Journal of Genomic Medicine and Pharmacogenomics
JGMP, 1(2): 210-224
www.scitcentral.com

ISSN: 2474-4670

Original Research: Open Access

Age and Genotype-Related Changes in Brain Bioactivity Networks: Potential Influence on Drug Monitoring and Neurodegeneration

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Received June 2, 2016; Accepted June 10, 2016; Published November 29, 2016

ABSTRACT

During life, the brain undergoes several structural and functional changes. The nature of such changes is of paramount importance to define the conditions of normality and to distinguish physiological changes from those resulting from neuropathological processes. The purpose of this study was to elucidate the major functional changes associated with age and with specific genotypes. We found that age produces non-linear regional changes in brain activity and disruptions between cortical networks affecting the *alpha2* band in particular. Increased *alpha1* oscillations in parietal lobe and decreased *alpha2* oscillations in occipital lobe, together with functional disruptions in parieto-frontal connections likely represent neurophysiological markers of normal aging. On the other hand, we found that the *APOE*-4 allele has an influence on brain activity even in non-demented healthy subjects. The *CYP* gene family may also affect brain function, and SNPs of the *AGT* gene associated with arterial hypertension and cerebrovascular pathology influence brain activity in patients with vascular dementia.

INTRODUCTION

The human brain is a dynamic system that shows both structural and functional changes from the fetus to the elderly. During this process, different brain regions and systems mature and degenerate along different timelines, finally resulting in the aging brain. The aging brain is characterized by (i) thinning of the cortex, (ii) loss of neural circuits and brain plasticity, (iii) alterations in gene expression and (iv) deficit in synthesis and transport of neurotransmitters [1-3]. All these signs associated with physiological aging are strongly influenced by the presence of risk variants in key genes associated with body homeostasis (e.g. *APOE*, *AGT*), drug metabolism (phase I (*CYPs*) and phase II reactions (*UGTs*, *NATs*)) and drug transporters (*ABCs*, *SLCs*). Similarly, chronic treatment with drugs affecting the central nervous system (CNS) and consumption of drugs of abuse and toxic substances induce dramatic changes in the brain. In addition, epigenetics affects life span and longevity. Epigenetic alterations are present in different tissues throughout the aging process and in neurodegenerative disorders, such as Alzheimer's disease (AD). AD-related genes exhibit epigenetic changes, indicating that epigenetics might exert a pathogenic role in dementia [4]. The different forms of dementia pose several challenges to our society and the scientific community: (i) they represent an epidemiological problem, and a socioeconomic, psychological and family burden; (ii) most of them have an obscure/complex pathogenesis; (iii) their diagnosis is not easy and lacks specific biomarkers; and (iv) their treatment is difficult and inefficient [5].

Neuroimaging studies have provided substantial evidence about structural changes but the functional alterations associated with age or genotype remain largely unclear. The quantitative analysis of electroencephalography (EEG) is a low-cost approach to study brain function, allowing the visualization of neural activity with a high time resolution. Previous EEG studies have revealed a slowing of EEG pattern in normal elderly subjects [6,7].

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Citation: Tellado I, Torrellas C, C Caarril J C, Fraile C, Cacabelos R. (2016) Age and Genotype-Related Changes in Brain Bioactivity Networks: Potential Influence on Drug Monitoring and Neurodegeneration. J Genomic Med Pharmacogenomics, 1(2): 210-224.

EEG is useful not only to discriminate patients from healthy subjects, but also for the prediction of treatment outcome in various brain diseases, yielding information about tailored therapy approaches for an individual [8]. AD patients treated with citicoline show more *alpha* (occipital electrodes) and *theta* (left side electrodes), accompanied by less *delta* activity in the left temporal lobe. Furthermore, significant differences with respect to placebo have been observed for *theta* activity in several fronto-parieto-temporal electrodes in the left hemisphere [9]. Cerebrolysin induces reductions in *delta* and *theta* activities in post acute moderate-severe traumatic brain injury (TBI) patients, showing good correlation with improvement of attention and working memory [10]. A decrease of *theta* activity over all cortical regions, increase of *beta* activity, and some restoration of the occipital *alpha* rhythm have been seen in Rett syndrome patients treated with cerebrolysin [11]; however, analysis of brain activity merely according to anatomically separated responses is insufficient to understand the complexity of functional changes in the brain. Functional connectivity is commonly assessed during performance of a cognitive task. Particular attention has been given to the inherent functional organization of brain networks in resting state. The brain resting state is an energetically costly condition characterized by a rich neural activity and long-range interneuron connections in specific brain circuits (e.g. DMN, default mode network). It has been suggested that resting-state networks may reflect an intrinsic property of brain functional organization that serves to stabilize brain ensembles, consolidate the past, and prepare us for the future [12, 13].

To visualize resting-state synchronization across frequency bands in large-scale functional networks, two lagged functional connectivity measures (lagged coherence and lagged phase synchrony), implemented in the eLORETA statistical package, have been proposed. These connectivity indices are resistant to non-physiological artifacts, in particular low spatial resolution and volume conduction [14].

AGE-RELATED CHANGES IN BRAIN ACTIVITY

Although age is the main source of physiological changes, little is known about the functional organization of neural networks and its connection with aging, neurodegenerative disorders and cerebro-vascular pathology. With the aim of identifying the main age-related functional changes, we investigated the brain activity of healthy subjects between 19 and 91 years of age. One hundred eighty-one healthy subjects that visited EuroEspes Biomedical Research Center for a clinical check-up were divided into three groups according to their age: 28 young (A group; age range: 19-35 years, mean: 28.45 ± 5.03), 92 middle-aged (B group; age range: 36-59 years, mean: 48.5 ± 6.81), and 61 older (C group; age range: 60-91 years, mean: 67.50 ± 6.82). No participants had any cognitive disturbance or history of neurological or psychiatric disorders. They were not taking any medication that might affect CNS at the time of the study, and underwent brain MRI screening to exclude any organic lesions.

EEG recordings were obtained in relaxed wakefulness with eyes closed by using 19 scalp electrodes located according to the international 10-20 system. The EEG activity was acquired using a linked ears reference, sampled at 500 Hz, and filtered offline between 1 and 30 Hz. Analysis was circumscribed to the resting, awake, eyes-closed state. For each subject, 20 non-overlapping, 2s artifact-free segments were randomly selected. In particular, we carefully avoided epochs containing ocular movements, muscle or cardiac contamination, drowsiness signs (i.e. emergence of slow wave activity with suppression of *alpha* rhythm), and even small baseline shifts so that reliable estimates of brain function in the awake resting-state could be obtained. Further analyses were performed using the eLORETA software. Functional images of spectral density were computed for six frequency bands: *delta* (1.5-4 Hz), *theta* (4-8 Hz), *alpha1* (8-10 Hz), *alpha2* (10-13 Hz), *beta1* (13-21 Hz) and *beta2* (21-30 Hz).

We performed a regression analysis including all participants. In addition, we searched for significant differences in source localization and functional connectivity between the three age groups.

