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Topological Biomarker of Alzheimer's Disease

Sanja Josef Golubic

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Abstract

For years, it has been assumed that the cerebral accumulation of pathologic protein forms is the main trigger of Alzheimer's disease (AD) pathology; however, recent studies revealed strong evidences that the alternations in synaptic activity precede and affect the homeostasis of amyloid-beta and tau, both of which aggregate during AD. Given that the neuropathological changes, characteristic for AD, start decades before the onset of the first symptoms, when alternations become irreversible, it is crucial to find a biomarker that can detect the preclinical signs of disease, presumably synaptic dysfunction of specific cerebral areas. Here is presented a novel, a high potential neuroimaging biomarker that can detect the postsynaptic dysfunction of specific neural substrate located in medial prefrontal cortex (mPFC) during sensory gating processing of a simple auditory stimulus. The magnetoencephalography-based localization of mPFC gating activation has the potential not only to detect symptomatic AD but also to become a predictor of cognitive decline related to the pathophysiological processes of AD, both at the individual level. The strengths of proposed biomarker lie in the simplicity of using a binary value, i.e., activated or not activated a neural generator along with its potential to follow the evolution of the pathophysiological process of disease from preclinical phase. The novel biomarker does not require estimation of uniform cutoff levels and standardization processes, the main problems of so far proposed biomarkers. Ability to individually detect AD pathology during putative preclinical and clinical stages, absolute noninvasiveness, and large effect size give this biomarker a high translation capacity and clinical potential.

Keywords: Alzheimer's disease, preclinical Alzheimer's disease, Alzheimer's disease biomarker, neuroimaging biomarker, auditory sensory gating, prefrontal cortex, magnetoencephalography

1. Introduction

Alzheimer's disease (AD), a long-lasting progressive neurodegeneration, characterized by synaptic dysfunction, an increase in extracellular amyloid plaques, intracellular tauopathy, extensive neuronal loss in several cerebral areas, and enhanced neuroinflammation. Highly disrupted cholinergic transmission is proving to be a featured biochemical sign of disease. Clinical manifestations include progressive loss of ability to encode new memories, impairment of both declarative and non-declarative memory, and finally the invincible decline of overall intellectual capacity. Today, worldwide spreading of Alzheimer's type dementia is one of the major public health challenges confronting this generation.

Extensive AD research, especially in the last 40 years, brought a significant progress in the development of diagnostic approaches and understanding the etiology. However, despite accumulated knowledge, the cause of the disease has not been found, a postmortem histopathological evaluation is still required to confirm the clinical diagnosis, and finally, effective treatment that would at least slow progression of the disease has not yet been found. As a result, if Augusta Deter, the first patient who had been described with the hallmarks of the disease, was alive today, her prognosis would be the same as in 1906.

1.1. Amyloid hypothesis

Since the first documentation by Alois Alzheimer, spread of abnormal protein filaments (plaque) throughout the brain, the main histopathological sign of Alzheimer's dementia, had a prominent role in a broad spectrum of proposed mechanisms related to disease pathogenesis. Amyloidogenic fragments were described structurally in extracellular plaques, and tau protein was documented as the main component of intracellular neurofibrillary tangles [1, 2].

According to amyloid hypothesis, the neurotoxic forms of amyloid-beta polypeptides, derived from amyloid precursor protein (APP), induce synaptic injuries followed by substantial intracellular damage in form of tauopathy and subsequently produce the pathological presentations of neurodegeneration leading to dementia [3]. There are reliable evidences, provided by the systematic work of Braak and Braak [4, 5], that the pathological progression of extracellular and intracellular deposits of pathological protein forms starts decades before the onset of clinical symptoms.

The genetic mutations identified on chromosome 21 are conferred to trigger AD through abnormal processing of APP, causing the elevated cerebral concentrations of amyloid-beta or increased production of its specific forms [6]. Also, three other different autosomal dominant mutations that might cause AD have been identified on chromosomes 14 and 1, leading to mutations of presenilin 1 and presenilin 2 proteins, respectively, along with late-onset apolipoprotein genotype ἐ4 [7–9].

The discoveries of mutations in amyloid-beta-related proteins have had significant influence in promoting the amyloid theory. However, while these mutations account for the majority of early-onset AD (<65 years; familial AD), the risk genes linked with late-onset AD (> 65 years; 95% of all AD cases) are subtle, with no direct genetic relation to the APP gene or

its enzymes [10]. In addition, recent neuroimaging results strongly indicate that some non-demented individuals can have amyloid-beta aggregates equivalent in concentration to those found in demented patients [11], and also symptoms of AD can emerge regardless of amyloid deposition [12].

The evidences, provided by the animal studies, that amyloid clearance produces decreased symptoms of disease in mouse models of AD [13, 14] had turned the drug development in the direction of targeting beta-amyloid in human brains. The deployment of drugs comprised active and passive immunization directly against amyloid-beta accumulation and inhibition of beta- and gamma-secretase APP cleaving enzyme. Regrettably, none of testing drugs have resulted in recovery of functional abilities or alleviating symptoms of the disease in humans. The treatments did not slow down the course of the disease; on the contrary, some drugs even accelerate the progression of the symptoms. The recently emerged evidences confirmed the low correlation of the cerebral distribution of beta-amyloid plaques with neuropathology, decrease of neural function, or cognitive deficits [3]. A possibility that insoluble plaque is not the primary cause of progressive AD pathology is a strong argument for failure of anti-amyloid vaccination trials to improve patient outcome, even when cerebral amyloid plaque was removed [15]. Consequently, failure of amyloid-based AD treatments shifts research hypothesis to the soluble amyloid beta oligomers rather than plaques to be the main cause of neuronal degeneration [16]. However, there is still not reliable evidence in human studies that soluble amyloid oligomers are toxic in vivo. Notably, the cause of pathological cascade, resulting in redundant amyloid forms production and ejection, is still poorly understood along with the issue concerning the role of different amyloid beta forms in AD pathogenesis [17].

1.2. Synaptic function failure hypothesis

Synapse loss generates a loss of dendritic mass [18] and promotes neuron loss [19], a hallmark of AD pathology. It is interesting that amyloid plaque can show up without synapse loss [20]; moreover, synapse loss can occur without associated amyloid deposition [21]. High quantitative correlations of postmortem cytopathology to premortem cognitive impairments suggest that the decrease in density of synapses and decrease in the number of synapses per neuron are more linked to AD symptoms than are the concentration of amyloid plaques, the number of intracellular tau-tangles, or cortical gliosis [22]. These results appoint synapses as the key feature of AD, strongly indicating that the disease pathogenesis could be the outcome of synaptic failure [23].

