Published in final edited form as:

Biochem Pharmacol. 2014 April 15; 88(4): 677–681. doi:10.1016/j.bcp.2013.11.017.

The End of Alzheimer's disease - from biochemical pharmacology to ecopsychosociology: a personal perspective

Peter J Whitehouse

Department of Neurology Case Western Reserve University, Cleveland, Ohio, USA and

Department of Medicine, University of Toronto, Toronto, Ontario, Canada

Abstract

The future of the Alzheimer's disease (AD) field involves a more complete understanding not only the state of current scientific approaches, but also the linguistic and cultural context of preclinical and clinical research and policy activities. The challenges surrounding dementia are large and growing but are only part of broader social and health concerns. In this latter context, the current state of research in the AD area is reviewed together with necessary priorities in moving forward. Creating a more optimistic future will depend less on genetic and reductionist approaches and more on environmental and intergenerative approaches that will aid in recalibrating the study of AD from an almost exclusive focus on biochemical, molecular and genetic aspects to better encompass "real world" ecological and psychosocial models of health

Keywords

dementia; Alzheimer's disease; amyloid; psychosocial

1. Introduction

Identifying future directions by which to travel on the complex map of what has become called the Alzheimer's field involves understanding not only the state of the art in current day science, but also the language that is used to characterize the challenges and the cultural context in which basic and clinical research and policy making activities occur. The future of this key area of human endeavor is critically dependent on what happens to human beings in general and while the social concerns surrounding dementia, including Alzheimer's disease (AD), are huge by no means do they represent the only social, economic, and health challenges. A more hopeful future can- and must - be created but this depends on learning the lessons from the last few decades of AD research. The principal lesson for this quarter century veteran basic and clinical scientist researcher is that we need less genetic and reductionist science and more environmental and intergenerative approaches to move from biochemical/ molecular pharmacology to ecopsychosociology [1,2]. For those committed to applying scientific approaches to dementia, as I am, appreciating the bigger social picture is critical.

© 2013 Elsevier Inc. All rights reserved.

Correspondence 2895 Carlton Road, Shaker Heights, OH 44122 Ph 216 464 6449 peter.whitehouse@case.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Words and stories matter greatly in this process of change. *Intergenerative* is a new word that focuses attention on innovation via the exploration of the spaces between concepts like disciplines and professions. Thus the future poses intergenerational ethical issues that the relative distribution of resources to children and elders and to those with dementia now and those threatened by it in the future. *Ecopsychosocial* is another new term designed to extend the biopsychosocial model of health by making explicit the need to view ecology as a dominant form of biological thinking in relationship to disease (1). Ultimately evolutionary anthropological approaches in medicine are needed that look at changes in genes and environment over time in relationship to each other and to culture.

In this review I will explore the larger context of work in dementia focusing on aging, health, the environment, economics and ethics and will then examine the state of the science in relationship to these broader perspectives. Finally I will end with a brief discussion of priority setting and next steps that should be considered.

2. Context

Aging demographics are often repeated like a mantra in the field of AD to emphasize the growing number of elders at risk for dementia. Statistics are used to calculate that someone is newly affected (diagnosed or labeled?) by AD every minute and that in the future that rate will accelerate. Moreover we are driven to believe that early diagnosis will improve outcomes, although how early and of what and for what purpose are questions that are only rarely asked. Moreover, language such as the metaphor of the “silver tsunami” creates fear in individuals and social planners alike [2] with the implicit message that hope can only be attained via initiatives like the National Plan to Address AD targets 2025 that are intended to end (cure?) this condition (<http://aspe.hhs.gov/daltcp/napa/natlplan.shtml>). For decades and year after year there has been an almost obsessive ritual of making claims that within five years there will be cure or at least an effective intervention for AD, the outcome from which is inevitably unrealized. How long: i) can the assertion that we are close to a cure maintain its credibility (if it has not already been lost) and, ii) do repeated claims of breakthroughs lead to a breakdown of trust?

