National Alzheimer's Project Act (NAPA)

The information that follows was included as an attachment to an email submitted by the public.

For more information about NAPA, visit the NAPA website at:

http://aspe.hhs.gov/national-alzheimers-project-act

Journal of Alzheimer's Disease 26 (2011) 1–11
DOI 10.3233/JAD-2011-111142
IOS Press

Hypothesis

What to Look for Beyond "Pathogenic" Factors in Senile Dementia? A Functional Deficiency of Ca^{2+} Signaling

Ming Chen[a,b,*], Huey T. Nguyen[a] and Darrell R. Sawmiller[a]
[a]*Aging Research Laboratory, Bay Pines VA Healthcare System, Bay Pines, Florida, USA*
[b]*Department of Molecular Pharmacology and Physiology, University of South Florida College of Medicine, Tampa, Florida, USA*

Accepted 3 August 2011

Abstract. We have contended that senile conditions—illnesses after age 60 and fully age-penetrating, such as tooth, hearing or memory loss—are not distinct "diseases" in medical nature, because they are caused by aging. Since the pace of aging varies among individuals and is much influenced by risk factors, senile conditions will only affect some but not all elderly. However, perhaps due to its unusually heavy burdens and tremendous social pressures, senile dementia (SD) has been singled out from other senile conditions and redefined as a curable "disease" (Alzheimer's). This highly popular definition has thus opened a Pandora's box that has been confusing us up until now and warrants further scrutiny. In this article we discuss: a) what should we logically look for in SD beyond "pathogenic" factors? b) why Ca^{2+}, a central regulator in neurotransmission, should be the primary player in SD; c) why the functionality of Ca^{2+} signaling, or its vibrant wave frequency and amplitude, must undergo down-regulation during aging, though this is intriguingly accompanied by an increase of Ca^{2+} "levels"; d) why intervention for SD should target Ca^{2+} function by promoting energy metabolisms and by Ca^{2+} agonists such as caffeine and nicotine, but not by "antagonists" as widely believed; and e) why our study should focus on aging, not "cell death", a seemingly attractive paradigm but perhaps too late for intervention. We also seek answers for why unproven hypotheses can become dogmas and inhibit self-correcting mechanisms of science.

Key words: Alzheimer's disease, amyloid, calcium, review

THE RISE OF THE QUESTION

Senile dementia (SD), discussed here mainly as its plaque-tangle subtype; also known as "SD of Alzheimer type", or "Alzheimer's disease" (AD), is a heart-breaking and socially threatening disease. Its pathogenesis has remained a conundrum after most intense studies for over three decades [1, 2] and, despite rhetoric to the contrary, there seems no major progress expected any time soon. This stagnation contrasts sharply with many other distinct diseases whose pathogenic causes were found in much shorter time with much fewer researchers involved (e.g., polio and AIDS).

This has prompted us to undertake an independent analysis of the SD features and realize that the current definition for SD by the National Institute on Aging (NIA) is the starting point of the problem [3, 4]. Our main viewpoints are as follow:

- Among the loosely defined "age-related" diseases, there should be a group of clearly and easily defined ones: those that occur after age 60

*Correspondence to: Ming Chen, Aging Research Laboratory, Bay Pines VA Healthcare System, Bay Pines, Florida, USA. E-mail: ming.chen@va.gov.

ISSN 1387-2877/11/$27.50

and eventually affect >50% of the elderly, such as atherosclerosis, osteoporosis, and SD. These illnesses, referred to here as "senile conditions", may not be explained by "abnormal" factors anymore, but logically should be explained by "normal" elements, most likely by "advanced aging plus risk factors".

- This model points to a "new" direction for SD prevention: motivate society as a whole to better support the elderly in healthy lifestyles and develop medications to extend the lifespan of old neurons by activating their lifeline metabolisms, rather than "inhibiting" the far-fetched "pathogenic" factors.
- Current dominant hypotheses in the "AD" study field [1, 10–12] have almost all assumed a "pathogenic" factor as the single "cause". These theories do not explain the role of the demographic change and its diverse end results in the elderly, and thus are off-target to the scientific nature of SD.
- What is the starting point of all these misconceptions? It is the NIA's definition, "SD = AD". Promoted by social and political interests and "proven" by some scientists, this definition has not only defied Alois Alzheimer's view, but also the scientific foundation of modern Geriatric Medicine and the NIA itself, thereby confusing the research field up to now, and perhaps forever if not revisited.

Today, similar views have been presented by other investigators [5–9] and together they suggest a paradigm shift in the research of "AD". In this endeavor, a scientific model that seeks a mechanistic and coherent explanation of SD features for reason and curiosity and a new path for pharmaceutical intervention would be needed. Here we present our opinions for scholarly discussion.

WHAT SHOULD WE LOOK FOR IN SD BEYOND "PATHOGENIC" FACTORS?

If, as we argued, senile conditions are not caused by pathogenic factors as in discrete diseases, then what should we logically and practically look for in the SD study?

To this paramount question, we first consider other senile conditions for a clue. It is known that cholesterol and gallstone deposits, for example, are the results of inefficient metabolisms (degradation and clearance) of lipid and minerals, respectively; and bone loss originates from the inefficient calcium absorption and ossification (Fig. 1A). These examples suggest that