Regression analysis revealed a significant age-related decrease in the *alpha* activity (8-13 Hz) in posterior regions (**Figure 1(a)).** Dividing *alpha* activity in *alpha1* (8-10 Hz) and *alpha2* (10-13 Hz) oscillations, we found a significant increase in *alpha1* oscillations in parietal regions (best match in Brodmann area 7), and a significant decrease in *alpha2* oscillations in occipital cortex (best match in Brodmann area 18) according to age (**Figure 1(b)).**

The middle-aged subjects (B group) exhibited significantly fewer *theta*, *alpha1* and *alpha2* oscillations, and more *beta2* activity than the young subjects (A group), with the limbic lobe (posterior cingulate) showing the highest significance for *theta*, *alpha1* and *beta2* activities, and the cuneus for *alpha2* band (**Figure 2).**

The connectivity pattern was characterized by reduced *alpha2* lagged linear connectivity (LLC) between occipital and temporal cortex (O2-T8) in the right hemisphere, and reduced *alpha2* lagged non-linear connectivity (LNL) between bilateral occipital and right temporal cortex (O1-T8 and O2-T8) in middle-aged subjects. In addition, there was increased LNC in the *beta2* band, involving right centro-frontal connections (C4-F8) (**Figure 3).**

The older subjects (C group) exhibited significantly more *alpha1* and *alpha2* oscillations and fewer *beta2* oscillations than the middle-aged subjects (B group), with the right

parietal lobe showing the highest significance for *alpha1* and *alpha2* activities, and the limbic lobe for *beta2* oscillations **(Figure 4).** We found no significant difference in functional connectivity. However, a decrease in *beta1* connectivity in centro-parietal regions (Cz-P7) nearly reached statistical significance (p<0.07, corrected).

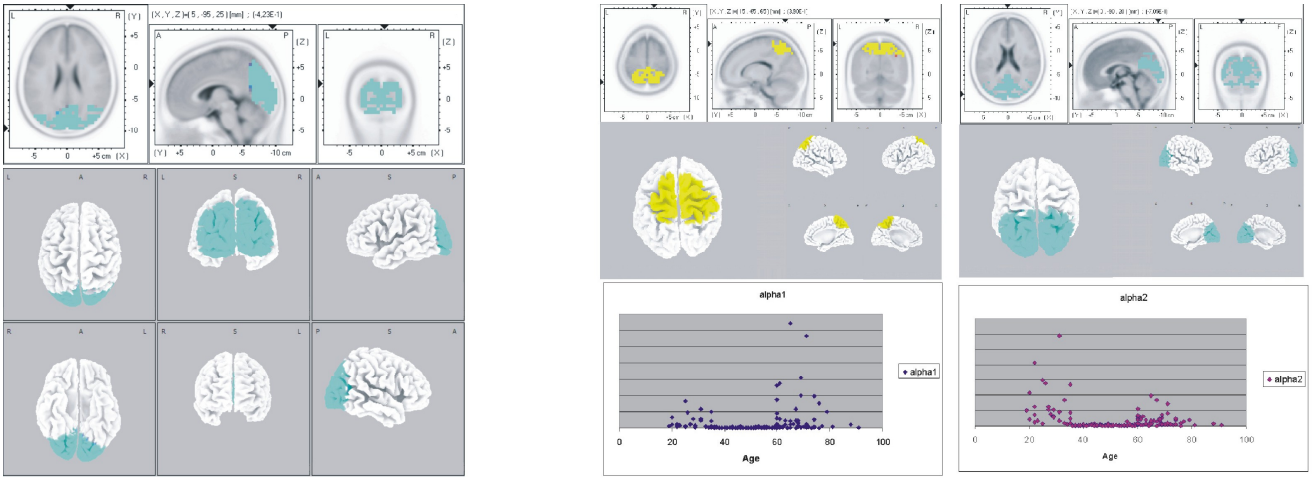


Figure 1. (a) eLORETA regression maps of *alpha* activity. Colored areas represent the spatial extent of age-related decrease in *alpha* activity (p<0.05, corrected. r=0.232). **(b) eLORETA regression maps of *alpha1* and *alpha2* oscillations.** Colored areas represent the spatial extent of age-related increase (p<0.05, corrected. r=0.233) and decrease (p<0.01, corrected. r=0.271) in *alpha1* and *alpha2* oscillations, respectively.

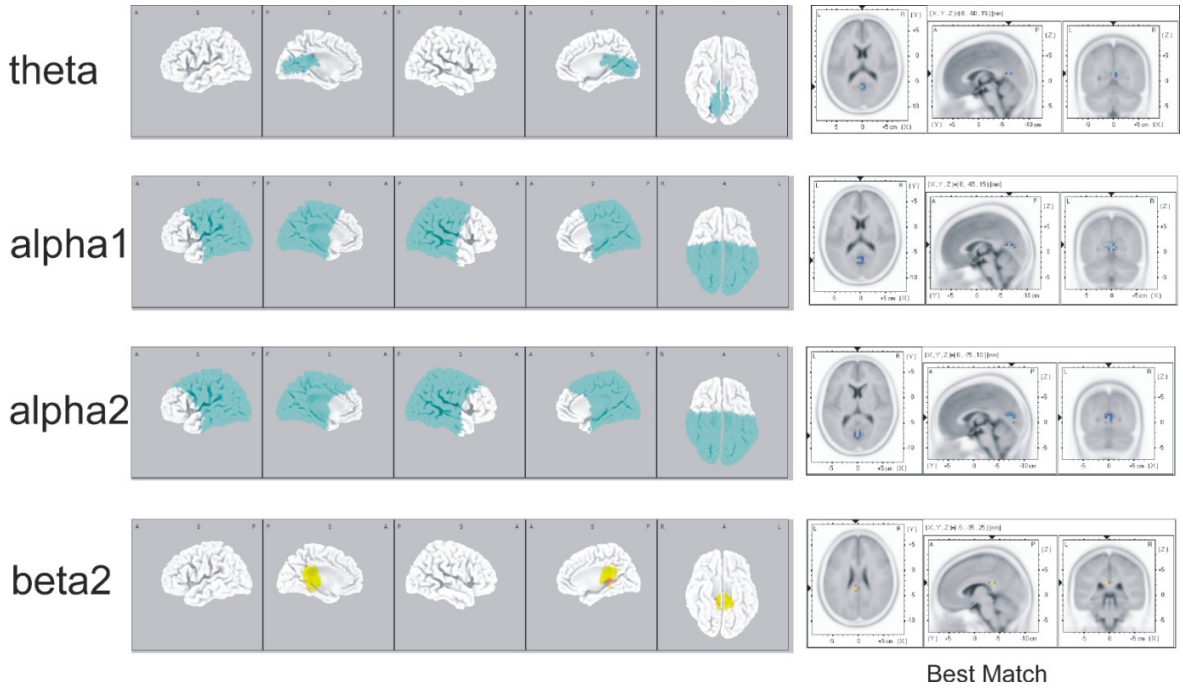


Figure 2. eLORETA statistical maps of *theta*, *alpha1*, *alpha2* and *beta2* oscillations in middle-aged vs. young subjects. Colored areas represent the spatial extent of voxels with significant difference in source current density (p<0.05, corrected). The MRI slices are located at the MNI-space coordinates of the voxel with highest significance. The best match for each frequency band is represented at the right side of the picture. The color scale represents logF-ratio values (threshold: log F= -1.364, p<0.05, for *theta*, *alpha1* and *alpha2* oscillations; threshold: log F= 1.165, p<0.05, for *beta2* oscillations). L, left; R, right; A, anterior; P, posterior.

