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Editorial

The Dark Side of Alzheimer's Disease: Neglected Physiological Biomarkers of Brain Hyperexcitability and Abnormal Consciousness Level

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THE MOONRISE: *IN VIVO* BIOMARKERS OF ALZHEIMER'S DISEASE

The National Institute of Aging and Alzheimer's Association have recently proposed a framework for the neurobiological diagnosis of Alzheimer's disease (AD) for research applications [1]. That framework states that the AD diagnosis can be based on biomarkers derived from *in vivo* measurement of amyloidosis ('A'), tauopathy ('T'), and neurodegeneration ('N') from the brain of patients with AD, regardless of the clinical manifestations of the disease in the continuum from subjective cognitive complaint, mild cognitive impairment (MCI), and mild, moderate, or severe degree of dementia [1]. Specifically, the brain amyloidosis and tauopathy can be measured by biomarkers derived from a laboratory analysis of cerebrospinal fluid or positron emission tomography (PET) mapping, while neurodegeneration can be probed by biomarkers derived from structural magnetic resonance imaging or fluorodeoxyglucose PET mapping [1]. According to this framework, brain amyloidosis would be the AD neuropathology, the brain amyloidosis and tauopathy would be AD, and the brain tauopathy and neurodegeneration would mainly explain the AD clinical manifestations ('C'). Those manifestations include 1) cognitive deficits in episodic memory, visuospatial abilities, frontal executive, and language functions and 2) disabilities in the activities of daily living in dementia [2]. Abnormalities in these cognitive functions alter consciousness contents related to object recognition, naming, autobiographic memory recall, etc. [1].

As an important merit, the ATN(C) framework defines a coherent brain disease model able to explain the neurobiological, neuroanatomical, and core cognitive deficits associated with the AD onset and progression. The biomarkers of the brain amyloidosis would be an indicator of the disease trait, while those of the brain tauopathy and neurodegeneration would be informative on the disease status (progression).

Despite the above merit, the ATN(C) framework received two major criticisms. The first criticism focused on the limited sensitivity of the biomarkers of brain amyloidosis and tauopathy in AD diagnosis. It was claimed that a significant number of old cognitively unimpaired persons positive to the mentioned

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biomarkers of brain amyloidosis and tauopathy do not develop the clinical manifestations of the disease (e.g., MCI and dementia) within a period of several years [3]. For this reason, it was proposed that the presence of positive biomarkers of brain amyloidosis and tauopathy may merely represent a risk factor for the development of AD rather than an ultimate diagnosis of AD [3]. In this line of reasoning, it was proposed that the diagnosis of AD should be based not only on brain amyloidosis and tauopathy but also on the presence of progressing clinical phenotypic manifestations compatible with AD [3].

The second criticism focused on the limited specificity of the biomarkers of brain amyloidosis and tauopathy in AD diagnosis. It was claimed that the biomarkers of brain amyloidosis and tauopathy can have abnormal values not only in AD patients but also in old patients with other aging-related progressive neurodegenerative diseases such as Lewy body disease and Parkinson's disease with dementia [4, 5]. Therefore, the presence *per se* of abnormal values in the biomarkers of brain amyloidosis and tauopathy would not ensure a correct diagnosis of AD in old patients with progressing cognitive deficits.

THE DARK SIDE OF THE MOON: MISSING NEUROPHYSIOLOGICAL BIOMARKERS IN AD

As explained above, the ATN(C) framework is grounded on the view that AD-related neuropathology (i.e., brain amyloidosis and tauopathy) represents the neurobiological cause of cerebral neural neurodegeneration and cognitive deficits from MCI to dementia. In this cause-effect model, there is surprisingly no mention of the disruptive effects of the AD-related neuropathology on the physiology of the collective oscillatory activity within large inter-connected neuronal populations (networks) underpinning human higher brain functions such as the regulation of vigilance within the sleep-wake cycle and cognitive functions. In a healthy brain, such an oscillatory activity reflects the adaptive functioning of neurophysiological mechanisms controlling the temporal synchronization of the neuronal activity with significant effects on the cortical arousal underpinning vigilance and cognitive performance. The temporal synchronization of that oscillatory neural activity and the related neurochemical synaptic transmission are associated with the summation of action and post-synaptic potentials producing detectable changes in the electromagnetic fields at different spatial scales from cellular to brain levels [6–8]. These changes may be measured by electrophysiological techniques to produce physiological biomarkers at various spatial scales in preclinical and clinical research in AD. Keeping in mind these considerations, an additional criticism of the ATN(C) framework is the lack of conceptual terms explaining when, how, and how much the AD neuropathology can exert an interference with the mentioned neurophysiological oscillatory mechanisms from the beginning of brain amyloidosis to the neurodegenerative outcome. This interference is expected to produce effects measured by pathophysiological 'P' biomarkers. In the past decades, the relevance of the pathophysiological 'P' biomarkers in the AD model has been grounded on converging findings derived from both preclinical and clinical studies [6–10].

