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Commentary

Hidden functional derangement of somatosensory cortices in Alzheimer's Disease.

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Alzheimer's Disease (AD) is a neurodegenerative disorder and represents the main cause of dementia worldwide, accounting 60-80% of cases who are diagnosed with dementia [1]. Clinically, AD is typically featured by memory loss, progressive cognitive decline and impairment of previous levels of functioning and performing at work or at usual activities. Additional knowledge about the pathophysiology of the disease might contribute to better understand AD course in order to mitigate social and familial burdens. Neurodegeneration has been attributed and is driven by extracellular aggregates of amyloid β (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) made of hyperphosphorylated tau protein in human brain [2]. Interestingly, accompanying these early proteinopathies are measurable changes in the patterns of functional neuronal activity, structural neuronal morphology, integrity and connectivity [3]. In fact, the natural history of AD includes significant alterations in the human connectome, considering AD as a disconnection syndrome. Significant changes in neural networks have been shown from structural and functional magnetic resonance imaging (MRI), magnetoencephalopathy (MEG) and electroencephalography (EEG) all even prior to the onset of clinical dementia [4].

Several studies described a decreased functional connectivity in the Default Mode Network (DMN) in AD patients. DMN includes brain regions with high degrees of functional connectivity and is active in the brain at rest, but becomes deactivated when task performance is initiated. Moreover, it seems to be relevant in self-related information processing, episodic memory, recollection of autobiographical information and decision making [5]. Since these changes have also been found in prodromal phases of AD, it has been suggested that they may provide potential biomarkers for AD.

Besides the involvement of associative cortices, it has been suggested that motor and auditory dysfunctions may occur in early phases of AD and seem not to be negligible [6,7]. In fact, primary motor cortex (M1) volume has also been long ago associated with gait performance in mild cognitive impairment (MCI) and alteration of intracortical motor connectivity confirmed the involvement of motor areas in the early stage of AD [8]. Concerning auditory disfunctions, studies on Event Related Potentials (ERPs) highlighted an increased amplitude of the P50 peak in patients with MCI: in fact, MCI patients who later converted to probable AD had larger amplitude P50s than those with a stable MCI diagnosis [9]. Moreover, through the use of MEG, some authors showed that the functional gating of redundant auditory information seems to be aberrant in patients with AD [7].

Very little evidence supported somatosensory disfunctions in AD patients (9), leading to the hypothesis that this function seems to be spared in AD. Nevertheless, the paper by Wiesman et al [10], published in this issue of EBioMedicine, has examined somatosensory function in amnestic MCI and mild AD patients. For the first time, the authors took into account attention and processing speed abilities as potential confounding factors in the evaluation of somatosensory dysfunction in AD spectrum. Through the use of MEG, this work highlighted a robust pattern of stronger somatosensory gating in AD patients: however, this alteration in functional somatosensory processing in primary sensory cortices is masked by variability in cognitive decline across individuals. In particular, variability in attention and processing speed abilities, whose deficits are both well documented in patients with AD, masks the detection of changes in somatosensory neural functions. Consequently, the detection of these somatosensory alterations led the authors to suggest considering cognitive variability in future studies regarding not only primary sensory function but also other less explored systems, for example visual and auditory processing. This could help to better understand the nuanced effects of AD.

Moreover, the authors suggested that their findings should guide future studies focusing on the mechanistic bases of functional alterations in AD. In fact, the analysis of these features would be useful to determine the inter-regional functional connections that potentially mediate AD-related changes in connectivity.

In conclusion, according to the results of this study, neurophysiological techniques might be potentially useful instruments to detect alterations in neural processing in order to better understand neurophysiological changes in AD and also to identify connectivity

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disfunctions suggestive for AD and that could represent an early signature of the disease.

Considering that the development of *in-vivo* biomarkers moved the diagnosis of AD from the dementia stage towards the prodromal phases, the identification of connectivity biomarkers could be helpful to make a preclinical diagnosis (ie, before symptom onset). In fact, these early stages of AD seem to be the perfect target for potential therapies for secondary prevention. Very early identification and multimodal treatment of patients will be real and concrete in a not-too-distant future.

Contributors

VB and GG co-wrote this commissioned Commentary.

Declaration of Competing Interest

Valentina Bessi and Giulia Giacomucci declare no competing interests.

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