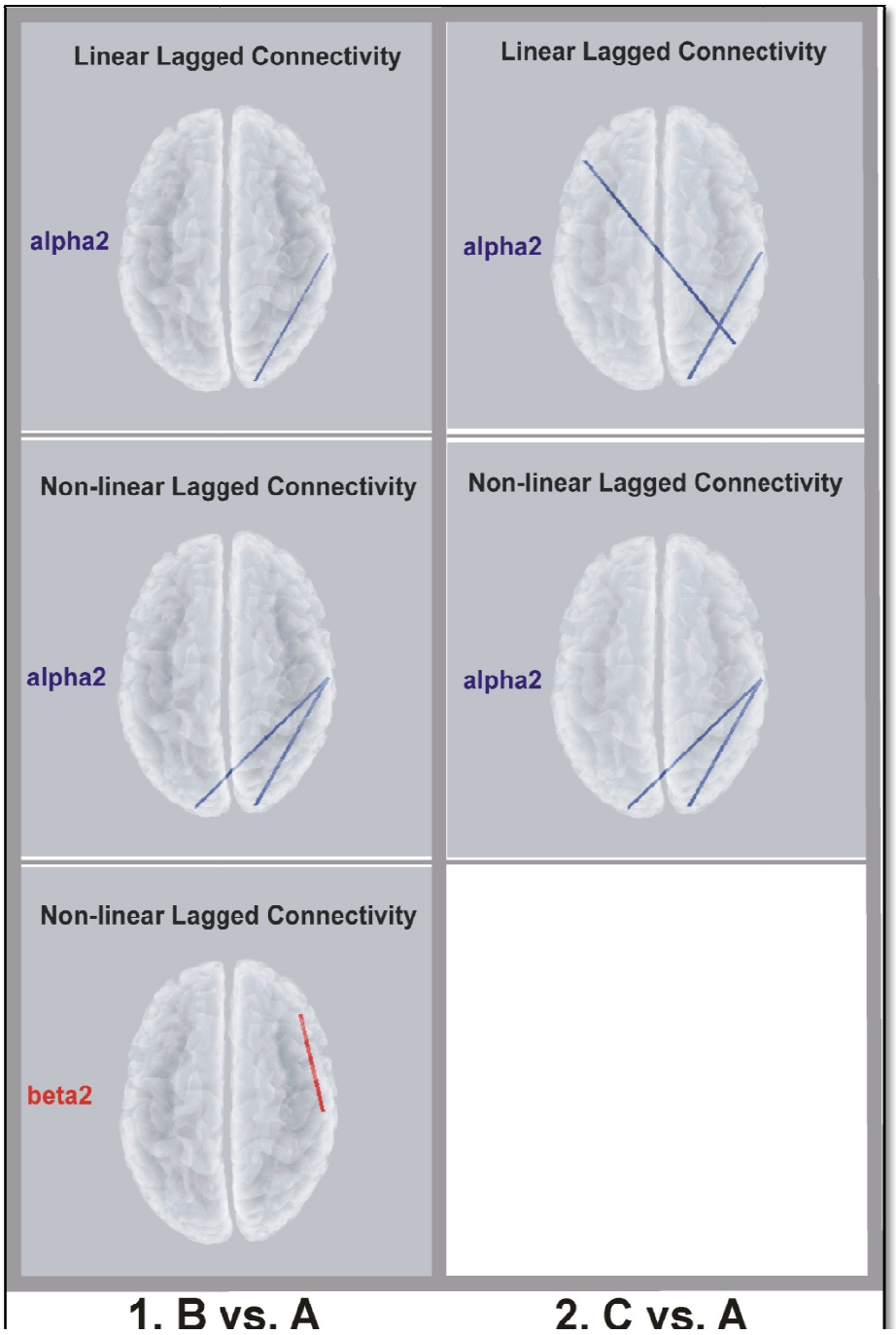


Figure 3. eLORETA wire diagram illustrating cortical areas with significantly decreased (blue wires) and increased (red wires) *alpha2* and *beta2* functional connectivity, respectively, in 1.middle-aged vs. young subjects (decreased *alpha2* linear lagged connectivity, threshold: t=-3.848, p<0.01, corrected; Decreased *alpha2* non-linear lagged connectivity, threshold: t=-4.065, p<0.01, corrected; Increased beta2 non-linear lagged connectivity, threshold: 4.773, p<0.05, corrected), and 2.older vs. young subjects (decreased *alpha2* linear lagged connectivity, threshold: t=-3.950, p<0.01, corrected; Decreased *alpha2* non-linear lagged connectivity, threshold: t=-4.047, p<0.01, corrected). Results are displayed on a transparent fiducial cortical surface. The points to which the lines are connected represent the center os the ROIs.

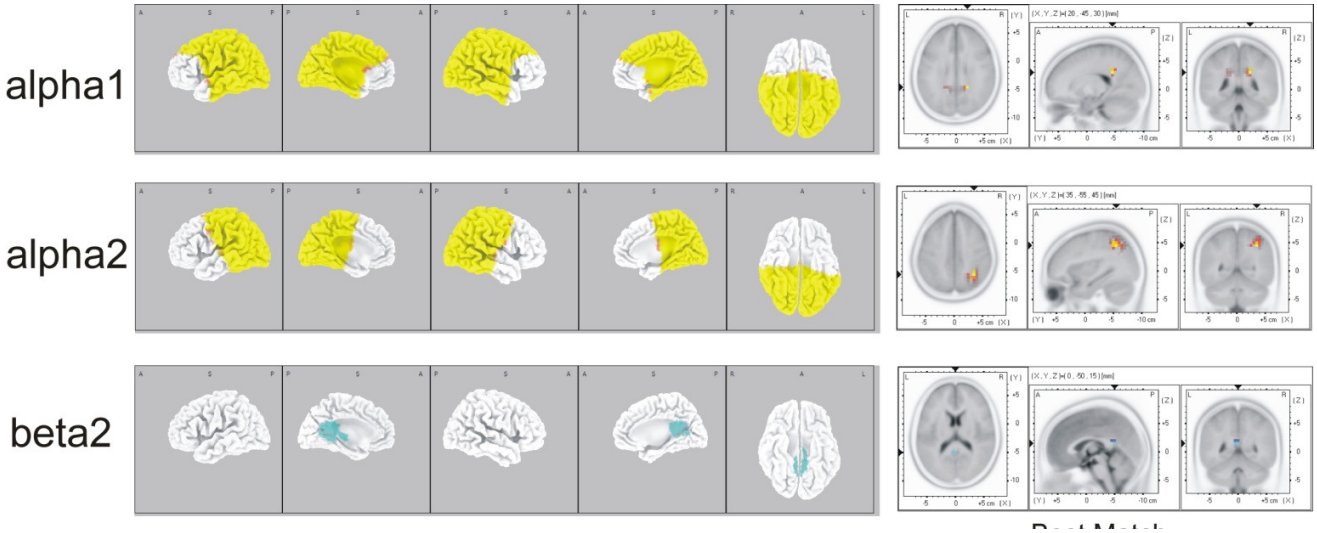


Figure 4. eLORETA statistical maps of *alpha1*, *alpha2* and *beta2* oscillations in older vs. middle-aged subjects. Colored areas represent the spatial extent of voxels with significant difference in source current density (p<0.01, corrected). The MRI slices are located at the MNI-space coordinates of the voxel with highest significance. The best match for each frequency band is represented at the right side of the picture. The color scale represents logF-ratio values (threshold: log F= 1.524, p<0.01, for *alpha1* and *alpha2* oscillations; threshold: log F= -1.428, p<0.01, for *beta2* oscillations). L, left; R, right; A, anterior; P, posterior.

