietal, occipital, temporal, and limbic) alpha 2 and alpha 3 sources. This effect was higher in the AD than the PD group. Furthermore, the AD and PD groups showed a substantial increase of the eLORETA solutions in widespread delta sources. This effect was higher in the PD than the AD group.

The Duncan planned post-hoc testing showed that the discriminant pattern Nold > PD > AD was fitted by parietal, occipital, temporal, and limbic alpha 2 (p < 0.01 to p < 0.000001) as well

as parietal, occipital, temporal, and limbic alpha 3 ($p < 0.05$ to $p < 0.000001$) sources. Furthermore, the discriminant pattern Nold < AD < PD was fitted by frontal and temporal delta sources ($p < 0.01$ to $p < 0.000001$). Of note, these findings were not due to outliers from those individual eLORETA solutions, as shown by Grubbs' test with an arbitrary threshold of $p < 0.0001$ (see Figure 2).

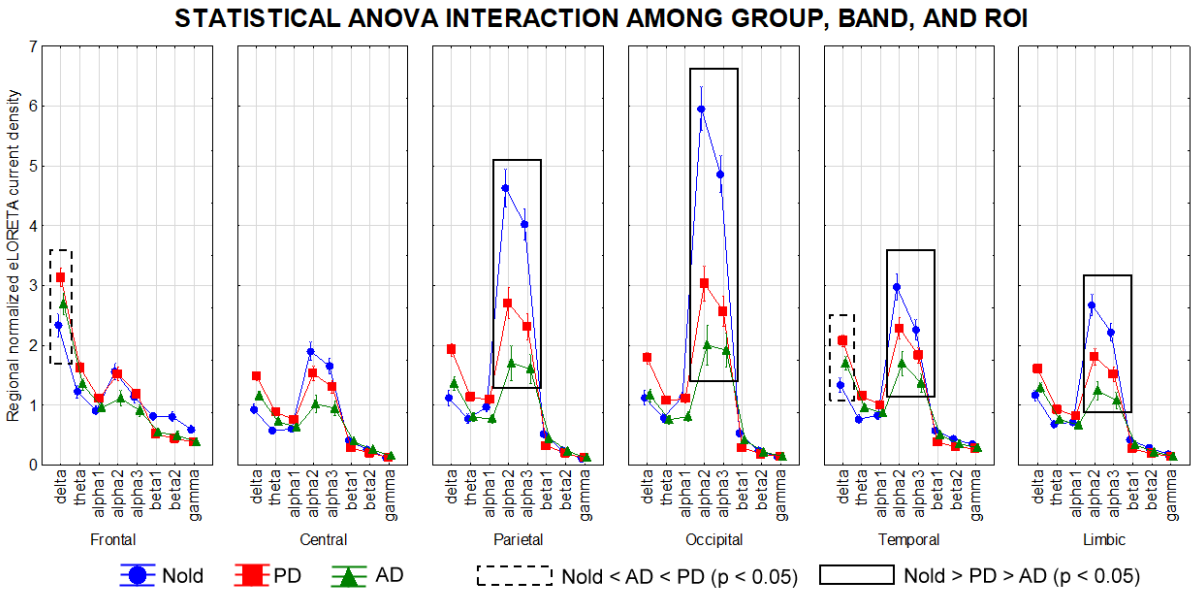

Figure 1. *Regional normalized exact low-resolution brain electromagnetic tomography (eLORETA) solutions (mean across subjects) of cortical sources of eyes-closed resting state electroencephalographic (rsEEG) rhythms relative to a statistical ANOVA interaction among the factors Group (healthy elderly subjects, Nold; Alzheimer's disease patients, AD; Parkinson's disease patients, PD), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2 and gamma), and Region of interest, ROI (central, frontal, parietal, occipital, temporal, limbic). This ANOVA design used the regional normalized eLORETA solutions as a dependent variable. Regional normalized eLORETA solutions modeled the rsEEG relative power spectra as revealed by a sort of "virtual" intracranial macro-electrodes located on the macro-cortical regions of interest. Legend: the rectangles indicate the cortical regions and frequency bands in which the eLORETA solutions statistically presented a significant eLORETA patterns "Nold ≠ AD ≠ PD" ($p < 0.05$).*

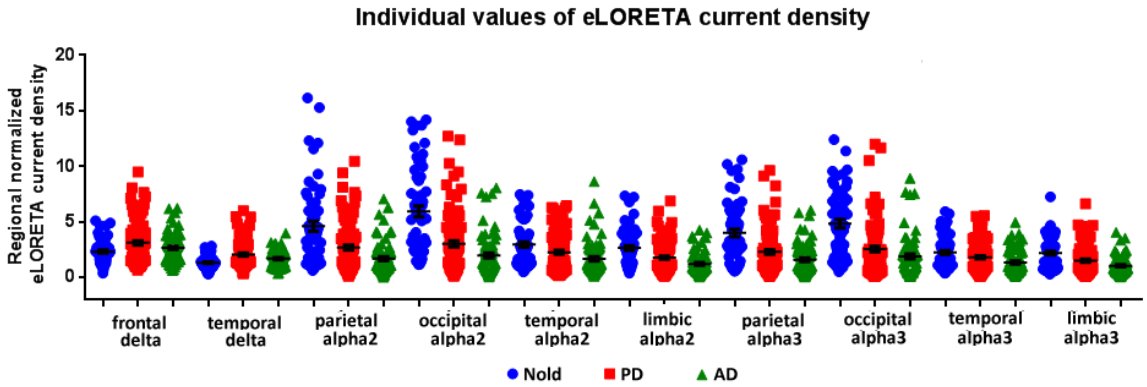

Figure 2. *Individual values of the regional normalized eLORETA solutions of the rsEEG rhythms showing statistically significant ($p < 0.05$) differences among the Nold, AD, and PD groups (i.e., frontal delta, temporal delta, parietal alpha 2, occipital alpha 2, temporal alpha 2, limbic alpha 2, parietal alpha 3, occipital alpha 3, temporal alpha 3, and limbic alpha 3). Noteworthy, the Grubbs' test showed no outliers from those individual values of the eLORETA solutions (arbitrary threshold of $p < 0.0001$).*

rsEEG source activities in the Nold, AD, and PD-MMSE(-/+) sub-groups

Table 6 reports the mean values of TF and IAF for the four sub-groups (i.e., Nold, AD, and PD-MMSE-, and PD-MMSE+), together with the results of the statistical comparisons between the sub-groups (ANOVA, $p < 0.05$). The mean TF was 6.0 Hz (± 0.2 SE) in the Nold sub-group, 5.7 Hz (± 0.3 SE) in the AD sub-group, 5.4 Hz (± 0.3 SE) in the PD-MMSE- sub-group, and 5.2 Hz (± 0.2 SE) in the PD-MMSE+ sub-group. Furthermore, the mean IAF was 9.3 Hz (± 0.2 SE) in the Nold sub-group, 8.3 Hz (± 0.4 SE) in the AD sub-group, 7.9 Hz (± 0.4 SE) in the PD-MMSE- sub-group, and 8.0 Hz (± 0.3 SE) in the PD-MMSE+ sub-group. The ANOVAs using these values as an input showed the following statistically significant findings: the mean IAF was greater ($F = 6.8$, $p < 0.0005$) in the Nold than the AD ($p < 0.05$), PD-MMSE- ($p < 0.005$), and PD-MMSE+ ($p < 0.005$) sub-groups.

MEAN VALUES (± SE) OF TRANSITION FREQUENCY (TF) AND INDIVIDUAL ALPHA FREQUENCY PEAK (IAF)					
	Nold	AD	PD-MMSE-	PD-MMSE+	Statistical analysis
TF	6.0 (± 0.2 SE)	5.7 (± 0.3 SE)	5.4 (± 0.3 SE)	5.2 (± 0.2 SE)	ANOVA: n.s.
IAF	9.3 (± 0.2 SE)	8.3 (± 0.4 SE)	7.9 (± 0.4 SE)	8.0 (± 0.3 SE)	ANOVA: $F = 6.8$; $p < 0.0005$

					(Nold > AD, PD-MMSE-, PD-MMSE+)

Table 6. *Mean values (± SE) of TF and IAF computed from rsEEG power density spectra in the Nold, AD, PD-MMSE-,and PD-MMSE+ groups. The table also reports the p values of the statistical comparisons of these values between the groups ($p < 0.05$). Legend: Nold = healthy elderly subjects; AD = Alzheimer's disease patients; PD-MMSE- = Parkinson's disease patients with low global cognitive deficits; PD-MMSE+ = Parkinson's disease patients with high global cognitive deficits.*

Figure 3 shows the grand average of regional rsEEG source activities (i.e., regional normalized eLORETA solutions) relative to a statistically significant ANOVA interaction effect ($F = 11.3$; $p < 0.00001$) among the factors Group (Nold, AD, and PD-MMSE-, and PD-MMSE+), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal, and limbic). Compared to the Nold sub-group, the AD, PD-MMSE-, and PD-MMSE+ sub-groups showed a substantial decrease of the eLORETA solutions in posterior alpha 2 and alpha 3 sources and a substantial increase of the eLORETA solutions in widespread delta sources. The decrease of the alpha eLORETA solutions was higher in the AD than the PD-MMSE- and PD-MMSE+ sub-groups, whereas the increase of the delta eLORETA solutions was higher in the PD-MMSE+ than the AD sub-group. Remarkably, widespread alpha 2 and alpha 3 eLORETA solutions showed a paradoxical greater magnitude in the PD-MMSE+ than the PD-MMSE- sub-group as a function of the global cognitive deficits. Furthermore, widespread delta eLORETA solutions showed a greater magnitude in the PD-MMSE+ than the PD-MMSE- sub-group as a function of the global cognitive deficits.

The Duncan planned post-hoc testing showed that the discriminant pattern PD-MMSE+ > PD-MMSE- was fitted by: (i) frontal, occipital, temporal, and limbic delta eLORETA solutions ($p < 0.05$ to $p < 0.000005$); (ii) frontal, parietal, occipital, temporal, and limbic alpha 2 eLORETA solutions ($p < 0.01$ to $p < 0.000001$); and (iii) frontal, parietal, occipital, temporal, and limbic alpha 3 eLORETA solutions ($p < 0.05$ to $p < 0.000001$). Of note, these findings were not due to outliers from those individual eLORETA solutions, as shown by Grubbs' test with an arbitrary threshold of $p < 0.0001$ (see Figure 4).

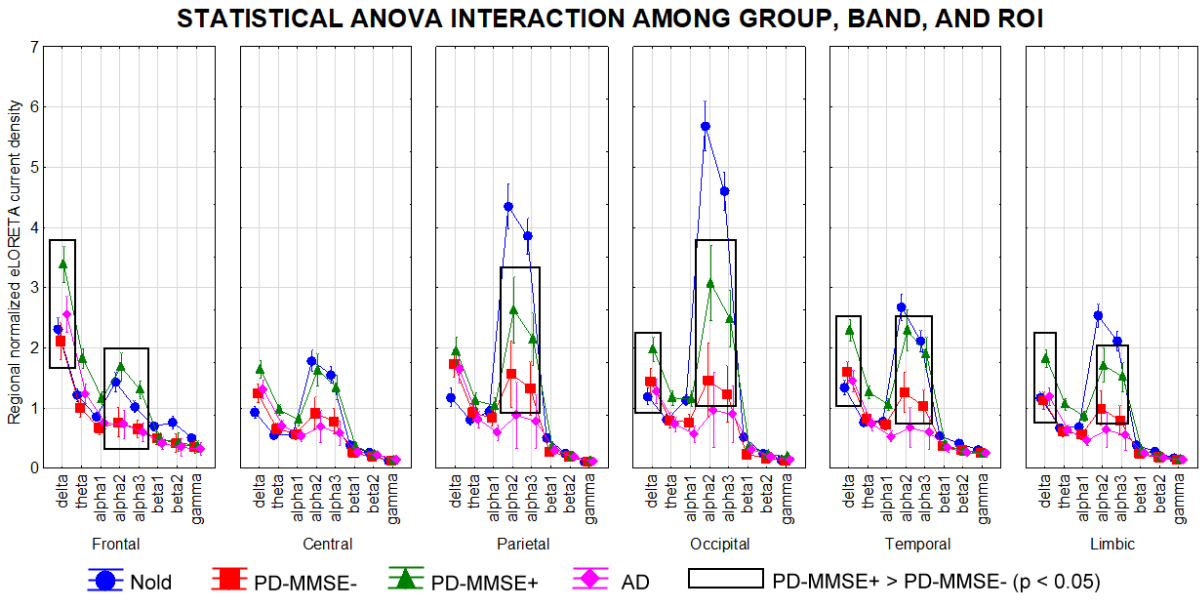

Figure 3. *Regional normalized eLORETA solutions (mean across subjects) of the rsEEG rhythms relative to a statistical ANOVA interaction among the factors Group (Nold; AD; PD patients with low global cognitive deficits, PD-MMSE-; PD patients with high global cognitive deficits, PD-MMSE+), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2 and gamma), and ROI (central, frontal, parietal, occipital, temporal, limbic). This ANOVA design used the regional normalized eLORETA solutions as a dependent variable. Legend: the rectangles indicate the cortical regions and frequency bands in which the eLORETA solutions statistically presented a significant eLORETA patterns "PD-MMSE- ≠ PD-MMSE+" (p < 0.05).*

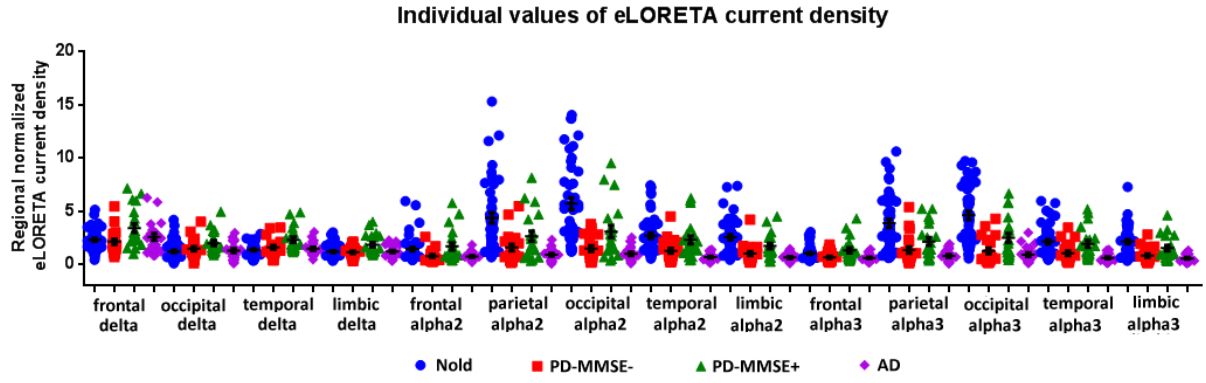

Figure 4. *Individual values of the regional normalized eLORETA solutions of the rsEEG rhythms showing statistically significant (p < 0.05) differences between PD-MMSE- and PD-MMSE+ groups (i.e., frontal delta, occipital delta, temporal delta, limbic delta, frontal alpha 2, parietal alpha 2, occipital alpha 2, temporal alpha 2, limbic alpha 2, frontal alpha 3, parietal alpha 3, occipital alpha 3, temporal alpha 3, and limbic alpha 3). Noteworthy, the Grubbs' test showed no outliers from those individual values of the eLORETA solutions (arbitrary threshold of p < 0.0001).*

To disentangle the possible influence of psychoactive drugs and acetylcholinesterase inhibitors, two control ANOVAs were performed using the same design of the main analysis. The only difference was in the PD patients considered. In the first ANOVA, we excluded all PD-MMSE+

patients (N = 2) assuming psychoactive drugs. In the second ANOVA, we excluded the only PD-MMSE+ patient assuming acetylcholinesterase inhibitors. The first ANOVA showed a statistically significant ANOVA interaction effect among the factors Group, Band, and ROI ($F = 11.2$; $p < 0.00001$). The Duncan planned post-hoc testing showed that the discriminant pattern PD-MMSE+ > PD-MMSE- was fitted by: (i) frontal, temporal, and limbic delta eLORETA solutions ($p < 0.005$ to $p < 0.000005$); (ii) frontal, parietal, occipital, temporal, and limbic alpha 2 eLORETA solutions ($p < 0.005$ to $p < 0.000001$); and (iii) frontal, parietal, occipital, temporal, and limbic alpha 3 eLORETA solutions ($p < 0.05$ to $p < 0.000001$). The second ANOVA showed a statistically significant ANOVA interaction effect among the factors Group, Band, and ROI ($F = 11.3$; $p < 0.00001$). The Duncan planned post-hoc testing showed that the discriminant pattern PD-MMSE+ > PD-MMSE- was fitted by: (i) frontal, occipital, temporal, and limbic delta eLORETA solutions ($p < 0.05$ to $p < 0.000005$); (ii) frontal, parietal, occipital, temporal, and limbic alpha 2 eLORETA solutions ($p < 0.005$ to $p < 0.000001$); and (iii) frontal, parietal, occipital, temporal, and limbic alpha 3 eLORETA solutions ($p < 0.05$ to $p < 0.000001$). These findings confirmed those observed in the main analysis performed in the whole PD-MMSE- and PD-MMSE+ groups including few patients assuming psychoactive drugs and acetylcholinesterase inhibitors.

rsEEG source activities in the Nold, AD, and PD-UPDRS(-/+) sub-groups

Table 7 reports the mean values of TF and IAF for the four sub-groups (i.e., Nold, AD, and PD-UPDRS-, and PD-UPDRS+), together with the results of the statistical comparisons between the sub-groups (ANOVA, $p < 0.05$). The mean TF was 6.0 Hz (± 0.2 SE) in the Nold sub-group, 5.5Hz (± 0.2 SE) in the AD sub-group, 5.1 Hz (± 0.2 SE) in the PD-UPDRS- sub-group, and 5.3 Hz (± 0.2 SE) in the PD-UPDRS+ sub-group. Furthermore, the mean IAF was 9.3 Hz (± 0.2 SE) in the Nold sub-group, 8.4 Hz (± 0.5 SE) in the AD sub-group, 7.8 Hz (± 0.3 SE) in the PD-UPDRS- sub-group, and 7.9 Hz (± 0.3 SE) in the PD-UPDRS+ sub-group. The ANOVAs using these values as an input showed the following statistically significant findings: (1) the mean TF was greater ($F = 3.6$, $p < 0.05$) in the Nold than the PD-UPDRS- ($p < 0.05$) and PD-UPDRS+ ($p < 0.05$) sub-groups; (2) the mean IAF was greater ($F = 10.8$, $p < 0.00001$) in the Nold than the AD ($p < 0.01$), PD-UPDRS- ($p < 0.001$), and PD-UPDRS+ ($p < 0.001$) sub-groups.

MEAN VALUES (± SE) OF TRANSITION FREQUENCY (TF) AND INDIVIDUAL ALPHA FREQUENCY PEAK (IAF)					
	Nold	AD	PD-UPDRS-	PD-UPDRS+	Statistical analysis
TF	6.0 (± 0.2 SE)	5.5 (± 0.2 SE)	5.1 (± 0.2 SE)	5.3 (± 0.2 SE)	ANOVA: F = 3.6; p < 0.05 (Nold > PD-UPDRS-, PD-UPDRS+)
IAF	9.3 (± 0.2 SE)	8.4 (± 0.5 SE)	7.8 (± 0.3 SE)	7.9 (± 0.3 SE)	ANOVA: F = 10.8; p < 0.00001 (Nold > AD, PD-UPDRS-, PD-UPDRS+)

Table 7. *Mean values (± SE) of TF and IAF computed from rsEEG power density spectra in the Nold, AD, PD-UPDRS-,and PD-UPDRS+ groups. The table also reports the p values of the statistical comparisons of these values between the groups (p < 0.05). Legend: Nold = healthy elderly subjects; AD = Alzheimer's disease patients; PD-UPDRS- = Parkinson's disease patients with low motor deficits; PD-UPDRS+ = Parkinson's disease patients with high motor deficits.*

Figure 5 shows the grand average of regional rsEEG source activities (i.e., regional normalized eLORETA solutions) relative to a statistically significant ANOVA interaction effect (F = 10.8; p < 0.00001) among the factors Group (Nold, AD, and PD-UPDRS-, and PD-UPDRS+), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal, and limbic). Compared to the Nold sub-group, the AD, PD-UPDRS-, and PD-UPDRS+ sub-groups showed a substantial decrease of the eLORETA solutions in posterior alpha 2 and alpha 3 sources and a substantial increase of the eLORETA solutions in widespread delta sources. The decrease of the alpha eLORETA solutions was higher in the AD than the PD-UPDRS- sub-group, whereas the increase of the delta eLORETA solutions was higher in the PD-UPDRS- and PD-UPDRS+ sub-groups than AD sub-group. Remarkably, widespread alpha 2 and alpha 3 eLORETA solutions showed a lower magnitude in the PD-UPDRS+ than the PD-UPDRS- sub-group as a function of the motor deficits.