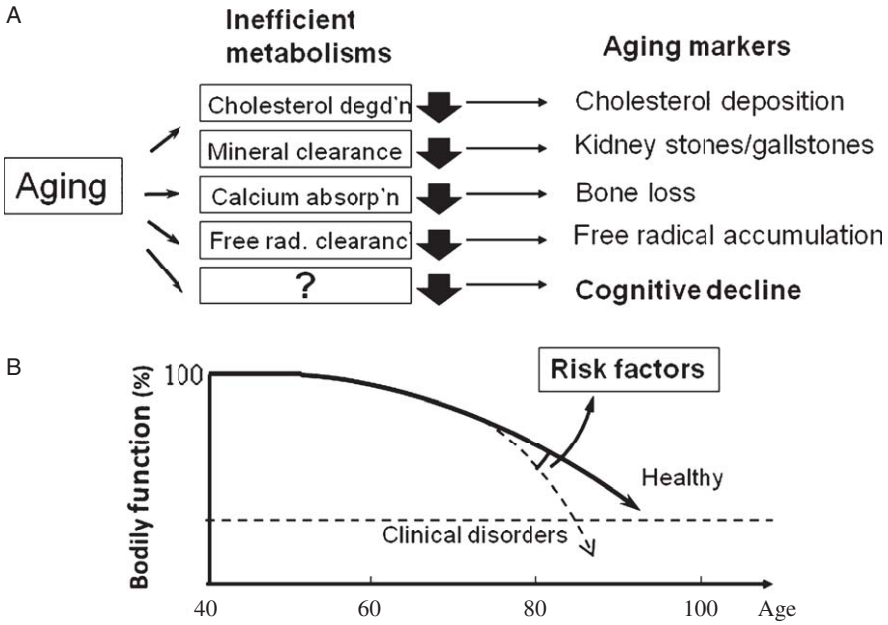

Fig. 1. What should we logically look for in SD? A) There is a specific inefficient metabolic pathway underlying each particular "aging marker" in the elderly. We thus believe that cognitive decline (with its concomitant appearance of plaques and tangles) should be no exception. B) The pace of aging varies in the individuals and can be critically influenced by lifestyles and other risk factors, therefore aging will end up in a diversity of consequences in the elderly population. Again, SD should be no exception. ⬇, functional decline.

while a myriad of metabolic pathways become inefficient as a result of aging, there is a specific one that primarily underlies each particular age-related condition. As such this pathway would be a converging point around which the actions of many other factors are centered and thus would serve as the primary target for study and intervention.

We therefore think that SD should have such an underlying pathway as well. But which one could it be? Our attention is on the regulatory mechanism of neurotransmission. It is long-known that Ca^{2+} is a central regulator in neurotransmission. Classic studies on neuromuscular junctions have long established that no neurotransmitter can be released in the absence of Ca^{2+} entry even though action potential and other factors are present. Conversely, Ca^{2+} alone can trigger transmitter release even in the absence of all other factors. In addition, the amount of the transmitters released is related to the number of Ca^{2+} ions entering the cell [13–15].

Such a stringent and somewhat exclusive regulatory mechanism suggests that Ca^{2+} is to neurotransmission as key is to lock: everyone can unlock the lock, but no one can do so without using the key. Thus, Ca^{2+} should be the converging point around which the actions of any cognition-affecting factors are centered (e.g., aging, injury, disease, lifestyle, drugs). Indeed, it has been generally accepted that Ca^{2+} and Ca^{2+}-dependent enzymes play a central role in memory and cognition [16, 17].

This "Ca^{2+}-centric" model, in essence, can be compared to the role of insulin in diabetes. Diabetes is a glucose metabolic disorder caused by many factors and insulin, a central regulator in glucose metabolisms, is a central player in the disease, so that other factors would exert their actions through insulin (e.g., insulin insufficiency, desensitization, or altered receptors).

WHY CA^{2+} FUNCTION MUST BE DOWN-REGULATED DURING AGING

If Ca^{2+} is so important in cognition, how then will its function change during aging? Will it increase or decrease? To this pivotal question, we think it unquestionable that the functionality of the Ca^{2+} signaling system as a whole should be down-regulated as aging progresses. This assertion is based on the following common sense knowledge.

First, Ca^{2+} signaling is a basic life-supporting pathway. Since aging is a process in which life itself is progressively diminishing until it fully stops, it is reasonable to assume that most if not all life-supporting metabolisms (ATP genesis, cell signal systems, DNA replication, protein synthesis, etc.) should be all down-regulated as age advances. There is no reason to assume that Ca^{2+} signaling can be an exception.

Second, Ca^{2+} signaling is a highly energy-dependent process (a 10,000-fold gradient across the membrane maintained by ATP-driven pumps; no other ions have such a steep gradient) [18, 19]. Therefore Ca^{2+}-regulated processes in the body are also energy-dependent/consuming [19], such as fertilization, cell division, differentiation and growth, muscle contraction, and neurotransmission [20]. Needless to say, they are all down-regulated during aging.

In light of this knowledge, together with our overall model for SD [3, 4], we propose that a functional deficiency of Ca^{2+} signaling, among a myriad of age-related changes, is the underpinning of cognitive decline during aging (Fig. 2A). The downward trajectory of the brain function will intensify and old brains will die in the end, like all other organs (Fig. 1B). However, since the pace of aging varies among individuals and is significantly influenced by brain reserve, lifestyle, and other risk factors, the descending trajectory will divert in the population, allowing brain death to occur at quite different ages among individuals–much as old cars will die at different years [3, 21–23] (Fig. 2A).

This model can explain: a) why demographic changes are the root cause for SD and why SD is fully age-penetrating but does not affect all elderly; b) why cognitive decline is intimately accompanied by plaques and tangles [21, 23] but they are not accurate predictors to dementia; c) why active lifestyles are known as "the key for successful aging"and "use it or lose it" is a time-tested rule of thumb; d) why the long-sought "cause" for SD and "biomarkers" for its pre-symptomatic diagnosis have not been found; and e) why some Ca^{2+} agonists have displayed neuroprotective effects (see below), but high-profile anti-amyloid-β drugs have not.

The model implies that SD, by and large, is a "lifestyle disease" in essence. This view, in fact, has been shared by many in the medical and clinical community [24–26], but contrasts sharply with current dominant theories in the "AD" basic study field, which all assume a linear and "cause-effect" mechanism (Fig. 2B). Since they have not taken into account the fundamental roles of aging and risk factors, it is clear that these theories, though highly appealing to the public and researchers alike, are of little relevance to the scientific nature of SD.