The older subjects (C group) exhibited a significant reduction in *alpha2* oscillations in the occipital cortex compared with the young subjects (A group) (**Figure 5).** In comparison with young subjects, older subjects exhibited reduced *alpha2* LLC in occipito-temporal (O2-T8) and interhemispheric parieto-frontal circuits (P4-F7). In addition, reductions in *alpha2* LNC were seen between bilateral occipital and right temporal cortex (O1-T8 and O2-T8). (**Figure 3).**

Alpha activity (8-13 Hz) suffers a significant age-related decrease in posterior regions, notably in the occipital lobe (**Figure 1).** Decreased magnitude of posterior *alpha* source has been seen by other authors [6,7] and it may be associated with early changes in the functioning of the cholinergic basal forebrain system. Since the main *alpha* generators under resting conditions are the thalamus together with the cuneus and precuneus [15], our data may reveal an age-related alteration of functional integrity of thalamo-cortical circuits. Decreased resting *alpha* rhythms had been induced by experimental impairment of cholinergic pathways stemming from the basal forebrain [16] and patients that suffer an evident impairment of cholinergic basal forebrain, such as cases with AD, exhibit low posterior *alpha* power in EEG studies [17-21]. Following the methodology used by other authors, we divided the *alpha* activity into its *alpha1* (8-10 Hz) and *alpha2* (10-13 Hz) components. Interestingly, unlike Babiloni who saw less magnitude in both *alpha1* and *alpha2* sources [17], we found a significant age-related increase in *alpha1* oscillations in parietal regions, especially in the left Brodmann area (BA) 7 (**Figure 1).** Given that the *alpha* oscillations are inverse related to brain activity [22] and greater *alpha* power is indicative of less cortical activity in broad underlying regions [23], our data suggest that age induces a significant decrease in cortical activity affecting particular areas of the parietal lobe. Of note, these areas are part of the default mode network (DMN), a brain circuit typically active during rest, whose correlation with EEG *alpha* activity is well known [24,25]. Therefore, older subjects show an altered DMN due to a decreased parietal activity. Since the integrity of parietal cortex is fundamental to maintain good cognitive performance and sense-spatial perception, parietal impairment may be implicated in the decline of brain function traditionally associated with old age. Several studies have demonstrated the relationship between cognitive decline in both normal and demented elderly with impairment of the parietal lobe and/or the DMN [26-29]. However, since *alpha1* activity responds selectively to attentional demands [30], an increase at rest may be necessary to maintain an adequate level of attention and alertness in healthy non-demented subjects and it may be a cosubstantial sign of healthy aging. Interestingly, the loss of parietal *alpha1* activity has been related to pathological processes in AD [18]. The slowing and shift to anterior regions of alpha activity associated with age (less *alpha2* in occipital lobe and more *alpha1* in parietal lobe) are consistent with those of classical EEG studies that found slowing of the *alpha* peak during physiological aging [30,31].

Brain activity in young vs. middle-aged subjects

We found several significant differences in both cortical oscillations and functional connectivity. Compared with the young, middle-aged subjects showed: (i) significant reduction in *theta* oscillations and increase in *beta2* oscillations in the limbic lobe; and (ii) significant decrease of *alpha1* and *alpha2* oscillations in frontal, temporal, parietal, limbic and occipital lobes (**Figure 2**). In addition, we found both a significant increase in the *beta2* connectivity in right centro-frontal connections and a decrease in the *alpha2* connectivity between right temporal cortex and occipital lobe **(Figure 3**). These findings suggest that middle-aged subjects have an energetically more costly resting state characterized by higher activity in frontal, temporal, parietal, occipital (*alpha* desynchronization), and limbic lobes (more *beta2* together with less *theta* and *alpha* oscillations). On the other hand, both age groups may differ in their attention and cognition processes, as suggested by changes in cortical activity and the functional connectivity of long-range networks. In humans, previous studies have reported significant correlations between EEG data and simultaneously recorded BOLD signal fluctuations within specific resting networks. In particular, at rest, regions of the DMN associated with internal processing (e.g. PCC) increase their *beta* oscillations, and the resting state dorsal attention network, involved in attention and related cognitive processes, shows a decrease in its *alpha* oscillations [32]. Both functional signatures are present in middle-aged compared to young subjects. The observed changes in brain activity may originally be caused by the imbalance induced by an early loss of Temporo-Occipital (T-O) connectivity. In the middle-aged subjects, the decreased *alpha2* connectivity involves changes in the functional organization of long-range cortical networks presumably affecting sensorial processing, with disconnections between primary visual areas and right associative visual cortex. The loss of cortical connectivity in these subjects probably causes an increased level of cortical activity, namely decreases in *alpha1* and *alpha2*. In fact, since the *alpha* oscillations play a general inhibitory role on cognitive and sensory processing [33,34], the decrease in *alpha* oscillations at rest may involve a lower stimulus detection threshold (sensory processing) and/or stronger cognitive processing at rest (e.g. abortive orienting reactions or loadings of working memory loops that occur spontaneously during conscious rest). Furthermore, good perception performance is related to low alpha power at rest [35]. This may be interpreted in terms of cortical inhibition and excitation previous to task performance [33]. According to this interpretation, perception performance is enhanced if the cortex is already activated, whereas memory performance is enhanced if the cortex is deactivated at rest before a task is performed (several studies have shown that high resting alpha power is positively associated with task performance [36,37,38]). This interpretation is plausible if, for sensorial discrimination, a high level of cortical excitation is helpful to analyze a sensorial input. For memory performance (and other cognitive processes) initial activation of the cortex may be detrimental because it may interfere with the high selectivity that is required to access a memory trace [33]. In a scenario of high sensory input, a requirement of additional activity in areas of the limbic lobe may be necessary to avoid non-relevant stimuli. The high limbic system activity observed in the middle-aged subjects might be a compensatory mechanism that may help to maintain an adequate level of internal processes related to episodic memory, conceptual processing, stimulus-independent thought and self-reflection. The increased *beta2* connectivity found between anterior and central areas belongs to the frontal lobe and may be a functional signature in a network underlying the DMN. The high activity of the DMN likely helps to maintain internal cognitive processes at an acceptable level in the middle-aged subjects.