It has been shown that the early AD symptoms significantly correlate with a specific dysfunction of cholinergic synapses [24]. Interestingly, acetylcholine receptor agonists affect several of AD hallmarks, including cholinergic deficits, cognitive dysfunction, but also tau and amyloid-beta pathological burdens [25]. The electrophysiological measurements of basal synaptic transmission and long-term potentiation in transgenic mouse with mutations analog of human mutations causing AD suggest that change in synaptic function precedes amyloid plaque production. Increased synaptic activity increases amyloid secretion, while decreasing activity inhibits it [26, 27]. In turn, beta-amyloid burden inhibits synapses and alerts synaptic plasticity [28], implying the existence of a feedback loop between synaptic dynamics and associated amyloid production that might serve as a mechanism to prevent synaptic

hyperactivation and excitotoxicity [26]. In addition, recent studies demonstrate an important physiological role of cortical amyloid secretion, showing that low concentrations of beta-amyloid peptides increase long-term potentiation, needed for successful memory formation [29, 30]. There are also evidences that synaptic dysfunction occurs before changes in synaptic morphology or the number of synapses per neuron [31, 32]. These breakthroughs in the field provide strong evidences that amyloid homeostasis is controlled by the synaptic functions and emphasize prominent amyloid involvement in healthy memory coding.

Cerebral dysfunction found in non-demented elderly individuals with amyloid plaques before any memory disturbances [33] points at impairment in neural function as a very early pathophysiological sign of AD. Interestingly, functional changes may be driven in both directions, increased [34, 35] or decreased [36, 37] neuronal excitability, usually depending on the disease stage and a specific brain area and its function. The increased synaptic activity, found in early stages of symptomatic AD, might be an adaptive response driving neuroprotection [38]. On the other hand, the decreased neural network excitability could be induced by activation of gamma-aminobutyric acid (GABA) receptors, which decrease glutamate excitatory transmission, implying that in vivo glutamate-mediated neuronal excitability is controlled by interactions between inhibitory systems [39]. The co-transmission of acetylcholine and GABA, first found within the cholinergic system only, recently was demonstrated as a common feature of nearly all cholinergic forebrain neurons [40, 41]. These results appoint GABA as a fast neurotransmitter utilized throughout the forebrain cholinergic system and emphasized acetylcholine-GABA co-release as a major modulation factor of cortical functions transmitted by cholinergic neurons. Moreover, there is evidence that GABA receptor agonists defend neurons in culture from the toxicity of beta amyloids and of different glutamate receptor agonists [42]. In conclusion, given their major role in both sensory processing and cognition, and high susceptibility to AD pathology, the ability of the cholinergic neurons to co-release GABA could explain the failure of specific synaptic inhibitory processes found in AD that may trigger the cascade of events resulting in characteristic neuropathology.

1.3. Dynamic model of AD pathogenesis

The presence of cerebral amyloid aggregation in cognitively normal individuals, the lack of systematic correlation between amyloid plaque deposition and cognition, insufficiently explained influence of soluble amyloid oligomeric *in vivo*, the bias of preclinical disease models toward the amyloid hypothesis, and finally failures of clinical trials with anti-amyloid drugs are the strong arguments for urgent need to revise present model of AD to include alternative possibilities that could account for all the research results associated to AD.

Failures of clinical trials of anti-amyloid drugs in symptomatic AD patients (mild cognitive impairment (MCI) and moderate Alzheimer's disease patients) in addition to reliable evidence that the hallmarks of disease could be found in the brain decades before symptom onset set up a view that the onset of clinical symptoms is a sign of irreversible neural damage. Consequently, the concept of AD pathogenesis is evolving toward a view of the disease as a long-term continuum, which differs only by symptom appearance; that is, a non-symptomatic (preclinical) AD phase and an irreversible symptomatic AD phase [43, 44]. This dynamic concept of the disease emphasizes the neurobiological advantage of early intervention before of

widespread neurodegeneration, during the preclinical stage of disease, when neural injuries may still be reversible. Consequently, it is crucial to detect very early, possibly reversible, pathological changes related to AD in cognitively intact individuals, before the occurrence of the first symptoms, i.e., to reveal the reliable preclinical biomarker of the disease.

1.4. Conclusion

A wealth of evidence suggests that the amyloid hypothesis of AD etiology is insufficient to explain all pathological changes associated with AD and their temporal evolution. Considering the wide spectra of data in AD research, it cannot be overlooked their common link: synaptic dysfunction and degradation as a very early characteristic of the disease. Unlike neuron death, changes in synaptic functions are very likely still reversible. These subtle neurofunctional alternations are likely detectable by functional neuroimaging techniques. The neuroimaging has the capability to provide an assessment of the altered neurophysiology, before anatomical abnormalities and divergent neuropathology of the later disease stages. Focusing the synaptic level, at the phase when the neuron cell potentially is still healthy, provides an excellent opportunity to intervene at a reversible stage of the disease when neural networks are vulnerable, but not lost. With regard to focal neural activation during the early phases of processing external inputs, studying the early sensory responses enable unique insight into the synchronized synaptic activity of functionally related neural substrates, which are on the larger scale recognized as sensory networks. The first manifestations of declining synaptic function could involve desynchronization of synaptic transmission, which may cause the "virtual" absence of activation when it is measured extracranially. These alterations in topology of sensory networks could be even associated with specific patterns of attention, memory, or behavioral disorder that could indicate the preclinical stage of disease.

2. Biomarkers of AD

A biomarker in medicine is conceptualized as a measurable detector of a physiological, anatomic, or biochemical alternation that can distinct normal biologic processes from pathological. Biomarker should be able to provide reliable diagnosis, follow the development of disease, and measure responses to a therapeutic intervention. The development of a new biomarker for any clinical condition is based on the ability to accurately detect specific pathophysiology against the gold or reference standard. This creates problem specifically to AD because there is no in vivo gold standard. Currently, the final diagnosis of AD requires both the presence of amnestic symptoms and postmortem histopathological confirmation. Premortem diagnosis of AD is only "probable" or "possible" based on symptoms characteristic of Alzheimer's type of dementia and neuroimaging findings.

