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Cognitive Behavioral Therapy (CBT) for Preventing Alzheimer's Disease

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Abstract

This review provides the rationale for implementing cognitive behavioral therapy (CBT) for the prevention of Alzheimer's disease (AD). There are known risk factors associated with the development of AD, some of which may be ameliorated with CBT. We posit that treating the risk factors of inactivity, poor diet, hyposmia and anosmia, sleep disorders and lack of regularly engaged challenging cognitive activity will modify the physiology of the brain sufficiently to avoid the accumulation of excess proteins, including amyloid beta, causal events in the development of AD. Further, the successful treatment of the listed risk factors is well within our technology to do so and, even further, it is cost effective. Also, there is considerable scientific literature to support the proposition that, if implemented by well-established practices, CBT will be effective and will be engaged by those of retirement age. That is, we present a biologically informed CBT for the prevention of the development of AD, i.e., an aspect of applied behavioral neuroscience.

Keywords: behavior, prevention, olfaction, sleep, inactivity, cholesterol, computer games, fluid flow

Abbreviations:

Alzheimer's Disease (AD); Amyloid beta (Ab); Brain-nasal cavity (B-NC); Cognitive Behavioral Therapy for Insomnia (CBT-I); Finnish Geriatric Intervention Study to Prevent Cognitive

Impairment and Disability (FINGER); Late Onset AD (LOAD); Mild cognitive impairment (MCI); Low-density lipoprotein (LDL); High-density lipoprotein (HDL)

Contents

1.0 Introduction

Those who are at retirement-age (middle 60s) can expect to live for another two decades, a goodly portion of a life-time (actuarial data, USA Social Security Administration). Those decades can be and often are very satisfying. However, those decades are marred by fear of developing Alzheimer's disease (AD). AD is horrible, insidious, currently incurable and extremely costly in terms of palliative care. Retirees fear the loss of mind and the helplessness of advanced AD, and rightfully so. Epidemiological data confirm what retirees have observed: about 30 to 50% of those living to their mid-80s will have suffered a marked loss of cognitive ability, a harbinger of advanced AD, or will have suffered advanced AD. Further, the tragedy of AD affecting loved partners takes an enormous toll on their healthier partners.

Observations at autopsy, and now with the aid of modern brain-scan-technology, confirm that the behavioral manifestations of advanced AD are due to a massive loss of brain tissue. The loss is so extensive that no one can apprehend how to restore the loss. This fundamental fact implies that the only hope for dealing with AD, other than palliative care, is to prevent its advancement. Stated differently, treatments designed to correct end-stages of the disease are probably too late.

Given the gravity of AD and the realization that a large proportion of the population of prosperous nations is approaching retirement-age, research directed toward understanding and treating AD has increased. For example, PubMed (the search engine of the US National Library of Medicine) tabulates and lists articles germane to AD. In 1971, there were 11 articles on AD. In 1981, there were 161. During the 80s and beyond, there has been a steady yearly increase in articles on AD; and in 2016 there were over 9,000. As of early 2017, Pub Med has listed over 123,000 articles relevant to AD.

The extensive research on AD has yielded considerable knowledge. Much of the modern understandings of AD are embedded in the amyloid beta (Ab) theory of AD [1]. The Ab theory holds that a metabolic product of neuronal activity, the protein Ab, is causally related to the degeneration of neuronal tissue. There are various theories of how exactly Ab becomes toxic, but it seems clear that an *accumulation* of Ab in the interstitial fluid of the brain is associated with a process that leads to an insidious loss of brain tissue. Further, it is posited that when Ab accumulates in the fluid of the brain that it tends to combine with other proteins, including other molecules of Ab, to form large globs of proteins (amyloid plaques). The plaques induce immune processes that do not always succeed in removing them. The presence of large plaques and the induced inflammatory processes (i.e., accumulation of microglia and release of cytokines) likely contribute, in some way (probably interfering with blood flow near or in capillaries), to the toxicity leading to cell-death [2–6]. The debris of cell-death contributes to further accumulation of proteins and further toxicity. There are important implications that can be drawn from this summary of a version of the modern Ab theory of AD. We will attend to those implications subsequently.

The salient symptom of advancing AD is a progressive cognitive decline, measurable by psychological tests [7,8]. Also, modern technology allows assessment of features of the brain such a morphology and direct counts of amyloid plaques [9]. Psychological testing and brain-scans both support this conclusion [9]. The process that is AD probably begins as early as 10 or more years before full dementia is present [1]. Further, the time between dementia and death can last months and even years. Hence, AD is a progressive, slowly developing (but accelerates toward the end) disease. Consequently, there is a possibility of halting the progression. Further, the conclusion can be drawn that the earlier one might attempt to halt the progression, the more likely that a potentially salutatory intervention will, indeed, be salutatory.

In addition to developing advanced amyloid theories of AD, two additional advances are salient. They are (a) the understanding that the brain is considerably more plastic than previously recognized and that plasticity extends even to advanced ages [10,11], and (b) although limited, there is neurogenesis in the adult

brain, even aged brains [12]. Note that the term plasticity has two meanings. One meaning is the same as ordinary learning involving events at synapses. The other, more common meaning, is related to the observations that consistent activity not only involves learning in the traditional sense but actually molds the anatomy and general physiology of the brain enabling better performance at that consistent activity.

Brain plasticity is most apparent as we mature; a brain is organized by the challenges of learning to walk, talk and think abstractly. Plasticity is apparent as we witness the extraordinary skills of experts as they perform their beyond-ordinary skills in the arenas of art, hobbies, entertainment, sports, commerce and academia. These new understandings of the brain have important implications. For example, we have new treatments for brain-damage. Now, we aspire to restore lost functions rather than, as we did before, merely provide palliative care.

A tenant of the modern concept of brain plasticity is that persistent activity of a particular kind organizes the brain for efficiency at that persistent activity. Colloquially, practice makes perfect; and, the establishment of habits allows the efficient, nearly unconscious, execution of daily behaviors [13]. Although established as a result of apparently utilitarian consequences, habits often have, in the long run, aversive consequences. A basic idea is that regularly engaged activity is a means for modifying the brain for health as well as ill-health (establishing lifestyles amenable to health or disease). Much of what is modern cognitive behavioral therapy (CBT) is involved with attempts to modify habits of cognition and behavior which are not useful and often problematic.