Brain activity in middle-aged vs. elderly subjects

We found more *alpha1* and *alpha2* oscillations in frontal, temporal, parietal and occipital areas, and fewer *beta2* oscillations in the limbic lobe in elderly subjects. No statistically significant changes in functional connectivity were observed. The increase of resting *alpha* oscillations suggests that, at rest, the elderly subjects have less neural activity and more cortical inhibition than the middle-aged subjects. The main regions affected by the relative decrease of neural activity were located at the parietal lobe, namely precuneus and right inferior parietal lobe. Similar increases in parietal *alpha* oscillations in normal elderly have previously been reported in the literature [39]. Both precuneus and inferior parietal lobe are regions involved in attention, memory and visuospatial processing/interpretation. The relative cortical deactivation at rest may be necessary to maintain an acceptable memory performance in normal non-demented elderly subjects. This interpretation is probable if for cognitive processes the initial deactivation of the cortex is helpful because it prevents interferences in the highly selective access to memory trace [33]. Particularly, the increase in parietal *alpha* oscillations likely have a main role in the conservation of an adequate cognitive outcome. Recent research has found significant decreases in *alpha* oscillations at parietal lobe in AD [18] linking the loss of parietal alpha activity with cognitive decline. However, the relative cortical deactivation that enables the maintenance of the cognitive state may induce an impairment in perception performance in the elderly since the perception performance is in fact enhanced if the cortex is activated before stimulus [33]. Together with the functional changes seen at neocortex, we found less activity of the limbic lobe in the elderly. The hypoactivity of the limbic system may be a cause of alterations in awareness, memory and behavior that are characteristic of the elderly. In these individuals the episodic memory is especially affected. Although the participants had no cognitive decline, in our study we found that PCC (which plays a principal role in episodic memory) is the region that shows the most

significant loss of activity. The PCC forms a central node in the DMN; thus, together with the results of the *alpha* activity, our study suggests that DMN is less prominent in the elderly than in the middle-aged subjects. The impairment of the DMN (namely, loss of limbic lobe function and increased cortical inhibition affecting the parietal lobe) may be seen as a biomarker of physiological aging. Alterations in the DMN in elderly have been seen previously by other authors. Resting-state fMRI showed that older subjects may recruit additional resources in frontal and temporal cortex to compensate for these reductions in DMN [40]. We found no data in neural activity that supports the involvement of additional cortical areas for the DMN. We found, in fact, less neural activity in frontal and temporal lobe. These opposed results may be due to the fact that fMRI studies reflect age-related changes in neurovascular coupling not directly associated with neural activity.

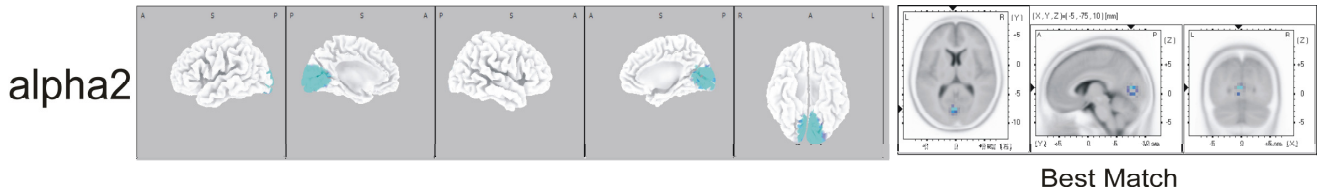


Figure 5. eLORETA statistical maps of *alpha2* oscillations in older vs. young subjects. Colored areas represent the spatial extent of voxels with significant difference in source current density ($p<0.05$, corrected). The MRI slices are located at the MNI-space coordinates of the voxel with highest significance. The best match for *alpha2* band is represented at the right side of the picture. The color scale represents logF-ratio values (threshold: log F= -1.284, $p<0.05$). L, left; R, right; A, anterior; P, posterior.

Brain activity in young vs. elderly subjects

Compared to young subjects, elderly individuals showed a significant decrease in *alpha2* oscillations in occipital lobe, mainly at the cuneus (**Figure 5**). Similar decreases had been seen by other authors in recent studies involving a slowing of occipital activity in the elderly [6,7]. The impaired function of the occipital lobe may be related to a reduction in grey matter volume and disruptions of thalamo-cortical circuits. Supporting this, previous studies have reported significant reductions in grey matter volume in the occipital lobe in older subjects [27]. The relation between decreased brain activity and decreased grey matter volume is well established in the literature [41]. Recent research shows an age-dependent decrease in thalamocortical synaptic transmission in healthy elderly subjects. Some authors found an impaired phase synchronization between thalamus and cuneus associated with *alpha2* oscillations and increased age [15]. Furthermore, the decrease in occipital *alpha2* EEG sources might be associated with changes in the functioning of the cholinergic basal forebrain system, which is supposed to induce a sustained increase in excitatory activity in the cholinergic brainstem pathway, desynchronizing the resting alpha rhythms at the cortical level and producing a mild enhancement of cortical excitability [6].

In addition to the source localization results, our connectivity analyses revealed significant decreases in LLC and LNC as measures of functional connectivity, affecting the *alpha2* frequency band (**Figure 3).** Decreased *alpha2* connectivity may indicate a disruption in neural communication affecting occipito-temporal and fronto-parietal circuits that occur in an intra- (O2-T8) and inter- (O1-T8 and P4-F7) hemispherical manner. Interestingly, these disconnections affect several regions that belong to the DMN. Recent research using fMRI showed an equivalent decrease in magnitude of the DMN in the elderly and its association with decline in the domains of attention/concentration/processing speed, memory function and executive functioning [27]. Our study shows that impaired DMN function is mainly caused by an interhemispheric disconnection between left prefrontal and right parietal cortex. Due to the principal role of the DMN in functional organization of the brain, it is presumable that the stabilization of brain ensembles, consolidation of the past and preparation for the future is impaired in some degree in older people. The amount of task-unrelated thoughts in this group is probably affected too, since the generation of spontaneous thoughts is related to DMN magnitude [42,43]. The reduced efficiency of brain networks observed, namely disruptions of long-range cortical circuits, may be associated with physiological aging through attenuated dopamine transmission [44] together with grey and white matter deficits in frontal and temporal regions [45,46].

In conclusion, age induces non-linear regional variations in cortical activity and disruptions in functional connectivity between specific brain areas. The functional changes affect regions belonging to several resting-state networks, including the DMN, and likely involve age-related differences in attentional and cognitive processes. At middle-age, the main finding is a loss of functional connectivity in occipito-temporal networks accompanied by an increase in occipito-temporal and parietal cortical activity, together with an increased magnitude of the DMN. In the elderly, in contrast, the frontal, temporal, parietal and occipital cortical activity decreases. The decreased cortical activity at rest, especially the increase in *alpha1* and *alpha2* activities at the parietal lobe, likely allows the conservation

of a good cognitive income, as indicated by recent research linking decreased parietal alpha with cognitive impairment.