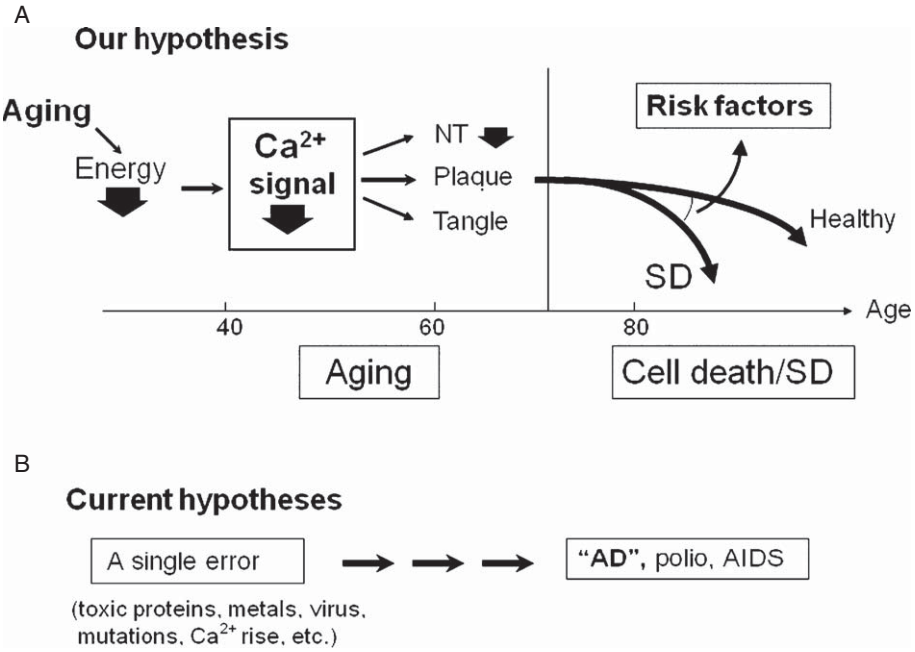

Fig. 2. Our "aging/Ca^{2+} deficits plus risk factors" model for SD. A) Aging will diminish energy and Ca^{2+} signaling, underlying neurotransmission (NT) decline with the concomitant appearance of plaques and tangles (21, 23). However, they will not always lead to SD, but rather to a heterogeneity of end results in the elderly population, thanks to the varying pace of brain aging among individuals and the key roles of risk factors in life. ⬇, functional decline. B) However, almost all of current hypotheses assume a "pathogenic" factor causing "AD" in a linear manner, like polio or AIDS. These theories are highly popular, but do not take into account aging and risk factors, thus do not explain the fundamental features of SD.

WHY HIGHER CA^{2+} "LEVELS" COULD MEAN LOWER FUNCTION

However, our "Ca^{2+} deficits" model for SD would confront the current "calcium overload" hypothesis [11]. This theory is based on the massive rises of intracellular Ca^{2+} levels observed in cells after stroke and infers that Ca^{2+} levels are rising throughout the aging process, leading to "overactivation" of Ca^{2+}-dependent processes/enzymes and to cell death (Fig. 3A).

But interestingly, a remarkable difference between the two models is that while ours is based on Ca^{2+} *function*, the other is based on its "levels". Since low intracellular Ca^{2+} levels are vital for life and maintained by energy, it is correct to deduce that they will gradually rise during aging as energy declines.

We thus encounter a fascinating dilemma: the *function* and *level* of Ca^{2+} may undergo opposite changes. Is this possible? As the issue carries considerable theoretical and practical significance, we propose the following explanations.

It is known today that, unlike other metals, Ca^{2+} functions as waves *in vivo* by changing its frequency and amplitude, like radio waves [27, 28], not by steady-state "levels" changes as traditionally conceived, like water level changes in the swimming pool (Fig. 3B). This means that Ca^{2+} channels and pumps would open/close extremely rapidly (within milli- or microsecond in the brain) [29] and intermittently like an alternator—driven by energy and producing alternate electric waves by rapidly changing the current directions. So, when energy supply declines, the turnover speed and output potency of the alternator (i.e., the wave frequency and amplitude) will diminish as well (Fig. 3B).

Intriguingly, however, the reduced wave frequency would mean a "Ca^{2+} overstay" in the cytosol, which can be manifested as "higher levels" if Ca^{2+} is measured at longer time intervals such as seconds or minutes (Fig. 4). Thus such studies do not measure the functionality of Ca^{2+}, but its average "levels". In other words, these steadily higher Ca^{2+} "levels" actually mean lower signaling function (Fig. 4).

It must be kept in mind that such age-related, irreversible and death-leading Ca^{2+} rises would be distinct from another type of Ca^{2+} rises that are transient, reversible, agonist- or action potential-induced

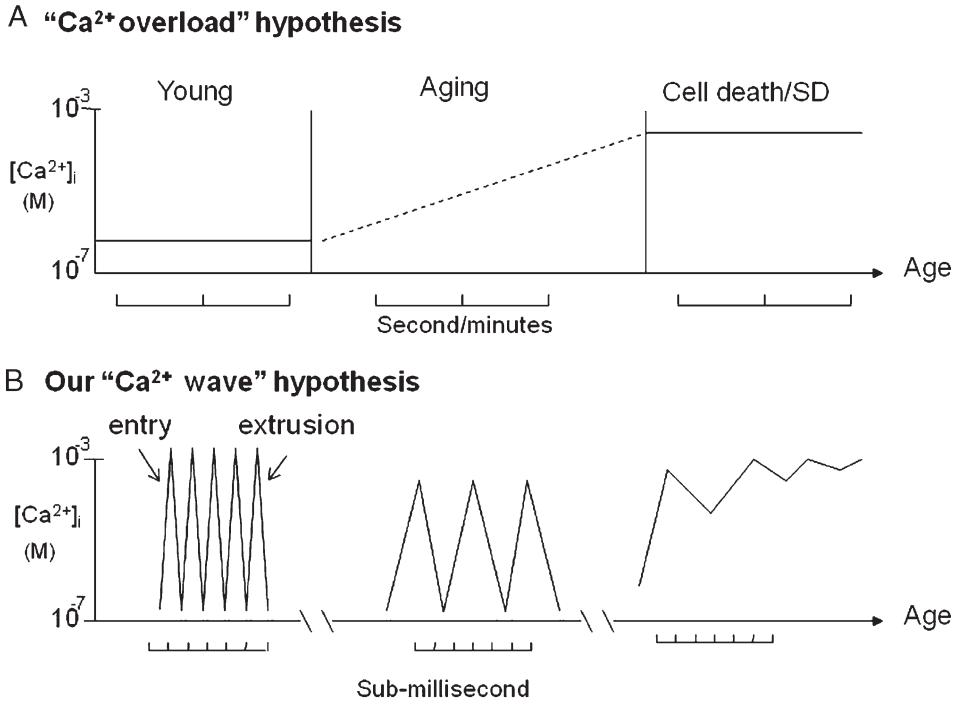

Fig. 3. Two opposing "Ca^{2+} hypotheses". A) The current "Ca^{2+} overload" hypothesis believes that the steady-state Ca^{2+} levels increase throughout aging, causing an "overactivation" of Ca^{2+}-dependent processes and cell death. It points to calcium antagonists as the only hope for intervention. B) But we propose that Ca^{2+} functions by rapidly changing its wave frequency and amplitude, which will decline during aging as energy declines and collapse at cell death. Such rapid wave changes perhaps can only be detected at sub-millisecond time intervals. The model points to promoting energy metabolisms and the use of Ca^{2+} agonists for SD intervention.

and life-supporting. Unfortunately, these two types of "Ca^{2+} rises", which can be distinguished by the wave model [22], have not been distinguished in the Ca^{2+} study field to our knowledge.