Given that: (a) AD is currently not curable. (b) AD develops slowly, hence may be preventable. (c) Ab is involved with the development of AD. (d) Brains remain plastic even to very old age. (e) Modification of brain in old age follows the same principles as when young; that is, activity (whether it be cognitive behavior or gross behavior, both being simultaneously manifestations of the full physiology of a living being) modifies brain, hence shaping the brain for reactivity with future circumstances. And (f) not all persons develop AD as they age, i.e., from 30 to 50% suffer AD if they live to their mid-80s [14] while the others retain their matured

cognitive abilities well into advanced ages [15]. It follows, we contend, that AD can be prevented by attending to *activities* of the elderly, i.e., by CBT for AD. It is one thing to conclude that modifying activity among those of retirement age can prevent AD, a generalization so broad and vague as to be almost meaningless. It is another thing to discover exactly what kind of activity might effectively halt the progression of AD. Also, once a salient or causal variable is identified (or a few salient and causal variables), there is still the issue of how to develop treatments that are practical enough to be widely implemented.

2.0 Loss of cognitive skill is both a risk factor for the development of AD and an index of the progression of AD.

There has been considerable research associated with the identification of risks associated with AD. There is a search for a reliable early sign of the progression of the disease to assess the utility of a medicine or procedure to treat AD. Also, there is an interest in treating the risks to see if such would halt the progression of the disease, even in its earliest stages. Treating risks, however, has not been explored as extensively as warranted by the prevalence and severity of AD.

Many individuals of retirement ages have a subtle change of cognition, being noticeable with some forgetfulness. If the losses are not sufficient to disrupt the routines of an earlier time, this change is labeled: a*ge-related cognitive decline*. Sometimes this initial cognitive decline progresses sufficiently to be manifest as a *preclinical stage* (measurable by sensitive cognitive tests) heralding a more problematic stage labeled *mild cognitive impairment* (MCI). MCI can be readily measured by standard tests of cognition. Further loss of cognition, including a profound loss of memory, is labeled *dementia*, the most common of which is advanced AD (obvious by even casual observation). The process from age-related cognitive decline to dementia and eventually death is considered a continuous process taking a decade or more [8].

A slow, but steady loss of cognitive ability is not only a risk for progression to dementia; it is the major symptom of AD. Periodic tests sampling facets of cognitive ability, particularly of memory (and perhaps most salient, episodic memory [16]), will surely track

the progression of untreated AD. A single measure of cognitive ability, however, may not be revealing, because a number of temporary factors can influence any given day's test-results. Furthermore, pathologic features of brain-scans and psychological tests indexing loss of cognition are concordant with one another [17]. For example, it has been known for decades that the hippocampus, a large segment of the limbic system (i.e., the olfactory brain, rhinencephalon, or paleomammalian brain) is critically involved in memory. In advanced AD, the space formally occupied by the hippocampus is literally a hole filled with fluid. Further, measurements of the size of the hippocampus are related to stages of memory loss [18]. For example, those suffering MCI have shrunken hippocampi [18,19].

Given that variations in measures of cognition reflect the anatomical and physiological status of the brain, the conclusion is: Any treatment preventing the *steady* decline in cognition often observed as one ages (measurable by periodic testing with well-developed psychological tests of cognition) will be a treatment preventing AD. Further, any measurable differences seen between those who age with sound cognition compared to those whose cognition is steadily declining are of particular interest in learning how to prevent AD [15,19].

3.0 Inborn risks for the development of AD

Aging and sex are two well-established risk factors for developing AD. Clearly, the older an individual becomes, the more likely that they will suffer AD [14,20]. A number of theorists seem to imply that aging *causes* AD (via a variety of mechanisms, e.g., [2,21–24]). Although the concept of aging reflects events which are real, it is not a nuanced concept. The proposition that AD is caused by aging surely does not, by itself, explain in any detail why about a third (maybe more) of the citizens who reach the age of 85 are stricken with MCI or advanced AD whereas the other proportion is not [14]. If one lives long enough, AD, or something like it, may eventually be inevitable. However, the perspective guiding research is that it is good to postpone any putative inevitability as long as possible (i.e., it would be good if brain-health outlasted bodily health). The observation that aging is highly related to AD is

useful because it may lead to a variable that accounts for why aging for some leads to AD while for other it does not [15]. The same line of thinking is applicable to the concept relating sex to AD. Readers are referred to recent reviews detailing the role of sex and steroids for AD [25,26]. In brief, AD is more prevalent among women [14,25]. Until one specifies the critical differences between men and women that increase women's risk for AD, knowledge of the greater prevalence of AD among women is interesting but, by itself, of little value. However, the actions of cholesterol and cholesterol-based steroids (e.g., sex and stress steroids) may be a potential target that warrants further investigation [25]. As one might expect there are significant interactions between age and sex and propensity to develop AD, i.e., being old and female is riskier than being only old or female. Indeed, women diagnosed with AD more rapidly experience diminished cognitive functions and neuropsychiatric status compared to men diagnosed with AD [27,28]. Unless one specifies what it is about aging and sex that is critical, then positing these two interesting variables as special circumstances in the development AD is merely a setting condition for further research. Fortunately, knowledge from advancing research (e.g., specifying the products of certain genes) is specifying functionalities associated with aging and sex that may be causally related to the development of AD.

There are two developmental tracks for the development of AD: (a) the very rare one, the early onset form which manifests in the mid-30s years old and which develops into dementia by late 40s, and (b) the more prevalent one that manifests in individuals of retirement age and beyond. The development of both early and late onset AD leads to a massive loss of brain tissue, hence produces similar behavioral changes, e.g., eventually complete loss of memory and becoming helpless.

The early onset AD is common in a town, Yarumal, in the district of Antioquia, Columbia and it clearly affects a large number of those who share a common ancestry. Research has identified genetic mutation conferring a very high risk of developing AD among young citizens of Yarumal [29]. The consequences of inheriting the risky genetic profile for early-onset AD are physiological processes leading to an accumulation of Ab [4,29]. That is: the mutations in

the genes for the human amyloid precursor protein and the enzymes cleaving the protein (secretases) generate elevated levels of the Ab, which eventuates in excess Ab and Ab plaques [1]. It follows from that general conclusion (embedded in modern Ab theories of AD) that treatments slowing the accumulation of Ab, among those carrying the genetic mutation, might be therapeutic. Also, treatments facilitating a greater rate of removal of Ab might also be beneficial [30].