GENOTYPE-RELATED CHANGES IN BRAIN ACTIVITY

Genomic factors potentially related to changes in brain bioactivity include at least five categories of gene clusters: (1) genes associated with disease pathogenesis (e.g. *AGT* in vascular dementia); (2) genes associated with the mechanism of action of drugs; (3) genes associated with drug metabolism (phase I and II reactions); (4) genes associated with drug transporters; and (5) pleiotropic genes involved in multifaceted cascades and metabolic reactions (e.g. *APOE*) [5].

***APOE* gene**. The *APOE*-4 allele is associated with genetic predisposition to suffering AD and with both AD-related abnormalities in cortical rhythms and disintegration of functional connectivity pattern in AD patients. Specific patterns of functional network disruption affecting *theta* and *alpha* band associated with the level of cognitive disturbance or with the *APOE* genotype have been found in AD [18]. Namely, AD patients had less parieto-occipital *alpha* activity than controls, and those carrying the *APOE*-4 allele exhibited reduced *alpha* oscillations in left parietal and temporo-occipital regions in comparison with noncarriers. The reduction in *alpha* power found in patients with AD most likely represents disease- and genotype-related resting-state regional dysfunction. There was a decreased *alpha2* connectivity pattern in AD, involving the left temporal and bilateral parietal cortex. Several regions exhibited increased lagged phase synchronization in the *theta* band across and within hemispheres, where temporal lobe connections were particularly compromised. In patients with early AD, there was an *APOE*-4 allele-related decrease in interhemispheric *alpha* connectivity in frontal and parietal regions.

Despite an increasing body of literature on *APOE*-brain network relationship in AD, little is known about the influence of *APOE* genotype on resting-state functional connectivity in cognitively healthy individuals. There are controversial data concerning the impact of the *APOE* genotype on cognitive functioning and brain activity in older healthy subjects. Some PET and fMRI studies have shown that *APOE*-4 carriers have reduced activity in the PCC, parieto-temporal and frontal cortex [47,48]. Other authors found altered connectivity between regions implicated in the DMN and subcortical regions and recent studies have shown increased connectivity between the DMN and hippocampus [49], and better cognitive performance in healthy *APOE*-4 carriers [50]. To investigate the potential *APOE*-4 allele influence on brain activity in healthy elderly, we compared 12 *APOE*-4 carriers and 28 non-carriers with no signs of cognitive deficit. The averaged eLORETA solutions show that the bioelectrical neural activity was higher in *APOE*-4 carriers compared to non-carriers in all frequency bands (**Figure 6).** Higher current density maxima were found particularly in *delta* (*APOE*-4 carriers: 3.74, *APOE*-4 non-carriers: 2.98), *theta* (*APOE*-4 carriers: 2.3, *APOE*-4 non-carriers: 1.09), *alpha1* (*APOE*-4 carriers: 7.21, *APOE*-4 non-carriers: 1.69) as well as in the *alpha2* band (*APOE*-4 carriers: 4.01, *APOE*-4 non-carriers: 1.38). There was a similar cortical distribution of maximal activity across groups; *alpha1* and *alpha2* activity were maximal in occipital regions. *Delta* and *theta* bands were predominant in the prefrontal cortex; however the *theta* band had maximum values in occipital cortex in *APOE*-4 carriers. Statistical analysis revealed significant differences between groups exclusively in the *alpha1* band. *APOE*-4 carriers exhibited significantly increased current density in the *alpha1* band in the right temporal cortex (**Figure 7).** *APOE*-4 carriers had significantly increased functional connectivity in the *alpha1* band compared to non-carriers. This increased connectivity was found in the left hemisphere between the posterior parietal and temporal cortex **(Figure 8).** Both findings, namely more *alpha1* in right temporal and more connectivity in the *alpha1* band between left parieto-temporal regions in healthy elderly *APOE*-4 carriers, implies singular differences in brain function associated with the *APOE*-4 allele. More *alpha1* oscillations may indicate less activity in right temporal cortex (more *alpha* is indicative of less cortical activity). The temporal lobe is a key region in AD pathogenesis. Our data may be interpreted as a sign of cortical disturbance in these subjects even in an asymptomatic stage. Interestingly, since decreased connectivity in *alpha* range between parieto-temporal regions is a trait observed in AD, our increased *alpha1* connectivity in the left hemisphere may be a potential compensatory mechanism that preserves a good cognitive status in these individuals with genetic vulnerability. The increased connectivity observed may be a primary stage of increased connectivity in temporal regions, as observed by Canuet et al in AD patients. Our findings may indicate that: (i) cortical dysfunction affects the right temporal lobe, and (ii) some compensatory mechanism may involve parieto-temporal resources in the left hemisphere.

***AGT* gene**. The *AGT* gene belongs to the renin-angiotensin system that regulates blood pressure and plays a principal role in the control of vascular function. *AGT* is a key factor in the occurrence and progression of vascular dementia (VD). VD is nowadays the second cause of dementia in the world, after AD. In a recent work, our team investigated the influence of two SNPs in the *AGT* gene (235T and 174M) associated with arterial hypertension and cerebrovascular pathology, on brain activity in VD patients [51]. We observed that VD patients with genomic risk (carriers of allelic variants associated with vascular pathology) had more connectivity in *delta* band between frontal, fronto-temporal and fronto-parietal regions. Our findings show that in VD high blood pressure disturbs the functional connectivity at the frontal level. The slow hyperconnectivity observed may

be a direct reflection of neural damage caused by high blood pressure in susceptible individuals.

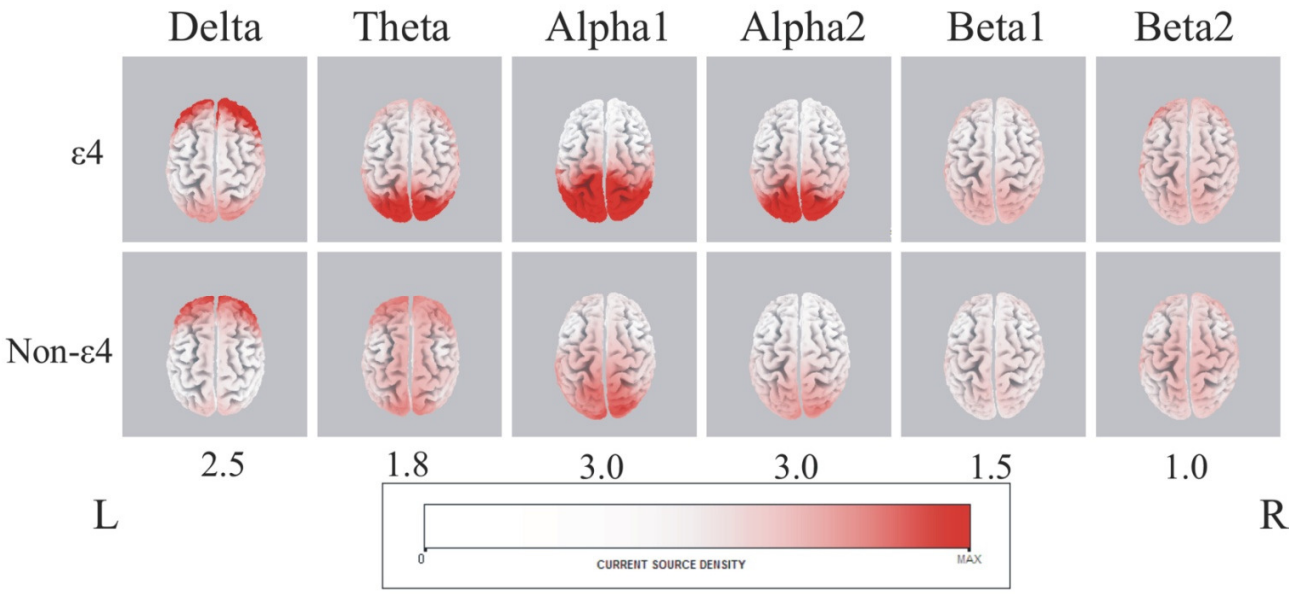


Figure 6. Averaged eLORETA solutions (current density at cortical voxels) of EEG sources for each frequency band. The maximum current density values for each frequency are given below the corresponding column. *ε4*, *ApoE epsilon4* carriers; Non- *ε4*, *ApoE epsilon4* non-carriers; L, left; R, right.