The Duncan planned post-hoc testing showed that the discriminant pattern PD-UPDRS+ < PD-UPDRS- was fitted by frontal, central, parietal, occipital, temporal, and limbic alpha 2 eLORETA solutions ($p < 0.001$ to $p < 0.000001$) as well as frontal, central, parietal, occipital,

temporal, and limbic alpha 3 eLORETA solutions ($p < 0.05$ to $p < 0.000001$). Of note, these findings were not due to outliers from those individual eLORETA solutions, as shown by Grubbs' test with an arbitrary threshold of $p < 0.0001$ (see Figure 6).

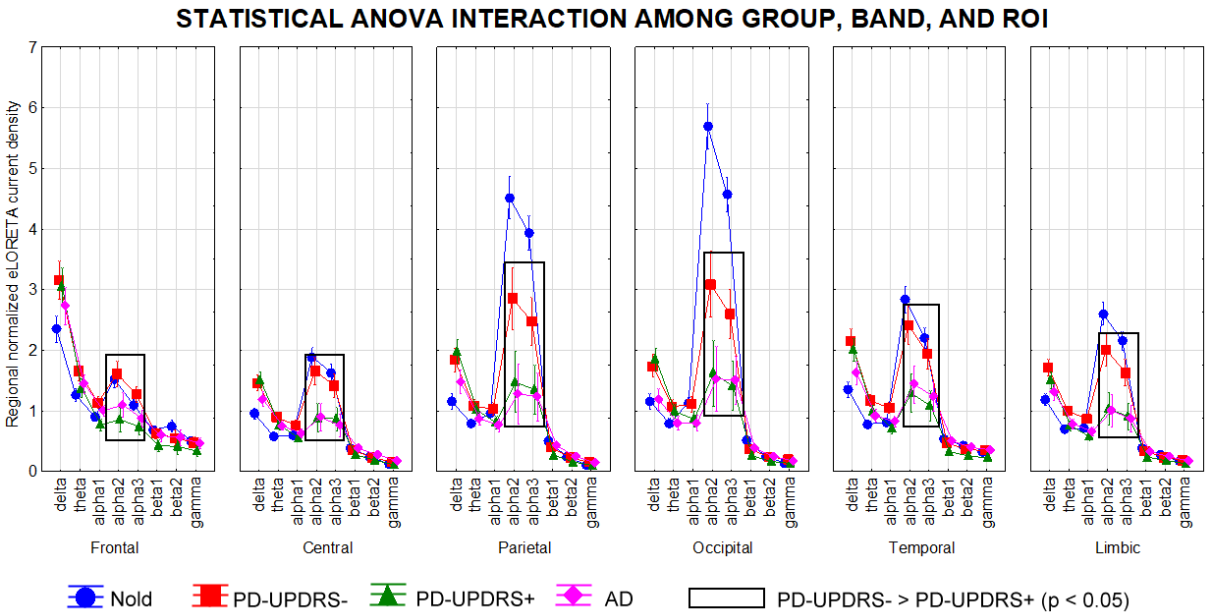

Figure 5. *Regional normalized eLORETA solutions (mean across subjects) of the rsEEG rhythms relative to a statistical ANOVA interaction among the factors Group (Nold; AD; PD patients with low motor deficits, PD-UPDRS-; PD patients with high motor deficits, PD-UPDRS+), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2 and gamma), and ROI (central, frontal, parietal, occipital, temporal, limbic). This ANOVA design used the regional normalized eLORETA solutions as a dependent variable. Legend: the rectangles indicate the cortical regions and frequency bands in which the eLORETA solutions statistically presented a significant eLORETA patterns "PD-UPDRS- ≠ PD-UPDRS+" ($p < 0.05$).*

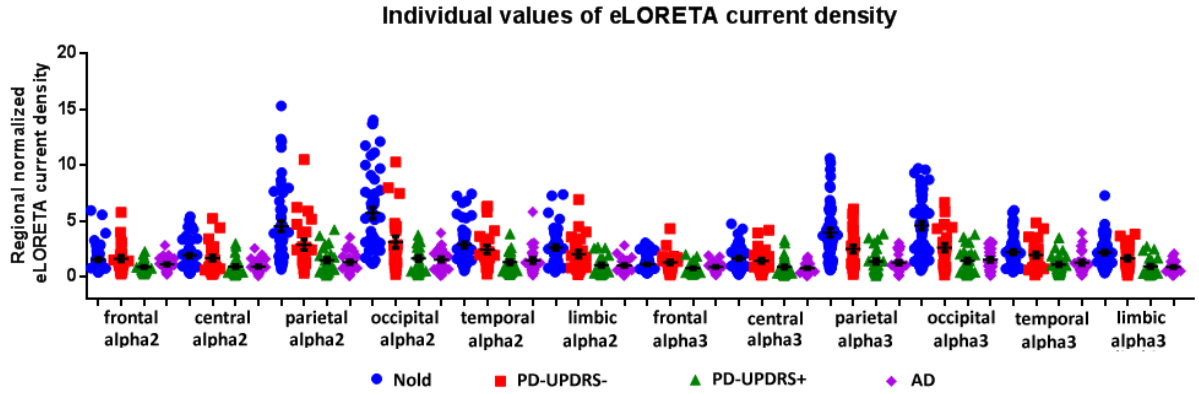

Figure 6. *Individual values of the regional normalized eLORETA solutions of the rsEEG rhythms showing statistically significant ($p < 0.05$) differences between PD-UPDRS- and PD-UPDRS+ groups (i.e., frontal alpha 2, central alpha 2, parietal alpha 2, occipital alpha 2, temporal alpha 2, limbic alpha 2, frontal alpha 3, central alpha 3, parietal alpha 3, occipital alpha 3, temporal alpha 3, and limbic*

alpha 3). Noteworthy, the Grubbs' test showed no outliers from those individual values of the eLORETA solutions (arbitrary threshold of $p < 0.0001$).

To disentangle the possible influence of psychoactive drugs and acetylcholinesterase inhibitors, two control ANOVAs on rsEEG source activities were performed with the same design of the main analysis (i.e. Group, Band, and ROI). The only difference was in the PD patients considered. In the first ANOVA, we excluded all PD-UPDRS+ patients assuming psychoactive drugs (N = 2). In the second ANOVA, we excluded all PD-UPDRS+ patients assuming acetylcholinesterase inhibitors (N = 3). The first ANOVA showed a statistically significant ANOVA interaction effect among the factors Group, Band, and ROI ($F = 11.1$; $p < 0.00001$). The Duncan planned post-hoc testing showed that the discriminant pattern PD-UPDRS+ < PD-UPDRS- was fitted by frontal, central, parietal, occipital, temporal, and limbic alpha 2 eLORETA solutions ($p < 0.001$ to $p < 0.000001$) as well as frontal, central, parietal, occipital, temporal, and limbic alpha 3 eLORETA solutions ($p < 0.05$ to $p < 0.000001$). The second ANOVA showed a statistically significant ANOVA interaction effect among the factors Group, Band, and ROI ($F = 10.5$; $p < 0.00001$). The Duncan planned post-hoc testing showed that the discriminant pattern PD-UPDRS+ < PD-UPDRS- was fitted by the discriminant pattern PD-UPDRS+ > PD-UPDRS- was fitted by frontal, central, parietal, occipital, temporal, and limbic alpha 2 eLORETA solutions ($p < 0.001$ to $p < 0.000001$) as well as frontal, central, parietal, occipital, temporal, and limbic alpha 3 eLORETA solutions ($p < 0.05$ to $p < 0.000001$). These findings confirmed those observed in the main analysis performed in the whole PD-UPDRS- and PD-UPDRS+ groups including few patients assuming psychoactive drugs and acetylcholinesterase inhibitors.

To disentangle the possible influence of cognitive over motor deficits, the following control ANOVA was performed with the same design of the main analysis (i.e., Group, Band, and ROI). The only difference was that the PD patients considered had high scores of the MMSE (group mean of about 28). Specifically, two additional sub-groups of PD patients (N = 15 for each sub-group) with good cognitive status were matched for demographic features, namely the PD sub-groups with lowest (UPDRS III ≤ 24; PD-UPDRS-) and highest (UPDRS III ≥ 26; PD-UPDRS+) motor deficits. These additional PD-UPDRS- and PD-UPDRS+ sub-groups with good cognitive status were paired for the MMSE score and were characterized by the absence of visual hallucinations. This additional PD-UPDRS- sub-group was formed by 5 PDNC and 10 PDMCI, while the additional PD-UPDRS+ sub-group was formed by 13 PDNC and 2 PDMCI. Demographic-matched sub-groups of ADMCI patients (N = 15) and Nold subjects (N

= 30) as controls were also used in the analysis. Table 8 summarizes the most relevant demographic and clinical features of the Nold, AD, additional PD-UPDRS-, and additional PD-UPDRS+ sub-groups. Furthermore, the Table 9 reports the results of the statistical analysis ($p < 0.05$) among the four sub-groups for the age (ANOVA), gender (Freeman-Halton), education (ANOVA), and MMSE score (Kruskal-Wallis) and the two PD-subgroups for the UPDRS III score (t-test). As expected, a statistically significant difference was found for the UPDRS III score ($p < 0.000001$), showing higher UPDRS III score in the additional PD-UPDRS+ than the additional PD-UPDRS- group. Furthermore, a statistically significant difference was also found for the MMSE score ($H = 59.1$; $p < 0.00001$). Specifically, there was a higher MMSE score in the Nold than the AD, additional PD-UPDRS-, and additional PD-UPDRS+ sub-groups ($p < 0.0001$). On the contrary, a statistically significant difference was found neither for the MMSE score among the AD, additional PD-UPDRS-, and additional PD-UPDRS+ sub-groups nor the age, gender, and education among the four sub-groups ($p > 0.05$).

Figure 7 shows the grand average of regional rsEEG source activities (i.e., regional normalized eLORETA solutions) relative to a statistically significant ANOVA interaction effect ($F = 6.28$; $p < 0.00001$) among the factors Group (Nold, AD, and additional PD-UPDRS-, and additional PD-UPDRS+), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal, and limbic). Compared to the Nold sub-group, the AD, additional PD-UPDRS-, and additional PD-UPDRS+ sub-groups showed a substantial decrease of the eLORETA solutions in central and posterior alpha 2 and alpha 3 sources. The decrease of the alpha eLORETA solutions was higher in the additional PD-UPDRS+ than the additional PD-UPDRS- and the AD sub-groups.

The Duncan planned post-hoc testing showed that the discriminant pattern additional PD-UPDRS+ > additional PD-UPDRS- was fitted by central, parietal, occipital, temporal, and limbic alpha 2 eLORETA solutions and alpha3 eLORETA solutions ($p < 0.001$ to $p < 0.000001$). Of note, these findings were not due to outliers from those individual eLORETA solutions calculated by Grubbs' test with an arbitrary threshold of $p < 0.0001$. It was concluded that the effect of the motor deficits on the reduction of the alpha eLORETA solutions was independent of the cognitive deficits and visual hallucinations in these PD patients.

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS					
	Nold	AD	PD-	PD-	Statistical analysis

			UPDRS-	UPDRS+	
N	30	15	15	15	-
Age (years)	69.2 (± 1.2 SE)	69.1 (± 1.6 SE)	68.8 (± 1.8 SE)	69.2 (± 2.7 SE)	ANOVA: n.s.
Gender (F/M)	11/19	7/8	3/12	6/9	Freeman-Halton: n.s.
Education (years)	9.7 (± 0.5 SE)	9.7 (± 0.4 SE)	9.5 (± 1.0 SE)	8.6 (± 0.8 SE)	ANOVA: n.s.
MMSE score	28.8 (± 0.2 SE)	27.6 (± 0.4 SE)	27.7 (± 0.3 SE)	28.6 (± 0.4 SE)	Kruskal-Wallis: n.s.
Visual hallucinations	-	-	N = 0	N = 0	-
UPDRS III Motor	-	-	15.5 (± 2.1 SE)	35.8 (± 2.7 SE)	T test: $p < 0.000001$

Table 8. *Mean values (± SE) of the demographic and clinical data as well as the results of their statistical comparisons ($p < 0.05$) in the sub-groups of Nold subjects (N = 30), AD patients (N = 15), PD patients with good cognition and low motor deficits (PD-UPDRS-, N = 15), and PD patients with good cognition and high motor deficits (PD-UPDRS+, N = 15). Legend: MMSE = Mini Mental State Evaluation; UPDRS III= Unified Parkinson Disease Rating Scale-III ; M/F = males/females; n.s. = not significant ($p > 0.05$).*

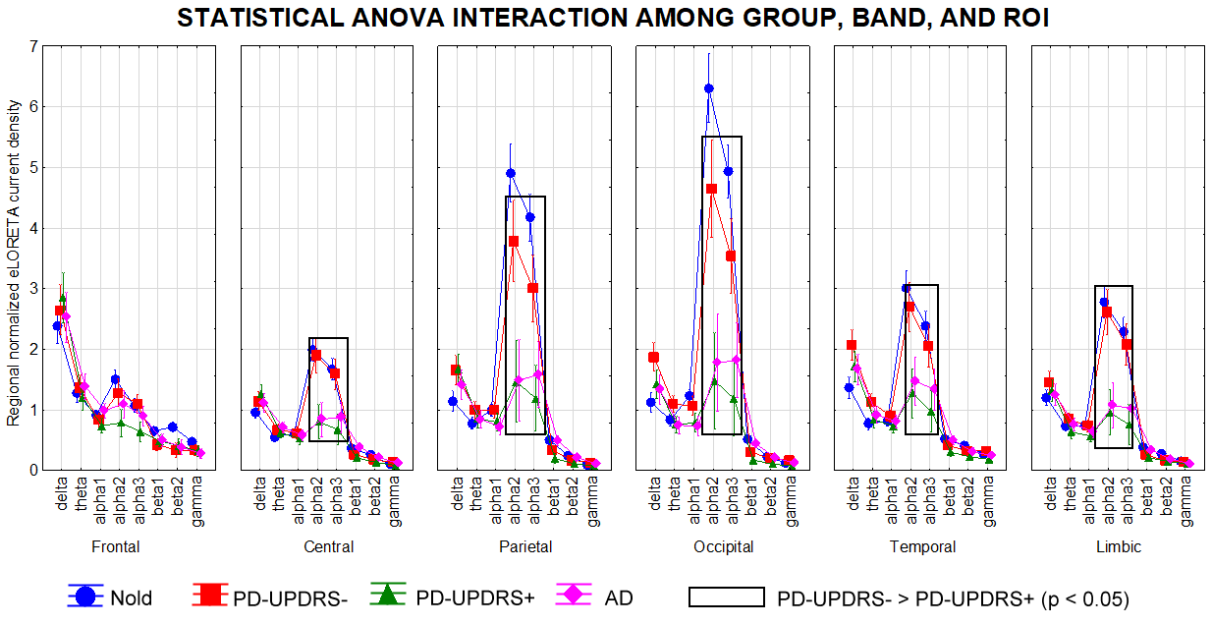

Figure 7. *Regional normalized eLORETA solutions (mean across subjects) of the rsEEG rhythms relative to a statistical ANOVA interaction among the factors Group (Nold; AD; PD patients with good cognition and low motor deficits, PD-UPDRS-; PD patients with good cognition and high motor deficits, PD-UPDRS+), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2 and gamma), and ROI (central, frontal, parietal, occipital, temporal, limbic). This ANOVA design used the regional normalized eLORETA solutions as a dependent variable. Legend: the rectangles indicate the cortical regions and frequency bands in which the eLORETA solutions statistically presented a significant eLORETA patterns "PD-UPDRS- ≠ PD-UPDRS+" (p < 0.05).*

rsEEG source activities in the Nold, AD, and PD-VH(-/+) sub-groups

Table 9 reports the mean values of TF and IAF for the four sub-groups (i.e., Nold, AD, and PD-VH-, and PD-VH+), together with the results of the statistical comparisons between the sub-groups (ANOVA, $p < 0.05$). The mean TF was 6.1 Hz (± 0.2 SE) in the Nold sub-group, 5.8 Hz (± 0.3 SE) in the AD sub-group, 5.2 Hz (± 0.3 SE) in the PD-VH- sub-group, and 5.1 Hz (± 0.2 SE) in the PD-VH+ sub-group. Furthermore, the mean IAF was 9.3 Hz (± 0.2 SE) in the Nold sub-group, 8.3 Hz (± 0.4 SE) in the AD sub-group, 7.8 Hz (± 0.3 SE) in the PD-VH- sub-group, and 7.6 Hz (± 0.3 SE) in the PD-VH+ sub-group. The ANOVAs using these values as an input showed the following statistically significant findings: (1) the mean TF was greater ($F = 3.8$, $p < 0.05$) in the Nold than the PD-VH- ($p < 0.05$) and PD-VH+ ($p < 0.05$) sub-groups; (2) the mean IAF was greater ($F = 7.8$, $p < 0.00001$) in the Nold than the AD ($p < 0.05$), PD-UPDRS- ($p < 0.005$), and PD-UPDRS+ ($p < 0.005$) sub-groups.

MEAN VALUES (± SE) OF TRANSITION FREQUENCY (TF) AND INDIVIDUAL ALPHA FREQUENCY PEAK (IAF)					
	Nold	AD	PD-VH-	PD-VH+	Statistical analysis
TF	6.1 (± 0.2 SE)	5.8 (± 0.3 SE)	5.2 (± 0.3 SE)	5.1 (± 0.2 SE)	ANOVA: F = 3.8; p < 0.05 (Nold > PD-VH-, PD-VH+)
IAF	9.3 (± 0.2 SE)	8.3 (± 0.4 SE)	7.8 (± 0.3 SE)	7.6 (± 0.3 SE)	ANOVA: F = 7.8; p < 0.0001 (Nold > AD, PD-VH-, PD-VH+)

Table 9. *Mean values (± SE) of TF and IAF computed from rsEEG power density spectra in the Nold, AD, PD-VH-, and PD-VH+ groups. The table also reports the p values of the statistical comparisons of these values between the groups (p < 0.05). Legend: Nold = healthy elderly subjects; AD = Alzheimer's*

disease patients; PD-VH- = Parkinson's disease patients with absence of visual hallucinations; PD-VH+ = Parkinson's disease patients with presence of visual hallucinations.

Figure 8 shows the grand average of regional rsEEG source activities (i.e., regional normalized eLORETA solutions) relative to a statistically significant ANOVA interaction effect ($F = 20.6$; $p < 0.00001$) among the factors Group (Nold, AD, and PD-VH-, and PD-VH+), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal, and limbic). Compared to the Nold sub-group, the AD, PD-VH-, and PD-VH+ sub-groups showed a substantial decrease of the eLORETA solutions in posterior alpha 2 and alpha 3 and a substantial increase of the eLORETA solutions in widespread delta sources. The decrease of the alpha eLORETA solutions was higher in the AD than the PD-VH- and PD-VH+ sub-groups, whereas the increase of the delta eLORETA solutions was higher in the PD-VH- and PD-VH+ sub-groups than AD sub-group. Remarkably, posterior alpha 2 and alpha 3 eLORETA solutions showed a higher magnitude in the PD-VH+ than the PD-VH- sub-group as a function of the psychiatric deficits (i.e., visual hallucinations).

The Duncan planned post-hoc testing showed that the discriminant pattern PD-VH+ > PD-VH- was fitted by, parietal, occipital, and temporal alpha 2 eLORETA solutions ($p < 0.01$ to $p < 0.00005$) as well as occipital alpha 3 eLORETA solutions ($p < 0.005$). Of note, these findings were not due to outliers from those individual eLORETA solutions, as shown by Grubbs' test with an arbitrary threshold of $p < 0.0001$ (see Figure 9).