Within the context of a demographic shift in the number of at-risk elders is also a cultural shift towards reinventing aging itself. Many, but not all baby boomers, will live healthier, longer lives with 72 now being described as the “new 30” [3] creating a new phase of life between career and/or family raising-oriented adulthood and post-career, frail elder hood. This “encore” period has been called many things, including Adulthood II, and may represent a new phase of life as important as adolescence, a similar type of age category concept invented in the early 1900s [4] The next generation of elders will be different and is, for example, slowly beginning to take more charge of their own brain health in creative ways through life-style and nonmedical integrative alternatives.

Attitudes about health care are also changing resulting in significant transformations in existing healthcare systems. Chronic diseases of all kinds are becoming more common, not only in elders, but also in children [5]. Individuals are being increasingly asked to take more responsibility for their own health through programs of chronic disease self-management (4) such that the provision of healthcare services in homes and the community, rather than institutions such as hospitals, is desirable. How individuals with varying degrees of cognitive impairments will deal with this increased responsibility and control of their own health is uncertain. Navigating healthcare systems is difficult enough for people with normal intellectual abilities, let alone those with dementia. Chronic disease self-management programs will therefore have to have as a priority the need to adapt to having participants who might have trouble learning and ultimately changing their behaviors.

An even larger and more troubling context of research and care in AD includes the interrelated issues of global climate change, economic inequity, and social/political/religious unrest (6). The epidemiology of dementia will change with, for example, more head injuries related to global conflict and natural disasters and changes in the patterns of infectious diseases affecting the nervous system, like malaria. Individuals with dementia will similarly be more at risk for harm from environmental events like droughts, floods, and storms. As public health disasters will likely consume more and more of our health care dollars, economics will likely continue to stutter along as a focus on growth and development reaches the limits of available and essential natural resources. The education and health of children will also become even more important social priorities as dependency ratios (number of old retirees to young working citizens) increase. The foundations of modern industrial and agricultural capitalism, e.g., dependency on fossil fuels, are crumbling as society looks for new ways of accounting natural resources through the triple business bottom lines of people, planet and profits. Capitalism itself is being reframed as conscious or natural capitalism with greater attention to social and environmental responsibility [7].

The emergence of information technology is a vital source of innovation. Mobile computing, social networking, augmented reality, gamification, digital multimedia and transmedia, together with increasingly smarter and more sympathetic computers and other digital devices, e.g. Google Glass, will transform the consequences of aging and help humans in general with their own cognitive challenges (including dementia). But this technology will not only support intellectual activities like education and research, but the arts and humanities and other aesthetic and value-related endeavors. Dance, supported by multimedia or not, is an ideal form of integrated physical movement, music, cognitive and social activity and storytelling. So-called brain fitness approaches e.g. Luminosity, Brain HQ, while subject to exaggeration offer real promise (8). Creating new narratives (9) in innovative learning spaces will also provide a beacon of new hope (10,11,12).

A new intergenerational ethic is needed in this complex world in which “presentism” (choosing priorities based on the needs of current rather than future generations, ironically a form of belief which might be due for some more emphasis in the AD field) often dominates. Whether it be the materialistic me-too generation or the next quarter financial performance orientation of corporations, we need to change to frameworks of engagement with the world that support thinking and valuing for the long-term. Science as a religion, i.e. scientism, needs to be challenged when unbridled faith in progress leads to unrealistic and self-serving claims for future therapeutic breakthroughs. An extreme example of this false hope is the anti-aging medicine practitioners of the world who claim that aging itself is a disease process that can be eliminated or even reversed [13]. The agenda of these anti-aging “scientists” resembles that of “legitimate” biogerontologists who share similar expectations that better understanding of the biology of aging will lead to treatments for age-related infirmities. But the anti-aging movement claims that aging is an actual disease and that we can slow aging today with various pills and potions and eventually cure it tomorrow. If AD shares the same biology as forms of severe brain aging (and there is really no convincing and consistence evidence to the contrary), then how do we distinguish quackery and pseudoscience from the excessive promises of the mainstream AD science establishment? How can an evangelical genomics that claims an understanding of DNA as the foundation for defining health be challenged for ignoring the effects of the environment on genes and health i.e. microepigenetic as well as macroecological disease-related issues? The promises of financially rewarding intellectual property (IP) is the basis of the pharmaceutical industry with even the patenting of genes being possible, although is now more controversial [14]. The pharma industry has become perceived as a “for profit” monster lacking in ethics where billions of dollars of fines (for inappropriate influences on physicians and excessive marketing claims) appear to be a standard part of business planning [15, 16]. This unethical

behavior all too often extends to physicians and other health care practitioners but may be in the process of achieving balance with grassroots pushbacks on drug prices [17, 18]. Since the AD field is based on true hype and much false hope, expectations for the future will be based on taking a deep and honest look at where the field has been, is currently and then being open to other possibilities that may well change current concepts about the nervous system, aging, expertise, science, and for-profit models.