The mutation characteristic of early onset AD is not common among those who develop AD at retirement age and beyond. Like other disorders with several symptoms, it would not be expected that late-onset AD (LOAD) risk is only due to a single gene; there are likely several genes, and their many alleles, involved. As an example, another genetic factor is related to developing AD is the ApoE gene. Interestingly, ApoE variants which seem to confer greater risk for development of LOAD are less determinant than the variants of early onset AD [31]. The function of ApoE is to transport cholesterol in the circulatory system as well as the brain. As it relates to LOAD, human alleles of ApoE seem to have different roles; some may be protective (ApoE2), others confer risk (ApoE4) or produce no differences (ApoE3) [32,33]. For example, about 50% of individuals that are diagnosed with LOAD, carry the ApoE4 allele compared to about 15% of the general population [32,34]. The product of the APOE gene is a protein associated with the transport of cholesterol throughout the circulatory system [15]. Knowledge of the protein produced by the APOE gene leads to the conclusion that features of cholesterol homeostasis might be significant in sustaining brain-health. In sum, genetic risk alone, or a specific genetic by sex interaction, is not sufficient to contribute to the majority of AD cases. What is important here is that cholesterol links these two general classes of inborn risks and is a potential target for therapy.

Cholesterol is an important target to consider. The brain is considered to be “cholesterol-rich” (or contains 25-30% of the entire volume of the body’s cholesterol) [35]. The primary use of cholesterol in the brain is oligodendrocytes’ production of myelin sheaths. Other important functions of cholesterol in the brain is the formation of steroids (neurosteroids). There is a functional role of brain-derived cholesterol for cognitive processes [36]. Indeed, a

controversial and not yet entirely understood consequence of cholesterol-lowering drugs, like statins, may be to alter these key glial and neuronal processes and thereby alter cognitive function or risk for AD [37,38]. Schreurs [36] citing a large number of studies concluded that high serum cholesterol levels were related to reduced cognitive ability, MCI and AD (as well as cardiovascular disease). However, there are studies indicating that among persons of retirement age that high cholesterol levels may sustain cognitive ability. Interestingly, serum cholesterol does not cross the blood-brain barrier. Further, the brain (glia in adults) synthesizes cholesterol meeting the CNS's high demand for cholesterol [36]. Recently, Schreurs and colleagues showed that 27-hydroxycholesterol (a breakdown product of cholesterol) crosses the blood-brain barrier. Further, when there is a high cholesterol diet, 27-hydroxycholesterol is increased in the hippocampus where it is associated with the characteristic signs of AD including cell death. Of further interest is that 27-OHC is an endogenous estrogen modulator which in turn led to the hypothesis that diet-induced hypercholesterolemia might disrupt estrogenic neuroprotection [39].

In recent years, there has been a renewed focus on the role of cholesterol metabolism for AD. This has been partly spurred by the rich animal literature showing that genetic models of AD, which overexpress genes associated with AD, have altered cholesterol metabolism in association with Ab deposition, cognitive function deficits, and changes in affective behaviors (all which mimic what is observed in people with AD) [25,26,40–43]. For example, mice with the APPswe and presenilin overexpression have evidence of altered cholesterol, i.e. greater turnover as measured by cholesterol/steroid levels and enzymes responsible for this in key brain structures, such as the hippocampus and prefrontal cortex [25]. Readers are referred to a recent review describing the translational work in support of a role of cholesterol metabolism, including steroid synthesis in the brain, for AD [25]. Indeed, among people with AD, a correlation between high cholesterol levels in circulation and cognitive impairment has been reported [44,45]. As well, lower levels of cholesterol-based neurosteroids, such as allopregnanolone, has been proposed as an early biomarker of AD [46]. The role of cholesterol is an important

consideration given sex differences in AD, described above, that may be related to differences in cholesterol metabolism. As well, these differences in circulating cholesterol levels may be associated with poor clearance of Ab and neurotoxic effects [47]. It is important to further understand these links between cholesterol transport, metabolism, and general homeostasis in the brain with aging, and risk and progression of AD.

Knowing the genetic risks associated with early- and late-developing AD has allowed further characterization of the physiology related to those profiles. An advantage of knowing the genetic risks of developing AD is that further research can specify the proteins produced by the salient genes. That knowledge will be helpful in specifying the physiological processes usually maintaining the health of neuronal tissue. Of course, that knowledge will also be critical to understanding the failures to maintain healthy neuronal tissue. For example, the study of early-onset AD (familial AD) provides support for the hypothesis that, with familial AD, it is excessive production of Ab that overwhelms the capacity of the usual way of clearing metabolic products, particularly Ab, from the brain. With respect to LOAD (sporadic AD), a hypothesis is that it is a failure to regularly clear the ongoing production of Ab that leads to an accumulation of Ab [48]. In both forms of AD, the idea is that it is a failure to maintain homeostasis with respect to metabolic products of neuronal functioning that is critical to the development of AD. This has given rise to a number of ideas about how to modify the resulting physiologies with respect to halting the development of AD. For example, it is posited: an accumulation of metabolic products in the brain, whether it be Ab or 27-OHC, is germane to the development of AD. That, in turn, leads to a focus on fluid flow within the brain; in as much as, such flow might regularly clear the excesses from interstitial fluid [21]. There are other risks associated with the development of AD, and they may also affect the development of AD.

4.0 Other risk factors (other correlates) of developing AD

There is an extensive longitudinal study done in Finland (the Cardiovascular Risk Factors, Aging, and Dementia study, CAIDE) studying potential risk factors for age-related ill-health including

dementia. That assessment [49] indicated that obesity at midlife, plus vascular risk factors (high systolic blood pressure and high total cholesterol level) were significant risks for later dementia. With the recognition of the results of the CAIDE study, the medical records and survey data of participants in a large health care system were assembled [50]. Data on midlife health and subsequent signs of dementia including AD were available. As with the CAIDE study, being somewhat older (within the boundaries of midlife, i.e., older than 53), having a large body mass index (> 30 kg/m^2), having a high cholesterol level (>251 mg/dl), and high systolic blood pressure (> 140 mm/Hg) were risks for dementia and AD during post-retirement ages. Interestingly, adding new measures to a salient model of risk for dementia such as depressed mood, diabetes mellitus, head trauma, poor lung functioning and smoking did not add much, if any, to the derived model of risk for dementia and AD [50].