In preclinical cellular models of AD at a microscopic spatial scale, recordings of oscillatory electrophysiological signals from rodent brain slices taken at the hippocampus and cerebral cortex showed that the general neuronal excitability, signal transmission, and synaptic contacts in that tissue were pathophysiologically deranged by the inclusion of amyloid protein in the experimental platform [11, 12]. At a larger spatial scale, behaving transgenic rodents producing AD neuropathology in the brain showed abnormal oscillatory local field potentials recorded from large populations of neurons in the hippocampus and cerebral cortex. Those abnormal potentials may be considered pathophysiological 'P' biomarkers of the effects of AD neuropathology on neural synchronization and connectivity in relevant cerebral networks elaborating cognitive processes [13–15]. Remarkably, several transgenic rodent AD models also displayed epileptiform intracerebral electroencephalographic (EEG) activity related to the amyloid accumulation and the trans-synaptic spread of tau pathology [16–18]. This epileptiform activity in rodent AD models can be considered an intriguing new pathophysiological 'P' biomarker of the effect of the AD neuropathology on the synchronization of neural activity determining the level of excitability in brain neural networks.

Concerning the clinical research, experts of the Electrophysiological Profession Interest Area (EPIA) of the International Society to Advance Alzheimer's Research and Treatment (ISTAART; http://www.alz.org) have recently reviewed the scientific studies comparing eyes-closed resting-state electroencephalographic (rsEEG) rhythms in AD

patients with MCI and dementia over matched control normal elderly (Nold) persons. There were converging findings summarized as follows: 1) rsEEG rhythms were abnormally higher at delta (<4 Hz) and theta (4–7 Hz) frequency bands in widespread scalp regions, while they were abnormally lower at the alpha (8–12 Hz) frequency band (as a sign of hyperexcitability) in posterior scalp regions; 2) the use of those abnormal rsEEG rhythms as biomarkers allowed classifications with >80% accuracy in discriminating between AD patients with MCI or dementia versus matched Nold individuals and patients with other progressive neurodegenerative diseases; 3) rsEEG rhythms at delta, theta, and alpha frequency bands showed increasing abnormalities at 12–24-month follow-ups and some signs of beneficial effects during 6–24-month intervention trials using standard symptomatic cholinergic drugs [6, 7]. In the same line, ISTAART-EPIA experts also reviewed the scientific studies investigating EEG activity related to cognitive tasks in AD patients. They found converging findings about event-related EEG activity, especially using oddball paradigms probing attention and working memory, in AD patients with MCI and dementia when compared to matched Nold persons and patients with other progressive neurodegenerative diseases and some signs of beneficial effects on that event-related EEG activity during 6–24-month intervention trials using standard symptomatic cholinergic drugs [9, 10].

In line with preclinical research, a bulk of studies showed an increased risk of overt epileptic seizures or subclinical, non-convulsive, epileptiform EEG signatures in AD patients with fast clinical deterioration [19–21]. Most of those epileptiform EEG signatures were observed during sleep, especially the non-rapid eye movement, pointing to the use of long EEG recordings [22]. These findings confirmed the strict relationship between AD neuropathology and pathophysiological mechanisms regulating general brain neural excitability and arousal. They also confirmed the translational value of the evidence showing epileptiform activity in the rodent AD.

