Journal of Alzheimer's Disease 33 (2013) 1191–1193
DOI 10.3233/JAD-2012-121124
IOS Press

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

ISSN 1387-2877/13/$27.50

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).

REFERENCES

[1] Rubial-Álvarez S, de Sola S, Machado M-C, Sintas E, Böhm P, Sánchez-Benavides G, Langohr K, Muñiz R, Peña-Casanova J (2013) The comparison of cognitive and functional performance in children and Alzheimer's disease supports the retrogenesis model. *J Alzheimers Dis*, in press.

[2] Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189-198.

[3] Reisberg B, Ferris SH, de Leon MJ, Crook T (1982) The global deterioration scale for assessment of primary degenerative dementia. *Am J Psychiatry* **139**, 1136-1139.

[4] Reisberg B, Franssen EH, Hasan SM, Monteiro I, Boksay I, Souren LE, Kenowsky S, Auer SR, Elahi S, Kluger A (1999) Retrogenesis: Clinical, physiologic, and pathologic mechanisms in brain aging, Alzheimer's and other dementing processes. *Eur Arch Psychiatry Clin Neurosci* **249**(Suppl 3), 28-36.

[5] Ashford JW, Kumar V, Barringer M, Becker M, Bice J, Ryan N, Vicari S (1992) Assessing Alzheimer severity with a global clinical scale. *Int Psychogeriatr* **4**, 55-74.

[6] Ashford JW, Kolm P, Colliver JA, Bekian C, Hsu LN (1989) Alzheimer patient evaluation and the mini-mental state: Item characteristic curve analysis. *J Gerontol* **44**, P139-P146.

[7] Ashford JW, Shan M, Butler S, Rajasekar A, Schmitt FA (1995) Temporal quantification of Alzheimer's disease severity: 'Time index' model. *Dementia* **6**, 269-280.

[8] Ashford JW (2008) Screening for Memory disorder, dementia, and Alzheimer's disease. *Aging Health* **4**, 399-432.

[9] Ashford JW, Schmitt FA (2001) Modeling the time-course of Alzheimer dementia. *Curr Psychiatry Rep* **3**, 20-28.

[10] Ashford JW, Schmitt F, Kumar V (1998) Diagnosis of Alzheimer's disease. In *Advances in the Diagnosis and Treatment of Alzheimer's Disease*, Kumar V, Eisdorfer C, eds. Springer Publishing Company, New York.

[11] Choi SJ, Lim KO, Monteiro I, Reisberg B (2005) Diffusion tensor imaging of frontal white matter microstructure in early Alzheimer's disease: A preliminary study. *J Geriatr Psychiatry Neurol* **18**, 12-19.

[12] Brun A, Englund E (1981) Regional pattern of degeneration in Alzheimer's disease: Neuronal loss and histopathological grading. *Histopathology* **5**, 549-564.

[13] Braak H, Braak E (1991) Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol* **82**, 239-259.

[14] Ashford JW, Shih WJ, Coupal J, Shetty R, Schneider A, Cool C, Aleem A, Kiefer VH, Mendiondo MS, Schmitt FA (2000) Single SPECT measures of cerebral cortical perfusion reflect time-index estimation of dementia severity in Alzheimer's disease. *J Nucl Med* **41**, 57-64.

[15] Shih WJ, Ashford JW, Coupal JJ, Ryo YU, Stipp VV, Magoun SL, Gross K (1999) Consecutive brain SPECT surface three-dimensional displays show progression of cerebral cortical abnormalities in Alzheimer's disease. *Clin Nucl Med* **24**, 773-777.

[16] Bohnen NI, Djang DS, Herholz K, Anzai Y, Minoshima S (2012) Effectiveness and safety of 18F-FDG PET in the evaluation of dementia: A review of the recent literature. *J Nucl Med* **53**, 59-71.

[17] Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, Trojanowski JQ (2010) Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol* **9**, 119-128.

[18] Morris JC, Roe CM, Xiong C, Fagan AM, Goate AM, Holtzman DM, Mintun MA (2010) APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. *Ann Neurol* **67**, 122-131.

[19] Vlassenko AG, Mintun MA, Xiong C, Sheline YI, Goate AM, Benzinger TL, Morris JC (2102) Amyloid-beta plaque growth in cognitively normal adults: Longitudinal [11C] Pittsburgh compound B data. *Ann Neurol* **70**, 857-861.

[20] Ashford JW, Jarvik L (1985) Alzheimer's disease: Does neuron plasticity predispose to axonal neurofibrillary degeneration? *N Engl J Med* **313**, 388-389.

[21] Teter B, Ashford JW (2002) Neuroplasticity in Alzheimer's disease. *J Neurosci Res* **70**, 402-437.

[22] Liu L, Drouet V, Wu JW, Witter MP, Small SA, Clelland C, Duff K (2012) Trans-synaptic spread of tau pathology *in vivo*. *PLoS One* **7**, e31302.

[23] de Calignon A, Polydoro M, Suarez-Calvet M, William C, Adamowicz DH, Kopeikina KJ, Pitstick R, Sahara N, Ashe KH, Carlson GA, Spires-Jones TL, Hyman BT (2012) Propagation of tau pathology in a model of early Alzheimer's disease. *Neuron* **73**, 685-697.

[24] Ashford JW, Soultanian NS, Zhang SX, Geddes JW (1998) Neuropil threads are collinear with MAP2 immunostaining in neuronal dendrites of Alzheimer brain. *J Neuropathol Exp Neurol* **57**, 972-978.

[25] Scheff SW, Price DA, Schmitt FA, Scheff MA, Mufson EJ (2011) Synaptic loss in the inferior temporal gyrus in mild cognitive impairment and Alzheimer's disease. *J Alzheimers Dis* **24**, 547-557.

[26] Buell SJ, Coleman PD (1981) Quantitative evidence for selective dendritic growth in normal human aging but not in senile dementia. *Brain Res* **214**, 23-41.