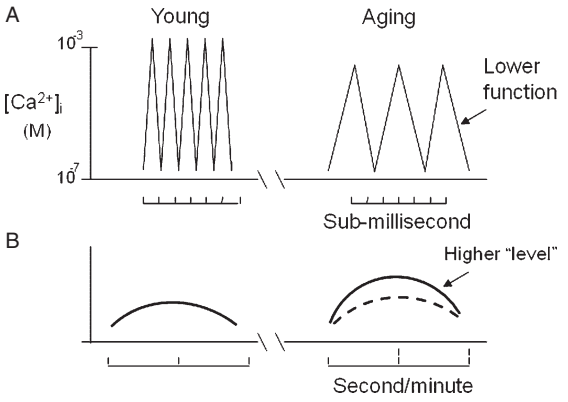

Fig. 4. Why higher Ca^{2+} "levels" could mean lower function. A) Changes of the Ca^{2+} wave frequency and amplitude in the brain are extremely fast (within milli- or micron-second) and difficult to measure in most laboratories by current technology. B) If Ca^{2+} is measured in second or minute instead, the reduced frequency and amplitude would manifest themselves as higher average "levels" or "overstay" in the cytosol, which actually means a lower signaling functionality.

Our analysis concludes that the intervention of SD should aim to activate basic metabolisms in general, and Ca^{2+} signaling in particular. The latter can be boosted by Ca^{2+} agonists such as caffeine and nicotine, two natural and blood brain barrier-penetrating neuroprotective agents [30, 31], which can have many positive effects in the cell [32, 33]. Other Ca^{2+} effectors such as agonists of muscarinic, nicotinic, and AMPA receptors have also been shown to have neuroprotective effects [34–36]. Along this line, it is anticipated that more effective, long-lasting, safe and affordable derivatives from these prototypical agents will be developed for pharmaceutical intervention in SD–a perspective that could be compared to the drugs delaying atherosclerosis and osteoporosis today.

It is worth noting that activating Ca^{2+}, a life-supporting process, would mean to protect life itself in a broader sense. So any foodstuffs that help protect brain cells would be expected to protect Ca^{2+} function. At the same time any cognitive stimuli that benefit the aged brain such as psychologically enriched environments, social connection, music, and story-telling [37–40] would involve activating Ca^{2+} as well. These practices will not cure or eradicate SD, but together they can delay or ameliorate its symptoms to a

certain extent, thereby realistically reducing social burdens. This is akin to better maintenance and handling expanding the lifespan of old cars.

WILL CALCIUM CHANNEL BLOCKERS HELP IN SD?

But contrary to our predictions, the "Ca^{2+} overload" hypothesis points to calcium antagonists for SD intervention. As this idea offers great hope, a number of high profile clinical trials on such drugs have been carried out over the last two decades and vigorously watched. One can be sure that any positive and consistent results would immediately run headlines on the mass media. Yet such reports have not come out until now.

Nevertheless, calcium channel blockers are known to benefit hypertension, a condition related to vascular dementia, not typical "AD" (the latter entity was originally introduced to be distinguished from the former [41]). But this distinction has been deliberately blurred in recent years and ignored by policymakers.

But even in hypertensive patients, calcium channel blockers may not always have positive effects. At least two studies have found that frequent users of the blockers are more likely than those using other types of antihypertensive drugs to be associated with lower scores in the mental ability test [42, 43].

Why are calcium channel blockers effective for hypertension, a common condition in the elderly, but not for cognition? It is noteworthy that the smooth muscle cells on the vessel walls are *constricted* in hypertension and the blockers can *relax* them (vasodilation [44]; muscle constriction is Ca^{2+}-dependent). But old neurons may need frequent *stimulation* to stay healthy, so the two conditions may differ by medical nature.

If Ca^{2+} acts by waves, then strictly speaking, there would be no Ca^{2+} "levels" at all (can radio waves be measured by "levels"?). As such Ca^{2+} effectors would not change its "levels" as traditionally thought, but only alter wave shapes, an effect that has been well-established for Ca^{2+} agonists [45, 46]. By the same token, therefore, calcium channel blockers would not reduce Ca^{2+} "levels" anymore, but actually diminish its wave frequency and amplitude [47], or functionality. Do old brains need such a "help"? It should be pointed out that blocking a lifeline pathway in the frail elderly, by theory or by practice, should be a skeptical idea at its inception.

Although "Ca^{2+} overload" hypothesis dominates the field, a growing number of important reports are worth mentioning. For example, protein kinase C, a Ca^{2+}-dependent enzyme, is well-known to be inactivated in aging [48]. The function of Ca^{2+} pumps, calpains and calcineurin has been found to diminish in aging (not in cell death, see below) [49–52]. And gene expression of almost all Ca^{2+}-dependent enzymes/proteins such as Ca^{2+}/calmodulin-dependent kinases, calcineurin, PKC, Ca^{2+} pumps and calbindin are reduced in the old brain [53]. Above all, perhaps the most compelling and logical indication for Ca^{2+} inefficiency in brain aging is simply the cognitive decline *per se* and the concomitant deposition of plaques and tangles [21, 23].

Of great importance is that the two opposing "Ca^{2+} hypotheses" can be directly tested: to see whether a long-term use of calcium antagonists will enhance, or impede, learning and memory in old animals. Needless to say, this test will carry not only the hope to create a much-needed animal model for SD (late-onset sporadic AD), but also the danger to become another never-ending controversy (like "toxic" amyloid-β; where science is entangled with social interests) [3].

SHOULD OUR STUDY FOCUS ON AGING OR "CELL DEATH"?

The "Ca^{2+} overload" hypothesis is not only based on the "level" model, but also on another solid conviction, that is, the central question in SD should be "why do some neurons die?" [2]. This question has officially steered the study focus from aging to "cell death" perhaps at the beginning of modern SD research.

The idea sounds indisputable at first glance, because aging, the passage of time, is a slow and insidious process in which changes are only marginal and difficult to measure. And targeting aging in elderly will take decades yet does not guarantee a definitive success.