The growing body of evidences evolves AD research field toward the concept of disease pathogenesis as a continuum of long-term phases in which clinical symptomatology and underlying pathophysiological process have different temporal development rates [45]. The existing findings indicate that the onset of the first symptoms marked the already irreversible stage of the disease [44]. Therefore, only detection of preclinical phase, before the occurrence of the first

symptoms, but with present neuropathological changes characteristic of AD, would provide a major opportunity for therapeutic intervention in possible still reversible stage of disease. The main problem of AD research lies in the fact that is not yet found a solid link between the specific biomarker occurrence in presymptomatic individuals and the subsequent appearance of clinical symptoms [44, 45]. Although major advances in brain imaging, neurochemistry, and genetic research that highly accelerated the field, there still remains a need for the establishment of accurate biomarkers of preclinical AD, which will differentiate subjects without the risk of progression to dementia from those at risk for developing symptomatic AD. Today, five state-of-the-art diagnostic measures of AD are proposed for diagnostic criteria [46, 47]. Three of these are neuroimaging measures, and the other two are the laboratory indicators related to cerebrospinal fluid (CSF) proteins. Laboratory measures of AD include a reduced level of amyloid-beta 42 or an increase in p-tau concentration in the CSF. Imaging measures include tracers that allow detection of fibrillary amyloid-beta deposits in the cortex by positron emission tomography (PET) and detectors, also known as injury or topographical biomarkers, of a medial temporal lobe atrophy and reduced glucose metabolism in temporoparietal regions, as determined by magnetic resonance imaging (MRI) and fluorodeoxyglucose (FDG) PET, respectively. However, proposed biomarkers have limited efficiency in detecting preclinical changes associated with the disease [45–50] and are invasive for subjects because there are risks associated with lumbar puncture (CSF), exposure to radiation (PET/CT), or claustrophobic time-consuming scanning (MRI). Moreover, the classification results of proposed biomarkers are based on the difference between group means of measured variables that generally cannot provide a clear boundary between normal and pathological responses. The underlying reason for the limited discriminatory accuracy of proposed biomarkers lies in the high individual heterogeneity and variability of neural responses, cerebral anatomy, and metabolism [51], especially in the elderly population. Consequently, there is an urgent need for additional, noninvasive, more accurate tool that can be used to differentiate presymptomatic and symptomatic AD from normal aging.

2.1. Topological biomarker of AD

Besides high sensitivity and specificity, ideal AD biomarker should be individual, robust, and must be able to follow the evolution of the pathophysiological process of AD from early preclinical changes to symptomatic aggravation of the disease. A promising, but so far underutilized line of biomarker research is the alternation of basic neural network topography as a consequence of AD pathology [52]. An efficient way to start topographic search for AD biomarker is studying the most fundamental, still focal neural mechanisms that occur very early in the processing stream of simple sensory inputs. Dominantly cholinergic modulation of a sensory gating processing [53, 54] indicates that sensory gating network would likely be alerted in AD pathophysiology because the leading neurochemical feature of AD is a deterioration of the cholinergic signal transmission by selective impact on the plasticity of nicotinic (nAChr) and muscarinic (mAChr) synaptic receptors [55]. On a large scale, this synaptic dysfunction is likely to cause subtle alterations in sensory gating processing years before meeting criteria for symptomatic AD [56, 57].

2.2. Sensory gating

Sensory gating is a fundamental process of sensory processing, arising within the first 50 ms of exposure to a stimulus, much earlier than conscious perception. It is a phenomenon

by which the neural system rapidly adjusts its response to subsequent stimuli, a neural feature with an essential impact in everyday life [58, 60]. This fast inhibition or enhancement of the neural response provoked by the external stimuli refers to different gating mechanisms: by gating-out neural system selectively suppresses its responses to irrelevant or redundant stimuli and by gating-in reinforcing responses on task-relevant or novel stimuli [59, 60]. Gating-out has been proposed as a mechanism of habituating to redundant stimuli that protect working memory overload by preventing irrelevant information from recurrent sensory processing, while at the same time, gating-in processing enables recognition of relevant environment inputs that are essential for survival [59–61].

2.2.1. Clinical correlates of sensory gating

Sensory gating deficits have been associated with several clinical conditions. Patients with schizophrenia [62–64], Alzheimer's disease [60, 64, 65], bipolar disorder [66], post-traumatic stress disorder [67], Parkinson's disease [68], or Huntington's disease [69] show alerted sensory gating dynamics compared to controls. Abnormality in extracranially measured auditory gating responses is recognized as one of the best established marks for schizophrenia [70, 71]. In addition, alerted sensory gating has been associated with impaired performance on tasks measuring sustained attention [72], inhibition of distractors [73], or performance on neurocognitive tasks [64].

2.2.2. Neurochemistry of sensory gating

Multiple neurotransmitters are found to be involved in sensory gating processing, including the cholinergic, dopaminergic, GABAergic, glutamatergic, noradrenergic, and serotonergic systems [74]. Pharmacological studies have emphasized the particular importance of the cholinergic system in regulating the decreased response to repeated stimuli (gating-out) through stimulation of the α-7 nicotinic receptor [75] and the muscarinic M1 receptor [76]. More recently, a marker of the gene for the α-7 nicotinic receptor has been strongly linked to sensory gating abnormalities [75]. Notably, $\alpha7$-containing receptors are also known for fast desensitization in the presence of agonist and high Ca^{2+} permeability [77].

2.2.3. Assessment of sensory gating

Sensory gating is typically assessed using a paired stimulus or oddball paradigm during an electrophysiological recording. In a paired-click paradigm, the event-related potential (ERP) component P50 or its magnetic counterpart M50, elicited about 50 ms after stimulus presentation, is measured during the presentation of two identical stimuli (S1 and S2) with an inter-stimulus interval (ISI) of 500 ms [72, 78]. The habituation of the response to the redundant second stimulus, expressed as the ratio between responses amplitudes (S2/S1), indicates the strength of gating-out inhibition [79]. Auditory oddball paradigm is characterized by the varying occurrence probability of a deviant (novel) stimulus between a series of repeated standard stimuli and therefore evokes both gating mechanisms, habituation of redundant information (standard stimuli) and pre-attentive memory-based comparison processes (deviant stimuli) [60, 64].

2.2.4. Neuroimaging of sensory gating

Notably, there is a problem in noninvasively studying the gating function in vivo. Only functional neuroimaging technique with millisecond temporal resolution can capture the sensory gating dynamics, which occurs within the first 100 ms after stimulus input. Positron emission tomography (PET), functional magnetic resonance imaging (fMRI), single-photon emission computed tomography (SPECT), and near-infrared spectroscopy (NIRS) are neuroimaging techniques that provide indirect look at the brain at work. These techniques provide measures of metabolic and vascular signals that are associated with neuronal activity, which are assumed to be linearly correlated, although reliable functional relations are not yet established. The temporal resolution of these functional techniques is rather low, on a minute scale, compared to underlying neural activity, which extends from 1 to 3 ms of action potential firing to a few tens of milliseconds of synchronous synaptic activity of thousands of postsynaptic neurons.