EXPLORING THE DARK SIDE OF THE MOON: EEG BIOMARKERS OF BRAIN HYPEREXCITABILITY IN AD

Keeping in mind the above data and considerations, the ISTAART-EPIA Steering Committee has promoted this Mini Forum entitled "Alzheimer's Disease, Brain Over-Excitation, and EEG Signatures: Preclinical and Clinical Evidence" in order to survey recent findings and concepts about the use of neurophysiological techniques such as transcranial magnetic stimulation (TMS) and EEG to investigate pathophysiological abnormalities in brain excitability due to AD neuropathology, including those belonging to the epileptiform activity. Overall, the pathophysiological mechanisms underpinning alterations of the vigilance in the sleep-wake cycle, the so-called consciousness level, can significantly affect the ability of AD patients to follow a TV talk show or a quiet social conversation among relatives. Such a disability may have a significant impact on the AD patients' daily quality of life and needs to be much better explored, understood, and treated not only with pharmacological agents but also with adequate non-invasive brain stimulations [23].

The Mini Forum includes six articles covering some relevant areas of the pathophysiological 'P' biomarkers of brain hyperexcitability in AD. These articles provide significant examples of the preclinical (three articles) and clinical (three articles) research in AD using non-invasive brain stimulation and EEG techniques.

PRECLINICAL RESEARCH

Dr. Tok and colleagues [24] reviewed the literature testing the hypothesis that AD neuropathology may induce clinically relevant brain network hyperexcitability. As a major contribution, they enriched that review of the field literature with their straightforward view on how the development of rodent models showing AD-specific network hyperexcitability may provide physiologically relevant translational data. In a twist, the authors revealed the methodological limitations and caveats in some reviewed preclinical studies in the literature, helping readers to prevent the design of experiments with poor translational validity. Based on the lessons from the literature, the authors also shared the treasure map on how to develop effective rodent models incorporating AD-specific network hyperexcitability and specific electrophysiological techniques to produce physiologically relevant translational data for a successful early drug discovery pathway in patients with sporadic AD.

Dr. Stoiljkovic and colleagues [25] provided an admirable example of the experimental approaches recommended by Tok et al. [24]. Specifically, the

authors tested the contribution of triggering receptor expressed on myeloid cells-2 (TREM2) of microglia on the control of hippocampal network hyperexcitability in transgenic mice overproducing cerebral amyloid-β (Aβ). As is well known, TREM2 protein is expressed only on microglia in the brain and may drive the development of AD neuropathology. The research focus was on the role of microglia on the modulation of the causal effective connectivity from the brainstem nucleus *pontis oralis* to the hippocampus. To this aim, the authors used an elegant combination of brain electric stimulation, the recording of local field potentials in the hippocampus, and the manipulation of TREM2 haploinsufficiency. Core findings suggest that the TREM2 plays a role not only in the regulation of hippocampal neuronal excitability during physiological conditions but also in moderating that network hyperexcitability in the case of brain Aβ overproduction.

Dr. Jin and other independent experts [26] dealt with the other face of the network hyperexcitability, namely the epileptiform activity recordable in transgenic rodents producing AD neuropathology. This activity has a significant translational value for a better understanding of the subclinical epileptiform EEG spikes that can be recorded in AD patients (also see articles by Babiloni et al. [27] and Costa et al. [28]). In this article, the authors recommended optimal EEG markers and experimental designs to 1) measure epileptiform activities from the hippocampus/cerebral cortex in transgenic rodents producing AD neuropathology and 2) evaluate the effects of drugs for the mitigation of those activities. The reported recommendations may facilitate the harmonization of experimental procedures in future field studies, thus enhancing the comparability of experimental findings and their impact in early preclinical drug discovery pathways.

CLINICAL RESEARCH

Dr. Joseph and colleagues developed both a literature review and a meta-analysis on cortical hyperexcitability in AD patients. The literature review unveiled converging evidence that the TMS over the motor cortex did induce greater motor-evoked electromyographic potentials recorded from upper limbs in AD patients over controls, as a biomarker of corticospinal network hyperexcitability. In this line, the meta-analysis of some reviewed studies showed higher cortical excitability in AD patients with dementia over the healthy controls, as revealed by resting and active motor thresholds for the TMS released over the motor cortex.

Dr. Costa and colleagues [28] explored the relationship between brain network hyperexcitability and the risk of dementia in old patients with late-onset epilepsy of unknown etiology (LOEU). The study tested the hypothesis that the graph topology of the EEG source functional connectivity in the baseline resting-state recordings may predict the development of cognitive deficits over years. All enrolled LOEU patients showed intact cognition at the baseline recording. Compared with the LOEU patients with stable cognitive status over time, those (about 50%) showing cognitive deficits after 5 years were characterized by certain signatures in the graph topology of the EEG source functional connectivity. Specifically, they presented alterations at delta and alpha frequency bands in the graph topology called "small world network," thus confirming the working hypothesis. These results are intriguing as that graph topology typically reflects the resilience of complex systems to the insults deranging network nodes.