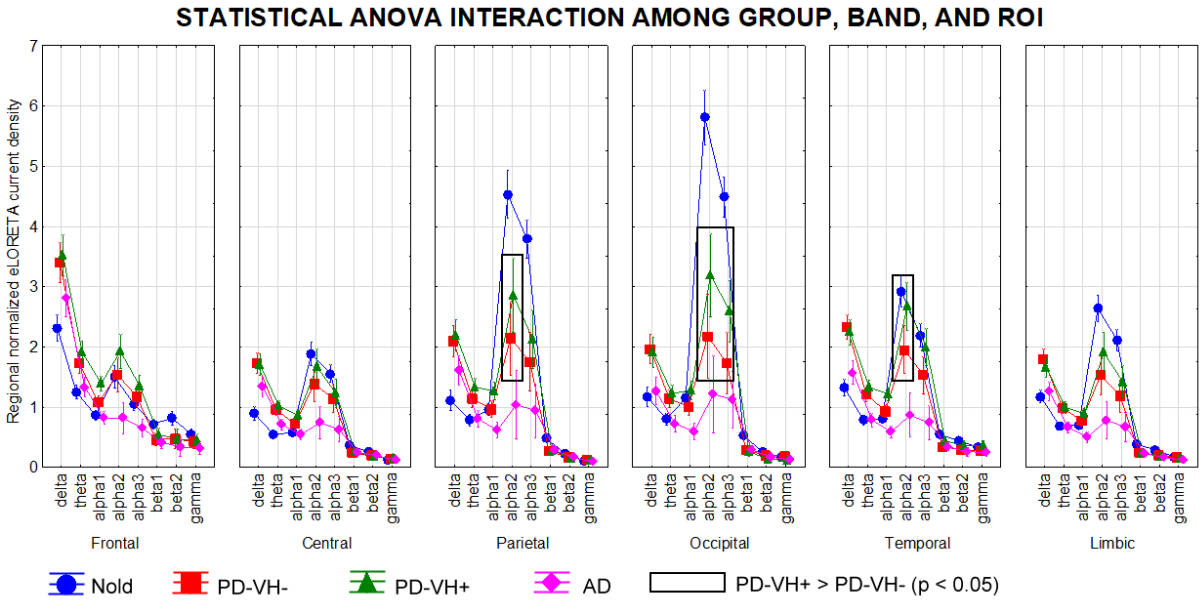

Figure 8. *Regional normalized eLORETA solutions (mean across subjects) of the rsEEG rhythms relative to a statistical ANOVA interaction among the factors Group (Nold; AD; PD patients with absence of visual hallucinations, PD-VH-; PD patients with presence of visual hallucinations, PD-VH+), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2 and gamma), and ROI (central, frontal, parietal, occipital, temporal, limbic). This ANOVA design used the regional normalized eLORETA solutions as a dependent variable. Legend: the rectangles indicate the cortical regions and frequency bands in which the eLORETA solutions statistically presented a significant eLORETA patterns "PD-VH- ≠ PD-VH+" (p < 0.05).*

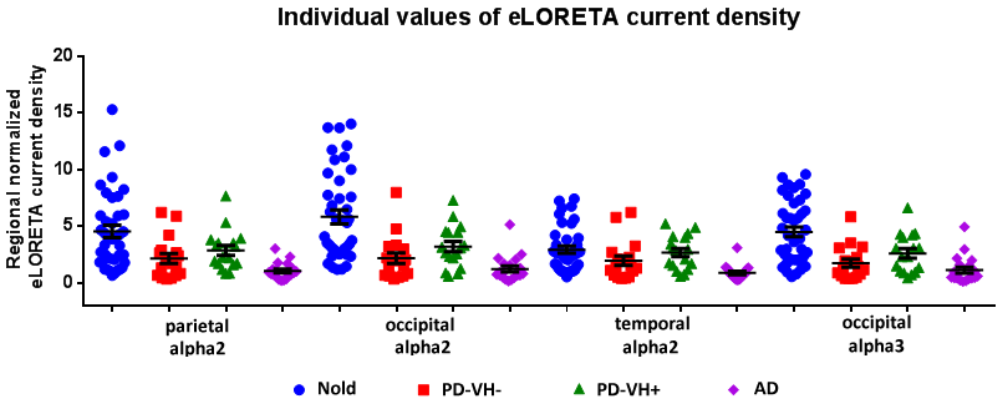

Figure 9. *Individual values of the regional normalized eLORETA solutions of the rsEEG rhythms showing statistically significant (p < 0.05) differences between PD-VH- and PD-VH+ groups (i.e., parietal alpha 2, occipital alpha 2, temporal alpha 2, and occipital alpha 3). Noteworthy, the Grubbs' test showed no outliers from those individual values of the eLORETA solutions (arbitrary threshold of p < 0.0001).*

To disentangle the possible influence of psychoactive drugs and acetylcholinesterase inhibitors, two control ANOVAs were performed using the same design of the main analysis (i.e., Group, Band, and ROI). The only difference was the PD patients considered. In the first ANOVA, we excluded all PD-VH- (N = 2) and PD-VH+ (N = 3) patients assuming psychoactive drugs. In the second ANOVA, we excluded all PD-VH- (N = 2) and PD-VH+ (N = 7) patients assuming acetylcholinesterase inhibitors. The first ANOVA showed a statistically significant interaction effect among the factors Group, Band, and ROI ($F = 8.2$; $p < 0.00001$). The Duncan planned post-hoc testing showed that the discriminant pattern PD-VH+ > PD-VH- was fitted by, parietal and occipital alpha 2 eLORETA solutions ($p < 0.05$ to $p < 0.01$). The first ANOVA showed a statistically significant interaction effect among the factors Group, Band, and ROI ($F = 8.4$; $p < 0.00001$).The Duncan planned post-hoc testing showed that the discriminant pattern PD-VH+ > PD-VH- was fitted by, parietal and occipital alpha 2 eLORETA solutions ($p < 0.05$ to $p < 0.0005$) as well as occipital alpha 3 eLORETA solutions ($p < 0.01$). These findings confirmed

those observed in the main analysis performed in the whole PD-VH- and PD-VH+ groups including few PD patients assuming psychoactive drugs and acetylcholinesterase inhibitors.

Correlation analysis and classification

The above findings showed effects of the PD on delta and alpha source activities at the group level. In the following, we reported the results of three analyses performed to test the effects of the PD on delta and alpha source activities at the individual level.

As a first exploratory analysis, the Spearman test ($p < 0.05$) evaluated the correlation between the MMSE score, as an index of global cognitive deficits, and rsEEG source activities (i.e., regional normalized eLORETA solutions) showing statistically significant differences between the PD-MMSE- and PD-MMSE+ groups. A statistically significant negative correlation was found between the MMSE score vs. widespread (= averaged across all cortical regions) delta, alpha 2, and alpha 3 eLORETA solutions in all PD patients ($r = -0.34$ to -0.48, $p < 0.05$ to 0.001; see Table 10). The higher the global delta, alpha 2, and alpha 3 eLORETA solutions, the lower the MMSE score (the greater the global cognitive deficits).

Correlation between (eLORETA) source activity of the rsEEG rhythms and MMSE score	
	Spearman R and p
Frontal delta vs. MMSE	R = -0.48, p = 0.001
Occipital delta vs. MMSE	R = -0.34, p = 0.03
Temporal delta vs. MMSE	R = -0.34, p = 0.03
Limbic delta vs. MMSE	R = -0.41, p = 0.009
Frontal alpha 2 vs. MMSE	R = -0.41, p = 0.009
Temporal alpha 2 vs. MMSE	R = -0.32, p = 0.04
Limbic alpha 2 vs. MMSE	R = -0.34, p = 0.03
Frontal alpha 3 vs. MMSE	R = -0.40, p = 0.01
Occipital alpha 3 vs. MMSE	R = -0.35, p = 0.03
Temporal alpha 3 vs. MMSE	R = -0.35, p = 0.03
Limbic alpha 3 vs. MMSE	R = -0.37, p = 0.02

***Table 10**. Results of the correlation analysis (Spearman test, $p < 0.05$) performed between the MMSE score and rsEEG cortical sources at delta, alpha 2 and alpha 3 bands in PD-MMSE- and PD-MMSE+ subjects considered as a whole group. In particular, these results include Spearman's correlation coefficient (R) and the associated level of significance (p). Legend: MMSE = Mini Mental State Evaluation.*

As a second exploratory analysis, the Spearman test ($p < 0.05$) evaluated the correlation between the UPDRS III score, as an index of motor deficits, and rsEEG source activities (i.e., regional normalized eLORETA solutions) showing statistically significant differences between

the PD-UPDRS- and PD-UPDRS+ groups. A statistically significant negative correlation was found between the UPDRS III score vs. widespread alpha 2 and alpha 3 eLORETA solutions in all PD patients ($r = -0.34$ to -0.48, $p < 0.05$ to 0.001; see Table 11). The lower alpha 2 and alpha 3 eLORETA solutions, the higher the UPDRS III score (the higher the motor deficits).

Correlation between (eLORETA) source activity of the rsEEG rhythms and UPDRS III score	
	Spearman R and p
Frontal alpha 2 vs. UPDRS	R = - 0.35, p = 0.01
Central alpha 2 vs. UPDRS	R = - 0.36, p = 0.01
Parietal alpha 2 vs. UPDRS	R = - 0.34, p = 0.02
Occipital alpha 2 vs. UPDRS	R = - 0.31, p = 0.03
Temporal alpha 2 vs. UPDRS	R = - 0.29, p = 0.04
Limbic alpha 2 vs. UPDRS	R = - 0.35, p = 0.01
Frontal alpha 3 vs. UPDRS	R = - 0.35, p = 0.01
Central alpha 3 vs. UPDRS	R = - 0.36, p = 0.01
Parietal alpha 3 vs. UPDRS	R = -0.35, p = 0.01
Occipital alpha 3 vs. UPDRS	R = - 0.34, p = 0.02
Temporal alpha 3 vs. UPDRS	R = - 0.29, p = 0.04
Limbic alpha 3 vs. UPDRS	R = - 0.36, p = 0.01

Table 11. *Results of the correlation analysis (Spearman test, $p < 0.05$) performed between the UPDRS III score and rsEEG cortical sources at alpha 2 and alpha 3 bands in PD-UPDRS- and PD-UPDRS+ subjects considered as a whole group. In particular, these results include Spearman's correlation coefficient (R) and the associated level of significance (p). Legend: UPDRS III= Unified Parkinson Disease Rating Scale-III.*

As a third exploratory analysis, we computed AUROC curves aimed at indexing the classification accuracy in the discrimination between: (i) PD-MMSE- and PD-MMSE+, (ii) PD-UPDRS- and PD-UPDRS+, and (iii) PD-VH- and PD-VH+ individuals. The significant delta and alpha source activities (i.e., regional normalized eLORETA solutions) in the above ANOVAs served as discriminant input variables. The results of this analysis are reported in detail in Table 12. In general, moderate accuracies (AUROC values = 0.71 - 0.74) between PD-MMSE- vs. PD-MMSE+ individuals were obtained using widespread delta and alpha eLORETA solutions. Similarly, moderate accuracies (AUROC values = 0.71 - 0.73) between PD-UPDRS- vs. PD-UPDRS+ individuals were obtained using widespread alpha eLORETA solutions. Finally, classification accuracy was low (AUROC values < 0.7) for the contrast between PD-VH- and PD-VH+ individuals.

Summarizing, the results of three analyses confirmed some effects of the PD on delta and alpha source activities at the individual level.

Classification among PD individuals based on source activity of the rsEEG rhythms				
PD MMSE- vs PD-MMSE+				
	Sensitivity	Specificity	Accuracy	AUROC
Frontal delta	85.0%	50.0%	67.5%	0.72
Limbic delta	75.0%	60.0%	67.5%	0.72
Frontal alpha 2	85.0%	60.0%	72.5%	0.74
Occipital alpha 2	75.0%	65.0%	70.0%	0.71
Frontal alpha 3	95.0%	50.0%	72.5%	0.73
Occipital alpha 3	70.0%	70.0%	70.0%	0.73
Temporal alpha 3	75.0%	65.0%	70.0%	0.71
Limbic alpha 3	75.0%	70.0%	72.5%	0.72
Frontal delta	85.0%	50.0%	67.5%	0.72
Limbic delta	75.0%	60.0%	67.5%	0.72
PD UPDRS- vs PD-UPDRS+				
	Sensitivity	Specificity	Accuracy	AUROC
Frontal alpha 2	66.7%	75.0%	70.8%	0.72
Central alpha 2	70.8%	75.0%	72.9%	0.73
Temporal alpha 2	70.8%	70.8%	70.8%	0.72
Limbic alpha 2	75.0%	66.7%	70.8%	0.72
Frontal alpha 3	66.7%	70.8%	68.7%	0.71
Central alpha 3	66.7%	75.0%	70.8%	0.72
Parietal alpha 3	75.0%	62.5%	68.8%	0.72
Temporal alpha 3	70.8%	70.8%	70.8%	0.72
Limbic alpha 3	70.8%	66.6%	68.7%	0.73

Table 12*. Results of the classification among the PD individuals based on delta and alpha source activities. These source activities were those showing statistically significant differences between the groups in the main statistical analyses. The classification rate is computed by the analysis of the area under the receiver operating characteristic (AUROC) curve. The table reports the classification accuracy for all the rsEEG source activities having a value higher than 0.70 in the AUROC curves. Legend: PD-MMSE- = Parkinson's disease patients with low global cognitive deficits; PD-MMSE+ =*

Parkinson's disease patients with high global cognitive deficits; PD-UPDRS- = Parkinson's disease patients with low motor deficits; PD-UPDRS+ = Parkinson's disease patients with high motor deficits.

Discussion

In the present retrospective study, we hypothesized that cortical sources of eyes-closed rsEEG rhythms at delta and alpha frequencies may differ as a function of relevant clinical features in PD patients such as the severity of motor and cognitive deficits and the presence of visual hallucinations. The hypothesis of the study was evaluated by comparing rsEEG source activities estimated between matched PD groups with different clinical symptoms. In this framework, the cortical sources of delta and alpha rhythms were considered as readouts of oscillatory neural synchronization mechanisms regulating cortical arousal and vigilance in quiet wakefulness, as one of the neurophysiological bases of motor, cognitive, and visual perceptive functions.

An initial control analysis contrasted delta and alpha source activities in the whole PD group compared to control Nold and AD groups. The aim was to evaluate the hypothesis that those delta and alpha source activities may characterize the PD status at the group level. Compared to the Nold group, the AD and PD groups showed greater delta source activities in widespread cortical regions and lower alpha source activities in occipital, temporal, and parietal lobes. Noteworthy, those abnormalities in the delta source activity were greater in the PD than the AD group, while the mentioned abnormalities in the alpha source activity were more prominent in the AD than the PD group. The findings of the control analysis are in general agreement with previous rsEEG evidence (Bonanni et al., 2008, 2015; Caviness et al., 2007, 2016; Babiloni et al., 2018a,b,c, 2017a,b).

To explain these findings, we speculate that PD and AD neurodegenerative processes may have a diverse impact on the ascending activating reticular and thalamocortical neural synchronization systems that regulate the cortical arousal and vigilance in the quiet wakefulness. More specifically, the AD neuropathology (i.e., brain amyloidosis and tauopathy) might mainly impinge on ascending systems from the cholinergic basal forebrain, while the PD neuropathology (i.e., brain α-synucleinopathy and intracellular Lewy bodies) might mainly impinge on (1) ascending dopaminergic systems from the substantia nigra/ventral tegmental area and (2) serotoninergic systems from the brainstem raphe. Both AD and PD neuropathologies may summate their effects on cholinergic, dopaminergic, serotoninergic and possibly other ascending activating systems regulating cortical neural synchronization

mechanisms generating delta and alpha source activities with a pathological impact on vigilance/sleep-wake, posture/motor, cognitive, and reality-sense functions.
In this speculative line, on one hand, the present abnormalities of cortical alpha source activities might reflect an alteration in the interplay of cholinergic and glutamatergic neurons, high-threshold thalamocortical, GABA interneurons, thalamocortical relay-mode, and cortical pyramidal wakefulness (see details of this neurophysiological model in Hughes & Crunelli, 2005 and Lörincz et al., 2008, 2009). This neural network may generate cycles of inhibition and excitation in thalamic and cortical neurons framing perceptual events as discrete snapshots of about 70–100 ms (Hughes & Crunelli, 2005; Lörincz et al., 2008, 2009). On the other hand, the present abnormalities of cortical delta source activities might be due to an abnormal thalamus and cortical interaction, related to PD and AD neuropathologies with the consequent loss of functional connectivity in widespread cortical modules (Valladares-Neto et al., 1995; Pugnetti et al., 2010; Babiloni et al., 2013, 2015; Caviness et a., 2016b).

To test one core hypothesis of this study, we contrasted delta and alpha source activities in two matched PD sub-groups with a different degree of motor deficits, assessed by the standard UPDRS III clinical scale. The aim was to evaluate the relationship between these rsEEG source activities and motor deficits. Compared to the PD patients with relatively mild motor deficits (PD-UPDRS-), those with the greatest motor deficits (PD-UPDRS+) showed lower alpha source activities in widespread cortical regions. Furthermore, there was a negative correlation between the alpha source activities and the UPDRS III motor scores across all PD patients. The lower the alpha source activities, the greater the UPDRS III motor scores (i.e., the strongest the motor deficits). This effect was unrelated to global cognitive deficits, visual hallucinations, psychoactive therapies (i.e., dopaminergic, anti-psychotic and cholinergic), and disease duration. Furthermore, it was specific in alpha frequencies, as no difference between the two PD sub-groups was observed in the delta or other source activities. Noteworthy, the lowering of the alpha source activities was very pronounced as a function of the motor deficits even when both PD groups (PD-UPDRS- and PD-UPDRS+) showed relatively high cognitive status, as revealed by a mean MMSE score of about 28 (30 = highest cognitive status).
These results extend to the resting state condition previous evidence in PD patients, reporting a poor reduction in the power of fronto-parietal alpha rhythms during the preparation and execution of voluntary movements compared to a rest pre-movement period (Delval et al., 2006; Defebvre et al., 1994, 1996). This poor reduction can be considered as a sign of low

event-related activation of cortical somatomotor systems (Pfurtscheller and Lopes da Silva, 1999).

In PD patients, this effect might be partially due to a low alpha power in the rest pre-movement period. Indeed, it may make smaller the gradient for the event-related reduction in alpha power during the movement preparation and execution (the so-called movement-related alpha desynchronization). In a previous study performed in PD patients, an acute dose of levodopa enhancing the neurotransmission of dopaminergic projects induced a greater event-related reduction of Rolandic alpha and beta rhythms during voluntary movements, in correlation with an enhancement in size and speed of the motor act (Brown and Marsden, 1999). In other studies carried out in PD patients, a deep brain stimulation of the subthalamic nucleus produced the following effects: (1) enhanced early electromyographic responses (~45-80 ms post-stimulus) evoked by transcranial magnetic stimulation (TMS) of primary motor cortex and increased EEG oscillations at alpha frequency (Casula et al., 2017) and (2) the correlation between Rolandic alpha/beta source activities and UPDRS rigidity score (Airaksinen et al., 2010). These findings confirm the deep relationship between the excitation of cortical somatomotor systems and the amplitude of cortical alpha rhythms in PD patients.

Keeping in mind the above findings, we speculate that in PD patients with significant motor deficits, low levels of the cortical alpha power during the somatomotor relaxation are associated with a background cortical overexcitation. This overexcitation may depend on tonic dis-inhibitory signals through thalamocortical circuits, due to the dysfunction of dopaminergic neural projections modulating the activity in the external globus pallidus/subthalamus (i.e., indirect pathway). This effect may be related more to nigrostriatal than mesolimbic/mesocortical dysfunctions, as the lower alpha source activities in the PD-UPDRS+ over the PD-UPDRS- group were unrelated to the typical manifestations of mesolimbic/mesocortical dysfunctions such as depression, cognitive deficits, and visual hallucinations.

Future studies in PD patients with different motor deficits may challenge the above speculative explanation correlating resting-state alpha source activities with (1) makers of single photon emission computed tomography (SPECT) with Ioflupane I123 injection (DaTscan™; Isaacson et al., 2017) and 18-F-fluorodeoxyglucose positron emission tomography (FDG-PET; Brajkovic et al., 2017) mapping the functionality of substantia nigra and (2) markers of motor cortical overexcitation, derived from TMS (Benussi et al., 2018), and electromyographic measurements of muscle rigidity and tremor.

To test another core hypothesis of this study, we contrasted delta and alpha source activities in two matched PD sub-groups with a different degree of global cognitive deficits, assessed with the standard MMSE scale. The aim was to evaluate the relationship between these rsEEG source activities and cognitive deficits. Compared to the PD patients with relatively mild cognitive deficits (PD-MMSE-), those with the highest cognitive deficits (PD-MMSE+) exhibited higher delta and alpha source activities in widespread cortical regions. Furthermore, there was a negative correlation between delta or alpha source activities and the MMSE scores across all PD patients. The higher the delta or alpha source activities, the lower the MMSE scores (i.e., the strongest the cognitive deficits).

These results were unrelated to motor deficits, hallucinations, psychoactive therapies (anti-psychotic, dopaminergic, and cholinergic), and disease duration. Furthermore, they are in agreement with a bulk of previous findings showing that in the quiet wakefulness, PD patients with cognitive deficits exhibited abnormally higher delta rhythms in widespread cortical regions (Bonanni et al., 2008, 2015; Caviness et al., 2007, 2016, 2017; Guner et al., 2017; Babiloni et al., 2018a,b,c, 2017a,b). Furthermore, such abnormality in the delta rhythms was related to the cortical Lewy type synucleinopathy, with maximum values in anterior cingulate regions, and AD neuropathology (Calviness et al., 2018). Moreover, it was related to the total phosphorylated α-synuclein in posterior cingulate cortex, as a hub of the cortical default mode network (Calviness et al., 2016b).