CYPs:

Pharmacogenomic factors may account for 60-90% of drug variability in drug disposition and pharmacodynamics. Approximately 60-80% of CNS drugs are metabolized via enzymes of the CYP gene superfamily. About 57.76% of patients with AD are extensive metabolizers (EMs) for CYP2D6 enzymes, 31.06% are intermediate metabolizers (IMs), 5.28% are poor metabolizers (PMs), and 5.90% are ultrarapid metabolizers (UMs); 73.71% are CYP2C19-EMs, 25.12% IMs, and 1.16% PMs; 60.87% are CYP2C9-EMs, 34.16% IMs, and 4.97% PMs; 82.75% are CYP3A4/5-EMs, 15.88% IMs, and 1.37% UMs. A trigenic cluster integrating CYP2D6+CYP2C19+CYP2C9 polymorphic variants yields 82 different haplotype-like profiles, representing 36 different pharmacogenetic phenotypes in which only 26.51% of patients show a pure 3EM phenotype[52]. These data clearly indicate that the incorporation of pharmacogenomic protocols to dementia research and clinical trials can foster therapeutic optimization by helping to develop cost-effective pharmaceuticals and improve drug efficacy and safety.

CYP2D6: The *CYP2D6* gene is a genetically polymorphic gene involved in the metabolism of several psychoactive drugs. Recent studies show that CYP2D6 may be involved in the production and biotransformation of neurotransmitters, such as dopamine and serotonin, whose influence on brain function and behavior is well established in the literature [53,54]. In individuals that have gene variants that lead to a complete lack of functional enzyme (*CYP2D6* poor metabolizers) both hepatic and brain levels of CYP2D6 are reduced. Increased anxiety and impulsivity have been associated with being a *CYP2D6* poor metabolizer [55]. Compared with *CYP2D6* extensive metabolizers, poor metabolizers show a significant increase in the activity of the thalamus and hippocampus, two regions with high expression of CYP2D6 protein and *mRNA* [56].

CYP2D6 poor metabolizers are at a higher risk for developing Parkinson's disease (PD) [57], and this risk is further increased when these individuals are exposed to pesticides [58]. This suggests that *CYP2D6* poor metabolizers may be unable to inactivate environmental toxins that increase the risk for developing PD. CYP2D6 is expressed within PD-affected brain regions (for example within the pigmented neurons of the substantia nigra) and is thus ideally situated to participate in the local inactivation of PD-causing neurotoxins. In contrast, inhibition of CYP2D6 in human neuroblastoma cells increased the neurotoxic effects of neurotoxins [59].