3. State of the science

During the past 25 years we have seen two hypotheses dominate the AD research field, the arguably true but limited so-called cholinergic hypothesis [19,20] and the currently fashionable but weakening amyloid hypothesis [21,22]. Both can be framed more narrowly in clinical and scientific terms but as general claims to importance they reflect more the current practices, politics, and fads of the Alzheimer field and science in general. The cholinergic hypothesis was based on a systems focus on neurotransmitters, their receptors and neural circuits and claimed that acetylcholine, especially nicotinic cholinergic systems, were important for memory and attention [19]. In AD and related dementias the cholinergic basal forebrain is characterised by neuronal loss. One could argue that this hypothesis was actually somewhat successful clinically as cholinesterase drugs were approved based on the scientific understanding of the role these networks play in normal cognition and disease. However at a social level these drugs have largely failed because economically, in terms cost utility analysis, they do not produce adequate benefit, i.e. improvements in quality of life, for individuals, particularly given the opportunity and social costs entailed (20).

When medical science in general moved from a systems neuroscience perspective to genetics and molecular biology, an opportunity emerged to replace the cholinergic hypothesis with one that was said to be more powerful, i.e. the amyloid hypothesis. Here the identification of the genes that affect amyloid processing in early onset, familial AD (EOAD) appeared to suggest that interventions at this level could lead to therapies that might more directly alter the basic pathogenesis and prevent cell death rather than merely improve neurotransmitter function [23]. The excitement, if not frenzy in the field, could be felt as scientists began to promise cures in a matter of years [24,25]. However, despite billions of dollars being spent on the basic biology and extensive clinical trials, largely focusing on therapeutics and vaccines that modified aspects of the amyloid cascade, there have been no effective therapies [22, 26]. Based on this science the study of mouse models almost literally replaced the study of human brains obtained at autopsy. Yet even though genetically manipulated mice do get “mouseheimers” disease, they do not get AD. While it is relatively easy to engineer transgenic mice to produce plaques and tangles, the genes, brains, behaviors and life span of mice are so different those of humans such that drawing conclusions from (especially often unreplicated) mouse studies is very difficult. Recent advances in imaging amyloid in the human brain using positron emission tomography [27] have reinforced efforts to identify a biomarker(s) to diagnose the disease and monitor therapy [28] although the government agency responsible for reimbursement decisions (Committee of Medicare and Medicaid Services; CMS) has, despite FDA approval, have declined to pay for amyloid imaging except under very limited clinical trial circumstances [29].

The problems with the amyloid hypothesis are many (21, 22, 26, 30,31,32) The so-called cascade from amyloid accumulation to cell death to clinical dementia includes many hypothetical steps that may not occur at all in all cases and especially not in a linear fashion one molecular step after another. It is unknown what amyloid-related proteins do normally [33] and it is unclear whether it is larger proteins or smaller oligomers that are responsible for any neural damage. The relationship between the amyloid plaque formation and

neurofibrillary tangles which themselves seem more closely related to neuronal dysfunction and death is also unclear [34]. Perhaps, most importantly it is well known that individuals can have considerable amyloid plaque in their brain and not have a clinically apparent dementia [35].

Perhaps the greatest problem with the amyloid hypothesis is not the lack of understanding regarding normal function, the role in pathogenesis or the myriad failure of current therapeutic approaches, but rather a set of problems identified during the earlier decades of study of the cholinergic hypothesis- AD is a heterogeneous disease state. Thus it is becoming clear that AD should not be considered a single condition (as a singular noun). Many competing hypothesis have emerged based on tangle formation, inflammation, oxidative damage, mitochondrial dysfunction, and others [26]. Perhaps the conclusion should not be that the amyloid hypothesis is somehow wrong and another one is correct but rather that they may all have an element of truth as “Alzheimer’s” likely includes a number of processes that affect people in different ways. Moreover despite the billions of dollars that have been spent it has not been established that there are fundamental differences between normal brain aging processes and what is viewed as AD could be viewed as severe brain aging (2).