More challenging is to explain why resting state cortical alpha source activities were higher in the PD patients with the highest (PD-MMSE+) than mild (PD-MMSE-) cognitive deficits, when motor and other relevant variables were matched. This effect contrasts with the typical evidence showing that those alpha source activates are typically lower in AD and PD patients compared to healthy subjects (Babiloni et al., 2018a,b,c, 2017a,b). At the present early stage of the research, we can just speculate about it. We posit that in PD patients with cognitive deficits, two neurophysiopathological processes may have an opposite effect on the thalamocortical circuits generating cortical alpha rhythms in the quiet wakefulness. The first neurophysiopathological process was explained in the previous section. Summarizing, dysfunctions in dopaminergic nigrostriatal projections to thalamocortical systems may reduce the synchronization (i.e., resulting in a desynchronizing effect) in cortical pyramidal neurons generating alpha rhythms, thus inducing a tonic cortical overexcitation of somatomotor systems and motor deficits. The effects of this process might be paradoxically mitigated by the consequence of the second neurophysiopathological process involving dopaminergic

mesolimbic/mesocortical systems. In normal conditions, dopaminergic mesolimbic/mesocortical systems may maintain a background tonic cortical arousal and slightly desynchronized alpha rhythms even in the quiet wakefulness, maybe to ensure a background alert for salient/motivational stimuli. The second neurophysiopathological process may impinge on these mesolimbic/mesocortical systems, thus reducing such slight desynchronization (i.e., resulting in a synchronizing effect) in cortical pyramidal neurons generating alpha rhythms. The consequence may be the mitigation of the overexcitation of somatomotor systems due to the first neurophysiopathological process. Unfortunately, the parallel abnormal increase of cortical delta rhythms may not allow to observe beneficial clinical effects of the interaction between the two neuropathological processes on the generation of alpha rhythms. This speculation is consistent with previous findings of our Consortium showing that in PD patients with normal cognition, the acute administration of levodopa reduced both delta and alpha source activities recorded in quiet wakefulness (Babiloni et al., 2018c).

Future studies in PD patients with different cognitive deficits may challenge this speculative explanation correlating resting-state delta and alpha source activities with (1) makers of DaTscan™ (Isaacson et al., 2017) and FDG-PET (Brajkovic et al., 2017) mapping ventral tegmental area, medial septum, nucleus accumbens and prefrontal cortex and (2) psychophysical measurements of performance in tasks related to the motivation, reward seeking, avoidance learning, impulsive-compulsive behavior in response to novel stimuli and the effect of the reward/punishment.

To test another core hypothesis of this study, we contrasted delta and alpha source activities in two matched PD sub-groups with and without visual hallucinations, assessed with standard clinical scales (of note, all PD subject had cognitive deficits). The aim was to evaluate the relationship between these rsEEG source activities and neuropsychiatric visual-perceptive deficits. Compared to the PD patients without visual hallucinations (PD-VH-), those with these symptoms (PD-VH+) showed higher alpha source activities localized in parieto-occipital regions. This effect was unrelated to global motor and cognitive deficits, hallucinations, therapies (anti-psychotic, dopaminergic, and cholinergic), and disease duration. Noteworthy, it was specific in alpha frequencies, as this effect was not observed in the delta or other source activities.

To our knowledge, the present study reports the first evidence of the relationship between parieto-occipital rsEEG rhythms at alpha frequencies and visual hallucinations in PD patients with cognitive deficits. This localization is in line with previous evidence showing that PD

patients with visual hallucinations were characterized by neuroimaging abnormalities in parietal, temporal, and occipital areas (Boecker et al., 2007; Ramírez-Ruiz et al., 2007; Yao et al., 2015; Prell, 2018), although other neuroimaging findings in those patients showed main abnormalities in frontal rather than posterior cortical regions (Nagano-Saito et al., 2004; Stebbins et al., 2004; Sanchez-Castaneda et al., 2010). In an interesting FDG-PET study, pareidolia (i.e., visual illusions involving ambiguous forms that are perceived as meaningful objects) was observed in all PD patients with visual hallucinations and the amount of pareidolic illusions did correlate with bilateral parietal, temporal, and occipital hypometabolism (Uchiyama et al, 2015).

The present findings complement those obtained investigating event-related potentials (ERPs) and sleep EEG in PD patients. In those previous investigations, PD patients with visual hallucinations showed a later latency of posterior peaks of positive potentials evoked by flickering-checkboards and facial discrimination, as a sign of delayed visual information processing in parieto-occipital cortex (Matsui et al., 2005; Kurita et al., 2010). Other evidence unveiled visual hallucinations in PD patients with marked motor symptoms and abnormal posterior visual ERPs (Onofrj et al., 2006). Concerning the sleep EEG studies, there is converging evidence that in PD patients, visual hallucinations are related to rapid-eye-movement behavioral sleep disorders (RBDs) and mixed states of vigilance and consciousness between sleep and wakefulness daytime and nighttime (Onofrj et al., 2002, 2006; Manni et al., 2002; Pacchetti et al., 2005).

Why are resting state parieto-occipital alpha source activities higher in the PD patients with (PD-VH+) than without (PD-VH-) visual hallucinations? We speculate that this paradoxical effect may be due to a neurophysiopathological process similar or overlapping to that hypothesized for PD patients with greatest cognitive deficits but no visual hallucinations. In PD patients with visual hallucinations, dysfunctions in mesolimbic/mesocortical dopaminergic systems might reduce the normal slight desynchronizing effect of those systems on parieto-occipital alpha source activities even in the quiet wakefulness. This neurophysiopathological process may interact with the two neurophysiopathological processes hypothesized (see the previous section) for the PD patients with cognitive deficits in the determination of the level of parieto-occipital alpha source activities in quiet wakefulness.

Future studies in PD patients with visual hallucinations may challenge the present speculative explanation correlating resting-state parieto-occipital alpha source activities with (1) markers of DaTscan™ (Isaacson et al., 2017) and FDG-PET (Brajkovic et al., 2017) mapping ventral tegmental area, medial septum, nucleus accumbens and prefrontal cortex, and (2)

psychophysical measurements of visual hallucinations induced by proper visual stimuli including flickering annulus and pareidolic images (Uchiyama et al., 2015; Pearson et al., 2016).

Interactions among the cholinergic, dopaminergic, and serotoninergic ascending systems in PD

In the speculative interpretation of the present findings, we did not take into account the probable interaction among serotoninergic, dopaminergic, and cholinergic systems in the modulation of delta and alpha rsEEG source activities. In normal subjects, this interaction is crucial for the modulation of cortical arousal and vigilance (Aosaki et al., 2010; Stahl, 2016; Lozovaya et al., 2018). For example, when the quiet wakefulness is perturbed by biologically relevant stimuli, cortical and thalamic neurons may inhibit the spontaneous firing of cholinergic interneurons in the striatum while dopaminergic neurons in the substantia nigra (pars-compacta) may increase their firing (Aosaki et al., 2010). The inter-relatedness between these two neuromodulatory systems may affect the generation of alpha source activities and underpin motor learning for rewarding stimuli (Lozovaya et al., 2018), attentional shifts, and regulation of motor activity for salient stimuli (Ding et al., 2010). Furthermore, ascending pedunculopontine projections of cholinergic neurons to dopaminergic neurons in the ventral tegmental area and the substantia nigra may increase reward-seeking and energizes motor functions, respectively (Yeomans, 2012). In parallel, descending pedunculopontine projections of cholinergic neurons to dorsal reticular formation in the pons may regulate thalamocortical activity and the generation of alpha source activities with an impact on visual cortical arousal in the vigilance/consciousness states underlying hypnagogic imagery, visual hallucinations, and dreams (Yeomans, 2012). Moreover, cholinergic forebrain neurons may regulate top-down and bottom-up attention to optimize cortical sensory information processing with a reflection on parieto-occipital alpha source activities (Bentley et al., 2004 and 2008; Yarnall et al., 2011; Janzen et al., 2012).

In the PD process, Lewy bodies accumulation in the substantia nigra is known to cause neurodegeneration of dopaminergic neural projections to the dorsal striatum (i.e., caudate and putamen), resulting in a disinhibition of local cholinergic interneurons innervating striatal GABAergic neurons; this effect may be related to abnormal delta and alpha source activities with an impact on significant motor symptoms (Schwarz et al., 1986; Hammond et al., 2007; Stahl, 2016; Aosaki et al., 2010) and alteration in attentional shifts and cessation of motor activity in response to salient stimuli (Ding et al., 2010; Lozovaya et al., 2018). In the same

vein, abnormalities in serotoninergic raphe neurons and serotoninergic projections in the dorsal striatum are known to relate to motor symptoms in PD patients (Buddhala et al., 2015; Joutsa et al., 2015). Furthermore, those abnormalities concur to the overexcitation in the ventral striatum (i.e., nucleus accumbens and olfactory tuberculum) and cerebral cortex, possibly inducing cognitive deficits and psychotic symptoms including visual hallucinations (Joutsa et al., 2015; Stahl, 2016). It can be hypothesized a correlation between these abnormalities and delta/alpha source activities in quiet wakefulness, as observed in PD patients with motor, cognitive deficits, and visual hallucinations in the present study.

III study

Abnormal cortical sources of resting state EEG rhythms are related to cognitive deficits, rem sleep behavior disorders, and visual hallucinations in patients with dementia with Lewy Bodies

Introduction

Dementia with Lewy Bodies (DLB) presents major abnormalities in frontal executive and motor functions, due to the progressive neurodegeneration not only in nigrostriatal dopaminergic but also frontostriatal, mesocortical, mesolimbic, and fronto-parietal neural networks in relation to intracellular Lewy bodies and neurofibrillary tangles (Weisman et al., 2007). As a result, DLB clinical manifestations extend to visual hallucinations, fluctuation of cognitive disorders, and disturbances of rapid eye movement (REM) sleep (McKeith et al., 1996; 2017; Donaghy and McKeith 2014). In this clinical framework, visual hallucinations are very frequent (> 80%) in DLB patients (McKeith et al., 2017).

Unfortunately, the mentioned clinical phenotype of the DLB partially overlaps with that of other neurodegenerative dementing disorders such as dementia due to Parkinson's disease (PDD) and Alzheimer's disease (ADD). The diagnostic process may imply the clinical and instrumental re-evaluation of ADD, PDD, and DLB patients over time every 6 or 12 months. Therefore, the clinical practice in millions of PDD, DLB, and ADD patients would benefit of biomarkers that are noninvasive, cost-effective, repeatable over time, and largely accessible worldwide. For an ideal precision medicine approach, these biomarkers should be sensitive to different brain neural substrates underpinning these neuropathological clinical manifestations.

Among various candidates, biomarkers derived from the spectral analysis of resting state eyes-closed electroencephalographic (rsEEG) rhythms show all the mentioned characteristics in principle. For this reason, rsEEG markers were tested in several DLB studies as indexes of brainstem-thalamus-cortical neural synchronization mechanisms underpinning the regulation of vigilance in quiet wakefulness (Bonanni et al., 2008; Bosboom et al., 2009, 2006; Caviness et al., 2016; Fünfgeld, 1995; Kamei et al., 2010; Melgari et al., 2014; Pugnetti et al., 2010; Serizawa et al., 2008). Results of those studies have shown that when compared to normal healthy elderly (Nold) individuals, DLB patients were characterized by higher rsEEG rhythms

at delta (< 4 Hz) and theta (4-7 Hz) frequencies in topographically widespread cortical regions, associated with a reduction in rsEEG rhythms at alpha frequencies (8-12 Hz; Bonanni et al., 2008; Jackson and Snyder, 2008).

To enhance the spatial and frequency details of the above rsEEG results, our Consortium used a methodological approach including (1) the estimation of rsEEG cortical sources by the popular exact low-resolution brain electromagnetic tomography (eLORETA) freeware (Pascual-Marqui, 2007) and (2) the definition of delta, theta, and alpha frequency bands on individual basis using the frequency with the maximum rsEEG power density in the alpha range (individual alpha frequency peak, IAF peak) as a reference in the rsEEG power density spectrum averaged across all electrodes (Babiloni et al., 2017ab, 2018abc). Main results of this approach can be summarized as follows (Babiloni et al., 2017ab, 2018abc). Compared with Nold subjects, DLB showed a reduced activation in occipital, parietal, and temporal cortical sources of alpha rhythms around the IAF, associated with an increase in topographically widespread delta source activities. Such abnormalities in the delta and alpha source activities were intermediate between those observed in ADD and PDD patients, where PDD and ADD showed maximum abnormalities in delta and alpha, respectively. Similar results were observed in those patients even at the prodromal stage of mild cognitive impairment. From a neurophysiological point of view, those abnormal reduction in alpha source activities may reflect a background cortical overexcitation in quiet wakefulness (Pfurtscheller and Lopes da Silva, 1999). Furthermore, those abnormalities in both delta and alpha source activities in resting state conditions may reflect alterations in the neurophysiological oscillatory systems regulating vigilance in quiet wakefulness. To support this tentative explanation, previous studies investigating rsEEG rhythms have reported that sleep deprivation induces an increase in posterior cortical delta rhythms and a reduction in widespread alpha rhythms recorded in healthy adults resting in quiet wakefulness, while the acute administration of a pharmacological agent enhancing the vigilance (i.e., Modafinil) partially recovers these effects (Chapotot et al., 2003; James et al., 2011; Bodenmann et al., 2009; Saletu et al., 2004, 2007). The relationship between cortical delta and alpha rhythms in the resting state condition and the neurophysiological regulation of quiet vigilance makes these rsEEG markers extremely interesting for investigating the clinical neurophysiology of fluctuations of cognitive functions, visual hallucinations, and rapid eye movement (REM) sleep behavior disorders in DLB patients.

In the present study, we used the mentioned methodological approach to test the hypothesis that in DLB patients, cortical sources of rsEEG rhythms at delta and alpha frequencies may show differences as a function of relevant clinical features such as the severity and fluctuation of cognitive deficits, REM behavioral disorders, and visual hallucinations. To test this hypothesis, cortical sources of rsEEG rhythms were compared between matched DLB sub-groups with high vs. low global cognitive status, and the presence or absence of the fluctuation of cognitive disorders, visual hallucinations, and REM sleep behavior disorders. In this framework, Nold and AD subjects were used as control groups to address the specificity of the effects.

Materials and Methods

Subjects

In the present exploratory and observational study, clinical and rsEEG data were taken from an international archive formed by the Clinical Units and E-DLB Consortia. Specifically, the DLB group (N = 46) was formed by 29 patients with dementia and 17 patients with mild cognitive impairment (MCI). As mentioned above, age-, sex-, and education-matched groups of AD patients (N = 60) and Nold subjects (N = 20) were also taken from the same archive for control purposes. In detail, the AD group was formed by 20 patients with dementia (ADD) and 40 patients with mild cognitive impairment (ADMCI). Table 1 summarizes the most relevant demographic (i.e., age, gender, and education) and clinical (i.e., mini mental state evaluation, MMSE score; visual hallucinations, VH; Unified Parkinson Disease Rating Scale-III, UPDRS III score;) features of those Nold, AD, and DLB groups. Furthermore, the Table 1 reports the results of the presence or absence of statistically significant differences ($p < 0.05$) among the three groups for the age (ANOVA), gender (Freeman-Halton), education (ANOVA), and MMSE score (Kruskal-Wallis). As expected, there was a higher MMSE score in the Nold than the AD and DLB sub-groups ($p < 0.00001$). On the contrary, statistically significant differences were found neither for the MMSE score between the AD and DLB groups ($p > 0.05$) nor the age, gender, and education among the Nold, AD, and DLB groups ($p > 0.05$).

Local institutional Ethics Committee approved the present observational study. All experiments were performed with the informed and overt consent of each participant or caregiver, in line with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the local Institutional Review Board.

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS				
	Nold	AD	DLB	Statistical analysis
N	20	60	46	-
Age	75.0 (± 1.1 SE)	75.2 (± 0.5 SE)	76.4 (± 0.8 SE)	ANOVA: n.s.
Gender (F/M)	10/10	35/25	22/24	Freeman-Halton: n.s.
Education	8.5 (± 0.6 SE)	9.6 (± 0.6 SE)	8.2 (± 0.6 SE)	ANOVA: n.s.
MMSE	28.2 (± 0.2 SE)	22.6 (± 0.5 SE)	20.8 (± 0.7 SE)	Kruskal-Wallis: H = 47.64; p < 0.00001 (Nold > AD, DLB)
Visual hallucinations	-	-	N= 31	-
UPDRS III	-	-	20.1 (± 2.0 SE)	-

***Table 1**. Mean values (± standard error of the mean, SE) of the demographic and clinical data as well as the results of their statistical comparisons (p < 0.05) in the groups of healthy elderly subjects (Nold, N = 20), Alzheimer's disease patients (AD, N = 60), and Lewy Body disease patients (DLB, N = 46). Legend: MMSE = Mini Mental State Evaluation; UPDRS III= Unified Parkinson Disease Rating Scale-III ; M/F = males/females; n.s. = not significant (p > 0.05).*

To test the relationship between the rsEEG source activities of interest and visual hallucinations in the DLB patients, two sub-groups of DLB patients (N = 31 with visual hallucinations, DLB VH+; N = 15 without visual hallucinations, DLB VH-) matched for the demographic features and drugs assumption (i.e. levodopa, acetylcholinesterase inhibitors -AChEI, benzodiazepines and antipsychotics) were considered. The confounding influence of cognitive and motor deficits was mitigated matching these two DLB sub-groups for the MMSE and UPDRS III scores. Specifically, the DLB VH- sub-group was formed by 9 DLB, and 6 DLBMCI, while the DLB VH+ sub-group was formed by 20 DLB, and 11 DLBMCI. Furthermore, all DLB patients performed the rsEEG recording within two years from the clinical diagnosis. In the same line, 40% DLB VH- patients and 58.0% DLB VH+ patients used psychoactive drugs, 33.3% DLB

VH- patients and 58.0% DLB VH+ patients used acetylcholinesterase inhibitors. No statistically significant difference between the DLB VH- and DLB VH+ sub-groups was found for the use of psychoactive drugs and acetylcholinesterase inhibitors (Fisher test: $p > 0.05$). To test the specificity of the statistical effects, demographic-matched sub-groups of AD patients (N = 60; 20 ADD and 40 ADMCI) and Nold subjects (N = 20) were used as controls in the statistical analysis. Table 2 summarizes the most relevant demographic and clinical features of the Nold, AD, and DLB VH-, and DLB VH+ sub-groups. Furthermore, the Table 2 reports the results of the statistical analysis ($p < 0.05$) among the four sub-groups for the age (ANOVA), gender (Freeman-Halton), education (ANOVA), and MMSE score (Kruskal-Wallis). As expected, the MMSE score was higher in the Nold than the AD, DLB VH-, and DLB VH+ sub-groups ($p < 0.00001$). On the contrary, a statistically significant difference was found neither for the MMSE scores among the AD, DLB VH-, and DLB VH+ sub-groups nor the age, gender, and education among the Nold, AD, DLB VH-, and DLB VH+ sub-groups ($p > 0.05$). Furthermore, there were significant differences neither in the UPDRS III scores between the DLB VH-, and DLB VH+ sub-groups ($p > 0.05$).

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS					
	Nold	AD	DLB VH+	DLB VH-	Statistical analysis
N	20	60	31	15	-
Age	75.0 (± 1.1 SE)	75.2 (± 0.5 SE)	75.7 (± 1.0 SE)	78.0 (± 1.5 SE)	ANOVA: n.s.
Gender (F/M)	10/10	35/25	15/16	7/8	Freeman-Halton: n.s.
Education	8.5 (± 0.6 SE)	9.6 (± 0.6 SE)	8.4 (± 0.8 SE)	7.9 (± 1.0 SE)	ANOVA: n.s.
MMSE	28.2 (± 0.2 SE)	22.6 (± 0.5 SE)	20.2 (± 0.8 SE)	22.0 (± 1.0 SE)	Kruskal-Wallis: H = 48.8; p < 0.00001 (Nold > AD, DLB VH-, DLB VH+)
UPDRS III	-	-	21.1 (± 2.4 SE)	18.2 (± 3.5 SE)	T test: n.s.

***Table 2**. Mean values (± SE) of the demographic and clinical data as well as the results of their statistical comparisons ($p < 0.05$) in the sub-groups of Nold subjects (N = 20), AD patients (N = 60), DLB patients with visual hallucinations (DLB VH+, N = 31), and DLB patients without visual hallucinations (DLB VH-, N = 15). Legend: MMSE = Mini Mental State Evaluation; UPDRS III= Unified Parkinson Disease Rating Scale-III ; M/F = males/females; n.s. = not significant ($p > 0.05$).*

To test the relationship between the rsEEG source activities of interest and the global cognitive status in the DLB patients, two sub-groups of DLB patients (N = 27 DLB with higher cognitive deficits; N = 15 DLB with low cognitive deficits) matched for the demographic features and levodopa therapy were considered, namely the DLB sub-groups with lowest (MMSE > 25; DLB MMSE-) and highest (MMSE < 24; DLB MMSE+) global cognitive deficits. The confounding influence of motor deficits and visual hallucinations was mitigated matching the DLB MMSE- and DLB MMSE+ sub-groups for the UPDRS III score and number of DLB patients with visual hallucinations. Specifically, the DLB MMSE- sub-group was formed by 3 DLB and 12 DLBMCI patients, while the DLB MMSE+ sub-group was formed by 22 DLB, and 5 DLBMCI. Furthermore, all DLB patients performed the rsEEG recording within two years from the clinical diagnosis. In the same line 40.0% DLB MMSE- patient and 55.6% DLB MMSE+ patients used psychoactive drugs, while 53.3% DLB MMSE- patients and 48.1% DLB MMSE+ patients used acetylcholinesterase inhibitors. As expected, no statistically significant difference between the DLB MMSE- and DLB MMSE+ sub-groups was found for the use of psychoactive drugs and acetylcholinesterase inhibitors (Fisher test: $p > 0.05$). To test the specificity of the statistical effects, demographic-matched sub-groups of AD patients (N = 24; 15 ADD and 9 ADMCI) and Nold subjects (N = 20) were used as control sub-groups in the statistical analysis. Table 3 summarizes the most relevant demographic and clinical features of the Nold, AD, and DLB MMSE-, and DLB MMSE+ sub-groups. Furthermore, the Table 3 reports the results of the statistical analysis ($p < 0.05$) among the four sub-groups for the age (ANOVA), gender (Freeman-Halton), education (ANOVA), and MMSE score (Kruskal-Wallis). In the same line, the two DLB sub-groups were compared for the UPDRS III score (t-test). As expected, a statistically significant difference was found for the MMSE score ($H = 65.7$; $p < 0.00001$). Specifically, there was a higher MMSE score in the Nold and DLB MMSE- than the AD and DLB MMSE+ sub-groups ($p < 0.0001$). On the contrary, statistically significant differences were found neither for the UPDRS III score between the DLB MMSE- and DLB MMSE+ sub-groups ($p > 0.05$) nor the age, gender, and education among the Nold, AD, DLB MMSE-, and DLB MMSE+ sub-groups ($p > 0.05$). Furthermore, the UPDRS III motor score was not different between the two DLB sub-groups ($p > 0.05$).