Unlike other functional neuroimaging techniques, electroencephalography (EEG) and magnetoencephalography (MEG) provide a critical opportunity to directly and noninvasively study the brain activity [80, 81]. Neurons in the human cortex generally process their information by means of electromagnetic signals and thus enable the direct recording of their activity. EEG and MEG are electrophysiological techniques that are both sensitive to the electrochemical currents within and between the brain cells. With sub-millisecond temporal resolution, these techniques can easily capture the dynamics of spontaneous and evoked neural responses. MEG and EEG provide a complimentary information about the underlying electromagnetic brain activity. MEG measures the magnetic field generated by the primary intracellular ionic currents through postsynaptic dendrites, while EEG measures the voltage scalp distribution generated by the secondary extracellular ionic flow, both produced by the normal brain activity [80, 81].

Though EEG can capture both radial and tangential components of a produced extracellular electrical field [80, 81], there was a widely accepted assumption that MEG detects only sources that are tangential to the scalp surface. However, recently, it was shown that source orientation is not a significant factor in limiting MEG sensitivity. Using both numerical simulation and empirical measurements, it has been demonstrated that source depth and spatial extent of activated assembly on convoluted cortical surface are the main factors that compromise the sensitivity of MEG to neural activity in the human cortex [82]. Although both techniques have high temporal resolution, MEG outperforms EEG in spatiotemporal localization of neural substrate underlying extracranially captured electromagnetic activity. Using modern signal analysis methods the centimeter spatial resolution of EEG approach that of conventional fMRI [83]. On the other hand, MEG technique has an excellent, millimeter spatial accuracy [82, 84]. Moreover, MEG can detect low-amplitude dipole current source in the deep tissue of dislocate cortex, which is simultaneously active with several times higher-magnitude dipole sources in the superficial regions of primary sensory areas [60], demonstrating a high spatial resolution of synchronously active sources within a neural network. Therefore, MEG can be used in two basic ways. The first, similar to the ordinary EEG recordings, utilizes studies of rhythmic brain activity, evoked neural processing, and clinical diagnostics to detect the presence or signs of abnormality in spontaneous or evoked brain activity. The second and more ambitious use of MEG is in the estimation of the location, strength, and time courses of neuronal current sources of spontaneous and evoked magnetic signals recorded outside the head. In conclusion, MEG is a unique method that enables the noninvasive spatiotemporal

mapping of elementary sensory gating processing that rises within first 100 ms after stimulus presentation. Moreover, the sources of MEG signals, primarily cortical intracellular postsynaptic currents, make MEG the first choice technique for the noninvasive study of synaptic function in real time. Consequently, MEG has an advantage in the neuroimaging search for early neurodegenerative biomarkers associated with synaptic alterations.

2.2.5. Cortical network underlying sensory gating

In line with the hierarchical model of neural processing [85], sensory gating responses have been long conceptualized to originate in the primary sensory areas [86, 87], due to the very early appearance in a sensory process stream. However, a report of the gating response presence after bilateral damage of the primary auditory areas [88] suggested a contribution from at least one source related to arousal level or state [89]. Efforts to delineate the neuroanatomy of the sensory gating network long have yielded inconsistent findings [90–93]. The recent works, relied on advanced MEG-based multi-dipole source localization, finally provide a reliable set of neural generators [60, 64, 94–96]. Moreover, our novel results revealed possible explanations concerning the problem of inconsistent reports regarding auditory gating network topology, suggesting that paired-click and oddball paradigms, which are often used to challenge sensory gating effects, evoke different gating generator topologies, even though they are both passive for the subjects [96].

2.2.6. Auditory sensory gating networks evoked by oddball and paired-click paradigm

Using the oddball paradigm, which evokes both gating-in and gating-out mechanisms, we have demonstrated that auditory gating network comprises a medial prefrontal (mPFC) generator along with the anticipated generators in the bilateral primary auditory cortices [60, 64, 96], as shown in panel A) of **Figure 1**. Our finding suggests the existence of a novel, very fast sensory processing stream (i.e., sensory gating loop), which links executive PFC to primary auditory cortex within the first 50 ms after stimulus presentation, alongside well-affirmed but slower limbic (dorsal) and somatic (ventral) sensory processing pathways [60, 96]. The existence of additional fast sensory processing stream, sensory gating loop, is anatomically supported by dense bidirectional connections between medial PFC and superior temporal cortices found in both primate and human anatomical studies [97, 98]. The mPFC possesses extensive cortico-cortical connections, including extensive local projections to and from other prefrontal regions, as well as with motor, limbic, and sensory cortices [99]. These structural properties of the connecting pathways provide the ability for localized primary auditory generators and PFC regions to work together as a large-scale neural network via fast sensory gating loop.