Many older people really have mixed dementias in which the cognitive abilities present in late age are a function of many factors acting throughout life including environmental factors such as toxins and head injuries. Above 65 or so, almost every CT or MRI scan shows atrophy (loss of neurons to some degree) and nonspecific white matter “ischemic” changes [36].

Twenty-five years ago it was thought that the ability to differentiate the two major common causes of dementia, claimed to be degenerative processes like AD and vascular pathologies causing multi-infarct dementia or vascular dementia would improve with further research. It was also thought that biological studies would allow a clearer differentiation between the different kinds of degenerative diseases e.g., AD, Lewy Body Dementia, and Frontal Lobe Dementia. None of these efforts to create clear diagnostic categories have worked consistently as it has become clear that there are overlapping features in the various forms of dementia.

Three sets of expert panels have suggested new diagnostic criteria for AD and dementia (37–40). The two focusing on AD from the National Institute of Aging and Alzheimer’s Association (37–39) and the International Working Group (40) are somewhat inconsistent with each other. For example, the relative importance of memory symptoms and the use of the term mild cognitive impairment differ across the panels. The American Psychiatric Association’s Diagnostic and Statistical Manual 5 [41, 42] not only largely ignored the challenges in labeling AD and mild cognitive impairment but contributed to the general havoc with psychiatric nosology. Specifically, the attempt to re-label dementia as Major Neurocognitive Disorder and introduce Minor then Mild forms is controversial. Will it reduce stigma or increase confusion?

The claims that the failure of current generation therapies relate to not making an adequate early diagnosis abound and are equally applicable to therapeutics purported to work via anti-inflammatory or oxidative stress mechanism as those involving amyloid, the only difference being that when indomethacin fails to show clinical efficacy [43], the data are used to conclude that NSAIDs do not work in AD while for amyloid targeted therapeutics the results are ignored [22, 26]. There is also no real evidence that the current generation drug candidates work better when given earlier. Moreover we have been promised new effective

amyloid drugs for so long that we can legitimately be concerned about their ultimate success.

However both groups looking at AD nosology going forward suggest preclinical categories, such as so-called Asymptomatic Alzheimer's as well as the still controversial term Mild Cognitive Impairment (38, 39, 40). Obviously these schemes are dependent on biomarkers as by definition no symptoms have become apparent. However no biomarker has been adequately validated to be used clinically, specifically the current CSF and/or amyloid imaging tests are inadequate for accurate diagnosis [44, 45, 46, 47]. In the United States the FDA "approved" the use of two amyloid imaging agents but this approval did not require demonstrating clinical utility, only biological validity, i.e. they measure what they purport to assess. For the reasons discussed above, knowing the amount of amyloid in the brain is imprecisely related to clinical dementia. Yes it provides some information but what is the value of that information to individuals, families, and additionally to healthcare systems in general, especially given other competing health priorities to address. Fortunately, the government agency responsible for reimbursement decisions decided against reimbursement. [29].

The next five years will be critical to the amyloid hypothesis and the future of molecular reductionistic strategies in the field in general. Tens of billions have been pumped into clinical trials, mainly for amyloid vaccines. Two studies [48 49] being conducted in Colombia by Genentech and Banner Health and the Dominantly Inherited Alzheimer's Network (DIAN) Therapeutic Unit that have started recently are enrolling people with early onset dementia with autosomal dominant mutations. Even if these trials are positive (however that might be defined), their generalizability to late onset dementia is very uncertain. Would biologics used to treat young people with mutations work in an older person who often have mixed dementia? The so-called A4 study (50) involves people at risk for late onset dementia because of their ApoE status and "positive" amyloid imaging. The selection of the agent was made late in the design because it was a choice among weak alternatives. Solanezumab was picked even though it failed in earlier trials. Even if there are positive signals, many questions will remain. What might the real effects in daily life be on people with these conditions? Would they improve quality of life and for how long? What will the side effects be of their long-term administration? What would drugs in this class cost, if they were ever approved? The results of earlier vaccine trials do not offer many people encouragement that we will have realistic and hopeful answers to these questions.