Within the context of the CAIDE program, there is the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) [51]. That study tested the idea that if risk factors for AD were attended to for 2 years, and hopefully modified for the better, that such would delay the onset of cognitive decline, the preeminent sign of advancing AD [51]. All participants were judged to be at risk for AD. In the intervention group, the risk factors attended to were exercise (actually change from a sedentary lifestyle), diet, vascular risk monitoring, and cognitive training. A control group received only advice on general health. A comprehensive neuropsychology test battery was used to measure cognition. In sum, the intervention-group improved or sustained cognition more than the control group (on the test battery, post intervention, the intervention group scored 25% higher than controls). The study provides support for the concept that attention to multiple risk factors might be particularly effective in sustaining cognitive health, even among those at risk for dementia.

The selection of risks to treat in the FINGER research is interesting. With the exception of cognitive training, the selected risks are associated with a variety of illness and, if moderated for the better would improve general health. Generally, better overall health is apt to be a condition for better health of the brain, hence

sustaining youthful cognition. Given the relatively small effect sizes associated with the major outcome (differences in cognition) [52] and given that it is unlikely that the treatment of any one of the risks would counter the beneficial effects of the other, there are some implications to be drawn from the FINGER research. A reasonable conclusion is that treating other known correlates of developing AD might improve the outcome of the combined treatments. Further, if a known risk factor is found to be more salient to AD, then, of course, that risk factor should be treated, if possible, with the hope of halting cognitive decline. Before discussing ways of improving the FINGER research, there is a review and commentary on the treatments used in the FINGER research.

4.1 Inactivity is a correlate of developing AD, and regular exercise reduces the overall risk.

It has been posited [53,54] that inactivity is a transdiagnostic condition of ill health. That proposition is similar to Selye's theory [55] that stress is a common factor associated with many different kinds of ill health, sufficient to be a disease in and of itself. Brain-scans indicate that lack of activity reduces signs of health in areas know to be salient to AD, for example, the hippocampus [56–58]. A meta-analytic study involving 42 studies and 3,781 older adults [59] supports the conclusion that aerobic fitness training enhanced or sustained cognitive ability with small to moderate effect sizes. Also, other reviews of preventable risks indicate that regular exercise will likely delay the onset of full-blown dementia [60–63].

Ethell [21] suggested that because intracranial pressure forces the flow of fluids through the cribriform-foramina, any event that might enhance optimal pressure, hence the optimal flow of cerebral spinal fluid (CSF) throughout the brain would aid and abet efficient removal of excess Ab. Citing research [64–66] showing that sedentary lifestyles risk the progression of AD, Ethell [21] implied that exercise would facilitate healthy CSF-flow, hence be therapeutic.

Advising and prescribing daily exercise to an elderly, inactive individual, however, is usually not sufficient for that person to engage in health-sustaining exercise. A potential beginning of a program of regular exercise that is boring (and, perhaps even,

embarrassing) and leaves the individual tired and sore is likely to be the of end the program. Rather than a “no pain, no gain” perspective, an alternative is more likely to succeed. The better approach is to encourage less intense activity, but more regular daily activity more compatible with the elderly, inactive citizen. Further, the general approach should be to start with modest goals and slowly increase the intensity and duration of exercise, in small achievable increments. Walking has been suggested with the goal of eventually attaining 10,000 steps a day.

One research program attempted to reduce the costs of treatment for inactivity by using a video presentation followed by a group discussion. This rather brief, remarkably cost-effective intervention did reduce sedentary behavior [67]. To achieve reinforcements for incrementing activity, motion-capturing technology can be used to enhance activity and use video-game-like situations to sustain interest, i.e., make use of the technology of exergaming [68]. Modern treadmills and stationary bikes can be used to increment the number of “steps” taken while making the walking or biking interesting [69]. In brief, treatments to increment activity and reduce sedentary behavior can make use of modern technology to facilitate activity and to reduce sedentary behavior and, thereby, reduce the costs of treatment.

There is strong support for the conclusion that increasing the activity of retirees presenting with minor signs of cognitive decline is helpful in reducing the likelihood of a rapid progression of cognitive decline (research cited above and these examples of a larger literature [70–74]). However, there is no support for increasing the activity of those experiencing dementia will modify major indices of cognition [75]. The implication is clear: Prevention of AD is more likely if begun before marked cognitive decline.

4.2 Some diets increase the risk of developing AD whereas others seem to reduce the risk.

As mentioned [74,75], overweight and obesity, having a high serum cholesterol level [36], and high systolic blood pressure are risks for AD. Obviously, these factors, each and all, are related to regular patterns of eating. Eating diets with *low* levels of salt, sugar, LDL fatty acids and *high* levels of fruits, nuts, vegetables and HDL is

the preferred habit because those patterns of eating reduce the risk of obesity and vascular ill-health [76–78].

There are two longitudinal studies conducted among the participants of the Rush Memory and Aging Project (Rush U. Med. Center) that assessed the effects of diets on cognitive decline with aging [79] and incidence of AD [80]. With reference to the available research, the authors selected food-groups they discerned to be helpful in sustaining the health of the brain during aging while excluding food-groups thought not to be healthy (the MIND diet). They developed scores indicative of the prevalence of using the MIND diet (the MIND diet score). The 10 brain-healthy food-groups were green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, seafood, poultry, olive oil and a very limited intake of wine. The 5 unhealthy food groups were red meats, butter and stick margarine, cheese, pastries and sweets, and fried/fast food. They also had considerable biographical and health data of the participants to use as co-variants of the prevalence of kinds of diets with respect to cognitive skills. Among the results was the finding that participants with higher education, greater cognitive and physical activity and more favorable cardiovascular conditions had a pattern of eating healthier foods than their counterparts. By statistical manipulations, the authors controlled for these variables, as well as a host of other covariates (including the incidence of ApoE4) in an attempt to isolate the effects of a pattern of eating the supposedly healthy diet in preference to an unhealthy pattern. Their findings: a pattern of eating the healthier diet tended to sustain cognitive health as one aged and reduced the incidence of AD significantly. An implication of this longitudinal study is that a favorable lifestyle, including a pattern of eating what has been posited as healthier foods, will reduce the prevalence of cognitive decline including that of AD.