But in contrast, cell death occurs when Ca^{2+} sharply rises and Ca^{2+}-dependent proteases relentlessly attack proteins [54], leading to innumerable cellular damages that are readily observed and manipulated *in vitro*. It thus appears that if these damages can be "arrested", then cell death and SD would be quickly and decisively prevented without having to tackle the aging process. The idea is especially eye-catching when stroke, where saving dying cells is a successful strategy, is taken as a role model for SD [11].

It should be pointed out, however, that dying cells in stroke (penumbra) can be rescued mainly because their Ca^{2+} rises result from a sudden energy shutdown (blood clots) while cell structures and functions

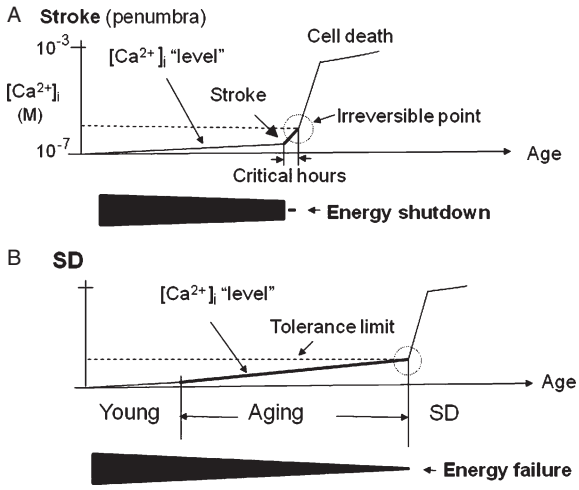

Fig. 5. Different mechanisms of cell death in stroke and SD, A) In stroke (penumbra), dramatic Ca^{2+} rises are caused by a sudden energy shutdown and can be reversed by restoring energy supply, if acting within the "critical hours" when Ca^{2+} levels have not surpassed the "irreversible limit" (like the water level limit in a leaky boat). B) In SD, the long aging process has progressively diminished energy supply and cell viability to zero. The resulting Ca^{2+} rises are unlikely to be reversed at this point because energy supply may not be restored anymore. Note the slow Ca^{2+} rises during aging can be slowed down, but the dramatic Ca^{2+}rises in the cell death stage, though easily detected, is too late for intervention.

are otherwise intact. Thus restoring energy supply (dissolving the clots together with anti-oxidative and other protective agents) will bring down Ca^{2+} levels and revitalize the cells [55, review], provided that action is taken within the "critical hours" when Ca^{2+} has not surpassed the "irreversible point" (Fig. 5A).

But in SD, cell death occurs at the end of the long aging process which has progressively diminished the cell viability (basic metabolisms) and energy supply to zero. The dramatic Ca^{2+} rises at this point are unlikely to be reversed, because the energy failure and other metabolic pathways may not be restored anymore (Fig. 5B). Thus caution must be taken when using stroke as the role model for SD.

Importantly, our analysis also suggests that the Ca^{2+} rises in both stroke and SD are due mainly to energy failure (energy-driven pumps), thus perhaps not to "leaky channel" or "excessive influx" [11]. This view would call into question current underlying assumptions for the use of calcium channel blockers in the elderly for preventing SD.

Cell death ("AD" brain) is invariably accompanied by a myriad of cellular damages (ion gradients collapse, rampant proteolytic activities, DNA fragmentation, etc.). These events are not physiological activation, but *autolysis*, an irreversible self-destruction process "activated" during cell death. In fact, many studies supporting the "Ca^{2+} overload" hypothesis have come from cell death studies [54, 56]. However, manipulating these damages in test tube, though data productive, would be perhaps too late to have any intervention significance in patients.

Thus, mixing aging and cell death is another profound misconception in the "AD" study field. In fact, some studies under the name of "aging research" are actually tackling the death process (e.g., apoptosis) or "errors" in aging (e.g., "activation" of some aberrant processes). These events are not parts of natural aging.

Although aging and cell death can substantially overlap in the old brain (where some cells are aging, others are dying) and difficult to separate in the clinic, they still should be conceptually distinguished in research. Clearly, only the natural aging process, the window for understanding of and intervening in senile conditions, should be our cogent study focus in SD (Fig. 2A and Fig. 5B).

WHY CELL DEATH HAS BECOME THE STUDY FOCUS

Under the prevalent "disease" definition, aging would be excluded as the root cause for SD (because aging does not lead all elderly to SD) [3]. As such, a policymaker has explicitly stated that aging and dementia are "two independent processes that appear to be correlated" [2]. Such an institutional perception would inevitably dictate SD study into an ever-lasting conundrum. By analogy, if aging is excluded as the cause of old cars' death (because other old cars may still be running), can such death ever be explained?

Indeed, the question of "why do some neurons die?" [2] has triggered an explosive hunting of almost all known pathogenic factors in human diseases, and the list is still expanding. We however believe that the correct central question should be: "Why do the *oldest* neurons die *faster* in some elderly?" It emphasizes two keywords: oldest (advanced aging) and faster (the pace of aging). Had the question been posed this way, perhaps the search would have been much focused and a substantial amount of research dollars saved.

HOW AN UNPROVEN THEORY HAS BECOME DOGMA

The dogmatic status of the "Ca^{2+} overload" hypothesis, an unproven theory, is problematic given that

competition among rival views is the lifeline and driving-force of science. But how has this happened? Perhaps first, as mentioned above, the two life-or-death different types of "Ca^{2+} rises" in our body have not been distinguished today. This critical knowledge gap has given rise to misconceptions that, for example, Ca^{2+} could mediate both life and death [20] and "excessive Ca^{2+}" be viewed to "cause" cell death. If a lifeline pathway can do this to cells, then will "excessive" water and air be held as the "cause" for human death?

Second, perhaps more important, "low Ca^{2+}" means a natural event in aging and thus long and hard work ahead with only incremental and nameless progress anticipated. But "high Ca^{2+}" immediately connotes "abnormality" and "disease"—relief, cure, fame and wealth.

Third, the "Ca^{2+} overload" hypothesis is enthusiastically promoted by a long-time and tireless NIA policymaker [11]. Is this good for science? The role of the policymakers, with their steering powers and resources, is to coordinate and ensure a fair play among the competing views before one is proven correct. In the delicate truth-seeking stage of science, any intrusion by social, political, ideological, financial or administrative forces would subtly shift the fragile balance of the views to their favor, thereby undermining the integrity and objectivity of science in an insidious way. Image: if a judge is also playing as athlete, can the tournament be fair?