Our novel research provides evidence that passive paired-click and oddball paradigms activate a different prefrontal generator within the auditory gating network [60, 96]. Spatiotemporal source localization of auditory gating responses evoked by the passive paired-click paradigm revealed a different gating topology consisting of a dorsolateral PFC (dlPFC) source in addition to the sources in the bilateral primary auditory cortices [78, 96], as shown in panel B) of **Figure 1**. This result implies the existence of early rerouting within prefrontal cortex by shifting prefrontal gating activation from dorsolateral to medial prefrontal region, depending on a paradigm [60, 96], suggesting that mPFC and dlPFC regions serve different functions involved during the early sensory processing. A passive paired-click paradigm characterized
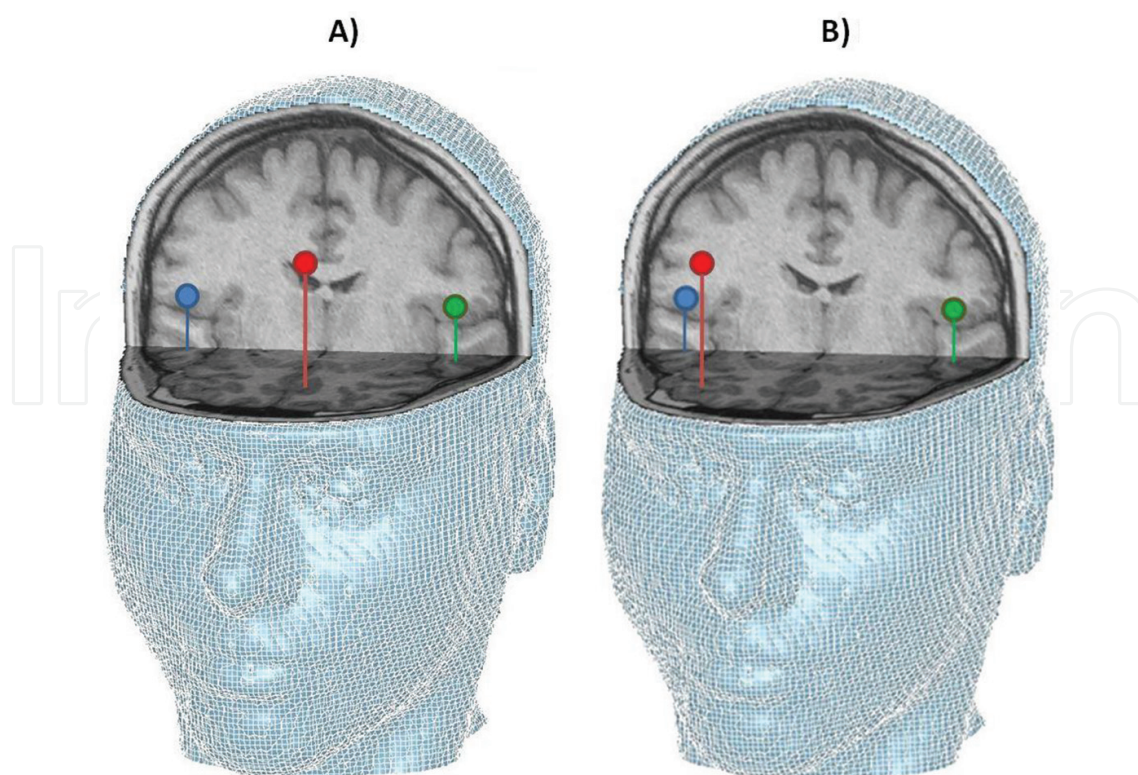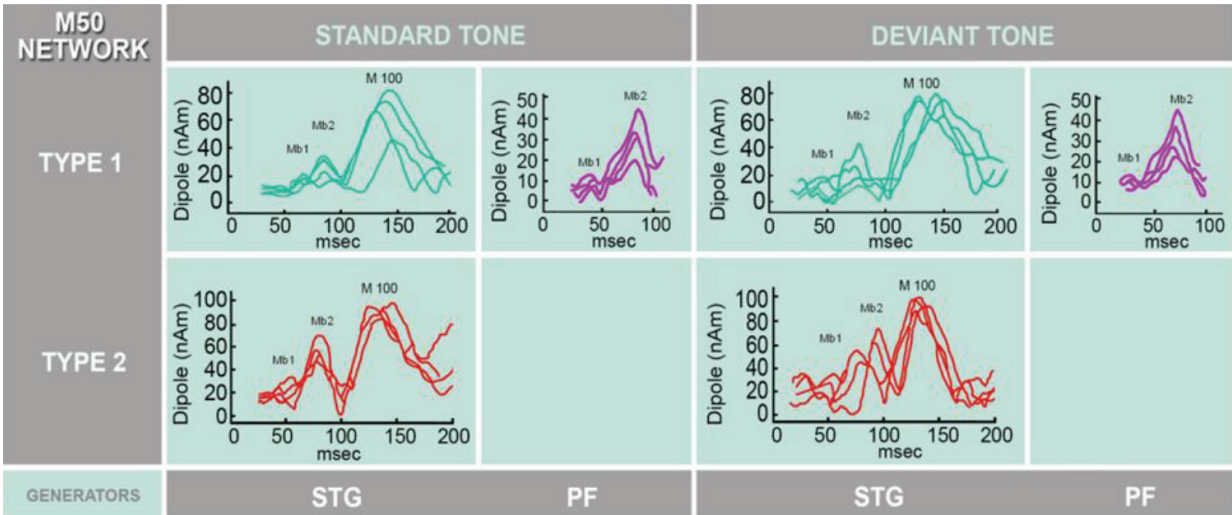
Figure 1. Auditory sensory gating network evoked by the oddball paradigm (panel A) and paired-click paradigm (panel B). The best-fitting source locations are superimposed on volumetric MRI head data to achieve a spatial (3D) rendering of the auditory gating topology. In addition to anticipated bilateral generators in primary auditory areas (blue and green dots), both paradigms evoke a prefrontal gating generator (red dot). While oddball tones provoke medial PFC activation, the tones of a paired-click paradigm activate dorsolateral PFC areas.

by the constant repetition of both short- and long-term patterns (S1–500 ms; S2–8 s) could result in long-term repetition suppression produced by the dlPFC. On the contrary, an oddball paradigm, characterized by the varying occurrence probability of a novel stimulus between a series of repeated stimuli, could put the neural network into a state of perceptual expectation (gating-in) while simultaneously suppressing redundant stimuli (gating-out). This phenomenon could be interpreted as the bottom-up, stimulus-driven initiation of attention during the very early sensory processing [100] executed by the mPFC region.

2.2.7. Functional mechanisms underlying auditory sensory gating

In addition to the spatial localization of auditory gating networks, we have disclosed the functional relation within network generators providing strong evidence of a modulatory role for the mPFC generator on bilateral superior temporal gyri (STG) sources dynamics during gating processing (**Figure 2**). This result discloses the long-sought mechanism underlying the auditory gating effect [60]. We demonstrated the complex form of estimated cortical morphology of the neural responses produced by the gating generators. In particular, gating response of STG generators is found to be composed of two consecutive cortical subcomponent, Mb1 peaking at 35–53 ms and Mb2 peaking at 75–95 ms post-stimulus, for both oddball paradigm tones [60]. We also provide the first estimates of cortical gating response produced by the mPFC generator, which has an analogous tandem form [60], as shown in **Figure 2**.

Figure 2. Estimated cortical dynamics of auditory gating network generators evoked by the oddball paradigm. Cortical dynamics of medial prefrontal (PF) and STG gating generators for both tones (standard and deviant) are shown for eight representative subjects (four of each network type). Gating network type 1 comprised bilateral STG and the PF source, while network type 2 was characterized by the absence of PF activation. The time courses of the STG activity were individually averaged across hemispheres and displayed for 30–200 ms time window to include M100, the most prominent STG response, for the amplitude comparison with earlier Mb1 and Mb2 components. Both components of STG gating response (Mb1 and Mb2) are significantly increased when PF source activation is absent.