4. Priorities for the future

We must essentially reverse priorities for the treatment of AD. Care must be viewed as more important than cure rather than the current message from the Alzheimer's Association and others that cure ("ending" Alzheimer's) is the answer. Even if effective drugs are developed, they might improve mortality (i.e. by keeping people out of nursing homes longer) and hence might not in the long term diminish the number of older people with cognitive impairment. If such drugs prolong life, they might actually increase health care costs and might even cause individuals to live longer with dementia rather than the hoped for goal of improving cognition but not affecting the age at which people die. Current drugs do not, and potential future drugs might not, improve quality of life. Evidence suggests psychosocial interventions, like educational and arts programs, do in fact have such a benefit (4,12). Supportive and enriching information technology (8) may be more important than biotechnology. Providing home-like community based programs should be more of a priority. In fact in the future society should work to improve the quality of eldercare communities in general. A dementia-friendly community is likely to be more comfortable for elders in general, children and in fact all the residents. AD is a cultural lever for social

change that is actually more important than even the enormous personal and social challenges age-related cognitive impairments themselves pose. Within the seeds of reconsidering the concept of AD lies the potential for deep reflection about the role of the brain in our lives, the processes of aging, the importance of science and also understanding its limitations, and the very nature of our individual human lives in community. Rethinking and revaluing so called AD can lead to social and economic benefits far beyond this unfortunate clinical label. Therein lies true hope in my view.

References

1. Whitehouse P, George D. The Aesthetics of Natural Elderhood. *Journal of Aging, Humanities, and the Arts*. 2010; 4:292–301.
2. Whitehouse PJ, George DR, D'Alton S. Describing the dying days of "AD". *Journal of AD*. 2011; 24(1):11–13.
3. Burger O, Baudischa A, Vaupela JW. Human mortality improvement in evolutionary context. *Proc. Natl. Acad. Sci. U.S.* 2013; 109:18210–18214.
4. Whitehouse P. Taking Brain Health to a Deeper and Broader Level. *Neurological Institute Journal*. 2010; (Spring Issue):17–22.
5. Murray CJL, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012; 380:2197–2223. [PubMed: 23245608]
6. Stein J, Schettler T, Rohrer B, Valenti M. Environmental threats to healthy aging with a closer look at Alzheimer's & Parkinson's disease. A Report by Greater Boston Physicians for Social Responsibility, Boston. 2008 http://www.agehealthy.org/pdf/GBPSRSEHN_HealthyAging1017.pdf.
7. Fyke JP, Buzzanell PM. The ethics of conscious capitalism: Wicked problems in leading change and changing leaders. *Human Relations*. 2013
8. George DR, Whitehouse PJ. Marketplace of memory: what the brain fitness technology industry says about us and how we can do better. *The Gerontologist*. 2011; 51(5):590–596. [PubMed: 21572161]
9. Whitehouse PW, George D. The Art of Personalized Medicine – Banking on Stories for Healthier Cognitive Aging. *The Lancet*. 2009; 373:1166–1167.
10. Whitehouse PJ, Bendezu E, Fallcreek S, Whitehouse C. Intergenerational Community Schools: A New Practice For a New Time. *Educational Gerontology*. 2000; 26(8):761–770.
11. George D, Whitehouse C, Whitehouse P. A Model of Intergenerativity: How the Intergenerational School is Bringing the Generations Together to Foster Collective Wisdom and Community Health. *J Intergenerational Relationships*. 2011; 9:389–404.
12. George DR, Whitehouse PJ. Intergenerational volunteering and quality of life for persons with mild-to-moderate dementia: results from a 5-month intervention study in the United States. *J Amer Geriatrics Society*. 2010; 58(4):796–797.
13. Holliday R. The extreme arrogance of anti-aging medicine. *Biogerontol*. 2009; 10:223–228.
14. Kesselheim AS, Cook-Deegan RM, Winickoff DE, Mello MM. Gene patenting - the Supreme Court finally speaks. *NEJM*. 2013; 369:869–875. [PubMed: 23841703]
15. LaMattina, J. Devalued and Distrusted: Can the Pharmaceutical Industry Restore its Broken Image?. Hoboken: Wiley; 2012.
16. Outtersson K. Punishing Health Care Fraud — Is the GSK Settlement Sufficient? *N Engl J Med*. 2012; 367:1082–1085. [PubMed: 22970920]
17. Hall SS. The Cost of Living. *New York* October 20, 2013. 2013 <http://nymag.com/news/features/cancer-drugs-2013-10/#print>.
18. Kantarjian HM, Fojo T, Mathisen M, Leonard A, Zwelling LA. Cancer Drugs in the United States: Justum Pretium—The Just Price. *J Clin Oncol*. 2013; 31:3600–3604. [PubMed: 23650428]
19. Bartus RT, DEarn RL III, Beer B, Lippa AS. The cholinergic hypothesis of geriatric memory dysfunction. *Science*. 217:408–414. [PubMed: 7046051]