In the politically-contentious scientific subjects, such as evolution, global warming and SD, the disruptive effects of the outside intrusions are especially profound. This may be why early studies on the low Ca^{2+} scenarios [57–59] have almost all disappeared afterwards, and also why "Ca^{2+} wave" theory has long been established, but has hardly been mentioned at all in the "AD" study field, a field that most needs it (see below).

HOW DO PRESENILIN MUTATIONS CAUSE DEMENTIA?

A scientific model, if reasonable, should have predictive values to help explain other puzzles. One such puzzle is the physiological function of presenilins (PSs), whose some-200 gene mutations have all caused early-onset dementia, a startling phenomenon suggestive of an important clue to the overall mechanism of the disease.

While most researchers believe that PSs function *in vivo* as proteases (i.e., "*r*-secretase") [1], based on the "Ca^{2+} deficits" model we unambiguously predicted in 1998 that "presenilins most likely act as calcium channels *in vivo*" and also that "functional reconstitution and electrophysiological studies should directly reveal whether or not presenilins in artificial membranes could act as Ca^{2+} channels" [21]. Eight years later, these purely theoretical analysis-based predictions are experimentally proven through the proposed approaches by other investigators [60].

But how do mutations cause dementia? To this central issue we also predicted that mutant PSs do so "by diminishing the Ca^{2+} channeling function" [21]. This seems to confront the current reports suggesting that the mutant PSs increase intracellular Ca^{2+} levels [60]. Nevertheless, this discrepancy perhaps can be readily conciliated by our "wave vs. level" model (Fig. 4).

By this model, mutant PSs would be inefficient channels (it takes longer time for them to channel-in Ca^{2+} in each entry/extrusion cycle), whereas aging cells would have inefficient pumps due to reduced energy (it takes longer time to pump Ca^{2+} out). Both cases would end up in the same net result: lower signaling function but higher Ca^{2+} "levels", if measured in time intervals longer than sub-millisecond (actually in second) [60].

It is possible that armed with advanced technology future studies in old primitive animals [61] or mutant PSs cells will be the first to demonstrate the age-related or mutation-related changes in Ca^{2+} wave shapes, or functionality changes.

SD IS A "CA^{2+} SIGNALING DEFICIENCY" DISORDER

Why should Ca^{2+} be conceived in an extremely complicated wave model, given that the simple "level" model has explained observations for many years? We think it is perhaps because only wave model can explain why Ca^{2+} is a "central regulator" in cognition.

A unique requirement for a central regulator is that it must be able to carry an enormous amount of information for coordinating neurotransmission among billions of neurons, let alone the large variations of the transmitters themselves (type, combination, intensity, interval and duration, etc.). This would be akin to a conductor in a symphony orchestra who has to carry the instructions for all instruments. But how can Ca^{2+}, a simple metal, carry such a large body of the information?

The wave model offers a clue. The frequency and amplitude changes can carry a body of information that is virtually unlimited, like radio waves can transmit

any TV pictures. During cognition, the wave-encoded "digital" information is "decoded" and executed by Ca^{2+}-dependent processes/enzymes or by transmitter's own variations, just like how instrument players decode conductor's instructions [27–29].

Additionally, a central regulator in the brain should display high sensitivity and response speed (within milli- or micro-second) in consistence with those of the cognitive stimuli (vision, hearing, touch, and thinking). No coincident, these are precisely the known characteristics of Ca^{2+} signaling system, the fastest and most sensitive one in the body [29]. On the other hand, no other factors have the comparable information-carrying capacity, delicacy and sensitivity (e.g., transmitters themselves, cAMP, NO, or any other metals).

It is thus reasonable to consider Ca^{2+} as a regulator that stands at the *central* position among the hierarchic orders of the innumerous elements in cognition. Thinking from this perspective, SD would be primarily a "Ca^{2+} signaling deficiency" disorder, since the concept explains the delicate, dynamic and progressive decline of cognitive ability in the elderly better than any other current static models. So a conceptual transition from static to vibrant/digital one is needed in the SD study field.

Nevertheless, the long-standing "level" model is still useful as it can explain many other biological processes (e.g., cell division and growth), but the "wave" model may be indispensable for understanding Ca^{2+} actions in the brain. And Ca^{2+} signaling, with its ultimate sophistication and intricacy, would be one of the last frontiers of science, in which theory development may need to go ahead of experimentation.

CONCLUSIONS

In this paper we try to make the following main points:

- Unlike the ongoing "shotgun" approach (pursuing all suspects) in SD, we undertake a "crime scene" analysis to rule out most suspects and pinpoint to "Ca^{2+} deficiency" as the primary one. It is not the singular "causation", but rather a key missing link necessary for explaining SD features for reason and curiosity. It can also serve as the primary target for rational drug design.
- Aging and Ca^{2+} deficits set the stage for SD, but do not always lead to SD in real life, thanks to the key roles of risk factors. Thus, targeting the risk factors by social supports and public awareness are indispensable but they should differ from some current ones that wind up in fear-mongering or promoting drug sale or "genetic test".
- The current "Ca^{2+} overload/activation" hypothesis is mainly derived from Ca^{2+} "level" measurements and cell death studies, neither of which represents the true Ca^{2+} functional changes during natural aging, the window for understanding of, and intervening in, perhaps all senile conditions.
- The two overwhelming concepts, "SD = AD" and "Ca^{2+} overload", have effectively blocked any meaningful progress of SD research and inhibited the self-correcting mechanisms of science, thereby rendering the bench-top "AD" study field an isolated island in the scientific and medical community as a whole. An independent scrutiny on the field may be helpful [39, 62, 63].

Science, the pursuit of fundamental truth (including inconvenient ones) and source of enlightenment, should be nurtured under its own laws and untangled from any outside interests to keep its values. Unfortunately this seems to be a far cry in SD. A soul-searching by policymakers and researchers on aging and aging research may be merited.

The single-minded pursuit of the unfalsifiable faith for a "cure" [64] by the "AD" laboratory research enterprise is armed with solid beliefs: Man has landed on the moon [65]; numerous once-incurable diseases have been cured; and science breaks new frontiers every day.