Taking advantage of the differences in the evoked gating networks between individuals whose PFC generator was activated (Type 1 in **Figure 2**) and cognitively impaired individuals whose PFC gating generator was not activated (Type 2 in **Figure 2**) by the tones of an oddball paradigm, we have carried out a differential analysis of the functional roles for each generator. Our results show that cortical gating dynamics of STG generators evoked by both the standard and deviant tones demonstrated highly increased strength of both gating components in all subjects lacking PFC generator activity [60]. This result is of extreme clinical importance because the prevalent view of the gating-related pathologies assumes that the larger amplitude of the extracranial gating response to the standard tone (i.e., redundant stimuli) reflects impaired gating out processing of neural substrate in primary auditory areas only (i.e., STG generators) [61–63, 66–69]. Our novel results provide strong evidence of sustained inhibitory activity of the PFC generator that suppresses or modulates the activity of the STG generators as an underlying mechanism of both gating phenomena. Consequently, impaired activity of a PFC gating generator could be a primary cause of impaired extracranially measured sensory gating responses, found in numerous neurological and psychological clinical conditions.

3. Link between impaired sensory gating and AD pathology

The initial symptoms of AD include subtle decline of the ability to learn new information along with diverse amnestic disorders without present brain injuries. Clinically indicated AD signs are pointing to the existence of functional impairment of synapses that are involved in converting and forming new declarative memory [32]. Whereas longer retention of sensory memory traces derive more successful memory encoding [101], sensory gating process, conceptualized

as the ability of the neural system to modulate its responses to subsequent stimuli, has a fundamental role in guiding successful encoding of new information. Impaired auditory gating processing may reduce pre-attentive signal-to-noise ratio and desynchronize synaptic consolidation in the initial phases of memory formation [58]. Augmentation of dysfunctional sensory gating process could yield to the first amnestic symptoms seen in AD neuropathology.

A range of EEG/MEG studies, measuring evoked sensory responses, have reported differences in early processing of auditory [102–104] stimuli in symptomatic AD patients, affirming the possibility of impaired inhibition of redundant information (gating-out) and processing of novel information (gating-in) in the initial phase of disease. Also, alerted connectivity among different brain regions and decline of long-distance synchronization are found to be responsible for some of the earliest cognitive changes in early phases of symptomatic AD [105]. Although the study of the extracranial neurophysiological (EEG/MEG) signals provides valuable information regarding the pathology-related changes in the amplitudes, latencies, frequency bands, spectral densities, and coherence of oscillatory brain dynamics, identified relations have received limited attention in the search for a biomarker of AD. The main reason is that classification based on the difference between group means of sensor-level measures generally cannot provide a clear individual boundary value between healthy and pathological responses and thus result in lower clinical significance. However, MEG spatiotemporal localization of cortical sources underlying extracranial magnetic field shows internal consistency and provides highly reliable and stable results of both cortical dynamics and topology of the activated network [60, 82, 84], enabling a search for an AD biomarker at the individual level.

3.1. Localization of auditory gating network generators: a topological biomarker of AD

Using MEG spatiotemporal source calculations, we have demonstrated [64] the potential of topological localization of mPFC generator within an auditory gating network as a discrete, binary, noninvasive tool for detection of AD at the individual subject level. We found three types of gating network topologies evoked by a simple auditory oddball paradigm across the research sample of elderly individuals, ranging from 63 to 87 years of age, which comprised patients with clinical diagnosis of symptomatic AD (MCI and moderate AD) and non-symptomatic elderly controls. Discrete localization/non-localization of mPFC gating generator absolutely discriminate symptomatic AD from controls confirm the indiscernibility between amnestic MCI (aMCI) and AD patients and differentiate two distinct gating network types within the elderly controls, one of which is suggested as preclinical AD. The lack of mPFC generator localization within an auditory gating network as a biomarker of symptomatic AD shows a large effect size (>0.9) and high accuracy, sensitivity, and specificity (100%) in respect of clinical diagnosis [64].

3.2. Sustained activation of mPFC gating generator: a sign of healthy cognitive aging

We have applied spectra of the multivariate analyses to disclose potentially hidden structure in complete set of our data, i.e., scores of wide neuropsychological screening and neurophysiological gating network topology results [64]. Clustering based on principal variables indicated the existence of three stable clusters across subjects as shown in **Figure 3**. Subsequent
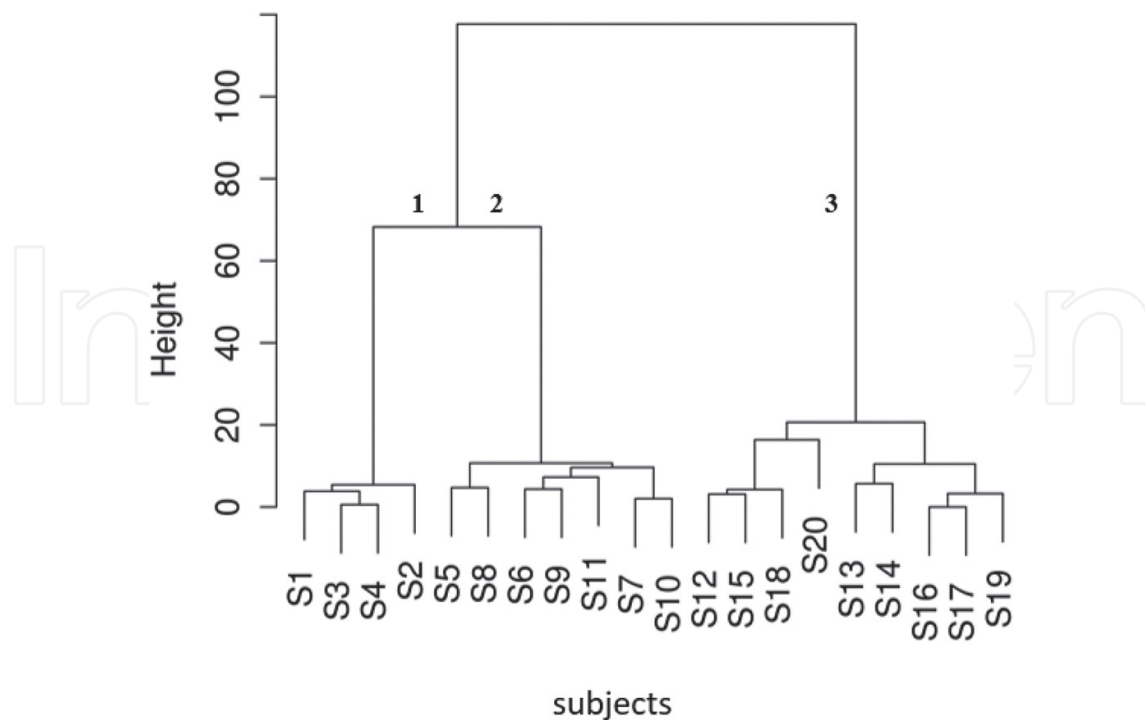
Figure 3. Dendrogram based on the neuropsychological and neurophysiological variables. Subjects were assigned numbers from 1 to 20 and grouped into clusters. Variables were normalized before using a clustering algorithm with Ward's minimum variance method as amalgamation rule and with Euclidean distance as a measure of dissimilarity. Cluster grouping disclosed three groups across two clinical categories (H-healthy subjects, MCI/AD—symptomatic AD subjects) suggesting the potential of the proposed approach to detect subgroup of control ("healthy") subjects who are in the possible preclinical phase of AD (cluster category 2).