Finally, Dr. Babiloni and colleagues [27] explored the relationship between brain network hyperexcitability and AD-related neuropathology in patients with amnesic MCI due to AD (ADMCI). None of those patients had a clinical diagnosis of epilepsy. The ADMCI patients were divided into those with (15%) and without silent, subclinical epileptiform EEG activity. Notably, the ADMCI patients showing the epileptiform EEG activity were characterized by greater AD-related amyloid neuropathology and enhanced EEG delta source activity in a standard resting-state condition, thus suggesting more abnormal pathophysiological mechanisms underpinning the regulation of cortical arousal and quiet vigilance. These results encourage further investigations on the clinical trajectory of those ADMCI patients and the pharmacological treatment of their subclinical epileptiform EEG activity using the validated EEG biomarkers.

CONCLUDING REMARKS

The data and considerations of this Mini Forum suggest that neurophysiological techniques such as TMS and EEG allow an informative investigation of the abnormalities in the pathophysiological mechanisms underpinning brain hyperexcitability in both preclinical and clinical AD research models,

Table 1
Theoretical proposal for an Alzheimer's disease model and the biomarkers for *in vivo* measurements of the model dimensions

Alzheimer's disease model and biomarkers			
A	Amyloid		CSF $A\beta_{42}$ or $A\beta_{42}/A\beta_{40}$ ratio
			Amyloid PET
T	Tauopathy		CSF phosphorylated tau
			Tau PET
P	Pathophysiology		EEG
			ERO/ERP
N	Neurodegeneration		Structural MRI
			FDG-PET
O	Output	Vigilance sleep/wake	Neuropsychology
			Psychophysics
		Cognition	Clinical scale

The proposed model is an extension of the well-known ATN(C) framework of the US-National Institute of Aging and Alzheimer's Association [1]. The model dimensions include the brain amyloidosis (A), tauopathy (T), pathophysiology (P), and neurodegeneration (N). The disease processes within those dimensions produce a clinical output (O) involving vigilance, wake-sleep cycle, cognitive functions, and abilities in the activities of daily living. The disease model is denoted by the abbreviations A-T-P-N-O. CSF, cerebrospinal fluid; PET, positron emission tomography; EEG, electroencephalography; ERO, event-related EEG oscillations; ERP event-related potentials; MRI, magnetic resonance imaging; FDG-PET, fluorodeoxyglucose PET.

including those focused on the evaluation of the epileptiform activity. Overall, those pathophysiological mechanisms may alter the regulation of the consciousness level in AD patients during wakefulness, with a significant impact on their quality of life.

The data and considerations of this Mini Forum also suggest more scientific consideration and investments in research lines able to speed up the discovery and further validation of pathophysiological 'P' biomarkers based on EEG activity/local field potentials reflecting 1) brain hyperexcitability for preclinical and clinical drug discovery pathways in AD and 2) the abnormal AD patients' consciousness level (e.g., quiet vigilance stability) for clinical applications. Remarkably, the ATN(C) framework [1] may be enriched with those pathophysiological 'P' biomarkers and the evaluation of vigilance, sleep-wake cycle, cognitive status, and abilities in the activities of daily living as a global clinical output 'O' (Table 1). Specifically, a theoretical proposal for an AD model may include the brain amyloidosis (A), tauopathy (T), pathophysiology (P), and neurodegeneration (N). The disease processes within those dimensions may produce a clinical output (O) involving vigilance, wake-sleep cycle, cognitive functions, and abilities in the activities of daily living. The disease model is denoted by the abbreviations A-T-P-N-O. Such integration may better explain the neurophysiological link between AD-related neuropathology, neurodegeneration, and clinical manifestations in AD patients at all stages of the disease. In this line, Clinical Neurophysiology may be exploited in the battle against AD. And the dream of German psychiatrist Dr. Hans Berger, the first human being to observe and name scalp-recorded EEG rhythms almost 100 years ago, may come true.

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