Optimism is good, but not half-truth. Man has landed on the moon and soon on Mars and beyond, but car aging has yet to be stopped; many diseases have been cured, yet none of them is a *senile* one; science breaks new frontiers every day, yet also sets limits to explorations (e.g., absolute zero, light speed, perpetual motion and, arguably, "fountain of youth").

NIA faces a deep dilemma today. After defining it a "disease", pressures has been building up from the public and Congress for the "pathogenic" factor it promised. But if so, then what does "A" in its name stand for? Can that definition be revisited? It would be unthinkable for *status quo*. So business-as-usual is perhaps its only choice, and thus "AD" research will go forever – and wander forever.

ACKNOWLEDGMENTS

This work is supported by the Department of the Veterans Affairs, the Biomedical Laboratory Research and Development program. The contents do not repre-

sent the views of the Department of Veterans Affairs or the United States Government.

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=965).

REFERENCES

[1] Selkoe DJ (2001) Alzheimer's disease: Genes, proteins, and therapy. *Physiol Rev* **81**, 741-766.

[2] Khachaturian ZS (2000) Toward a comprehensive theory of Alzheimer's disease–challenges, caveats, and parameters. *Ann N Y Acad Sci* **924**, 184-193.

[3] Chen M, Maleski JJ, Sawmiller DR (2011) Scientific truth or false hope? Understanding Alzheimer's disease from an aging perspective. *J Alzheimers Dis* **24**, 3-10.

[4] Chen M, Fernandez HL (2001) Alzheimer's disease revisited 25 years later: Is it a "disease" or senile condition? Front. *Biosci* **6**, e30-e40.

[5] Whitehouse PJ, George DR, and D'Alton S (2011) Describing the dying days of "Alzheimer's Disease". *J Alzheimers Dis* **24**, 11-13.

[6] Moalem S, Percy ME (2002) The quandary of reductionism: Relevance to Alzheimer disease research. *J Alzheimers Dis* **4**, 531-537.

[7] Castellani RJ, Zhu X, Lee HG, Smith MA, Perry G (2009) Molecular pathogenesis of Alzheimer's disease: Reductionist versus expansionist approaches. *Int J Mol Sci* **10**, 1386-1406.

[8] Swerdlow RH (2007) Is aging part of Alzheimer's disease, or is Alzheimer's disease part of aging? *Neurobiol Aging* **28**, 1465-1480.

[9] Bishop NA, Lu T, Yankner BA (2010) Neural mechanisms of ageing and cognitive decline. *Nature* **464**, 529-535.

[10] Brunden KR, Trojanowski JQ, Lee VM (2009) Advances in tau-focused drug discovery for Alzheimer's disease and related tauopathies. *Nat Rev Drug Discov* **8**, 783-793.

[11] Khachaturian ZS (1994) Calcium hypothesis of Alzheimer's disease and brain ageing. *Ann NY Acad Sci* **747**, 1-11.

[12] Aguzzi A, Haass C (2003) Games played by rogue proteins in prion disorders and Alzheimer's disease. *Science* **302**, 814-818.

[13] Katz B, Miledi R (1967) The timing of calcium action during neuromuscular transmission. *J Physiol* **189**, 535-544.

[14] Llinás RR (1982) Calcium in synaptic transmission. *Sci Am* **247**, 56-65.

[15] Miller RJ (1988) Calcium signalling in neurons. *Trends Neurosci* **11**, 415-419.

[16] Lynch G, Baudry M (1984) The biochemistry of memory: A new and specific hypothesis. *Science* **224**, 1057-1063.

[17] Kandel ER, Schwartz JH (1991) *Principles of Neural Science*, 3rd edn. Simon & Schuester, New York.

[18] Gunter TE, Pfeiffer DR (1990) Mechanisms by which mitochondria transport calcium. *Am J Physiol* **258**(5 Pt 1), C755-C786.

[19] Chen M, Fernandez HL (1999) The Alzheimer's plaques, tangles and memory deficits may have a common origin. Part V: Why is Ca2+ signal lower in the disease? *Front Biosci* **4**, a9-a15.

[20] Berridge MJ, Bootman MD, Lipp P (1998) Calcium – a life and death signal. *Nature* **395**, 645-648.

[21] Chen M (1998) The Alzheimer's plaques, tangles and memory deficits may have a common origin-Part I: A calcium deficit hypothesis. *Front Biosci* **3**, a27-a31.

[22] Chen M, Fernandez HL (1999) Ca2+signaling down-regulation in aging and Alzheimer's disease: Why is Ca2+ so difficult to measure? *Cell Calcium* **26**, 149-153.

[23] Chen M, Fernandez HL (2001) Where do plaques and tangles of Alzheimer's disease come from? Aging-related protein degradation inefficiency. *Front Biosci* **6**, e1-e11.

[24] Whitehouse P, George D (2008) *The myth of Alzheimer's: What you aren't being told about today's most dreaded diagnosis*, St. Martin's Press, New York.

[25] Fratiglioni L, Qiu C (2009) Prevention of common neurodegenerative disorders in the elderly. *Exp Gerontol* **44**, 46-50.

[26] Rolland Y, Abellan van Kan G, Vellas B (2008) Physical activity and Alzheimer's disease: From prevention to therapeutic perspectives. *J Am Med Dir Assoc* **9**, 390-405.

[27] Berridge MJ, Galione A (1988) Cytosolic calcium oscillators. *FASEB J* **2**, 3074-3082.

[28] Putney Jr. JW (1998) Calcium signaling: Up, down, up, down. . . .what's the point? *Science* **279**, 191-192.

[29] Llinás R, Moreno H (1998) Local Ca2+signaling in neurons. *Cell Calcium* **24**, 359-366.

[30] Eskelinen MH, Kivipelto M (2010) Caffeine as a protective factor in dementia and Alzheimer's disease. *J Alzheimers Dis* **20**, S167-S174.

[31] Gray R, Rajan AS, Radcliffe KA, Yakehiro M, Dani JA (1996) Hippocampal synaptic transmission enhanced by low concentrations of nicotine. *Nature* **383**, 713-716.

[32] Friel DD (1995) Calcium oscillations in neurons. *Ciba Found Symp* **188**, 210-223.

[33] Haass M, Kübler W (1997) Nicotine and sympathetic neurotransmission. *Cardiovasc Drugs Ther* **10**, 657-665.