statistical review of group differences on neuropsychological tests confirmed the low-magnitude but significant differences in Mini Mental State Exam (MMSE) and delayed Rey-Osterreith Complex Figure Test (dROCFT) scores across subjects in different cluster groups [64]. The first group of controls, characterized by sustained gating activation of mPFC generator for both oddball tones, had the highest MMSE scores and the highest performance on the dROCFT, thus considered to be cognitively healthy elderly group.

3.3. Partial activation of mPFC gating generator: a biomarker of preclinical AD

The second cluster group of controls was characterized by the first signs of neurophysiological gating alternation, which emerged as a partial activation of the mPFC gating generator to the deviant tone only, as shown in **Table 1**. The standard tone did not evoke mPFC activation, suggesting that a very early stage of impairment in sensory gating processing is manifested by an absence of mPFC gating transmission that corrupts habituation to redundant stimuli [64]. We confirmed the presence of insidious cognitive decline in this subgroup of controls, demonstrating the low-amplitude but significantly lower both MMSE and dROCFT scores in comparison with the high-functioning subgroup of controls [64]. Overall, both neuropsychological and neurophysiological impairments characteristic of an AD type of dementia found in low-functioning control group, although they did not yet meet clinical criteria for aMCI, indicate a possible preclinical AD phase. The additional weight to our speculation gave Takayama,

Subject	MMSE	dROCFT	mPFC standard	mPFC deviant	Clinical diagnosis	Cluster category
S1	30	26	1	1	H	1
S2	30	25	1	1	H	1
S3	30	23	1	1	H	1
S4	30	23	1	1	H	1
S5	30	22	0	1	H	2
S6	30	22	0	1	H	2
S7	30	17	0	1	H	2
S8	29	26	0	1	MCI	2
S9	29	25	0	1	H	2
S10	29	18	0	1	H	2
S11	26	20	0	1	H	2
S12	26	12	0	0	MCI	3
S13	26	7	0	0	MCI	3
S14	26	1.5	0	0	MCI	3
S15	25	13	0	0	MCI	3
S16	25	0	0	0	AD	3
S17	25	0	0	0	AD	3
S18	24	10.5	0	0	AD	3
S19	23	0	0	0	AD	3
S20	22	2	0	0	AD	3

Table 1. Subject scores on the MMSE, dROCFT, mPFC gating generator activation (1-activated, 0-non-activated), clinical diagnosis, and cluster group.

whose 10-year longitudinal study also discerns the dROCF test as highly assertive indicator of conversion to symptomatic phase of Alzheimer's disease, i.e., found significant sensitivity of dROCFT scores to early, possible preclinical AD pathology [106].

The possibility that partial gating activation of the mPFC generator in lower-functioning controls may be associated with preclinical AD phase is also confirmed by several recent findings. There are evidences that reduced functional connectivity affecting the PFC is associated with amyloid-β-related hypersynchronization [107] and p-tau pathology [108] in a very early phase of AD-type memory impairment. The impaired mPFC activity during endogenous brain activity or memory tasks is found in cognitively normal individuals who were AD APOE ε 4 carriers [109]. Also, evidence of decreased extracranial gating dynamics as a predictor of cerebrospinal amyloid-β reduction is demonstrated in MCI patients [65]. Alerted synaptic function along with subsequent synaptic loss and transneuronal spread of pathological tau forms [108] through PFC regions could result in the topological gating deficit that we found in a low-functioning subgroup of controls. This topological gating deficit could reflect a possible preclinical phase of AD pathology before widespread of cognitive symptoms.

3.4. Complete absence of mPFC gating generator activation: a biomarker of symptomatic AD

Subjects within the cluster group characterized by the complete absence of mPFC gating generator activation regardless of the tone condition (i.e., standard and deviant tone) had the lowest neuropsychological test results and belonged to the symptomatic AD patients with clinical diagnosis [64], as shown in **Figure 3**. Clearly, a topological deficit of mPFC gating generator activation is augmented in symptomatic AD phase, taking place during both gating out (inhibition of standard tone) and gating in (enhanced processing of novel tone), suggesting complete disruption of sensory gating process. This absolute break of a fundamental sensory process is associated with the onset of the amnestic AD symptoms. It is possible that progressive failure in sensory gating-out, found in possible preclinical phase of disease, is likely to lead to an overload of working memory due to noise accretion and consequent to the first symptoms of memory impairment.

There are numerous evidences of association between symptomatic AD pathology and alerted physiology of PFC region. Decreased frontal-parietal correlations of glucose metabolism [110], prefrontal glucose hypometabolism on 18F-fluorodeoxyglucose PET scans [111], and frontal retention of 11C-Pittsburgh compound [112] are found in AD patients. Klupp and colleagues [113] found a significant hypometabolism in PFC regions that are not loaded with amyloid plaques, suggesting that the deficit in mPFC gating activation may be related to longitudinal amyloid deposition in different but functionally connected brain regions. For instance, absence or desynchronization of mPFC gating activity could induce atrophy across fast auditory sensory gating loop, which may result in increased amyloid vulnerability of synapses terminated within primary auditory areas involved in the gating process. Inactivity of the mPFC generator during processing of repetitive stimuli (gating-out) likely impairs the ability to distinguish novel from repetitive information, which is critical for long-term memory encoding. It has been demonstrated that activation of presynaptic α-7-nAChRs, involved in gating transmission, induces long-term potentiation of the excitatory input [114]. Therefore, a topological deficit of mPFC generator activation during gating transmission could be a consequence of impaired nAChR levels found in PFC regions of AD patients. Alerted function of α-7-nAChRs could induce lower levels of intracellular calcium, consequently impairing the calcium cascade in producing synchronized postsynaptic signals required for effective both gating processing and long-term memory encoding.

