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Commentary

Retrogenesis: A Model of Dementia Progression in Alzheimer's Disease Related to Neuroplasticity

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Rubial-Alvarez et al. [1] analyzed 181 children (ages 4 to 12 years) and 148 adults, ranging from normal to severe dementia (approximate ages 65 to 95 years), using the Mini-Mental State Exam [2], an intelligence test, the Global Deterioration Scale [3], and an activities of daily living measure, in order to test the "retrogenesis model" of Alzheimer's disease (AD) [4]. The Rubial-Alvarez et al. analysis supports the concept that the general pattern of childhood development is approximately recapitulated in reverse order by the pattern of deterioration associated with the continuum of AD progression from normal adult cognition through "mild cognitive impairment" and the stages of dementia to the most profound, complete state. The specific comparisons indicate that normal adult function is fairly well approximated by a 12 year old individual, while mild dementia is comparable to the level of function of a 5 to 6 year old child, and moderate dementia is similar to the function of a 4 year old. However, there were some expectable deviations from the retrogenesis model, particularly in activities of daily living.

It has been well established that cognitive and functional deterioration in AD follows a generally uniform course [5]. While the retrogenesis model is compelling and useful, there are several points that should be carefully addressed in the examination of this model, including heuristic and neuropathological issues.

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First, the pattern of dementia deterioration does not precisely mirror the pattern of childhood development. Needless-to-say, children have excellent memories and learn age appropriate material quickly, while dementia itself begins selectively as a memory problem [6, 7]. Further, the specific ordinal pattern loss of items and functions during the course of the dementia associated with AD [8] is most closely related to the progressive deterioration of memory function (e.g., inability to remember what groceries need to be purchased or what objects are called, rather than being unable to organize a shopping trip or being unable to pronounce specific words). A specific "item-analysis" along the developmental continuum would highlight the divergences between the courses of childhood development and dementia. Further, a "time-index" analysis of the AD-type dementia progression [7, 9, 10] would provide direct contrast of the temporal patterns of development and dementia, which are only roughly comparable in this study.

The issue of great relevance regarding the retrogenesis model for AD pathology is the potential for understanding the neuronal vulnerability underlying AD. While the explanation of retrogenesis as a consequence of reversal of developmental myelination patterns [11] is interesting, the similarity is not close enough to be accepted as relevant. Further, with the definition by Brun & Englund of the pathological pattern of AD as affecting the posterior temporal and inferior parietal lobes [12] and the pathological analysis of Braak & Braak [13] showing the initiation

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and spread of tau pathology from the entorhinal cortex to the selected cortical regions, this pattern most closely follows the pattern of the AD dementia course, both through cross-sectional and longitudinal examination of brain blood flow [14, 15] and metabolism [16]. This well-established pattern of neuroanatomical progression demonstrates a much different pattern than the myelinization order. Specifically, the pattern of progressive development of tau pathology is what corresponds to the loss of all daily living and cognitive functions along the course of dementia progression. This tau pattern also contrasts with the deposition of amyloid-β, which has recently been shown to have a very long course, initially involving the frontal lobes and not corresponding to functional deficits [17–19].

In the examination of the progression of tau pathology, an important point to consider is the relationship of AD to neuroplasticity [20, 21]. Braak & Braak [13] have shown that the initial AD changes are in the entorhinal transitional neurons, which project through the perforant path to the dentate gyrus. Recent studies have shown in mouse models how tau pathology is manifest at the distal terminations of axons, and how the portions of dendrites most distant from the neuronal cell bodies are initially affected with hyperphosphorylated tau [22, 23]. Presumably the pattern of dendritic components most distal from the neuronal cell bodies, the most plastic and dynamic, being the most vulnerable to tau pathology, is a feature common to the regions of the brain affected by AD pathology. This characteristic of hyperphosphorylated tau developing in vulnerable distal dendrites followed by the hyperphosphorylated tau transformation into paired-helical filaments, twisting into neuropil threads, which get transported retrogradely back to the cell body to form neurofibrillary tangles, is the likely course of events most related to the development of dementia in AD. The neuropil threads likely clog neurons, leading to massive loss of distal dendrites and thus distal synapses [24], which is the factor most closely related to dementia in AD [25]. Loss of proximal synapses and the basal trunk of the dendrite's tree likely occur late in the process, and cell death is not clearly a contributor to dementia. Following this line of reasoning, the critical comparison between the course of dementia and child development is that neuronal processes, particularly dendrites, grow to increasingly greater lengths throughout life [26], initially laying down substrates of basic developmental functions (dendritic branch patterns and synaptic connections) closer to the neuronal cell bodies, and more complex function in the intricate connections of the distal components of the dendrites. This perspective of reversal of neuroplastic growth suggests how the retrogenesis model may support the currently developing concepts of how the progressive tau pathology may mimic the Piagetian course of cognitive and functional development. (A critical side note is that synapse counts progressively decline through later development from about age 3 years until adulthood, with massive losses occurring in AD. The constant, high-volume formation and removal of synapses is the central component of neuroplasticity affected by AD. Thus, synapse counts do not have a reciprocal relationship between childhood development and AD progression).

The important role of the retrogenesis model is to demonstrate both the central similarities and critical differences between development and the course of AD. This model can help to provide a foundation for the understanding of AD pathology, which really needs to be achieved before successful strategies for AD prevention or treatment can be found.

DISCLOSURE STATEMENT

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=1544).

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