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS					
	Nold	AD	DLB MMSE+	DLB MMSE-	Statistical analysis
N	20	24	27	15	-
Age	75.0 (± 1.1 SE)	76.4 (± 0.6 SE)	76.5 (± 1.1 SE)	75.7 (± 1.5 SE)	ANOVA: n.s.
Gender (F/M)	10/10	11/13	13/14	5/10	Freeman-Halton: n.s.
Education	8.5 (± 0.6 SE)	8.8 (± 1.0 SE)	8.3 (± 0.8 SE)	9.2 (± 1.1 SE)	ANOVA: n.s.
MMSE	28.2 (± 0.2 SE)	19.9 (± 0.7 SE)	18.4 (± 0.7 SE)	25.6 (± 0.3 SE)	Kruskal-Wallis: H = 65.7; p < 0.00001 (Nold, DLB MMSE- > AD, DLB MMSE+)
Visual hallucinations	-	-	19	18	Fisher's test: n.s.
UPDRS III	-	-	21.5 (± 2.7 SE)	18.3 (± 3.6 SE)	T test: n.s.

Table 3. *Mean values (± SE) of the demographic and clinical data as well as the results of their statistical comparisons (p < 0.05) in the sub-groups of Nold subjects (N = 20), AD patients (N = 24), DLB patients with high cognitive deficits (DLB MMSE+, N = 27), and DLB patients with less cognitive deficits (DLB MMSE-, N = 15). Legend: MMSE = Mini Mental State Evaluation; UPDRS III= Unified Parkinson Disease Rating Scale-III ; M/F = males/females; n.s. = not significant (p > 0.05).*

To test the relationship between the rsEEG source activities of interest and cognitive fluctuations in the DLB patients, two sub-groups of DLB patients (N = 27 with cognitive fluctuations, DLB Flu+; N = 18 without cognitive fluctuations, DLB Flu-) matched for the demographic features and the use of levodopa, AChEI and antipsychotics. The confounding influence of cognitive deficits and visual hallucinations was mitigated matching the DLB Flu-

and DLB Flu+ sub-groups for the MMSE score and visual hallucinations. Concerning the subjects' cognitive status, the DLB Flu- sub-group was formed by 9 DLB and 9 DLBMCI, while the DLB Flu+ sub-group was formed by 19 DLB, and 8 DLBMCI. Furthermore, all DLB patients performed the rsEEG recording within two years from the clinical diagnosis. In the same line, 38.9% DLB Flu- patients and 37.0% DLB Flu+ patients used levodopa, while 44.4% DLB Flu- patients and 55.6% DLB Flu+ patients used in the same measure acetylcholinesterase inhibitors and psychoactive drugs. As expected, no statistically significant difference between the DLB Flu- and DLB Flu+ sub-groups was found for the use of before mentioned drugs (Fisher test: $p > 0.05$). To test the specificity of the statistical effects, demographic-matched sub-groups of AD patients (N = 24; 15 ADD and 9 ADMCI) and Nold subjects (N = 20) were used as controls in the statistical analysis. Table 4 summarizes the most relevant demographic and clinical features of the Nold, AD, and DLB Flu-, and DLB Flu+ sub-groups. Furthermore, the Table 4 reports the results of the statistical analysis ($p < 0.05$) among the four sub-groups for the age (ANOVA), gender (Freeman-Halton), education (ANOVA), and MMSE score (Kruskal-Wallis). The MMSE score was higher ($H = 46.6$; $p < 0.00001$) in the Nold than the AD, DLB Flu-, and DLB Flu+ sub-groups ($p < 0.00001$). On the contrary, statistically significant differences were found neither for the MMSE score among the AD, DLB Flu-, and DLB Flu+ sub-groups ($p > 0.05$) nor the age, gender, and education among the Nold, AD, DLB Flu-, and DLB Flu+ sub-groups ($p > 0.05$). Furthermore, the UPDRS III motor score was not different between the two DLB sub-groups ($p > 0.05$).

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS					
	Nold	AD	DLB Flu+	DLB Flu-	Statistical analysis
N	20	24	27	18	-
Age	75.0 (± 1.1 SE)	76.4 (± 0.6 SE)	76.5 (± 1.1 SE)	77.2 (± 1.7 SE)	ANOVA: n.s.
Gender (F/M)	10/10	11/13	14/13	7/11	Freeman-Halton: n.s.
Education	8.5 (± 0.6 SE)	8.8 (± 1.0 SE)	8.0 (± 0.7 SE)	8.9 (± 1.0 SE)	ANOVA: n.s.

MMSE	28.2 (± 0.2 SE)	19.9 (± 0.7 SE)	20.2 (± 0.8 SE)	22.2 (± 0.9 SE)	Kruskal-Wallis: H = 46.6; p < 0.00001 (Nold > AD, DLB Flu-, DLB Flu+)
Visual hallucinations	-	-	21	9	Fisher's test: n.s.
UPDRS III	-	-	21.5 (± 2.6 SE)	18.3 (± 3.2 SE)	T test: n.s.

***Table 4**. Mean values (± SE) of the demographic and clinical data as well as the results of their statistical comparisons (p < 0.05) in the sub-groups of Nold subjects (N = 20), AD patients (N = 24), DLB patients with cognitive fluctuations (DLB Flu+, N = 27), and DLB patients without cognitive fluctuations (DLB Flu-, N = 18). Legend: MMSE = Mini Mental State Evaluation; UPDRS III= Unified Parkinson Disease Rating Scale-III ; M/F = males/females; n.s. = not significant (p > 0.05).*

Finally we tested the relationship between the rsEEG source activities of interest and REM sleep behavior disorders in the DLB patients, two sub-groups of DLB patients (N = 31 with REM sleep behavior disorders, DLB RBD+; N = 14 without REM sleep behavior disorders, DLB RBD-) matched for the demographic features and the use of levodopa and AChEI. The confounding influence of cognitive deficits and visual hallucinations was mitigated matching the DLB RBD- and DLB RBD+ sub-groups for the MMSE score and visual hallucinations. Concerning the subjects' cognitive status, the DLB RBD- sub-group was formed by 11 DLB and 3 DLBMCI, while the DLB RBD+ sub-group was formed by 18 DLB, and 13 DLBMCI. Furthermore, all DLB patients performed the rsEEG recording within two years from the clinical diagnosis. In the same line, 21.4% DLB RBD- patients and 45.2% DLB RBD+ patients used levodopa, while 57.1% DLB RBD- patient and 35.5% DLB RBD+ patients used AChEI. As expected, no statistically significant difference between the DLB RBD- and DLB RBD+ sub-groups was found for the use of before mentioned drugs (Fisher test: p > 0.05). To test the specificity of the statistical effects, demographic-matched sub-groups of AD patients (N = 60; 20 ADD and 40 ADMCI) and Nold subjects (N = 20) were used as controls in the statistical analysis. Table 5 summarizes the most relevant demographic and clinical features of the Nold, AD, and DLB RBD-, and DLB RBD+ sub-groups. Furthermore, the Table 5 reports the results of the statistical analysis (p < 0.05) among the four sub-groups for the age (ANOVA), gender (Freeman-Halton), education (ANOVA), and MMSE score (Kruskal-Wallis). The MMSE score was higher (H = 47.4; p < 0.00001) in the Nold than the AD, DLB RBD-, and DLB RBD+ sub-

groups ($p < 0.00001$). On the contrary, statistically significant differences were found neither for the MMSE score among the AD, DLB RBD-, and DLB RBD+ sub-groups ($p > 0.05$) nor the age, gender, and education among the Nold, AD, DLB RBD-, and DLB RBD+ sub-groups ($p > 0.05$). Furthermore, the UPDRS III motor score was not different between the two DLB sub-groups ($p > 0.05$).

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS					
	Nold	AD	DLB RBD+	DLB RBD-	Statistical analysis
N	20	60	31	14	-
Age	75.0 (± 1.1 SE)	75.2 (± 0.5 SE)	75.6 (± 1.0 SE)	76.4 (± 1.3 SE)	ANOVA: n.s.
Gender (F/M)	10/10	35/25	11/20	10/4	Freeman-Halton: n.s.
Education	8.5 (± 0.6 SE)	9.6 (± 0.6 SE)	8.4 (± 0.8 SE)	8.4 (± 0.8 SE)	ANOVA: n.s.
MMSE	28.2 (± 0.2 SE)	22.6 (± 0.5 SE)	21.7 (± 0.8 SE)	19.5 (± 1.2 SE)	Kruskal-Wallis: H = 47.4; p < 0.00001 (Nold > AD, DLB RBD-, DLB RBD+)
Visual hallucinations			20	10	Fisher's test: n.s.
UPDRS III	-	-	18.8 (± 2.5 SE)	20.9 (± 3.8 SE)	T test: n.s.

***Table 5**. Mean values (± SE) of the demographic and clinical data as well as the results of their statistical comparisons ($p < 0.05$) in the sub-groups of Nold subjects (N = 20), AD patients (N = 60), DLB patients with REM sleep behavior disorders (DLB RBD+, N = 31), and DLB patients without REM sleep behavior disorders (DLB RBD-, N = 14). Legend: MMSE = Mini Mental State Evaluation; UPDRS III= Unified Parkinson Disease Rating Scale-III ; M/F = males/females; n.s. = not significant ($p > 0.05$).*

Diagnostic criteria

The diagnosis of the probable DLB was carried out in agreement with the consensus guidelines (McKeith IG et al. 2005; 2017). Twenty-six out of 46 DLB patients performed DaTSCAN to confirm the diagnosis of probable DLB. Concerning the detection of the core and suggestive features of DLB, the Neuropsychiatric inventory (NPI) item-2 investigated the occurrence frequency and the severity of hallucinations (Cummings JL et al., 1994). Frontal Assessment Battery (FAB) (Dubois et al., 2000) and Clinician Assessment of Fluctuations (Walker et al., 2000a; 200b) were included to investigate, respectively, the severity of the frontal dysfunction and the presence and severity of the cognitive fluctuations. Unified Parkinson Disease Rating Scale-III (UPDRS-III) assessed the presence and severity of the extrapyramidal signs (Fahn et al., 1987). The presence and/or absence of rapid eye movement (REM) sleep behavior disorder (RBD) was determined according to minimal International Classification of Sleep Disorders criteria (1992). As this retrospective study was based on data of several clinical units that did not follow a harmonized protocol, the DLBMCI subjects underwent a different battery of clinical scales including the Neuropsychiatric Inventory (NPI), the scale for the assessment of Behavioral and Psychological Symptoms of Dementia (BPSD), the MMSE, the Epworth Sleepiness Scale (ESS) for estimating subjective sleep disturbances, and the Alzheimer's Disease Cooperative Study for the Activities of Daily Living (ADCS-ADL). Furthermore, DLBMCI subjects underwent different battery of neuropsychological tests to evaluate the status of MCI (Donaghy et al., 2018). This battery included neuropsychological tests assessing the general cognitive performance in the domains of memory, language, executive function/attention, and visuo-construction abilities (some of them received the CERAD-plus battery). The diagnostic criteria for ADD and ADMCI have been described diagnostic criteria of "I and II studies" as weel as inclusion criteria for Nold subjects.

Statistical analysis

Five statistical sessions were performed by the commercial tool STATISTICA 10 (StatSoft Inc., www.statsoft.com) to test the control hypothesis and the four working hypotheses. In all the statistical sessions, ANOVA was computed using the rsEEG source activities (i.e., regional normalized eLORETA solutions) as a dependent variable ($p < 0.05$). Mauchly's test evaluated the sphericity assumption and degrees of freedom were corrected by the Greenhouse-Geisser procedure when appropriate ($p < 0.05$). Duncan test was used for post-hoc comparisons ($p <$

0.05). The results of the following statistical analyses were controlled by the Grubbs test ($p < 0.001$) for the presence of outliers in the distribution of the eLORETA source solutions.

The first ANOVA tested the control hypothesis that the rsEEG source activities (i.e., regional normalized eLORETA solutions) differed among Nold, AD, and DLB groups. The ANOVA factors were Group (Nold, AD, and DLB), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal, and limbic). The confirmation of the control hypothesis may require: (1) a statistically significant ANOVA effect including the factor Group ($p < 0.05$) and (2) a post-hoc Duncan test indicating statistically significant ($p < 0.05$) differences in the rsEEG source activities among Nold, AD, and DLB groups (i.e., Nold ≠ AD ≠ DLB, $p < 0.05$).

The second ANOVA evaluated the first working hypothesis that the rsEEG source activities (i.e., regional normalized eLORETA solutions) are related to visual hallucinations in DLB patients (DLB VH- vs. DLB VH+; Nold and AD as control groups). The ANOVA factors were Group (Nold, AD, DLB VH-, and DLB VH+), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal, and limbic). The confirmation of the first working hypothesis may require: (1) a statistically significant ANOVA effect including the factor Group ($p < 0.05$) and (2) a post-hoc Duncan test indicating statistically significant ($p < 0.05$) differences in the rsEEG source activities between DLB VH- and DLB VH+ groups (i.e., DLB VH- ≠ DLB VH+, $p < 0.05$).

The third ANOVA evaluated the second working hypothesis that the rsEEG source activities (i.e., regional normalized eLORETA solutions) differed as a function of global cognitive deficits (i.e., MMSE) in DLB patients (DLB MMSE- vs. DLB MMSE+; Nold and AD as control groups). The ANOVA factors were Group (Nold, AD, DLB MMSE-, and DLB MMSE+), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal, and limbic). The confirmation of the second working hypothesis may require: (1) a statistically significant ANOVA effect including the factor Group ($p < 0.05$) and (2) a post-hoc Duncan test indicating statistically significant ($p < 0.05$) differences in the rsEEG source activities between DLB MMSE- and DLB MMSE+ groups (i.e., DLB MMSE- ≠ DLB MMSE+, $p < 0.05$).

The fourth ANOVA evaluated the third working hypothesis that the rsEEG source activities (i.e., regional normalized eLORETA solutions) differed as a function of cognitive fluctuations in DLB patients (DLB Flu- vs. DLB Flu+; Nold and AD as control groups). The ANOVA factors were Group (Nold, AD, DLB Flu-, and DLB Flu+), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal, and limbic). The confirmation of the first working hypothesis may require: (1) a statistically significant ANOVA effect including the factor Group ($p < 0.05$) and (2) a post-hoc Duncan test indicating statistically significant ($p < 0.05$) differences in the rsEEG source activities between DLB Flu- and DLB Flu+ groups (i.e., DLB Flu- ≠ DLB Flu+, $p < 0.05$).Finally, the fifth ANOVA evaluated the last working hypothesis that the rsEEG source activities (i.e., regional normalized eLORETA solutions) differed as a function of sleep rem behavior disorders (i.e., RBD) in DLB patients (DLB RBD- vs. DLB RBD+; Nold and AD as control groups). The ANOVA factors were Group (Nold, AD, DLB RBD-, and DLB RBD+), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal, and limbic). The confirmation of the first working hypothesis may require: (1) a statistically significant ANOVA effect including the factor Group ($p < 0.05$) and (2) a post-hoc Duncan test indicating statistically significant ($p < 0.05$) differences in the rsEEG source activities between DLB RBD- and DLB RBD+ groups (i.e., DLB RBD- ≠ DLB RBD+, $p < 0.05$).

Spearman test ($p < 0.05$) was used to evaluate the correlation between the MMSE score and rsEEG source activities (i.e., regional normalized eLORETA solutions) showing statistically significant differences ($p < 0.05$) between the DLB MMSE- and DLB MMSE+ groups. In the same line, Point Biserial Correlation Coefficient ($p < 0.05$) was also used to evaluate the correlation between the presence or absence of visual hallucinations, cognitive fluctuations, and REM sleep behavior disorders and rsEEG source activities (i.e., regional normalized eLORETA solutions) showing statistically significant differences ($p < 0.05$) between the DLB RBD- and DLB RBD+ groups.

Results

Table 6 reports the mean values of TF and IAF for the three groups (i.e., Nold, AD, and DLB), together with the results of the statistical comparisons between the groups (ANOVA, $p < 0.05$). The mean TF was 5.8 Hz (± 0.2 SE) in the Nold group, 5.5 Hz (± 0.1 SE) in the AD group, and

4.9 Hz (± 0.1 SE) in the DLB group. Furthermore, the mean IAF was 9.0 Hz (± 0.2 SE) in the Nold group, 8.6 Hz (± 0.1 SE) in the AD group, and 7.2 Hz (± 0.1 SE) in the DLB group. The ANOVAs using these values as an input showed the following statistically significant findings: (1) the mean TF was greater ($F = 9.9$, $p < 0.0005$) in the Nold and AD than the DLB group ($p < 0.0001$); (2) the mean IAF was greater ($F = 21.9$, $p < 0.00001$) in the Nold and AD than the DLB group ($p < 0.0001$). These findings stress the importance to use the TF and IAF in the determination of the delta to alpha frequency bands in the studies focused on AD and DLB patients.

MEAN VALUES (± SE) OF TRANSITION FREQUENCY (TF) AND INDIVIDUAL ALPHA FREQUENCY PEAK (IAF)				
	Nold	AD	DLB	Statistical analysis
TF	5.8 (± 0.2 SE)	5.5 (± 0.1 SE)	4.9 (± 0.1 SE)	ANOVA: F = 9.9, p < 0.0005 (Nold, AD > DLB)
IAF	9.0 (± 0.2 SE)	8.6 (± 0.1 SE)	7.2 (± 0.1 SE)	ANOVA: F = 21.9, p < 0.00001 (Nold, AD > DLB)

Table 6. *Mean values (± SE) of transition frequency (TF) and individual alpha frequency peak (IAF) computed from rsEEG power density spectra in the Nold, AD, and DLB groups. The table also reports the p values of the statistical comparisons of these values between the groups ($p < 0.05$). Legend: Nold = healthy elderly subjects; AD = Alzheimer's disease patients; DLB = Lewy Body disease patients.*

Figure 1 shows the grand average of regional rsEEG source activities (i.e., regional normalized eLORETA solutions) relative to a statistically significant ANOVA interaction effect ($F = 15.2$; $p < 0.00001$) among the factors Group (Nold, AD, and DLB), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal, and limbic). In the figure, rsEEG source activities have the shape of typical rsEEG relative power spectra. In the Nold group as a physiological reference in quiet wakefulness, the dominant values of the eLORETA solutions were observed in occipital (maximum), parietal, temporal, and limbic alpha 2 and alpha 3 sources. Low values of the eLORETA solutions were found in the widespread delta, theta, and alpha 1 sources. The eLORETA solutions in beta 1, beta 2, and gamma sources were very low. Compared to the Nold group, the AD and DLB

groups showed a substantial decrease of the eLORETA solutions in posterior (i.e., central, parietal, occipital, and limbic) alpha 2 and alpha 3 sources. This effect was higher in the AD than the DLB group. Furthermore, the AD and DLB groups showed a substantial increase of the eLORETA solutions in frontal, parietal and temporal delta sources. This effect was higher in the DLB than the AD group. The Duncan planned post-hoc testing showed that the discriminant pattern Nold > DLB > AD was fitted by central, parietal, occipital, and limbic alpha 2 and alpha 3 ($p < 0.0005$). Furthermore, the discriminant source pattern DLB > AD > Nold was fitted by frontal, parietal and temporal delta sources ($p < 0.005$ to $p < 0.05$). Of note, these findings were not due to outliers from those individual eLORETA solutions, as shown by Grubbs' test with an arbitrary threshold of $p < 0.0001$ (see Figure 2).