4. Conclusion

Identification of a novel biomarker of AD (**Figure 4**) with the potential to detect both putative preclinical and clinical stages at the individual subject level represents significant progress toward improving diagnosis of AD and accelerating the field toward the neurobiological advantage of earlier intervention. Although the study engaged only a research sample, the very large effect size (>0.98) of proposed test, thanks to its binary nature, provides high relevance to the finding. Such a large effect size enables this study with the research sample size to yield power greater than 85%.
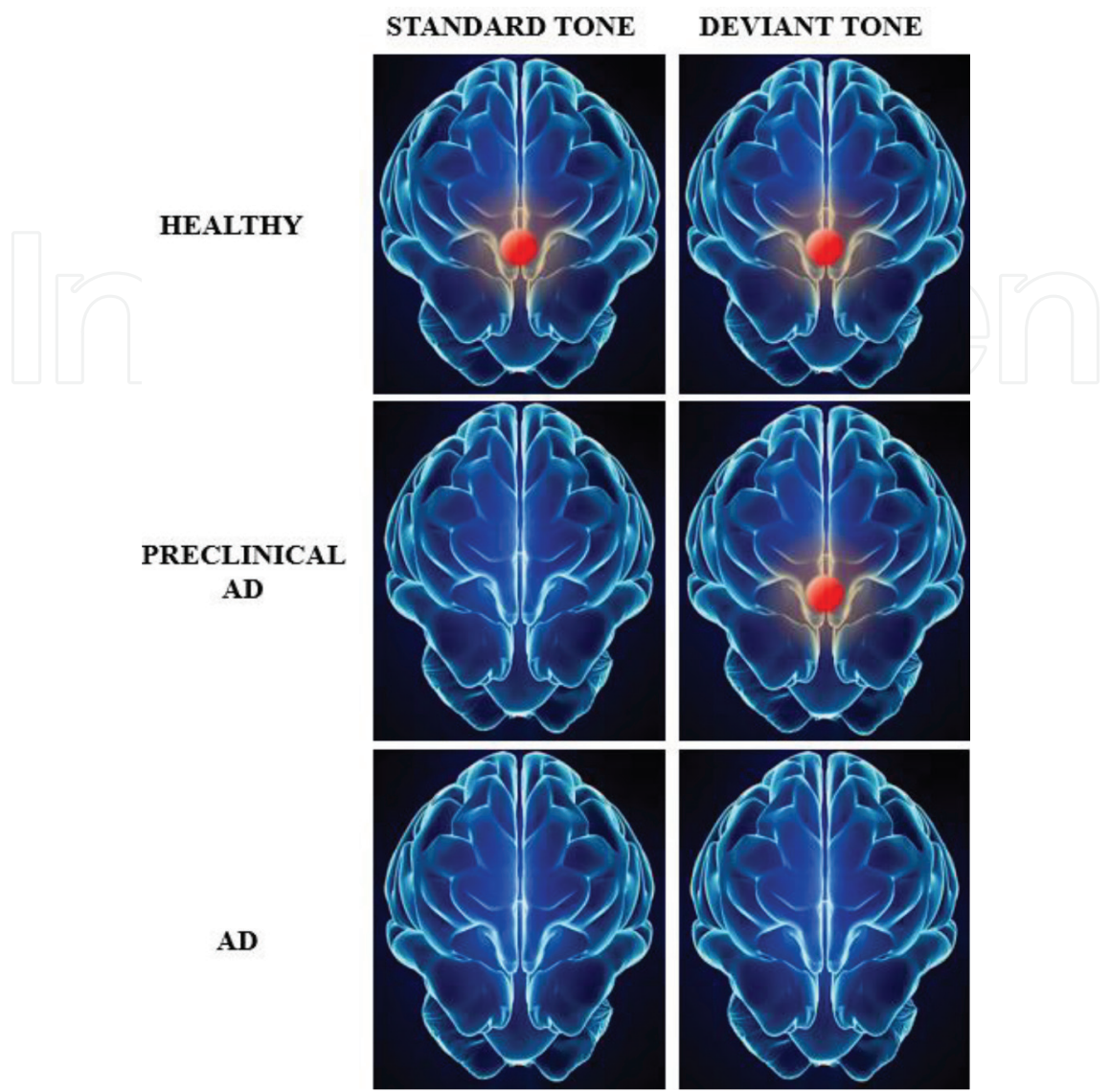
Figure 4. Proposed topological approach as biomarker of AD pathology. Three distinct types of mPFC auditory gating generator activation (red dot) were identified in healthy controls, possible preclinical AD and symptomatic AD patients. The healthy gating topology type requires mPFC activation in processing both oddball tones (standard and deviant). An altered gating topology, characterized by selective mPFC activation only by the deviant tone, presumably represents a presymptomatic phase of AD. Symptomatic AD gating topology lacks mPFC activation for both standard and deviant tones.

Novel topological biomarker, besides high accuracy, sensitivity, and specificity (100%) in identifying symptomatic AD patients in the research sample, shows the potential of following the evolution of the pathophysiological process of disease. The noninvasiveness and low sensitivity to individual heterogeneity and variability due to the discrete nature of impaired prefrontal gating activation are the most important properties of the novel biomarker. It is not based on the use of group means and is not associated with statistically significant changes in a continuous variable. The advantage of this biomarker lies in the simplicity of using a binary value, i.e., activated or not activated a prefrontal generator during gating processing of simple tones. The proposed biomarker is absolutely noninvasive; it is based on recordings of neuromagnetic fields that are produced by normal brain activity.

The new topographic tool certainly has properties, which place it within a group of high-potential biomarkers. The absolute noninvasiveness, individual detection of pathology, ability to detect the preclinical phase of the disease, discrete nature that does not require estimation of uniform cutoff levels and standardization processes, the low sensitivity to individual heterogeneity and variability, capability to follow the evolution of the pathophysiological process of AD, and finally high accuracy and sensitivity make it highly promising biomarker of AD.

However, despite mentioning highlights, the proposed biomarker requires to be tested in a large independent sample and requires assessment in longitudinal clinical MEG studies that would track nonsymptomatic elderly with partial activation of the prefrontal gating generator until the first clinical symptoms appear and finally to autopsy for confirmation of AD. It would also be necessary to investigate prefrontal gating dynamics in other dementias to determine the specificity of novel biomarker to discriminate AD from other etiologies of age-related cognitive decline.

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