There is research [81] indicating that retirees who regularly use alcoholic beverages might suffer thiamine deficiencies thereby risking Wernicke’s encephalopathy, which, in turn, is a risk factor for Korsakoff syndrome. The Wernicke-Korsakoff syndrome is manifest as memory loss. Wernicke-Korsakoff syndrome is, in essence, the death of particular neurons, i.e., those of the mammillary bodies. Disease of the mammillary bodies and fornix (a

major link to the hippocampus) have been linked to AD [82,83]. Death of neurons in the mammillary bodies occurs rapidly with the complete depletion of the thiamine reserve in the brain. The prevention of Wernicke's encephalopathy is clearly, easily treatable; i.e., provide thiamine by healthy eating or supplements. Before the complete loss of thiamine, there would probably be debris needing to be cleared from the area. Sustained regular exercise will further debris-removal. More difficult to treat is the alcoholism that interferes with thiamine homeostasis; however, there are reasonable improvements that can be made in the treatment of alcoholism [84].

Given the correlation between the variance in the APOE gene and the prevalence of AD and the relationship of the products of the APOE gene to homeostasis of cholesterol, there is an interest in variation in diets with respect to lipids. Essential fatty acids are particularly relevant in as much as there is research to indicate that supplements of them prevented indications of AD in mice who had bulbectomies [85] (also see [86] for a relevant, supportive study with elderly citizens).

Being overweight, obese, pre-diabetic, suffering Type II diabetes and Type II diabetes that evolves into Type I as well as a sedentary lifestyle are all correlated with an array of vascular problems including small infarcts in the brain. Each item of the list is correlated with the development of AD [5,87]. Each of these chronic conditions is related to what has come to be known as an unhealthy pattern of eating which involves excessive (more than "burned") calories taken nearly every day by way of considerable intake of palatable food. The palatable food often contains considerable sugar, fat, and salt without providing a sufficient variety of foods to provide adequate nutrition. The palatable food sold in many fast-food restaurants and in packaged-prepared foods contains too much sugar, fat and salt to be healthy (particularly if taken frequently). This is common knowledge (e.g., [78]).

Treatment of overweight and obesity (which obviously involves changing eating habits) are notoriously difficult to engage and, if engaged, to sustain. The crux of the issue involves behaviors (eating and physical exercise) and, therefore, should be amenable to behavioral interventions. There are tests of the potential for

behavioral therapy to be effective within the context of treatment of diabetes.

Weight-loss of somewhat greater than 7% of body-weight when evidencing Type II diabetes (or predictive signs of getting Type II) has been shown to be helpful in reducing blood glucose and relevant hormonal levels (indices of eventual serious disease). There have been two large-scale trials featuring behavioral interventions designed to effect weight loss. Each trial was discussed recently [88,89] (as part of an entire issue of the *American Psychologist*) on psychological contributions to control of diabetes. The conclusions drawn indicate that rather intensive therapy focusing of lifestyle changes did manage to get a reasonable proportion of those receiving treatment to meet the goal of weight loss and to sustain a loss for years. The weight loss and other features of the treatments reduced the incidence of advancing diabetes. Of course, the treatment did not succeed for all. However, the degree of success over control conditions (usual advice) and over the prescription of metformin (a standard medicine used to reduce blood glucose levels) is encouraging. Interestedly, there was a comprehensive study whose results were reported in 1980 that showed that CBT designed to reduce body weight was successful [90]. In brief, the CBT designed to control the progression of advanced diabetes is reasonably effective, can be implemented without excessive cost and can be improved. Better use of internet capabilities might reduce the cost of therapy, enhancing its practicality [88,89].

Diabetes and AD are both slowly developing, chronic diseases with common risk factors associated with unhealthy lifestyles known to produce overweight and obesity and accompanied by being sedentary. Treatments instilling a healthier lifestyle for one of these chronic conditions are apt to be of benefit in reducing the progression of both diabetes and AD. CBT specifically designed to modify eating behaviors and activity has been shown to be sufficiently effective to be implemented widely. We note the obvious: the costs of enhanced programs designed to prevent the progression to advanced diabetes and AD will be minimal compared to the cost of treating advanced diabetes and AD.

4.3. Monitoring known risks for vascular disease may reduce the risk of developing AD.

It is known that variables such as inactivity and unhealthy eating habits are associated with vascular diseases such artery and heart diseases and strokes. Of particular relevance to AD are hypertension (related to fluid flow) and hyperlipidemia (lack of optimal cholesterol homeostasis). Both can be treated by attending to lifestyle changes. However, a common treatment is to prescribe antihypertensive and antihyperlipidemic medications. Both kinds have been assessed for their ability to treat signs of AD. The results indicate a mixed picture [70]. Some studies indicate a benefit to prescribing antihypertensive and antihyperlipidemic medications medicines whereas others do not. For example, there are recent reviews addressing statins for their putative utility in preventing the progression to advanced AD; one suggested a benefit [91], whereas the others did not [92].
In 2012, the Food & Drug Administration (USA) added a warning to the labels for statins indicating that their use may raise the levels of sugar in the blood and could cause memory loss. Statins' benefit in reducing blood cholesterol may be offset by their side-effects. It is not known whether the prescription of antihypertensive and antihyperlipidemic medications are the cause of a gradually yearly (from 1969 to 2014) decrease in deaths due to heart attacks and strokes (deaths per 100,000 population) or other factors such as the adoption of healthier lifestyles. Given that the USA has about 5% of the World's population, but purchases 50% of the World's available medicines [93], but does not have better signs of good health, does gives rise to the idea that there might be an over-prescription of medicines with side-effects that outweigh possible therapeutic effects.

4.4. Specific cognitive training may reduce the risk of AD.

Individuals with more advanced levels of education and who regularly deal with complex intellectual challenges, probably involving extensive use of working memory, are at *less* risk of AD [50,60–63,94]. The converse is equally true; those with little formal education and who do not regularly engage intellectual challenges are at a *higher* risk. The question arises: Can we arrange educational opportunities at retirement ages that will do the same as having advanced levels of education that encourage intellectual

challenges and, thereby, reduce the risk of AD? The available research surely indicates that many interventions with the goal of enhancing cognition, and in particular memory, are not very effective in producing lasting enhancement of cognitive ability. For example, encouraging working at crossword puzzles, attempts to learn a second language, enhanced time spent reading and similar activities are not easy to instill among those who do not ordinarily engage such. Further, when there is some progress at getting individuals to engage these kinds of activities more than usual, there is no evidence that it modified ability to deal with other cognitive challenges [17,95–99]. That is, people may become somewhat more proficient at crossword puzzles, but still routinely forget where they left the car-keys. One can encourage a strategy that is beneficial such as always putting the keys in the same place. However, practicing that strategy does not help resolve other cognitive challenges such as remembering to buy needed toilet paper.