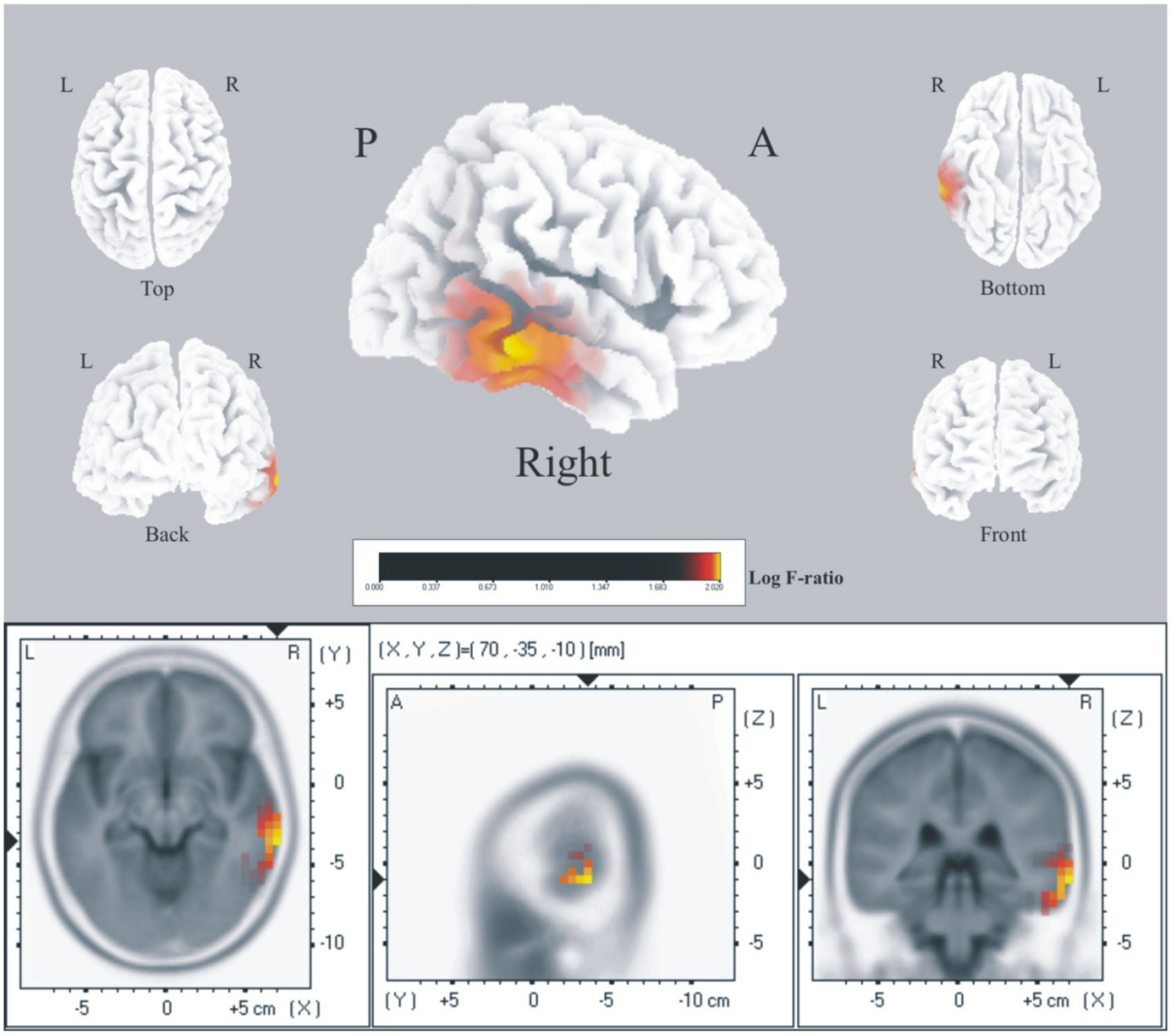


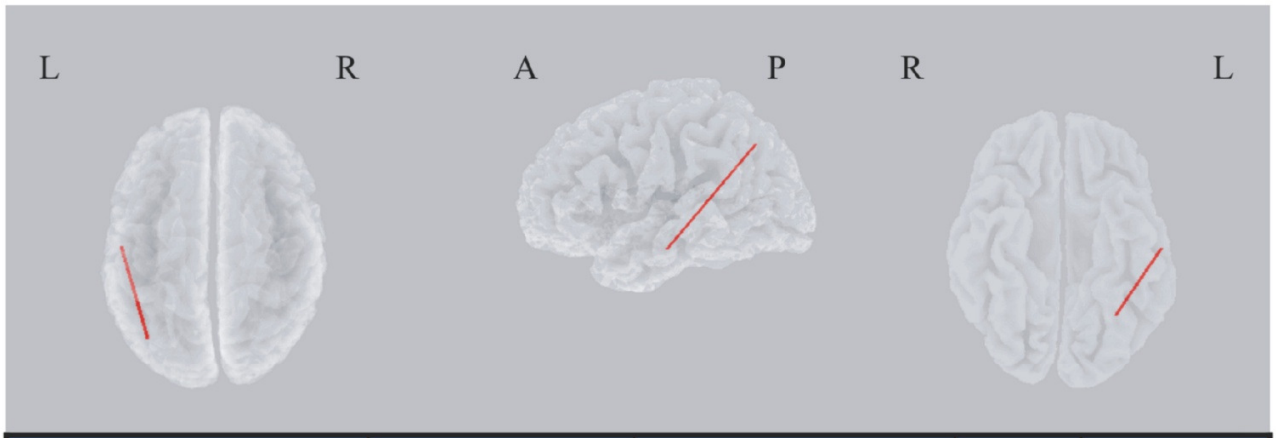
Figure 7. eLORETA statistical maps of *alpha1* oscillations. Colored areas represent the spatial extent of voxels with significant difference (red-coded for p<0.05; yellow-coded for tmax=2.02; p=0.018, corrected for multiple testing) in source current density in *ApoE epsilon4* carriers vs. *ApoE epsilon4* non-carriers. Significant results are projected onto a fiducial cortical surface (top panel) and a brain MRI template (bottom panel). The MRI slices are located at the MNI-space coordinates indicated in the figure that correspond to the voxel of highest significance. The color scale represents log F-ratio values (threshold: log-F=1.878, p<0.05). L, left; R, right; A, anterior; P, posterior.

CYP2C19: Genetic variation in *CYP2C19*, involved in the metabolism of serotonin and oxidation of sexual hormones, such as testosterone and progesterone, has also been associated with heritable personality traits such as reward dependence, cooperativeness and self-transcendence in females [60].

CYP2C9: It has recently been found that *CYP2C9* gene polymorphism is associated with phenytoin toxicity in infants with epilepsy [61] and with reductions in cerebellar volume in epileptic users of phenytoin [62].

CYP3A4: The induction of *CYP3A4* in the brain has been associated with cognitive and behavioral dysfunction. Potent inducers of *CYP3A4* in the brain, such as anti-epileptic drugs (e.g. oxcarbazepine, carbamazepine and phenytoin) increase the metabolism of testosterone and estradiol, which are involved in mood, behavior, sexuality, memory and cognition [63]. The endocrine dysfunction associated with

the induction of *CYP3A4* illustrates how brain *CYPs* can potentially modulate the local concentrations of endogenous molecules and affect brain function and behavior. Another example is the *CYP1A1*- and *CYP1A2*-mediated metabolism of arachidonic acid in the brain, which produces epoxyeicosatrienoic acid (ETTs) and hydroxyeicosatetraenoic acids (HETEs) known to participate in critical biological processes, such as calcium signaling, vesicle release and the vasodilation of cerebral arteries [64].



Interconneted Regions	*ApoE e4* carriers n=12	*ApoE e4* Non-carriers n=28	t	p (corrected)
Left Hemisphere: Parietal & Temporal (P3 & T7 electrodes)	0.420±0.152	0.224±0.117	4.089	0.05

Figure 8. eLORETA wire diagram illustrating significantly increased functional connectivity (lagged linear connectivity) in the *alpha1* frequency band in left parieto-temporal circuits in *ApoE epsilon4* carriers vs. *ApoE epsilon4* non-carriers (tmax=4.089; p<0.05, corrected). The significant connectivity wire is shown inside a transparent cortical surface with axial views from the top (left) and bottom (right), as well as left sagittal view (middle). The red color of the wire indicates relative increase in linear connectivity. Increased *alpha1* linear connectivity was observed between signals of the parietal region (P3 electrode) and the temporal region (T7 electrode) in the left hemisphere. The table at the bottom shows the linear connectivity values of the significant connection between groups.

Drug-induced brain toxicity is a typical finding in carriers of *CYP3A4* mutant variants associated with poor drug metabolism. Particularly, neurotoxicity has been found in therapies with anti-epileptic or anti-tumoral agents [65,66]. EEG is useful to detect early cortical dysfunctions associated with neurotoxicity, such as, abnormal beta activity, aberrant connectivity patterns, paroxysmal patterns and epilepto form discharges. EEG is a powerful tool to investigate the action and safety of drugs on CNS. However, a review of the literature reveals inconsistent operating procedures from one study to another. While this fact does not invalidate results per se, the lack of standardization constitutes a regrettable shortcoming, especially in the context of drug development programs [67]. The incorporation of pharmacogenetic programs to drug development and clinical drug assessment (efficacy and safety) may help to optimize therapeutics as well as the utility of brain mapping as a biomarker. It has been clearly demonstrated that in patients with dementia *APOE-4* carriers are poor responders to conventional treatments [68], and a good correlation has been found with EEG parameters in these patients [69,70].

CONCLUSION

Age and genotype dramatically influence brain function. We found that age induces non-linear changes in cortical activity and functional disruptions in brain networks. Functional changes affect regions that belong to several resting-state networks, including the DMN, and likely involve age-related differences in attentional and cognitive processes. The *APOE* gene is a key gene for brain activity despite the predisposition to suffer AD. We found significant differences in brain function associated with the *APOE*-4

allele even in healthy subjects. We also found that VD patients with genomic risk (carriers of *AGT* variants associated with vascular pathology) show disturbances in functional connectivity at the frontal level. Finally, we propose that the *CYP* superfamily may also play a possible role in brain activity.

ACKNOWLEDGEMENTS

This work was supported by EuroEspes and the International Agency for Brain Research and Aging (IABRA). The authors would like to thank the nurses Margarita Alcaraz and Laura Nebril for their collaboration in blood sampling as well as Yolanda González and Lucía López for their help with MRI studies.

DISCLOSURE STATEMENT

There are no actual or potential conflicts of interest including any financial, personal or other relationship with other people or organizations that could inappropiately influence this work.

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