EC Neurology Editor's Column - 2017

Alzheimer's Dementia and Global Self Circuits: A New Degenerative Model?

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ABSTRACT

Recent findings have helped to consolidate a dynamical portrait of Alzheimers dementia that show a specific impact on the brain's ability to construct a self-image used for regional entrainment.

Keywords: *Alzheimer's Dementia; Self-Image*

INTRODUCTION

Improved medical care has significantly extended life expectancies, shifting demographic profiles of the elderly world-wide; yet it has also greatly increased the numbers of patients suffering age-related cognitive deficits. According to United Nation's projections nearly 20% of the world population will be 60 or more years of age by 2050, with considerably higher percentages in developed nations, placing large numbers of individuals at risk [1]. The most prevalent neurodegenerative disease among the elderly is Alzheimer's Dementia (AD). Its lifetime risk above 60 is calculated at 33% in males and 45% in females, and its anticipated growth is expected to exceed nearly 100% that of current levels in developed nations. Disturbingly, a more than 300% increase is anticipated in Southeast Asian countries, including India, China, and their neighboring states [2].

AD displays an insidious onset and progresses relentlessly until the death of the patient in ten to fifteen years. Patients present with limb apraxia and exhibit neuropsychological profiling that includes dyscalculia, phonological alexia, and dysgraphia. Episodic memory loss is correlated with reduced hippocampal cholinergic markers, a finding that initially led to the cholinergic hypothesis for AD [3]. Based on the prevalence of b-amyloid plaques and hyper tau phosphorylation, today's prevailing model is the amyloid cascade hypothesis. This widely accepted model proposes that cleavage of b-amyloid precursor protein initiates a pathologic cascade involving caspases, enzymes participating in programmed cell death. Writing on the occasion of the 100th anniversary of Alloys Alzheimer's first description of the disease in 2006, however, Dr K Jellinger of the Institute of Clinical Neurobiology, Vienna, stated 'that despite considerable progress in the clinical diagnosis, neuroimaging, genetics, molecular biology, neuropathology, defining risk factors, and treatment, the etiology of the disease is still unknown and, therefore, a causal treatment of AD will not be available in the near future' [2].

The absence of causal therapies, despite the wide variety of investigative approaches undertaken to characterize its etiology seems to indicate, in fact, that rather than identifying the disease's causal origin, the hypothetical models and experimental techniques are characterizing disease features lying outside the critical etiological domain of

Citation: Denis Larrivee. "Alzheimer's Dementia and Global Self Circuits: A New Degenerative Model?". EC Neurology ECO.01 (2017): 30-32.

AD. Expanding the investigative range may offer, therefore, more promise for their identification. This new situation may be underway soon.

To date, how the brain coordinates behavioral activity has proved elusive, an understanding of global brain operation likely to prove significant for AD, which has been implicated in affecting a fundamental brain network needed for perception of the self, the default mode network (DMN) [4]. Experimental approaches have for the most part been incapable of directly monitoring behaviorally relevant, neural activity. For example, magnetic resonance imaging (MRI) has been widely used due to its relatively high spatial resolution, but the metric that it assesses, neuronal, activity dependent, hemodynamic flow, is several orders of magnitude slower than the neuronal activity it is intended to measure. Electropotential recording, on the other hand, while offering considerably improved temporal resolution is increasingly challenged on theoretical grounds for its inability to discriminate brain activity that is functionally significant. The challenge that is encountered is related to the brain's need to use dynamically stable elements like attractors that are only indirectly dependent on Hodgkin Huxley electrical activity. The assessing of dynamical activity has, in turn, generated theoretical models that are largely abstracted from the physical events the models are intended to represent.

Recent studies, however, are exploiting a novel parameter of dynamical activity termed the metastability index that assesses the ability of the brain to exercise global coordination over regional activity [5,6]. This index measures the variation of interareal coherence, which is high in DMN exploratory modes and low in coupled regionally entrained ones. The index, therefore, is likely to assess whether a basic perceptual construct associated with global brain dynamics is selectively altered in AD patients.

A paper from the Oslo University Hospital and Institute of Clinical Medicine, Norway, purports to have done just that [7]. Together with a cluster of other critical findings, this one is helping to consolidate a portrait that shows that the disease impacts the brain's ability to construct a dynamical self-image employed for regional entrainment.

The evidence for this specific effect on the self-construct is three fold, and is framed against the backdrop of a number of studies that demonstrate a basic need for structuring a coherent and stable self-image in order to intentionally engage external events in the world [8]. First, Alzheimers specifically affects DMN operation [7,9], a self-designated domain. First identified by nuclear imaging studies that showed consistently higher levels of activity during passive task conditions, the DMN was hypothesized to monitor the external environment, body, and even emotions [4]. Task related increases in activity in regional brain zones coincided with its decreased activity, indicating a reciprocal relation between the two zones related to the performative state of the task. Functional MRI shows that these relative activity levels are substantially and progressively altered by Alzheimers [9]. In AD patients posterior cingulate and right inferior temporal cortical activities, for example, decline whereas the activity of the bilateral inferior parietal cortex increases. Because the zones form causally significant, central connectivity hubs within the DMN the activity changes appear to reflect a weakening of causally influential relations among its principal nuclei [10]. Second, the impact of altered connectivity appears to implicate global dynamical activity, seen in altered oscillatory patterns of the electroencephalogram in the AD patient [11]. Global oscillatory profiles, notably, are invoked as mechanisms for conferring inter areal coupling between brain regions for synchronized activity. Third, metastability indices for AD patients are reduced in decoupled, desynchronized states, revealing the disease progression significantly reduces the brain's ability to locally entrain regional dynamical activity.

Together these data are significant for relating neuronally specific, temporally coincident events to a basic perceptual construct for self-identification, and are helpful for explaining why Alzheimers is cognitively devastating. By impacting the brain's ability to construct a sense of self-awareness the patient's capacity to interact with exterior events is progressively lost as this sense is gradually diminished. The identification of a physiologically pertinent global dynamic, on the other hand, offers promise for targeted research into AD's causal etiology. The promise of this research may also foreclose pessimistic prognostications.

CONFLICT OF INTEREST

None.

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