There is an approach, derived from the concepts of brain plasticity, that appears to have promise for enhancing global cognition. The basic idea is that the brain is continually being organized by perceptual input and that certain daily activities actually trains for less efficient cognition because it limits perceptual capabilities. For examples, we walk on smooth surfaces and lose skill at walking on rough, bumpy, uneven terrain. We spend hours looking straight ahead while watching television and driving a car and our brain responds by facilitating such viewing at the expense of peripheral vision [100,101].

The advent of the technology that allows for video games provides technology for a new approach with the goal of modifying established auditory and visual perceptual processes that are not utilitarian to perceptual processes that are more utilitarian. This technology has been used to develop computer-assisted game-like programs with the express purpose of enhancing cognition. A germane question: Can these computer-assisted game-like programs induce sufficient activity in relevant neural networks to strengthen overall cognitive ability? Further, if such programs can strengthen cognition, will such reduce the risk of AD?

One relevant example is associated with Prof. Merzenich and his colleagues, including a former student of his (Henry Mahnche) [11]. They formed a company, Posit Science, to market programs designed to enhance “brain fitness. Early in the history of Posit Science, a comprehensive, well-controlled, randomized study was conducted with the express purpose of testing the idea that a computer-assisted game-like program that was designed with ideas of brain plasticity in mind would enhance memory [102]. The study is a model of a scientific test of a complex proposition. For example, the statistical analyses of the results were done by an independent group. In brief, the trial involved citizens aged 60 to 87. There were 3 groups, a group that received the training designed to improve cognition based on brain plasticity rationale (sustained practice at enhancing visual and auditory perception), an active control group, and a no treatment group that was merely tested for memory at the same time the other groups were tested. Care was taken so that the active control group engaged activities that might enhance memory and cognition, e.g., watching educational lectures and taking tests on their contents. The active control group engaged the same duration of activity as the group with the experimental treatment, i.e., 60 min a day, 5 days a week for 8 to 10 weeks. In brief, the experimental treatment group demonstrated improved performance on tasks of memory that were different from those used in training whereas the two control groups did not. The difference in outcomes was indexed by an effect size of 0.25. The implication is that the approach developed by Merzenich and colleagues is different than what was attempted before in trying to improve cognition among the elderly; different in concept and different in effectiveness. Now 10 years after this demonstration and based on continuing research, many conclude that *specially-designed* computer-assisted game-like programs are useful and it would benefit healthy aging if widely used [8,10,100,101,103–107].

Prior to the work described above, there is the research of Prof. Ball of the University of Alabama at Birmingham. She and her colleagues, across the years and with multiple studies [100,101], have demonstrated that computer-assisted game-like training focusing on enhancing visual processing speed and spatial abilities (in particular, training for enhanced peripheral vision) can change

older participants' capabilities sufficiently to reliably reduce the incidence of motor vehicle crashes [107]. Thus, there is a precedent for incorporating game-based training for sensory processing to enhance other behaviors related to safety and well-being of aged individuals.

Based on these early demonstrations that computer-assisted game-like programs could enhance cognition among some persons and stoked by individuals' desires to improve their cognitive abilities, considerable commerce has developed selling programs advertised to improve such fundamental cognitive abilities as memory and attention. Some of these commercial programs are surely more sophisticated than others. If one takes as an index which of these programs is mostly based in the relevant science (e.g., numbers of germane published peer-reviewed articles and Federal grants awarded), then the scientists who developed the programs of Posit Science are surely the leaders in developing science-based programs with the possibility of actually improving memory and attention. The current programs offered by Posit Science are very sophisticated, designed to sustain practice and available at reasonable cost. Further, they allow the collection of data on the amount of use and progress with practice.

The advantage of practicing memory and attention might not be enhancing the ability to memorize and to attend directly, but rather the enhanced fluid flow that might be engendered by practice in networks involved in memory and attention. In other words, sustained cognitive activity likely induced enhanced fluid flow that may clear an accumulation of excess Ab in anatomical areas that are previously only periodically, but not regularly, active.

Consideration of the extensive research associated with treating the risks for AD that were treated in the FINGER research and the rather impressive research supporting the idea that treating those risks is likely to reduce the prevalence of AD, it seems that widespread implementation of treating those risks is a treatment of choice for a condition that appears to be incurable and not preventable. Further, we posit that a program of treating risks for AD can be improved by attending to other risks, namely treating loss of olfaction and difficulty sleeping. Loss of olfactory ability (hyposmia and anosmia) is an early sign of impending AD (e.g.,

[108–114]) and disturbance of sleep is also a known risk for developing AD [115,116].

5.0. AD and the olfactory brain

Much of the content of this section follows from an article by Prof. Ethell [21] and describes ideas about the role of fluid flow and olfaction for AD. In accordance with the amyloid theory of AD [1], Ethell posits that the essence of AD is an inability of CSF-flow to regularly clear metabolic products, particularly *excess* Ab, from the interstitial fluid of the brain [21]. More specifically, Ethell posits that disease at the brain-nasal cavity (B-NC) interconnection interferes with the steady removal of excess Ab. It was estimated that over 80% of the bulk flow exiting the cranium is by way of the functionalities of the B-NC interface [117]; however, new theories may challenge that value, which will be discussed. There are reasons to focus attention on the B-NC interface, one of which is that it is vulnerable to disease.

5.1. The tissues of the nasal cavity are vulnerable.

The dendrites and cell bodies of the olfactory nerves are actually outside of the cranium, embedded in the olfactory epithelium of the nasal mucosa. Olfactory nerves (axons) extend through the cranium by way of the numerous foramina of the cribriform plate of the ethmoid bone, which separates the nasal cavity from the meninges, with their CSF-filled subarachnoid space, and the olfactory bulb. At the nasal epithelium, flowing CSF merges into lymph vessels that are part of cervical lymphatics [21,118]. Any event disrupting the functionality of fluids exiting the cranium via the cribriform plate, as well as disrupting the olfactory nerves and their supporting tissues at the cribriform plate, would have unhealthy consequences. Those unhealthy consequences include less efficient bulk flow from the brain to the cervical lymphatics and hyposmia and anosmia.

