EDITORIAL

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The effect of neuronal activity and connectivity on Alzheimer's disease: a new direction and its implications for future treatment strategies

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“Should disturbed brain dynamics indeed play a significant role in Alzheimer's disease pathophysiology ... its systematic description and analysis could open up a whole new direction of diagnostic, prognostic and therapeutic strategies.”

Imagine troubleshooting a malfunctioning computer without turning it on or paying attention to the software installed on it. Imagine trying to understand traffic jams without looking at actual traffic flow, or the spread of epidemics without paying attention to human travel patterns. These approaches seem shortsighted, since ‘dynamics’ form an essential aspect of these systems, often influencing or even causing vulnerability and malfunction. Yet, this is exactly what is happening presently in Alzheimer's disease (AD) research, as the brain's core business, the coordination of neuronal communication, is largely ignored.

The relationship between AD pathology and symptomatology is still poorly understood. This is not very surprising when one considers two systematically overlooked but crucial aspects of cognitive processing: it is both dynamic and distributed. Most neuroscientists will agree that, particularly, our higher cognitive functions cannot be tied to a single location, but depend on efficient communication between many brain areas. It has been argued that AD can consequently be characterized as a disconnection syndrome [1]. Although this is an interesting notion, it is rather vague; how can it help us to understand the preferential impairment

of specific cognitive domains in AD? We need a more detailed understanding of how disturbed communication exactly relates to structural pathology and cognitive decline. For this purpose, methods that combine accurate acquisition of brain dynamics and connectivity with appropriate analytical tools to interpret the observed changes are required.

At the moment, exploration of *in vivo* ‘functional’ brain networks is booming. Owing to the application of modern network theory concepts to functional imaging techniques, such as functional MRI, PET, EEG and magnetoencephalography, the description of functional brain network topology is moving at a fast pace. Many links between brain network structure and function have already been found: network organization develops and degrades during life; is related to prominent mental features such as intelligence and consciousness; and is damaged in various diseases [2,3]. Interestingly, different forms of neurodegenerative dementia show specific patterns of functional network disruption [4,5]. This suggests that this system-level approach is sensitive to the different kinds of underlying pathology, and that it may provide clues about the relation between

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pathology and symptoms. It may even facilitate the development of a set of quantitative ‘cognitive brain function tests’, similar to those for heart or lung function.

The fact that we are not yet able to ‘benchmark’ the working brain does not mean we should leave brain dynamics out of the equation. A very well-known model in AD research sketches the order in which different biomarkers of dementia start to show abnormal values [6]. In this model, biomarkers are either structural or neuropsychological; markers of brain dynamics are missing. However, when neurons degenerate, their behavior will inevitably change. At what stage will dynamic disturbances become manifest; only once profound structural damage has been done? Increasing evidence suggests the opposite. First, for the major risk factors of AD (age and ApoE status), direct associations with altered patterns of brain activity and connectivity have been reported [7–10]. Second, neuronal activity and functional connectivity are often already altered in early-stage AD [11–13]. Third, and perhaps most intriguing, experimental animal studies have revealed that local neuronal activity levels can directly influence interstitial β -amyloid concentration [14,15].

In short, an increasing number of studies suggest early involvement of brain dynamics in AD pathology. To go one step further: could it be that dynamic disturbances actually cause brain damage and/or malfunction? Although probably counterintuitive for many, from a network perspective the idea is not so strange; in many systems, dynamic activity can cause network dysfunction. Similar examples can be found in traffic jams, or temporary Internet server failures due to massive demand. It is also well established that in many human organs excessive activity can lead to pathologic damage, for example, due to high metabolic demands and oxidative stress. The brain, by far the most active organ in our body, devotes approximately 80% of its energy to cellular communication. Considering the constantly high levels of neuronal activity throughout the brain, regardless of what we are doing, the idea may not sound so far-fetched after all.

In a recent computational modeling study, we have shown that an ‘activity dependent degeneration’ regime, which involves the simple assumption that high local levels of activity lead to degeneration, reproduces virtually all neurophysiological AD-related hallmarks such as oscillatory slowing, loss of functional coupling and specific

graph theoretical disturbances of functional network structure [16]. In addition, the observation that the most active and thus vulnerable regions show a striking overlap with the highest levels of amyloid deposition in AD may provide an explanation for the nonrandom pattern of pathology across the brain. We, therefore, conclude that there may well be a prominent role for dynamics in the AD mechanism. Of course, this prediction needs to be verified in patient data, but the resemblance of activity-dependent degeneration and AD-induced damage is intriguing.

A substantial role of disturbed dynamics in AD could have profound implications for therapeutic interventions, since neuronal activity can be influenced in many pharmacological and nonpharmacological ways. Recently, antiepileptic drugs have been shown to have a positive effect on cognition in mild cognitive impairment patients by reducing excessive hippocampal activity [17]. However, nonpharmacological approaches such as deep brain stimulation and transcranial magnetic stimulation have also shown encouraging results [18,19]. However, complex networks behave in unpredictable ways, and studies assessing the effect of various therapeutic agents on large-scale neuronal activity and functional network organization could help to inform future interventional strategies.

In summary, it is about time we start to focus on the brain’s software. A neglect of the brain’s dynamic nature and organization is a serious conceptual limitation, since it ignores the question of how cognitive processes are coordinated throughout the brain. We are getting better at describing and interpreting the disruption of coordinated brain dynamics, and this may fill the gap in our knowledge between brain damage and cognitive symptoms. Should disturbed brain dynamics indeed play a significant role in AD pathophysiology, as is suggested by the studies mentioned above, its systematic description and analysis could open up a whole new direction of diagnostic, prognostic and therapeutic strategies.

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