[34] Fisher A (2008) Cholinergic treatments with emphasis on m1 muscarinic agonists as potential disease-modifying agents for Alzheimer's disease. *Neurotherapeutics* **5**, 433-442.

[35] Chen M (1999) Do the intracellular Ca2+ states in Alzheimer's disease need to be revisited? *J Neuropathol Exp Neurol* **58**, 310-311.

[36] Jourdi H, Yanagihara T, Martinez U, Bi X, Lynch G, Baudry M (2005) Effects of positive AMPA receptor modulators on calpain-mediated spectrin degradation in cultured hippocampal slices. *Neurochem Int* **46**, 31-40.

[37] Lynch G (1998) Memory and the brain: Unexpected chemistries and a new pharmacology. *Neurobiol Learn Mem* **70**, 82-100.

[38] Fratiglioni L, Wang HX, Ericsson K, Maytan M, Winblad B (2000) Influence of social network on occurrence of dementia: A community-based longitudinal study. *Lancet* **355**, 1315-1319.

[39] Whitehouse P, George D (2008) The myth of Alzheimer's: What you aren't being told about today's most dreaded diagnosis, St. Martin's Press, New York.

[40] Chen M, Fernandez HL (2000) Revisiting Alzheimer's disease from a new perspective: Can "risk factors" play a key role? *J Alzheimers Dis* **2**, 97-108.

[41] Khachaturian ZS (1985) Diagnosis of Alzheimer's disease. *Arch Neurol* **42**, 1097-1105.

[42] Maxwell CJ, Hogan DB, Ebly EM (1999) Calcium-channel blockers and cognitive function in elderly people: Results from the Canadian study of health and aging. *CMAJ* **161**, 501-506.

[43] Heckbert SR, longstreth WT Jr, Psaty BM, Murros KE, Smith NL, Newman AB, Williamson JD, Bernick C, Furberg CD (1997) The association of antihypertensive agents with MRI white matter findings and with modified mini-mental state examination in older adults. *J Am Geriatr Soc* **45**, 1423-1433.

[44] Christ G, Wingard C (2005) Calcium sensitization as a pharmacological target in vascular smooth-muscle regulation. *Curr Opin Investig Drugs* **6**, 920-933.
[45] Woods NM, Cuthbertson KS, Cobbold PH (1986) Repetitive transient rises in cytoplasmic free calcium in hormone-stimulated hepatocytes. *Nature* **319**, 600-602.
[46] Kawanishi T, Blank LM, Harootunian AT, Smith MT, Tsien RY (1989) Ca2+oscillations induced by hormonal stimulation of individual fura-2-loaded hepatocytes. *J Biol Chem* **264**, 12859-12866.
[47] Holl RW, Thorner MO, Mandell GL, Sullivan JA, Sinha YN, Leong DA (1988) Spontaneous oscillations of intracellular calcium and growth hormone secretion. *J Biol Chem* **263**, 9682-9685.
[48] Sun MK, Alkon DL (2010) Pharmacology of protein kinase C activators: Cognition-enhancing and antidementic therapeutics. *Pharmacol Ther* **127**, 66-77.
[49] Zaidi A, Gao J, Squier TC, Michaelis ML (1998) Age-related decrease in brain synaptic membrane Ca2+-ATPase in F344/BNF1 rats. *Neurobiol Aging* **19**, 487-495.
[50] Baudry M, DuBrin R, Beasley L, Leon M, Lynch G (1986) Low levels of calpain activity in Chiroptera brain: Implications for mechanisms of aging. *Neurobiol Aging* **7**, 255-258.
[51] Guttmann RP, Johnson GV (1998) Oxidative stress inhibits calpain activity in situ. *J Biol Chem* **273**, 13331-13338.
[52] Kayyali US, Zhang W, Yee AG, Seidman JG, Potter H (1997) Cytoskeletal changes in the brains of mice lacking calcineurin A alpha. *J Neurochem* **68**, 1668-1678.
[53] Lu T, Pan Y, Kao SY, Li C, Kohane I, Chan J, Yankner BA (2004) Gene regulation and DNA damage in the ageing human brain. *Nature* **429**, 883-891.
[54] Saito K, Elce JS, Hamos JE, Nixon RA (1993) Widespread activation of calcium-activated neutral proteinase (calpain) in the brain in Alzheimer disease: A potential molecular basis for neuronal degeneration. *Proc Natl Acad Sci U S A* **90**, 2628-2632.
[55] Lee JM, Zipfel GJ, Choi DW (1999) The changing landscape of ischaemic brain injury mechanisms. *Nature* **399**, A7-A14.
[56] Mattson MP, Rydel RE, Lieberburg I, Smith-Swintosky VL (1993) Altered Calcium signaling and neuronal injury: Stroke and Alzheimer's disease as examples. *Ann NY Acad Sci* **679**, 1-21.
[57] Peterson C, Gibson G, Blass J (1985) Altered calcium uptake in cultured skin fibroblasts from patients with Alzheimer's disease. *N Engl J Med* **312**, 1063-1065.
[58] Shelanski ML (1989) Intracellular ionic calcium and the cytoskeleton in living cells. *Ann N Y Acad Sci* **568**, 121-124.
[59] Nixon RA (1989) Calcium-activated neutral proteinases as regulators of cellular function. Implication for Alzheimer's disease pathogenesis. *Ann N Y Acad Sci* **568**, 198-208.
[60] Tu H, Nelson O, Bezprozvanny A, Wang Z, Lee SF, Hao YH, Serneels L, De Strooper B, Yu G, Bezprozvanny I (2006) Presenilins form ER Ca2+ leak channels, a function disrupted by familial Alzheimer's disease-linked mutations. *Cell* **126**, 981-993.
[61] Llinás R, Steinber IZ, Walton K (1981) Relationship between presynaptic caclium current and postsynaptic potentials in squid giant synapse. *Biophys J* **33**, 323-351.
[62] Jacoby S (2011) Never say die: The myth and marketing of the new old age, Pantheon Books, New York.
[63] Gillick MR (1998) Tangled minds: understanding Alzheimer's disease and other dementia. Penquin Group, New York.
[64] Khachaturian ZS (2007) A chapter in the development of Alzheimer's disease research: A case study of public policies on the development and funding of research programs. *Alzheimers Dement* **3**, 243-258.
[65] Allen M (2009) Aiming to revolutionize dementia research, An interview with the president of the Lou Ruvo Brain Institute. *Las Vegas Sun* Jan. 7, 2009.