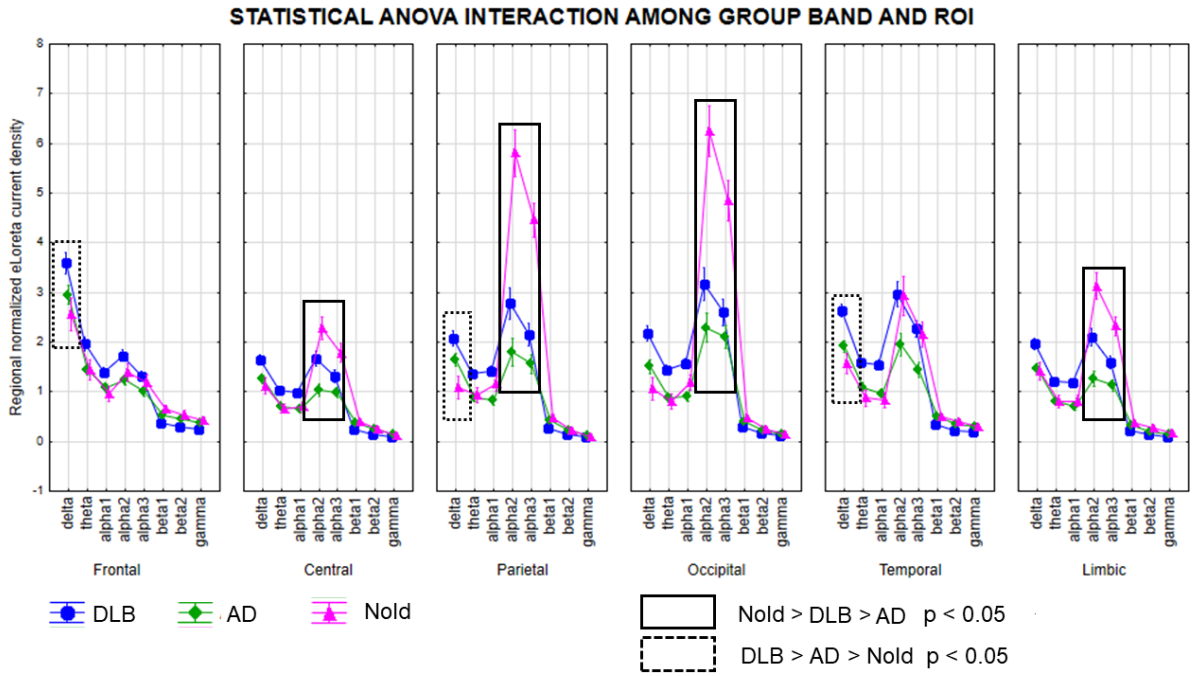

Figure 1. *Regional normalized exact low-resolution brain electromagnetic tomography (eLORETA) solutions (mean across subjects) of cortical sources of eyes-closed resting state electroencephalographic (rsEEG) rhythms relative to a statistical ANOVA interaction among the factors Group (healthy elderly subjects, Nold; Alzheimer's disease patients, AD; Lewy Body disease patients, DLB), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2 and gamma), and Region of interest, ROI (central, frontal, parietal, occipital, temporal, limbic). This ANOVA design used the regional normalized eLORETA solutions as a dependent variable. Regional normalized eLORETA solutions modeled the rsEEG relative power spectra as revealed by a sort of "virtual" intracranial macro-electrodes located on the macro-cortical regions of interest. Legend: the rectangles indicate the cortical regions and frequency bands in which the eLORETA solutions statistically presented a significant eLORETA patterns "Nold ≠ AD ≠ DLB" ($p < 0.05$).*

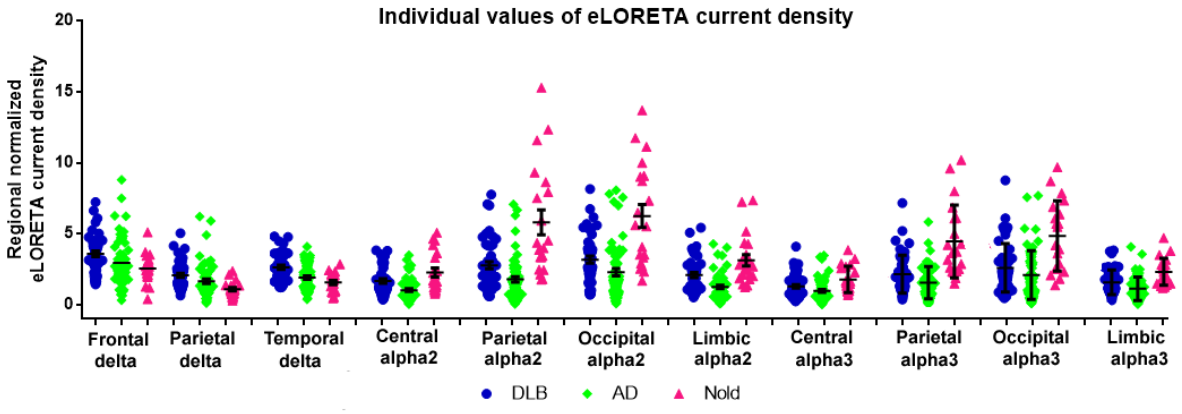

Figure 2. *Individual values of the regional normalized eLORETA solutions of the rsEEG rhythms showing statistically significant ($p < 0.05$) differences among the Nold, AD, and DLB groups (i.e., frontal, parietal and temporal delta; central, parietal, occipital, and limbic alpha 2 and alpha 3). Noteworthy, the Grubbs' test showed no outliers from those individual values of the eLORETA solutions (arbitrary threshold of $p < 0.0001$).*

rsEEG source activities in the Nold, AD, DLB-VH(-/+) sub-groups

Table 7 reports the mean values of TF and IAF for the four sub-groups (i.e., Nold, AD, DLB VH-, and DLB VH+), together with the results of the statistical comparisons between them (ANOVA, $p < 0.05$). The mean TF was 5.8 Hz (± 0.2 SE) in the Nold group, 5.5 Hz (± 0.1 SE) in the AD sub-group, 4.8 Hz (± 0.1 SE) in the DLB VH+ sub-group, and 5.1 Hz (± 0.2 SE) in the DLB VH- sub-group. Furthermore, the mean IAF was 9.0 Hz (± 0.2 SE) in the Nold group, 8.6 Hz (± 0.1 SE) in the AD sub-group, 7.0 Hz (± 0.2 SE) in the DLB VH+ sub-group, and 7.6 Hz (± 0.3 SE) in the DLB VH- sub-roup. The ANOVAs using these values as an input showed the following statistically significant findings: the mean TF was greater ($F = 6.6$, $p < 0.0005$) in the Nold ($p < 0.05$) than the AD, DLB VH- and DLB VH+ sub-groups; the mean IAF was greater ($F = 15.6$, $p < 0.00001$) in the Nold and AD ($p < 0.005$) than DLB VH- and DLB VH+ sub-groups.

MEAN VALUES (± SE) OF TRANSITION FREQUENCY (TF) AND INDIVIDUAL ALPHA FREQUENCY PEAK (IAF)					
	Nold	AD	DLB VH+	DLB VH-	Statistical analysis
TF	5.8	5.5	4.8	5.1	ANOVA:

	(± 0.2 SE)	(± 0.1 SE)	(± 0.1 SE)	(± 0.2 SE)	F = 6.6, p < 0.0005 (Nold > AD > DLBVH+; Nold > DLBVH-)
IAF	9.0 (± 0.2 SE)	8.6 (± 0.1 SE)	7.0 (± 0.2 SE)	7.6 (± 0.3 SE)	ANOVA: F = 15.6, p < 0.00001 (Nold, AD > DLBVH+, DLB VH-)

Table 7. *Mean values (± SE) of TF and IAF computed from rsEEG power density spectra in the Nold, AD, DLB VH-,and DLB VH+ groups. The table also reports the p values of the statistical comparisons of these values between the groups (p < 0.05). Legend: Nold = healthy elderly subjects; AD = Alzheimer's disease patients; DLB VH- = Lewy Body disease patients without visual hallucinations; DLB VH+ = Lewy Body disease patients with visual hallucinations.*

Figure 3 shows the grand average of regional rsEEG source activities (i.e., regional normalized eLORETA solutions) relative to a statistically significant ANOVA interaction effect (F = 10.2; p < 0.00001) among the factors Group (Nold, AD, and DLB VH-, and DLB VH+), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal, and limbic). Compared to the Nold group, the AD, DLB VH-, and DLB VH+ sub-groups showed a substantial decrease of the eLORETA solutions in posterior alpha 2 and alpha 3 sources and a substantial increase of the eLORETA solutions in widespread delta sources. The decrease of the alpha eLORETA solutions was higher in the AD than the DLB VH- and DLB VH+ sub-groups, whereas the increase of the delta eLORETA solutions was higher in the DLB VH+ than the DLB VH- and AD sub-groups. Moreover, the DLB VH+ sub-group showed increased temporal alpha 2 compared to DLB VH- and AD sub-groups.

The Duncan planned post-hoc testing showed that the discriminant source pattern DLB VH+ > DLB VH- was fitted by frontal and parietal delta (p < 0.005 to p < 0.05) as well as temporal alpha 2 (p = 0.05). Of note, these findings were not due to outliers from those individual eLORETA solutions, as shown by Grubbs' test with an arbitrary threshold of p < 0.0001 (see Figure 4).

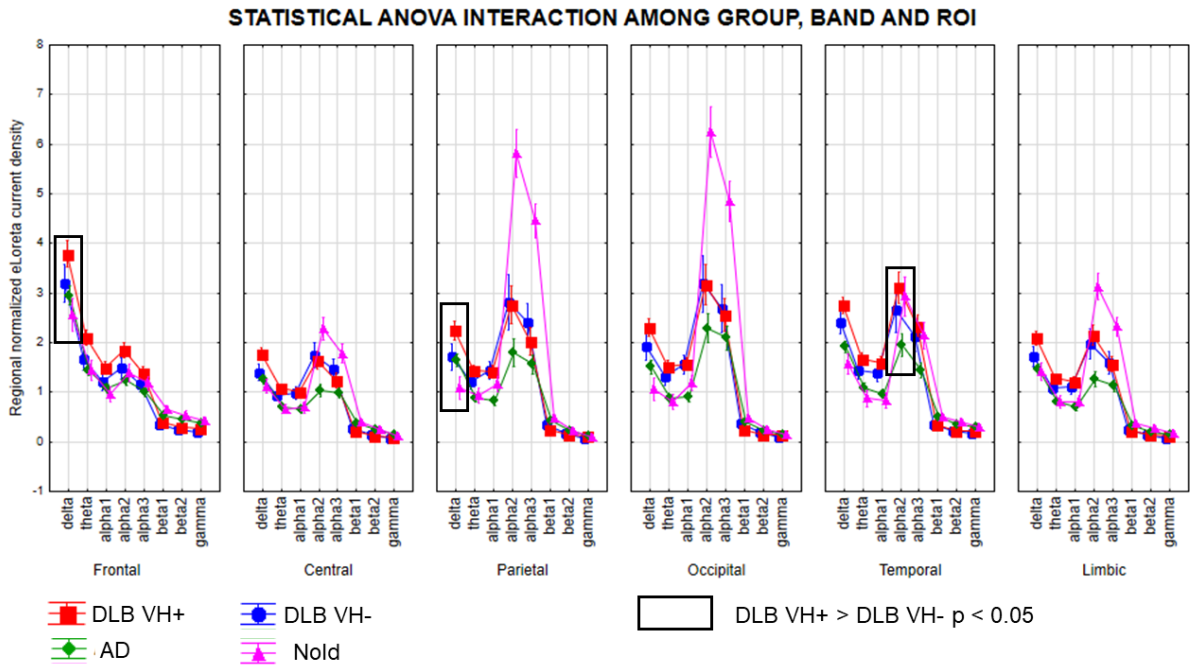

Figure 3*. Regional normalized eLORETA solutions (mean across subjects) of the rsEEG rhythms relative to a statistical ANOVA interaction among the factors Group (Nold; AD; DLB patients with absence of visual hallucinations, DLB VH-; DLB patients with presence of visual hallucinations, DLB VH+), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2 and gamma), and ROI (central, frontal, parietal, occipital, temporal, limbic). This ANOVA design used the regional normalized eLORETA solutions as a dependent variable. Legend: the rectangles indicate the cortical regions and frequency bands in which the eLORETA solutions statistically presented a significant eLORETA patterns "DLB VH- ≠ DLB VH+" (p < 0.05).*

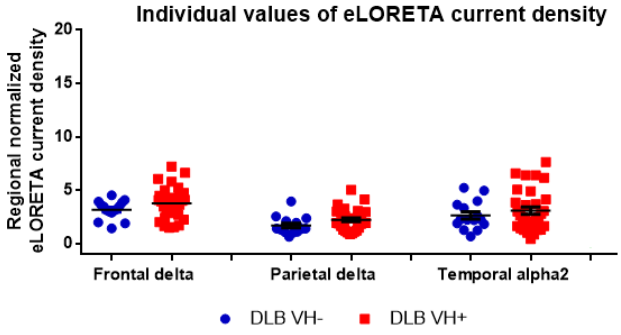

Figure 4. *Individual values of the regional normalized eLORETA solutions of the rsEEG rhythms showing statistically significant (p < 0.05) differences between DLB VH- and DLB VH+ groups (i.e., frontal and parietal delta; temporal alpha 2). Noteworthy, the Grubbs' test showed no outliers from those individual values of the eLORETA solutions (arbitrary threshold of p < 0.0001).*

rsEEG source activities in the Nold, AD, DLB-MMSE(-/+) sub-groups

Table 8 reports the mean values of TF and IAF for the four sub-groups (i.e., Nold, AD, and DLB MMSE-, and DLB MMSE+), together with the results of the statistical comparisons

between the sub-groups (ANOVA, $p < 0.05$). The mean TF was 5.8 Hz (± 0.2 SE) in the Nold group, 5.1 Hz (± 0.2 SE) in the AD sub-group, 4.8 Hz (± 0.1 SE) in the DLB MMSE+ sub-group, and 5.1 Hz (± 0.2 SE) in the DLB MMSE- sub-group. Furthermore, the mean IAF was 9.0 Hz (± 0.2 SE) in the Nold group, 8.0 Hz (± 0.3 SE) in the AD sub-group, 6.9 Hz (± 0.2 SE) in the DLB MMSE+ sub-group, and 7.7 Hz (± 0.3 SE) in the DLB MMSE- sub-group. The ANOVAs using these values as an input showed the following statistically significant findings: (1) the mean TF was greater ($F= 6.11$, $p < 0.001$) in the Nold ($p < 0.05$) than in AD, DLB MMSE- and DLB MMSE+ sub-group; (2) the mean IAF was greater ($F = 11.8$, $p < 0.00001$) in the Nold ($p < 0.005$) than AD, DLB MMSE- and DLB MMSE+ sub-groups.

MEAN VALUES (± SE) OF TRANSITION FREQUENCY (TF) AND INDIVIDUAL ALPHA FREQUENCY PEAK (IAF)					
	Nold	AD	DLB MMSE+	DLB MMSE-	Statistical analysis
TF	5.8 (± 0.2 SE)	5.1 (± 0.2 SE)	4.8 (± 0.1 SE)	5.1 (± 0.2 SE)	ANOVA: F = 6.11, p < 0.001 (Nold > AD, DLBMMSE-, DLBMMSE+)
IAF	9.0 (± 0.2 SE)	8.0 (± 0.3 SE)	6.9 (± 0.2 SE)	7.7 (± 0.3 SE)	ANOVA: F = 11.8, p < 0.00001 (Nold > AD, DLBMMSE-> DLBMMSE+)

Table 8. *Mean values (± SE) of TF and IAF computed from rsEEG power density spectra in the Nold, AD, DLB MMSE-,and DLB MMSE+ groups. The table also reports the p values of the statistical comparisons of these values between the groups ($p < 0.05$). Legend: Nold = healthy elderly subjects; AD = Alzheimer's disease patients; DLB MMSE- = Lewy Body disease patients with low cognitive deficits; DLB MMSE+ = Lewy Body disease patients with high cognitive deficits.*

Figure 5 shows the grand average of regional rsEEG source activities (i.e., regional normalized eLORETA solutions) relative to a statistically significant ANOVA interaction effect ($F = 8.6$; $p < 0.00001$) among the factors Group (Nold, AD, and DLB MMSE-, and DLB MMSE+), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal, and limbic). Compared to the Nold group, the AD, DLB MMSE-, and DLB MMSE+ sub-groups showed a substantial decrease of the eLORETA solutions in posterior alpha 2 and alpha 3 sources and a substantial increase of the eLORETA solutions in

widespread delta sources. The decrease of the alpha eLORETA solutions was higher in the DLB MMSE- than in DLB MMSE+ sub-group, whereas the increase of the delta eLORETA solutions was higher in the DLB MMSE+ than DLB MMSE- sub-group.

The Duncan planned post-hoc testing showed that the discriminant source pattern DLB MMSE+ > DLB MMSE- was fitted by temporal and parietal delta, parietal alpha 1, occipital delta and theta ($p < 0.05$) as well as parietal alpha 2 ($p < 0.005$). Of note, these findings were not due to outliers from those individual eLORETA solutions, as shown by Grubbs' test with an arbitrary threshold of $p < 0.0001$ (see Figure 6).

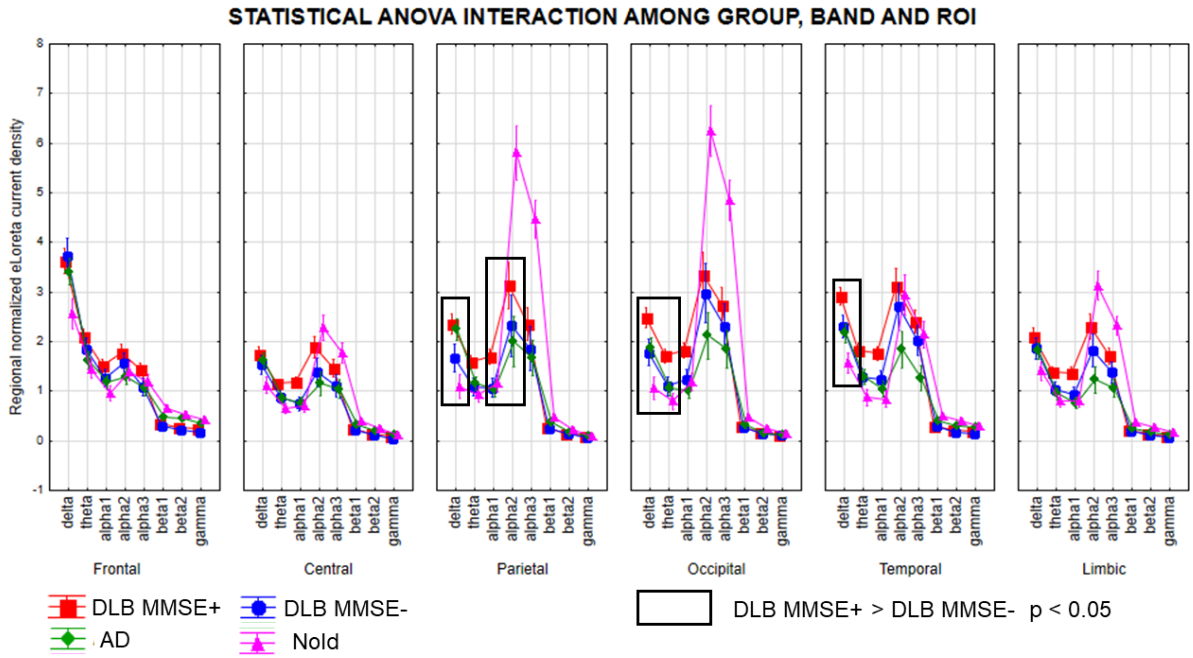

Figure 5. *Regional normalized eLORETA solutions (mean across subjects) of the rsEEG rhythms relative to a statistical ANOVA interaction among the factors Group (Nold; AD; DLB patients with low global cognitive deficits, DLB MMSE-; DLB patients with high global cognitive deficits, DLB MMSE+), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2 and gamma), and ROI (central, frontal, parietal, occipital, temporal, limbic). This ANOVA design used the regional normalized eLORETA solutions as a dependent variable. Legend: the rectangles indicate the cortical regions and frequency bands in which the eLORETA solutions statistically presented a significant eLORETA patterns "DLB MMSE- ≠ DLB MMSE+" ($p < 0.05$).*

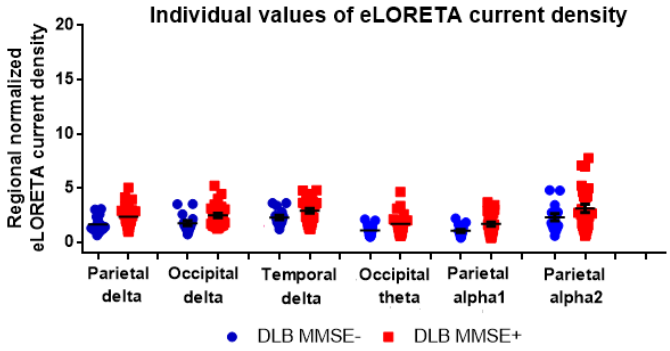

***Figure 6**. Individual values of the regional normalized eLORETA solutions of the rsEEG rhythms showing statistically significant (p < 0.05) differences between DLB MMSE- and DLB MMSE+ groups (i.e., parietal delta, parietal alpha 1, occipital delta and theta; parietal alpha 2). Noteworthy, the Grubbs' test showed no outliers from those individual values of the eLORETA solutions (arbitrary threshold of p < 0.0001).*

rsEEG source activities in the Nold, AD, DLB-Flu(-/+) sub-groups

Table 9 reports the mean values of TF and IAF for the four sub-groups (i.e., Nold, AD, DLB Flu- and DLB Flu+), together with the results of the statistical comparisons between them (ANOVA, $p < 0.05$). The mean TF was 5.8 Hz (± 0.2 SE) in the Nold group, 5.1 Hz (± 0.1 SE) in the AD sub-group, 4.9 Hz (± 0.2 SE) in the DLB Flu- sub-group, and 4.9 Hz (± 0.2 SE) in the DLB Flu+ sub-group. Furthermore, the mean IAF was 9.0 Hz (± 0.2 SE) in the Nold group, 8.0 Hz (± 0.3 SE) in the AD sub-group, 7.3 Hz (± 0.3 SE) in the DLB Flu- sub-group, and 7.1 Hz (± 0.1 SE) in the DLB Flu+ sub-group. The ANOVAs using these values as an input showed the following statistically significant findings: (1) the mean TF was greater ($F= 5.27$, $p < 0.05$) in the Nold ($p < 0.05$) than in AD, DLB Flu-, and DLB Flu+ sub-groups; (2) the mean IAF was greater ($F = 10.16$, $p < 0.00001$) in the Nold ($p < 0.005$) than AD, DLB Flu-, and DLB Flu+ sub-groups.