Because the tissues of the nasal cavity are exposed to the air of breathing and sniffing, they are subject to a variety of adversities. The most common of which are infections due to growth of virus, bacteria, fungi, protozoa and perhaps an accumulation of allergenic particles and immune processes which attempt to combat infections or allergens. Poisonous fumes can also severely damage the functionalities of fluid flow and olfaction.

Even the intense air pollution of some urban centers might be toxic [119,120]. Some commonly prescribed drugs may also affect olfaction [7,121]. Ethell pointed out that physical trauma to the head can disrupt the fragile structures of the cribriform plate hence disrupting fluid flow [21]. Physical trauma can also move the brain and olfactory nerves against the more stable skull shearing the olfactory nerves traversing the skull. Ethell posited a potential causal link between such physical damage and AD because the trauma would disrupt fluid flow regulating the concentration of Ab [21].

The loss of olfactory perception is an early sign of impending, fully developed AD (e.g.,[20,48,79,108–114]). Loss of olfactory perception has multiple consequences. Most individuals are disturbed by hyposmia and anosmia. Hyposmia and anosmia also reduce the pleasures of taste, thereby, contributing to the anhedonia characteristic of clinical and subclinical depression. It is notable that changes in mood/depression may be a very early sign of AD [122]. Also, olfactory bulbectomy is an animal-model of depression [123]. And, it has even been posited that olfactory bulbectomies might be an animal-model of AD because the consequences of bulbectomies resemble those of AD [124]. As well, animal models of AD show both cognitive and affective dysfunction [42,43].

Authors often conclude that neuro-degenerative diseases *cause* loss of olfactory perception. For example, Mackay-Sim and colleagues have described how "...many neurodegenerative diseases also induce loss of olfactory function." ([7] p. 763). However, it is equally plausible that a feature of olfactory dysfunction may induce neurodegeneration, a proposition finding support in a report showing anosmia is correlated to a loss of cortical gray matter [125,126].

Mackay-Sim et al. [7] related results from a survey of adults of various ages and confirmed that the quality of olfactory perception tends to decrease with age. However, a different perspective emerged when the tested participants were separated into two groups: one was characterized as having a history of nasal problems and taking a variety of medications, and the other group was characterized as having no history of nasal problems and not taking a variety of medications. The medications included those

routinely prescribed to an elderly population, i.e., antihypertensive and antihyperlipidemic medications that had been shown to be associated with reduced olfactory ability [121]. Those with known nasal problems and/or taking a variety of medications *did* show a marked decline in olfaction as a function of aging. The trouble-free group, with a small incidence of prescribed medications, *did not* show a marked reduction in olfactory perception as a function of age. Evidently, among the generally healthy elderly, the processes of neurogenesis known to occur in the olfactory epithelium was sustained sufficiently to maintain olfactory perception [127]. The conclusion: Degradation of olfactory perception is not an inevitable consequence of aging.
In addition to noting that loss of olfaction is a correlate of developing AD and noting that the olfactory anatomy is susceptible to disease, there is research supporting the idea that the distal portions of the olfactory brain are the sites where the development of AD begins.

5.2. Perhaps, AD begins in the distal portions of the olfactory brain.

Interesting differences were found in the first post-mortem study to directly compare the histology of the olfactory bulbs of patients with AD to those without AD [20]. Those with AD had extensive neurofibrillary tangles and reduced cell density in the anterior olfactory nucleus; and, those without AD had not suffered such. The distal portions of the olfactory system are clearly affected in those manifesting AD [20]. AD is characterized by a progression of ill health from the olfactory bulb, anterior olfactory nucleus to other segments of the limbic brain (importantly to the hippocampus thereby affecting memory) and eventually to nearly the whole brain [21,128–131]. There is an extensive review [132] detailing the information supporting the idea that onset of AD is likely to begin at the distal portions of the olfactory brain and then spread to the more central portions of the olfactory brain and then to nearly all of brain (also see [131]). Also, it is noted that olfactory bulbectomy in mice leads to accumulation of metabolic and cellular debris in the entorhinal cortex [133], a cortical area for olfactory perception and involvement in hippocampal functioning.

A recent article addressed the issue of whether AD starts in the basal forebrain or in the entorhinal cortex by measuring shrinkage in gray matter volume of the basal forebrain and the entorhinal cortex [134]. The issue was addressed by measuring the relative size of the two areas from those suffering various stages of AD during autopsy. The conclusion was drawn that the basal forebrain suffered somewhat earlier damage than the entorhinal cortex. Using advanced technology to estimate the number of neurons in an area of autopsied brains, an earlier study addressed the loss of tissue in selected areas of the brain with the advancing signs of AD (from no signs of AD to dementia) in each of three areas of the human brain: (a) nucleus basalis of Meynert, (b) locus coeruleus, and (c) entorhinal cortex [135]. For example, the neuron number of a heathy 80-year-old for nucleus basalis of Meynert is estimated to be 167,200 to 215,827; there is a small loss in neurons among those with earliest signs of cognitive decline and extensive loss among those with advanced AD (83% loss) [135]. There was progressive loss of neurons in each area sampled as AD advanced. The nucleus basalis of Meynert is a source of cholinergic innervation of the olfactory bulb. The locus coeruleus is a source of noradrenergic innervation of the olfactory bulb [136,137]. The entorhinal cortex is a place receiving innervation from the olfactory bulb as well as cholinergic innervation [138]. With the focus on determining which of these central areas of the brain has the earliest and most severe loss of tissue, the focus overlooked the possibility that the initial disease was likely at the B-NC interface. The idea is that induced disease of the olfactory bulb (vulnerable to disease at the B-NC interface), in turn, induces disease in areas providing both cholinergic and noradrenergic input to the bulb, i.e., the nucleus basalis of Meynert and locus coeruleus. Such tissue loss eventually proceeds to entorhinal cortex, the hippocampus and large segments of the cortex. It follows that any effect that might prevent or halt disease at the B-NC interface might also halt the progression of AD.