20. Commission de la transparence. Médicaments de la maladie d'Alzheimer : à éviter. Prescrire Int. 2012 Jun.21(128):150. [Drugs for AD: best avoided. No therapeutic advantage]. PMID 22822592. [PubMed: 22822592]
21. D'Alton S, George DR. Changing perspectives on AD: thinking outside the amyloid box. Journal of AD : JAD. 2011; 25(4):571–581.
22. Krstic D, Knusel I. The airbag problem - a potential culprit for bench-to-bedside translational efforts: relevance for Alzheimer's disease. Acta Neuropath. Comm. 2013; 1:62.
23. Karran E, Mercken M, DeStrooper B. The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. Nat Rev Drug Dis. 2011; 10:698–712.
24. Hope J. Daily pill that halts Alzheimer's is hailed as 'biggest breakthrough against disease for 100 years'. MailOnline. 2008 www.dailymail.co.uk/health/article-1039677.
25. Chernin N. UTSW doctor says, 'I think we're going to cure Alzheimer's disease, and we're not far away from it' Dallas Morning News May 28, 2013. 2013 <http://www.dallasnews.com/lifestyles/health-and-fitness/health/20130527-utsw-doctor-says-i-think-were-going-to-cure-alzheimers-disease-and-were-not-far-away-from-it.ece>.
26. Mullane K, Williams M. Alzheimer's Therapeutics: Continued clinical failures question the validity of the amyloid hypothesis -but what lies beyond? Biochem. Pharmacol. 2013; 85:289–305. [PubMed: 23178653]
27. Villemagne VL, Klunk WE, Mathis CA, Rowe CC, Brooks DJ, Hyman BT, et al. A β Imaging: feasible, pertinent, and vital to progress in Alzheimer's disease. Eur J Nuclear Med Mol Imaging. 2012; 39:209–219.
28. Jack CR Jr, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 2013; 12:207–216. [PubMed: 23332364]
29. Committee of Medicare and Medicaid Services. Decision Memo for Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease (CAG-00431N). 2013. (http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=265&utm_medium=email&utm_source=govdelivery)
30. Smith MA, Atwood CS, Joseph JA, Perry G. Predicting the failure of amyloidbeta vaccine. Lancet. 2002; 359(9320):1864–1865. [PubMed: 12044411]
31. Castellani RJ, Lee H-G, Zhu X, Nunomura A, Perry G, Smith MA. Neuropathology of Alzheimer's Disease: pathognomonic but not pathogenic. Acta Neuropathol. 2006; 111:503–509. **2006**. [PubMed: 16718346]
32. Castellani RJ, Lee H-G, Zhu X, Perry G, Smith MA. Alzheimer disease pathology as a host response. J. Neuropathol Exp. Neurol. 2008; 67:523–531. [PubMed: 18520771]
33. Hardy J. The relationship between amyloid and tau. J Mol Neurosci. 2003; 20:203–206. [PubMed: 12794314]
34. Luan K, Rosales JL, Lee KY. Viewpoint: Crosstalks between neurofibrillary tangles and amyloid plaque formation. Ageing Res Rev. 2013; 12:174–181. [PubMed: 22728532]
35. De Meyer G, Shapira F, Vanderstichele H, Vanmechelen E, Engelborghs S, De Deyn PP, et al. Diagnosis-independent Alzheimer disease biomarker signature in cognitively normal elderly people. Arch Neurol. 2010; 67:949–956. 2010. [PubMed: 20697045]
36. Brayne C, Richardson K, Matthews FE, Fleming J, Hunter S, Xuereb JH, Paykel E, Mukaetova-Ladinska EB, Huppert FA, O'Sullivan A, Denning T. The Cambridge City Over-75s Cohort CC75C Study Neuropathology Collaboration. Neuropathological Correlates of Dementia in Over-80-Year-Old Brain Donors from the Population-Based Cambridge City over-75s Cohort (CC75C) Study. J Alzheimer's Disease. 2009; 18:645–658. [PubMed: 19661624]
37. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, et al. The diagnosis of dementia due to AD: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for AD. Alzheimer's dementia. 2011; 7(3):263–269.
38. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of AD: recommendations from the National Institute on Aging-Alzheimer's