MEAN VALUES (± SE) OF TRANSITION FREQUENCY (TF) AND INDIVIDUAL ALPHA FREQUENCY PEAK (IAF)					
	Nold	AD	DLB Flu+	DLB Flu-	Statistical analysis
TF	5.8 (± 0.2 SE)	5.1 (± 0.2 SE)	4.9 (± 0.1 SE)	4.9 (± 0.2 SE)	ANOVA: F = 5.27, p < 0.05 (Nold > AD, DLB Flu-, DLB Flu+)

IAF	9.0 (± 0.2 SE)	8.0 (± 0.3 SE)	7.1 (± 0.1 SE)	7.3 (± 0.3 SE)	ANOVA: F = 10.16, p < 0.00001 (Nold > AD, DLB Flu- > DLB Flu+)

Table 9. *Mean values (± SE) of TF and IAF computed from rsEEG power density spectra in the Nold, AD, DLB Flu-,and DLB Flu+ groups. The table also reports the p values of the statistical comparisons of these values between the groups (p < 0.05). Legend: Nold = healthy elderly subjects; AD = Alzheimer's disease patients; DLB Flu- = Lewy Body disease patients without cognitive fluctuations; DLB Flu+ = Lewy Body disease patients with cognitive fluctuations.*

Figure 7 shows the grand average of regional rsEEG source activities (i.e., regional normalized eLORETA solutions) relative to a statistically significant ANOVA interaction effect (F = 9.0; p < 0.00001) among the factors Group (Nold, AD, and DLB Flu-, and DLB Flu+), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal, and limbic). Compared to the Nold group, the AD, DLB Flu-, and DLB Flu+ sub-groups showed a substantial decrease of the eLORETA solutions in posterior alpha 2 and alpha 3 and a substantial increase of the eLORETA solutions in widespread delta sources. Remarkably, posterior alpha 2 eLORETA solutions showed a higher magnitude in the DLB Flu+ than the DLB Flu- sub-group. No difference in delta source between the two sub-groups. The Duncan planned post-hoc testing showed that the discriminant source pattern DLB Flu+ > DLB Flu- was fitted by occipital, temporal alpha 2 (p < 0.005) as well as limbic alpha 2 (p < 0.05). Of note, these findings were not due to outliers from those individual eLORETA solutions, as shown by Grubbs' test with an arbitrary threshold of p < 0.0001 (see Figure 8).

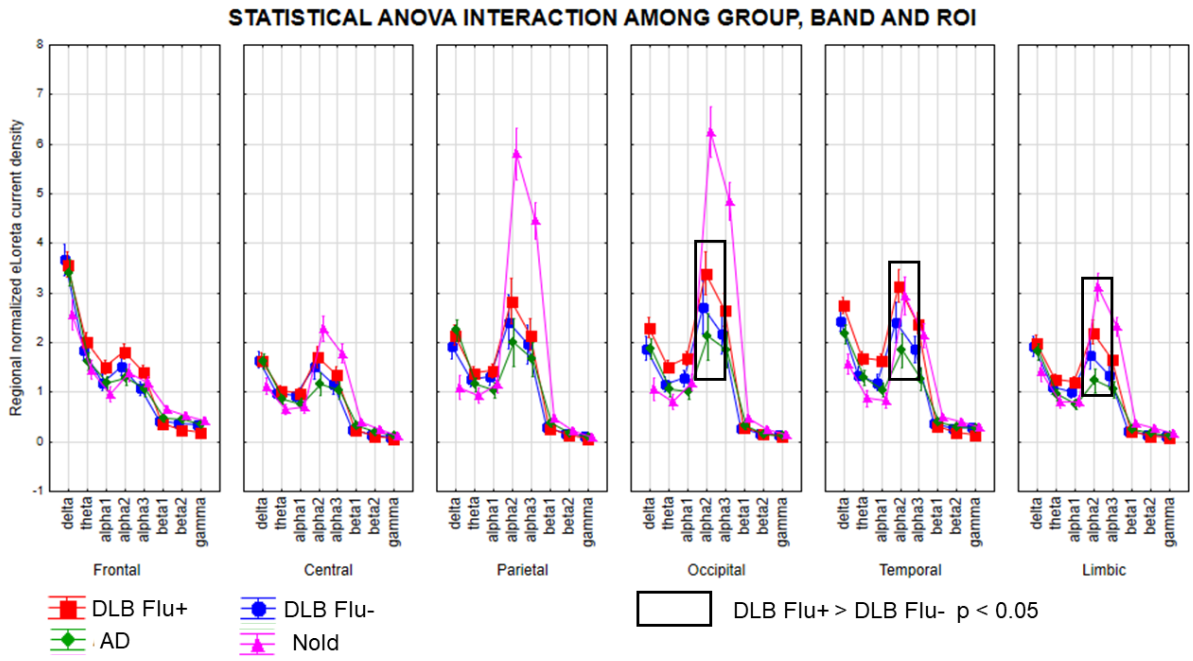

Figure 7. *Regional normalized eLORETA solutions (mean across subjects) of the rsEEG rhythms relative to a statistical ANOVA interaction among the factors Group (Nold; AD; DLB patients without cognitive fluctuations, DLB Flu-; DLB patients with cognitive fluctuations, DLB Flu+), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2 and gamma), and ROI (central, frontal, parietal, occipital, temporal, limbic). This ANOVA design used the regional normalized eLORETA solutions as a dependent variable. Legend: the rectangles indicate the cortical regions and frequency bands in which the eLORETA solutions statistically presented a significant eLORETA patterns "DLB Flu- ≠ DLB Flu+" (p < 0.05).*

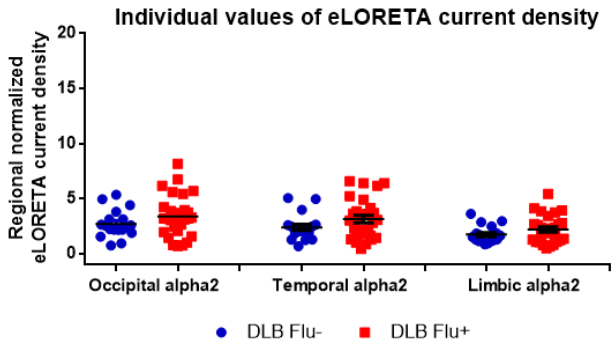

Figure 8*. Individual values of the regional normalized eLORETA solutions of the rsEEG rhythms showing statistically significant (p < 0.05) differences between DLB Flu- and DLB Flu+ groups (i.e., occipital, temporal alpha 2; limbic alpha 2). Noteworthy, the Grubbs' test showed no outliers from those individual values of the eLORETA solutions (arbitrary threshold of p < 0.0001).*

rsEEG source activities in the Nold, AD, and DLB-RBD(-/+) sub-groups

Table 10 reports the mean values of TF and IAF for the four sub-groups (i.e., Nold, AD, DLB RBD- and DLB RBD+), together with the results of the statistical comparisons between the sub-groups (ANOVA, $p < 0.05$). The mean TF was 5.8 Hz (± 0.2 SE) in the Nold group, 5.5 Hz (± 0.1 SE) in the AD sub-group, 4.8 Hz (± 0.3 SE) in the DLB RBD- sub-group, and 5.0 Hz (± 0.1 SE) in the DLB RBD+ sub-group. Furthermore, the mean IAF was 9.0 Hz (± 0.2 SE) in the Nold group, 8.6 Hz (± 0.1 SE) in the AD sub-group, 6.8 Hz (± 0.3 SE) in the DLB RBD- sub-group, and 7.5 Hz (± 0.2 SE) in the DLB RBD+ sub-group. The ANOVAs using these values as an input showed the following statistically significant findings: (1) the mean TF was greater ($F = 5.5$, $p < 0.0005$) in the Nold and AD ($p < 0.005$) than the DLB RBD- and DLB RBD+ (sub)groups; (2) the mean IAF was greater ($F = 14.7$, $p < 0.00001$) in the Nold and the AD ($p < 0.00001$) than in DLB RBD-, and DLB RBD+ sub-groups.

MEAN VALUES (± SE) OF TRANSITION FREQUENCY (TF) AND INDIVIDUAL ALPHA FREQUENCY PEAK (IAF)					
	Nold	AD	DLB RBD+	DLB RBD-	Statistical analysis
TF	5.8 (± 0.2 SE)	5.5 (± 0.1 SE)	5.0 (± 0.1 SE)	4.8 (± 0.3 SE)	ANOVA: F = 5.5, p < 0.005 (Nold, AD > DLB RBD-,DLB RBD+)
IAF	9.0 (± 0.2 SE)	8.6 (± 0.1 SE)	7.5 (± 0.2 SE)	6.8 (± 0.3 SE)	ANOVA: F = 14.7, p < 0.00001 (Nold, AD > DLB RBD+ > DLB RBD-)

***Table 10**. Mean values (± SE) of TF and IAF computed from rsEEG power density spectra in the Nold, AD, DLB RBD-,and DLB RBD+ groups. The table also reports the p values of the statistical comparisons of these values between the groups (p < 0.05). Legend: Nold = healthy elderly subjects; AD = Alzheimer's disease patients; DLB RBD- = Lewy Body disease patients without REM sleep behavior disorders; DLB RBD+ = Lewy Body disease patients with REM sleep behavior disorders.*

Figure 9 shows the grand average of regional rsEEG source activities (i.e., regional normalized eLORETA solutions) relative to a statistically significant ANOVA interaction effect ($F = 9.8$; $p < 0.00001$) among the factors Group (Nold, AD, and DLB RBD-, and DLB RBD+), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central,

parietal, occipital, temporal, and limbic). Compared to the Nold group, the AD, DLB RBD-, and DLB RBD+ sub-groups showed a substantial decrease of the eLORETA solutions in posterior alpha 2 and alpha 3 and a substantial increase of the eLORETA solutions in widespread delta sources. Remarkably, the DLB RBD+ sub-group shows an increment of posterior alpha source activity as well as occipital and temporal delta and theta sources compared to AD and DLB RBD- sub-groups.

The Duncan planned post-hoc testing showed that the discriminant source pattern DLB RBD- > DLB RBD+ was fitted by frontal alpha 3 and parietal alpha 1 ($p < 0.05$); occipital alpha 1 and limbic alpha 2 ($p < 0.01$); occipital and temporal delta, theta alpha 1, 2 and 3 and parietal alpha 1, 2, and 3 ($p < 0.005$) (see Figure 10).

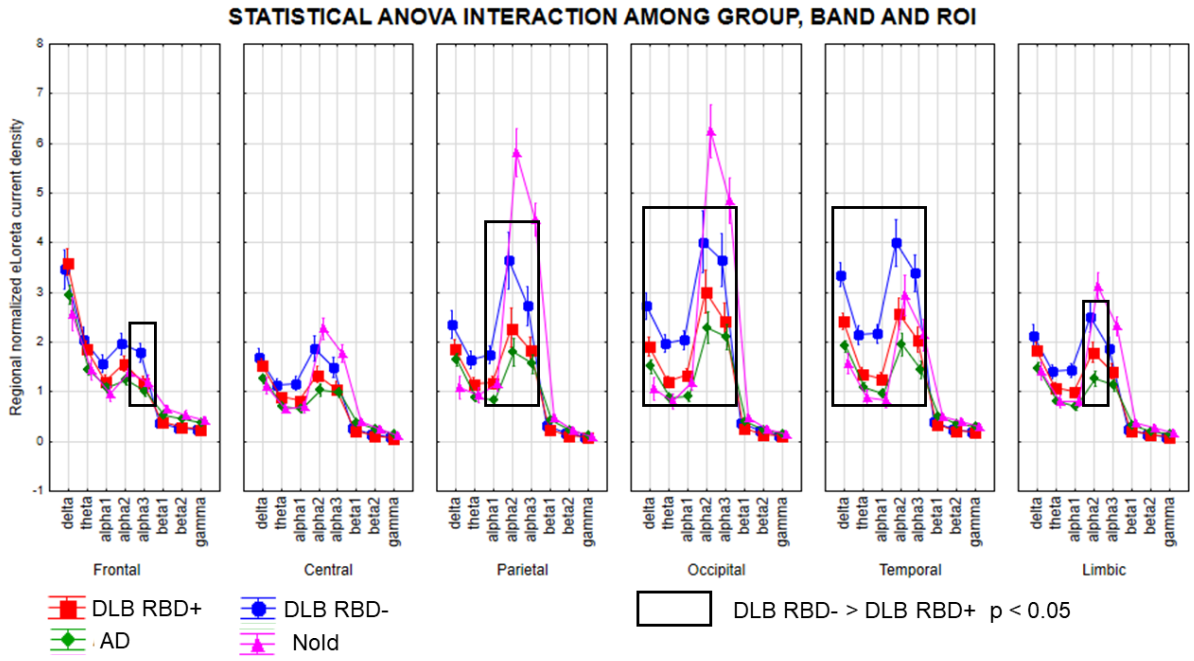

Figure 9. *Regional normalized eLORETA solutions (mean across subjects) of the rsEEG rhythms relative to a statistical ANOVA interaction among the factors Group (Nold; AD; DLB patients without REM sleep behavior disorders, DLB RBD-; DLB patients with REM sleep behavior disorders, DLB RBD+), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2 and gamma), and ROI (central, frontal, parietal, occipital, temporal, limbic). This ANOVA design used the regional normalized eLORETA solutions as a dependent variable. Legend: the rectangles indicate the cortical regions and frequency bands in which the eLORETA solutions statistically presented a significant eLORETA patterns "DLB RBD- ≠ DLB RBD+" ($p < 0.05$).*

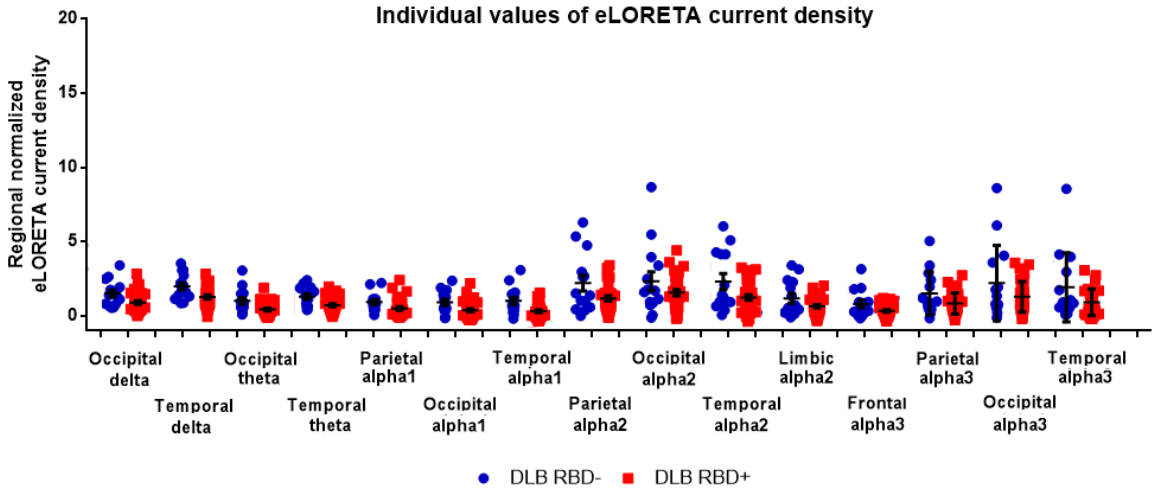

Figure 10. *Individual values of the regional normalized eLORETA solutions of the rsEEG rhythms showing statistically significant ($p < 0.05$) differences between DLB RBD- and DLB RBD+ groups (i.e., frontal alpha 3 and parietal alpha 1; occipital alpha 1 and limbic alpha 2; occipital and temporal delta, theta alpha 1, 2 and 3 and parietal alpha 1, 2, and 3). Noteworthy, the Grubbs' test showed no outliers from those individual values of the eLORETA solutions (arbitrary threshold of $p < 0.0001$).*

Correlation analysis

The above findings showed effects of the DLB on delta and alpha source activities at the group level. In the following, we reported the results of the analyses performed to test the effects of the DLB on delta and alpha source activities at the individual level.

The Spearman test ($p < 0.05$) evaluated the correlation between the MMSE score, as an index of global cognitive deficits, and rsEEG source activities (i.e., regional normalized eLORETA solutions) showing statistically significant differences between the DLB MMSE- and DLB MMSE+ groups. A statistically significant negative correlation was found between the MMSE score vs. parietal and temporal delta as well as occipital delta and theta eLORETA solutions in all DLB subjects ($r = -0.42$ to -0.26, $p < 0.05$; see Table 11). The higher delta source activities, the lower the MMSE score (the greater the global cognitive deficits). A statistically significant positive correlation was found between the MMSE score vs. parietal alpha 2 eLORETA solutions in all DLB patients ($r= 0.34$, $p < 0.005$). The higher alpha source activities, the higher the MMSE score.

Correlation between (eLORETA) source activity of the rsEEG rhythms and MMSE score	
	Spearman R and p
Parietal delta vs. MMSE	R = -0.42, p = 0.001

Occipital delta vs. MMSE	R = -0.40, p = 0.0005
Temporal delta vs. MMSE	R = -0.32, p = 0.005
Occipital theta vs. MMSE	R = -0.26, p = 0.05
Parietal alpha 2 vs. MMSE	R = 0.34, p = 0.01

***Table 11**. Results of the correlation analysis (Spearman test, p < 0.05) performed between the MMSE score and rsEEG cortical sources at delta, theta and alpha 2 bands in DLB MMSE- and DLB MMSE+ subjects considered as a whole group. In particular, these results include Spearman's correlation coefficient (R) and the associated level of significance (p). Legend: MMSE= Mini Mental State Evaluation.*

The point biserial correlation coefficient has been used to study the correlation between a continue variable (eLORETA sources) and dichotomous variable (yes/no for visual hallucination, cognitive fluctuations and REM sleep behavior disorders). The analysis showed a significant statistically negative correlation between occipital and temporal delta, theta, and alpha 1 eLORETA solutions and REM sleep behavior disorders in all DLB patients (r= -0.47 to -0.33, p < 0.05; see Table 12).

Correlation between (eLORETA) source activity of the rsEEG rhythms and RBD dichotomous score	
	Point biserial correlation coefficient R and p
Occipital delta vs. RBD	R = -0.37, p = 0.05
Temporal delta vs. RBD	R = -0.37, p = 0.05
Occipital theta vs. RBD	R = -0.33, p = 0.05
Temporal theta vs. RBD	R = -0.43, p = 0.005
Occipital alpha 1 vs. RBD	R = -0.39, p = 0.01
Temporal alpha 1 vs. RBD	R = -0.47, p = 0.005

***Table 12.** Results of the biserial correlation analysis (p < 0.05) performed between the RBD presence/absence (respectively 1/0) and rsEEG cortical sources at delta, theta and alpha 1 bands in DLB RBD- and DLB RBD+ subjects considered as a whole group. In particular, these results include Spearman's correlation coefficient (R) and the associated level of significance (p). Legend: RBD= REM sleep behavior disorders.*

Discussion

In the present retrospective rsEEG study, we hypothesize that the topography of cortical delta and alpha source activities may differ in sub-groups of demographically matched DLB patients as a function of characterizing disease symptoms such as cognitive deficits, REM sleep behavior disorders, fluctuations of cognitive deficits, and visual hallucinations. Here these

cortical sources are considered as an outcome of brainstem-cortical, forebrain-cortical, and thalamus-cortical oscillatory neural synchronization mechanisms regulating the brain arousal and vigilance in quiet wakefulness, as one of the neurophysiological bases of motor, cognitive, and visual perceptive functions in humans.

