Brain Connectivity as Potential Biomarker for Alzheimer’s Disease

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Abstract

One important challenge for the Alzheimer’s disease research field is developing new and efficacious biomarkers. In this regard we have devoted significant efforts towards finding biomarkers that are able to detect the prodromal pathological stage at an early phase. The idea behind this picture is to detect early stage points in order to provide better treatment options. Here, we firmly believe that this strategy will offer better hope for patients. With this in mind, we discuss the use of brain circuit alterations as a potential tool for early time point detection. Additionally, we briefly discuss the combination of powerful new techniques, like optogenetics and magnetic resonance imaging, for new diagnosis and treatment strategies.

The short document will be an important contribution towards exploring new strategies for AD diagnosis and treatment. Given the practical application of these data, we feel that this manuscript will be of significant interest to the audience of Journal of Neurology and Neuroscience.

Keywords: Alzheimer’s disease; Brain connectivity; Amyloid beta; Biomarker

Introduction

Alzheimer’s disease (AD) has being canonically defined by the aberrant accumulation of amyloid beta (Aβ) and tau protein aggregates [1]. The leading hypothesis postulates that accumulation in specific parts of the brain, i.e., hippocampus, causes neuronal death, translating into cognitive deficits [2]. It should be noted that the hippocampus is the paramount critical structure responsible for cognitive processing and memory formation [3]. The hypothesis could explain from a chronological perspective the pathogenesis and clinical signature of AD patients; however, one logical corollary is missing from the clinical manifestation. Aspects of the symptomatology of AD patients are not well correlated with protein deposition and the clinical AD diagnosis is not well correlated with aggregates, particularly Aβ deposition [4]. Indeed, several recent papers demonstrate the underlying clinical pathology is not fundamentally underscored by protein deposition; rather, certain protein fragments are generated long before the main aggregate, the Aβ plaque [5]. Currently, the soluble Aβ version oligomers that are formed during the early phase of the amyloidogenesis are now being blamed for the neurotoxicity [6]. Although, several pieces of evidence have correlated the oligomeric version of Aβ with synaptic plasticity and oscillatory network alterations, the precise relationship remains elusive [7]. For example, the newest peptide that is currently gaining attention among our research community is the b-CTF fragment [8]. This fragment has been correlated with alterations in oscillatory activity, which is critical for cognitive functions [8]. Alterations in two of the most important oscillatory rhythms, theta and gamma and their cross-frequency coupling, were found correlated with the b-CTF presence at one month of age in a transgenic mouse model that is characterized by developing Aβ deposits at 4 months of age [8,9]. Further supporting these findings, we have found alterations in hippocampal theta activity in a different transgenic AD mouse model which is characterized by Aβ deposits at 6 months of age (unpublished data). In agreement to published data [8], our data suggests that even in less aggressive forms of AD development, brain circuit activity is affected and consequently could be a putative critical marker during early stages of disease development.

The other eminent component in the proposed pathogenesis of AD development has been tau deposits, mainly comprised of abnormally phosphorylated tau protein [1]. Abnormally phosphorylated tau protein aggregates within a neuron prompting to neuronal malfunction and finally to neuronal cell death, collaborating the tau hypothesis [4]. However, mouse models of tauopathy are absent for markers of cell death at early time stages, although aberrant hippocampal network functioning has been found [10]. More recent data from our group has demonstrated that brain network alterations are happening as early as one month of
age in transgenic mouse models that are characterized by tau deposition at 8 months of age (unpublished data). Our data, along with published data [8], suggests that way before any potential tau deposits; brain circuit activity is drastically affected, thus supporting the idea of detecting malfunction in brain circuit activity as an early marker of disease progression [9]. This observation bridges the discussion for one of the current and therapeutic debates in the AD field, which is the treatment window for therapeutic intervention [10,11]. Here many authors, including us, believe that early intervention will offer better hope with better prognostic outcomes. Unfortunately, finding the early prodromal pathology of AD has become particularly difficult; the consummate goal is to find early markers for disease progression. In this regard, we have seen that specific phosphorylation levels in tau protein could be observed as an early marker; nonetheless, the accuracy still depends mainly on the disease stage [12]. Concomitantly, brain circuit alterations, as seen in the transgenic models, are emerging as a remarkably reliable tool for early AD diagnosis. The pending challenge now would be to translate these tools to human diagnosis. Nonetheless, less refined techniques currently used for brain circuit measurements like magnetic resonance imaging (MRI) are showing promising results [13]. In addition, new techniques like optogenetics, are helping us to dissect and understand brain circuit activity. The combination of powerful techniques such as optogenetics, MRI and electrophysiology, will become the key when designing protocols for diagnosis and treatment. In this regard, functional MRI studies in patients with mild cognition impairment (prodromal stage of AD) have shown intranetwork functional disruptions within the dorsal attention network and executive control network [14]. Another functional MIR study showed similar results concluding that longitudinal alterations of functional connectivity are more profound in earlier stages as opposed to later stages of the disease [15]. Overall, is evident that brain circuit alterations are gaining attention as the new biomarker for the prodromal stage of AD.

The last three decades of AD research has mainly focused on Aβ, which has been the main target for diagnosis and therapeutic approaches, but has shown little recuperative benefit [11]. In the last decade, a tau protein strategy has slowly become the newest Aβ target, for both, diagnosis and therapeutic treatment. A fundamental question must be raised: are we willing to spend time and effort in developing a new potential protein treatment that is probably the wrong target? For the new generation of scientists, we have to derive new and fresh approaches; herein, brain circuit alterations as a new option for early diagnosis could offer better hope for AD patients. Additionally, neural circuit alterations can become an interesting and more promising therapeutic strategy. In this vain, neural circuit stimulation has shown ameliorated effects in brain pathologies like Parkinson’s disease [16]. With this in mind and the correct stimulation protocols, brain circuit strategy could become a promising therapeutic target for AD patients.

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