- Association workgroups on diagnostic guidelines for AD. *Alzheimer's dementia*. 2011; 7:280–292.
39. Albert MS, DeKosky ST, Dickson DW, Dubois BB, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to AD: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for AD. *Alzheimer's Dementia*. 2011; 7:270–279.
40. Dubois B, Feldman H, Jacova C, Cummings J, DeKosky S, Barberger-Gateau P, et al. Revising the definition of AD: a new lexicon. *Lancet Neurol*. 2011; 9:118–1127.
41. Blazer D. Neurocognitive Disorders in DSM-5. *Am J Psychiatr*. 2013; 170:585–587. [PubMed: 23732964] George DR, Whitehouse PJ, Ballenger J. The evolving classification of dementia: placing the DSM-V in a meaningful historical and cultural context and pondering the future of "Alzheimer's". *Culture, Medicine and Psychiatry*. 2011; 35(3):417–435.
42. de Jong D, Jansen R, Hoefnagels W, Jellesma-Eggenkamp M, Verbeek M, et al. No Effect of One-Year Treatment with Indomethacin on Alzheimer's Disease Progression: A Randomized Controlled Trial. *PLoS ONE*. 2008; 3(1):e1475. [PubMed: 18213383]
43. Flood D, Marek G, Williams M. Developing predictive CSF biomarkers - a challenge critical to success in Alzheimer's disease and neuropsychiatric translational medicine. *Biochem Pharmacol*. 2011; 81:1422–1434. [PubMed: 21295552]
44. Anderson DC, Kodulka K. Biomarkers in Pharmacology and Drug Discovery. *Biochem. Pharmacol*. 2014 in press.
45. George DR, Qualls SH, Camp CJ, Whitehouse PJ. Renovating Alzheimer's: 'Constructive' Reflections on the New Clinical and Research Diagnostic Guidelines. *Gerontologist*. 2012:1–12. 2012.
46. Whitehouse PJ, George DR. Uncertain progress on the fuzzy boundaries of AD: reading between the guidelines. *J Alz Dis*. 2011; 26:1–5.
47. Belluck P. New Drug Trial Seeks to Stop Alzheimer's Before It Starts. *New York Times*. 2012 <http://www.nytimes.com/2012/05/16/health/research/prevention-is-goal-of-alzheimers-drug-trial.html>.
48. Corbyn Z. New set of Alzheimer's trials focus on prevention. *Lancet*. 2012; 381 614-5.47.
49. Langbaum JB, Fleisher AS, Chen K, Ayutyanont N, Lopera F, Quiroz YT, Caselli RJ, et al. Ushering in the study and treatment of preclinical Alzheimer disease. *Nature Rev Neurol*. 2013; 9:371–381. [PubMed: 23752908]

Fig 1.

Intergenerative relationships from a genetic biochemical pharmacology to nature-rooted ecopsychsociology. This diagram shows the many levels of analysis that required for a broader, integrated understanding of ageing associated cognitive challenges like so-called Alzheimer's disease.