In the present study, an initial analysis of rsEEG rhythms contrasted delta and alpha source activities in the whole DLB group compared with the control Nold and AD subjects. In relation to the Nold group, the AD and DLB groups were characterized by greater delta source activities in widespread cortical regions and lower alpha source activities in posterior cortical lobes. The abnormalities in delta source activities were greater in the DLB than the AD group, while those in alpha source activities were prominent in the AD than the DLB group. Overall, these findings replicated previous rsEEG evidence observed in AD and DLB patients (Bonanni et al., 2008, 2015; Babiloni et al., 2017a,b).

According to the neurophysiological animal model by Cardiff group (Hughes & Crunelli, 2005 and Lörincz et al., 2008, 2009), the present abnormalities in cortical alpha source activities might reflect an alteration in the interplay of cholinergic projections from basal forebrain to the following oscillating neural networks involving glutamatergic high-threshold and relay-mode thalamocortical neurons, GABA interneurons, and cortical pyramidal neurons. From a translational point of view, a recent rsEEG study has reported abnormal alpha source activities in resting-state brain neural networks in DLB patients (Aoki et al., 2019). In that study, occipital alpha source activity was reduced in DLB patients over healthy controls in a visual neural network, this abnormality being correlated with deficits in attention, visuospatial skills, and cognition possibly reflecting cholinergic impairment (Aoki et al., 2019).

Concerning the present abnormalities in delta source activities observed in AD and DLB patients, it may be generated by an abnormal synchronization of neurons of thalamus and cerebral cortex, possibly related to an altered functional connectivity in parietal, temporal, and occipital regions (Steriade and Llinas, 1988; Pfurtscheller and Lopez da Silva, 1999).

As novel findings of the present study, the DLB patients with greater cognitive deficits over the DLB controls exhibited higher delta source activities in widespread posterior (i.e., occipital, temporal, parietal) cortical regions. In the same vein, delta source activities and MMSE scores of global cognition showed a negative correlation across all DLB patients (i.e., the higher the delta source activities, the strongest the cognitive deficits as revealed by low MMSE scores). Furthermore, the DLB patients with the fluctuation of cognitive deficits over the DLB controls

were characterized by higher posterior (i.e., occipital, temporal, limbic) alpha source activities. As another different source pattern, the DLB patients with visual hallucinations over the DLB controls displayed higher frontal-parietal delta source activities and an increase in temporal alpha source activities. It should be remarked that the above differences in delta and alpha source activities were unrelated to basic confounding variables in the various statistical contrasts (i.e., global motor and cognitive deficits, visual hallucinations, REM behavioral disorders, disease duration, and psychoactive therapies with dopaminergic, anti-psychotic and cholinergic).

Concerning the above abnormalities in delta source activities, the present results complement previous rsEEG findings derived from the comparison of scalp rsEEG markers between DLB patients and subjects belonging to Nold, DLB, PDD, and ADD groups (Walker et al., 2000a,b; Kai et al., 2005; Andersson et al., 2008; Bonanni et al., 2008; Babiloni et al., 2017a). Summarizing, those previous findings showed the following effects. Compared with Nold and ADD groups, DLB patients exhibited greater delta and theta rhythms (Andersson et al., 2008; Kai et al., 2005; Stylianou et al.,2018). The temporal fluctuation of these rhythms characterized DLB patients (Walker et al., 2000a,b; Andersson et al. 2008; Bonanni et al., 2008; Stylianou et al.,2018) and correlated with clinical scores of cognitive fluctuations (Stylianou et al.,2018). In those DLB patients, the main localization of the fluctuations of delta rhythms was occipital (Bonanni et al., 2016). Furthermore, the fluctuation of delta rhythms was detectable at the individual level in most of the DLB individuals (Bonanni et al., 2008) and was used as an input to classify them from ADD patients with an accuracy higher than 90%. (Stylianou et al.,2018). Finally, previous findings showed that DLB patients with hallucinations have greater widespread delta rhythms when compared to ADD patients with hallucinations (Dauwan et al., 2018). In this framework, the present results demonstrated for the first time that DLB patients with greater cognitive deficits, cognitive fluctuations, and visual hallucinations can be distinguished by different spatial patterns of delta source activities. Therefore, future studies may test the association of this different symptoms-related delta source topography with DLB neuropathological processes such as cortical α-synucleinopathy and intracellular Lewy bodies (Caviness et al., 2018) as well as total phosphorylated α-synuclein (Caviness et al., 2016), beyond the concept of "global delta rhythms" in quiet wakefulness.

Concerning the above abnormalities in alpha source activities, the present results apparently challenge previous rsEEG evidence derived from the comparison of rsEEG markers among Nold, DLB, PDD, and ADD groups (Babiloni et al., 2017a; Dauwan et al., 2018; Aoki et al., 2019). Such previous rsEEG evidence pointed to lower posterior alpha source activities in DLB

patients compared with Nold subjects (Babiloni et al., 2017a; Aoki et al., 2019). It also showed higher frontal-parietal functional connectivity at scalp alpha rhythms in DLB patients with hallucinations compared with ADD patients with similar hallucinations (Dauwan et al., 2018). At the present early stage of the research, we can just speculate about this challenge, namely the present result of greater posterior alpha source activities in DLB patients with visual hallucinations over the DLB controls. Our speculation is grounded on the following results of our recent rsEEG studies in PD patients with cognitive deficits. In one study, we reported that (1) an acute dose of levodopa induced a decrease in both widespread delta and alpha source activities in these PD patients and (2) alpha source activities were greater in the PD patients with major cognitive deficits over the PD controls (Babiloni et al., 2019a). In another study, we reported that the PD patients with visual hallucinations over the PD controls had greater alpha source activities, while those with greater motor deficits were characterized by lower posterior alpha source activities with no effects on delta source activities (Babiloni et al., 2019b). These previous results suggest that PD processes might affect the activity of parallel dopaminergic sub-systems exerting opposite effects on the thalamus-cortical generation of alpha rhythms in quiet wakefulness. On one hand, the PD-related decrease in nigrostriatal dopaminergic neurotransmissions might induce a marked reduction in posterior alpha source activities related to motor deficits, possibly reflecting a background tonic increase in resting state cortical arousal. On the other hand, the PD-related decrease in mesolimbic and mesocortical dopaminergic neurotransmissions might induce a slight increase in posterior alpha source activities related to cognitive deficits and visual hallucinations. This reduction might be related to a tonic decrease in the cortical arousal. Here we extend this speculation to the present DLB patients with cognitive fluctuations and visual hallucinations. These patients might suffer from prevalent alterations in mesolimbic and mesocortical dopaminergic neurotransmissions inducing a background tonic decrease in the cortical arousal during the resting state condition and relatively higher posterior alpha source activities estimated from rsEEG rhythms compared with the DLB controls. This effect might be hidden in the comparison of rsEEG markers between DLB patients and the control groups including Nold subjects or patients with ADD and PDD, thus emphasizing the importance of statistical comparisons of rsEEG markers not only between DLB and other groups of Nold, AD, and PD patients but also between matched DLB sub-groups with characteristic clinical features. Of course, the present alpha source abnormalities in DLB sub-groups might not be only due to dysfunctions in the dopaminergic systems and might be associated with alterations in ascending activating systems using other

neurotransmitters (e.g., noradrenergic, cholinergic, etc.). More research is needed before any final conclusions.

With the same methodological approach, here we contrasted delta and alpha source activities in matched DLB sub-groups without vs. with REM sleep behavior disorders (i.e., parasomnia with vivid, often frightening dreams related to motor behaviors during REM sleep). The DLB patients with REM sleep behavior disorders over the DLB controls were characterized by both lower delta and alpha source activities in posterior cortical regions. This effect was unrelated to the mentioned confounding variables (global cognitive and motor deficits, fluctuation of these deficits, visual hallucinations, etc.) and complements previous evidence indicating abnormal spectral EEG features (i.e. frequency slowing of rsEEG rhythms) and poor muscular atonia in DLB patients examined during REM sleep (Fantini et al., 2003; Massicotte-Marquez et al., 2005; Iranzo et a., 2010; Inoue et al., 2015).

Unfortunately, we have no conclusive explanation why the present DLB patients with REM sleep behavior disorders specifically manifest a parallel reduction in both delta and alpha source activities in quiet wakefulness. Indeed, this effect is apparently in disagreement with the increase in delta rhythms observed in previous rsEEG studies carried out in patients with DLB compared with Nold and ADD subjects (Walker et al., 2000a,b; Kai et al., 2005; Andersson et al., 2008; Bonanni et al., 2008; Babiloni et al., 2017a). Furthermore, it is partially in disagreement with previous rsEEG findings showing that MCI patients with REM sleep behavior disorders have a higher parietal, temporal and occipital theta rhythms, and lower occipital alpha rhythms, when compared to subjects with REM sleep behavior disorders but no cognitive deficits (Rodrigues Brazete et al., 2013). In a previous rsEEG study, subjects with REM sleep behavior disorders pointed to greater frontal, temporal, and occipital theta rhythms and lower alpha rhythms in relation to Nold subjects (Fantini et al., 2003; Iranzo et al., 2010).

As a tentative explanation of the present findings, we still refer to the mentioned results of our recent rsEEG studies showing that PD patients with major cognitive deficits over PD controls had greater delta and alpha source activities, while an acute dose of levodopa decreased both widespread delta and alpha source activities (Babiloni et al., 2019a,b). Keeping in mind the tentative explanation given in the previous section on cognitive deficits and visual hallucinations, we speculate that the present DLB patients with REM sleep behavior disorders might suffer from a major impairment in nigrostriatal dopaminergic neurotransmissions inducing a background tonic increase in the resting state cortical arousal, reflected by a

desynchronization in alpha rhythms. Such impairment might involve brainstem neural circuits using several neurotransmitters. See the basis of this speculation in the following paragraphs.

In Lewy body diseases (i.e., PDD, DLB), poor muscle atonia and dream enactment behavior during REM sleep might be partially due to poor noradrenergic projections that origin from locus coeruleus and do target amygdala, thalamus, and cerebral cortex (Jones et al., 1977; Cash et al., 1987; Zweig et al., 1993; Del Tredici and Braak, 2013). Those projections also target raphe (serotoninergic) and substantia nigra (dopaminergic) nuclei of ascending activating systems regulating the brain arousal and possibly rsEEG rhythms (Vermeiren and De Deyn, 2017). As a matter of fact, DLB patients are characterized by significant neural losses in the locus coeruleus due to α-synuclein pathology, although the relation with REM sleep behavior disorders is still under discussion (Dugger et al., 2012; Del Tredici and Braak, 2013). Furthermore, lesions in the cat locus coeruleus interfered with muscle atonia and ponto-geniculo-occipital waves in REM sleep stages (Jones et al., 1977).

In the same line of speculation, REM sleep behavior disorders might be also related to poor cholinergic projections from pedunculopontine tegmental nucleus (PPT) and Meynert nucleus of cholinergic basal forebrain. As a matter of fact, DLB patients with REM sleep behavior disorders suffer from significant neural loss in PPT due to α-synuclein pathology (Del Tredici and Braak, 2013). Furthermore, DLB patients treated with acetylcholinesterase inhibitors showed a mitigation of REM sleep behavior disorders (Massironi et al., 2003). Finally, recent optogenetic evidence in mice hints that both PPT and cholinergic basal forebrain are directly (and diversely) involved in the modulation of brain arousal to enhance information processing of salient stimuli and behavioral reactions (Azzopardi et al., 2018; Aitta-Aho et al., 2018).In this speculative line, ascending pedunculopontine cholinergic projections to midbrain dopaminergic nuclei (i.e., substantia nigra and ventral tegmental area) might modulate reward-seeking and behavior (Yeomans, 2012), while parallel descending cholinergic pedunculopontine projections to pons reticular formation might modulate thalamocortical activity at alpha rhythms regulating cortical arousal in visual systems and relative functions such as vigilance and visual (hypnagogic) imagery. The alteration of these functions in DLB patients might be one of the neural bases of visual hallucinations and abnormalities in dreams and REM sleep (Yeomans, 2012). Finally, Meynert nucleus of cholinergic basal forebrain may enhance sensory information processing in the cerebral cortex via the regulation of parieto-occipital alpha rhythms in wakefulness (Bentley et al., 2008; Janzen et al., 2012).

Methodological remarks

In the interpretation of the findings of the above three rsEEG studies in AD, PD, and DLB patients, the following methodological limitations should be considered.

The data were collected in different clinical units without a single experimental protocol. As a result, some interesting biomarkers, clinical measurements, and neuropsychological scores were not available in all subjects, e.g. APOE genotyping, DAT scan, and ADAS-Cog as a measurement of the global cognitive status. Indeed, the only measurement of the global cognitive status common to all subjects was the mini mental state evaluation (MMSE) score. That measurement is widely used for the assessment of the global cognitive functions in elderly subjects, with special attention to the area of memory. However, it may be not equally sensitive to global cognitive deficits in all neurodegenerative dementing disorders.

The subjects were not given identical instructions in all clinical units, and the experimenters did not receive the same qualification training to set the environmental conditions for the rsEEG recording. However, we think that these aspects were minor sources of variance as they are very standard in the practice of the expert clinical units of the E-DLB and PDWAIVE Consortia.

The rsEEG data were recorded from different hardware systems and various recording parameters (i.e. frequency sampling, antialiasing passband, and reference electrode) in the clinical units. To mitigate these potential sources of variability, we performed the following steps of a centralized and well-standardized procedure of data analysis: a common antialiasing bandpass filtering and down-sampling to 128 Hz; a re-referencing of all rsEEG data to the common average reference; and a normalization of the eLORETA rsEEG sources to remove the effects of the local amplifier gain and electrode resistance.

Finally, the lack of serial rsEEG recordings within a day and in different days prevented the evaluation of the fluctuation of the rsEEG source activity in relation to the motor, cognitive, and behavioral symptoms. These recordings are important especially in DLB patients who suffer from a fluctuation of cognitive functions.

Furthermore, there are specifically methodological limitations for each experimental study explained as following:

In the first study, the relatively small number of the patients in the ADD, PDD, and DLB groups (N = 34-42) did not permit their stratification based on the pharmacological regimens (e.g. cholinergic, dopaminergic, serotoninergic), the severity of dementia and motor symptoms, and the disease duration;

In the second study, our clinical and rsEEG database was not sufficiently extended to form groups of PD patients without cognitive deficits to compare those with vs. without visual hallucinations. For the same reason, we could not form groups of PD patients (1) with visual hallucinations to compare those with vs. without hallucinations in other modalities and (2) de-novo as dopaminergic therapies. Therefore, we do not know if the neurophysiopathological processes hypothesized in the PD patients with cognitive deficits but without visual hallucinations and those with both cognitive deficits and visual hallucination are partially different or overlap in the determination of the level of parieto-occipital alpha source activities in the quiet wakefulness. Furthermore, we do not know if the neurophysiopathological processes hypothesized in the PD patients with visual hallucinations are specific compared with PD patients with hallucinations in other modalities. Finally, we could just match the dopaminergic therapies in the PD groups to take into account the effect of the dopaminergic intervention. A systematic pharmacological manipulation of these therapies in PD patients would allow a final confirmation of the different effect of the dopamine on different dopaminergic ascending systems in the generation of alpha source activities in the quiet vigilance.

In the last study, the size of the matched DLB sub-groups was just sufficient for statistical comparison and should be extended in future cross-validation prospective investigations manipulating the relevant clinical features such as cognitive deficits, fluctuation of these deficits, visual hallucinations, and REM sleep disorders. In those future rsEEG investigations, the data collection will have to be performed with harmonized instrumental recording and clinical protocols (i.e., clinical scales, neuropsychological testing, etc.). Ideally, those rsEEG investigations might include neuroimaging markers of single photon emission computed tomography with Ioflupane I123 injection (Isaacson et al., 2017), measuring dopaminergic function in the substantia nigra, and 18-F-fluorodeoxyglucose positron emission tomography (Brajkovic et al., 2017) and markers of structural magnetic resonance imaging mapping the integrity of noradrenergic and cholinergic functions in the coeruleus, PPT, and basal forebrain.

Conclusions

The three retrospective and exploratory rsEEG studies of the present PhD thesis tested hypotheses and generated results that support some main conclusions. Specifically, the first study tested the hypothesis that the cortical sources of rsEEG rhythms in quiet vigilance may characterize peculiar neurophysiological mechanisms of brain arousal in ADD, PDD, and DLB patients at the group and individual levels. Compared to the reference Nold group, all patients' groups exhibited a slower IAF, especially the PDD and DLB ones. Furthermore, all patient groups showed lower posterior alpha 2 source activities, especially ADD and DLB patients. Finally, they exhibited higher occipital delta source activities (especially the PDD and DLB groups). As a possible sign of clinical relevance, these rsEEG markers correlated with the MMSE score (i.e. global cognitive status) and allowed good classification accuracies (about 0.85-0.90) between Nold and diseased individuals and between ADD and PDD patients. These results suggest that ADD, PDD, and DLB patients might be characterized by different spatial and frequency features of their rsEEG sources, possibly unveiling an Alzheimer and Parkinson neuropathological axis related to neurophysiological mechanisms underpinning quiet vigilance where the Alzheimers' neuropathology may mainly affect cholinergic sub-systems and posterior cortical alpha rhythms in AD patients, while the Parkinson's neuropathology may mainly affect dopaminergic sub-systems and diffuse cortical delta rhythms in PD patients. DLB patients may be placed about halfway in that axes.

The second and the third studies evaluated the hypothesis that the abnormalities in cortical rsEEG rhythms underpinng cortical arousal in the quiet vigilance that have been observed in the first study may be related to clinical symptoms of the PD and DLB diseases.

Results of the second study showed the following main effects: (1) the PD patients with the most pronounced motor deficits exhibited very low alpha source activities in widespread cortical regions; (2) the PD patients with the strongest cognitive deficits showed higher delta and alpha source activities in widespread cortical regions compared to the PD patients with mild cognitive deficits; and (3) in relation to the PD patients without visual hallucinations, those with visual hallucinations were characterized by higher parieto-occipital alpha sources activities. These results suggest that in PD patients set in the quiet vigilance, abnormalities in

cortical neural synchronization at delta and alpha frequencies are differently related to cognitive and motor deficits as well as visual hallucinations. Interestingly, parallel PD neuropathological processes might have opposite effects on cortical neural synchronization mechanisms underpinning cortical alpha rhythms, quiet vigilance, and motor and cognitive systems. In contrast, cortical delta rhythms may abnormally increase as a function of PD neuropathological processes affecting cerebral vigilance and cognitive systems.

Results of the third study showed the following main effects: (1) the DLB sub-group with the greatest REM sleep behavior disorders showed lower delta and alpha source activities in widespread posterior cortical regions; (2) those with the greatest cognitive deficits mainly showed higher delta source activities posteriorly; (3) those with visual hallucinations pointed to greater parieto-frontal delta and parietal alpha source activities; and (4) those with cognitive fluctuations over controls manifested higher parietal alpha source activities. These results suggest that cortical neural synchronization mechanisms generating peculiar topographical abnormalities in delta and alpha source activities during quiet vigilance are related to relevant DLB patients' clinical features at the group level.

On the whole, the three studies unveiled specific abnormalities in rsEEG rhythms at delta and alpha frequencies in AD, PD, and DLB patients set in quiet vigilance. Interestingly DLB patients with visual hallucinations showed different abnormalities in cortical delta and alpha rhythms when compared to abnormalities revealed in PD patients with visual hallucinations (second study), thus unveiling different neural substrate and possibly different clinical features of this significant symptom maybe in relation to alterations in quiet vigilance. In the same line, DLB and PD patients with greatest cognitive deficits showed different abnormalities in cortical delta and alpha rhythms. Noteworthy, these effects may represent the neurophysiological correlates of abnormalities in ARASs, cortical arousal, and cholinergic and dopaminergic systems probed by EEG techniques in AD, PD, and DLB patients with indications that the cholinergic systems may mainly affect posterior cortical alpha rhythms of rsEEG activity in AD patients, while dopaminergic systems may mainly impinge on diffuse cortical delta rhythms in DLB and PD patients. These effects were strictly related to clinical manifestations of the mentioned diseases maybe in relation to alteration in quiet vigilance.

Future studies may cross-validate those results in prospective, harmonized, and longitudinal rsEEG studies in AD, PD, and DLB patients followed from prodromal to dementia stages of

the diseases. Specifically, the aims of such studies should cross-validate the present results and support the following main predictions. First, cortical sources of rsEEG rhythms might reflect different abnormalities of the core neurophysiological mechanisms underlying brain arousal in quiet vigilance in ADD, PDD, and DLB patients. Second, the mentioned rsEEG markers might reflect a neurophysiological continuum for patients with AD and Lewy body diseases at the dementia stage. Third, they may be clinically useful in the disease staging, monitoring over time, and drug discovery. Diagnosis of dementia being equal, a patient with abnormal rsEEG markers might reflect abnormalities in the brain arousal in quiet wakefulness and be a candidate to a quick progression of the disease and a critical clinical management. Furthermore, future studies should test those promising rsEEG markers for a Precision Medicine approach in AD, PD, and DLB patients in relation to different clinical manifestations in vigilance (sleep-wake cycle), cognitive, motor, and psychiatric domains.

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