We have information indicating that a major source of bulk flow from the brain to lymphatic system is at the brain-nasal cavity (B-NC) interface. We have noted that the distal portions of the olfactory brain are susceptible to a variety of illnesses. In addition, loss of olfactory perception is an early risk factor for the

development of AD. And, there is a progression in the development of AD that begins with the loss of neural tissue in the distal portions of the olfactory brain and progresses to the more central portions of the olfactory brain. An issue emerges: How could disease at the B-NC begin a progression of disease that would eventually destroy nearly all of the hippocampus and wide portions of the cerebral cortex. The next section addresses that issue.

5.3. Disease at the B-NC interface is apt to reduce fluid flow through the distal portions of the olfactory brain, hence lead to excess Ab with interesting consequences.

Neuro-vascular and neuro-metabolic coupling is a name given to the relationship between local neural activity and changes in the vascular and metabolic processes that provides the nourishment needed by heightened neural activity [87,138–140]. In brief, it is posited, that neural activation triggers vasodilation hence increases blood flow to an active area; and concordantly, and of necessity, less blood flow to areas of less activity (a functionality making functional magnetic resonance imaging, fMRIs, possible). Any area of the brain not activated beyond a basal state of readiness must nevertheless sustain energy-use to maintain membrane potentials; hence produce metabolic products, including Ab. If disease at the nasal epithelium has blocked olfactory stimulation by the olfactory nerve, then that malfunction would drastically reduce stimulation of the olfactory bulb. Consequently, the bulb would not be an area of high activity and be an area of reduced fluid flow and be subject to an accumulation of metabolic products that might have toxic effects. Further, the invasion of infectious agents along perineural pathways might cause death of neurons in the olfactory bulb and inflammation.

A chronically quiescent olfactory bulb (e.g., due to reduced olfactory sensation and a consequence of a variety of diseases at the B-NC interface) might lead to an accumulation of metabolic waste that may lead to events that are not healthy first for the anterior olfactory nucleus, and then progressively not healthy for the lateral olfactory tract, and its connections [132]. If there is cell death, there are likely to be immune processes (probably involving Ab [141] and, of course, microglia) that can be overwhelmed by the

extent of the damage and hence contribute to further ill health by forming even larger clumps of “trash” needing to removed [142]. Also, if fluid flow at the cribriform plate is totally blocked, then there would be considerably reduced means of removing the accumulated debris from the area. This line of thinking supports Ethell’s hypothesis that disease at the B-NC interface can be an initiating event in the development of AD [21,132]. There is also an implication that can be drawn from this line of thinking. Any activity that would restore any reduced levels of fluid flow to the distal portions of the olfactory brain is likely to be therapeutic.

5.4. Treating lost olfactory perception may halt the progression of disease in the limbic system that eventuates into full-blown AD.

There have been extensive reviews on the topic of addressing potentially preventable risks for developing AD (e.g., [60–63]). Notably, none have addressed the possibility that treating hyposmia and anosmia might be a way of reducing the risk for AD. Perhaps, that is the case because until recently there was not sufficient recognition that malfunctions at B-NC interface might be causally related to AD (however, see [21,132]). Also, until recently there were only a few studies indicating that hyposmia and anosmia were easily treatable. Physical blockage of the nasal passages (e.g., by tumors or infections) are often treatable, but the long-lasting effects of the disease at the B-NC interface may lead to chronic loss of olfaction. Until recently, there were no known cures for chronic anosmia or hyposmia due, for example, to lingering effects of infections.

Anosmia and hyposmia are associated with a number of problems, e.g., reduced ability to sense spoiled foods and smoke. The loss of pleasures from eating seem to be particularly problematic for the elderly [143]. Also, loss of olfactory perception is associated with clinical depression [144], which in turn is a risk factor for AD [145–147]. Consequently, the successful treatment of hyposmia and anosmia would be beneficial regardless of its potential benefits in halting the progression of AD.

5.4.1. New procedures have been developed that effectively treat hyposmia and anosmia.

Across the last few years, a few studies have demonstrated that daily training with scents has improved olfaction [148–159]. The regimen used is remarkably simple. The participants have merely been directed to every morning and evening, to sniff, for 10 seconds or so, each of four scents. By doing so for months, about 30% of those presenting with hyposmia or anosmia recovered some of their lost olfaction; a much larger percent than those who did not practice [149]. Recently the training regimen has been modified [148]. After many days sniffing the initial four scents twice daily, the participants were presented four new scents to sniff daily, again, for many days. This rather small change in the daily regimen led to 63% measurable improvements in olfaction [148]. Further, there was an indication that those who engaged olfactory training within a year of loss of olfaction were more likely to recover olfactory perception [148,149]. Together, these studies demonstrate the possibility of olfactory training to reduce olfactory dysfunction; albeit, there may be windows of sensitivity after the dysfunction manifests.

At issue: How does merely sniffing daily among those with anosmia engender the plasticity necessary for recovery of lost olfaction? Some recent findings are germane. Sniffing among those with anosmia enhances activity in olfactory cortical areas [155] as well as other areas of the brain [158] that might be critical to olfaction. For example, sniffing is critical to the perception of the source of a scent and for sensing the potential toxicity of the source of scents. In brief, sniffing is an integral component of olfactory perception [159]. The basis of fMRIs to index neural activity is that neural activity induces fluid flow and associated oxygenated blood, which can be indexed by MRI. Consequently, when there is recovery of lost olfactory perception, it is surmised that there is increased neural activity, hence increased vascular activity within the olfactory brain. Actually, it is difficult to imagine how it would be otherwise, neural activity demands constant nourishment and removal of metabolic products from interstitial fluids surrounding neurons. Sniffing, therefore, might enhance the relevant flow of CSF and, perhaps, neuropoiesis in portions of the olfactory brain.

5.4.2. Some caveats

The hypothesis that the B-NC is *the* place where CSF interacts with the lymphatic systems is incomplete. It does not account for the

fact that the blockade of the flow through the cribriform plate does not immediately lead to rather disastrous effects. Consequently, there must be alternatives for metabolic products generated in the brain to get to the lymphatic system other than at the B-NC interface. Recent discoveries [160,161] have confirmed [162] that there are functional lymph vessels lining sinuses of the dura mater thereby providing a connection between the CSF of the subarachnoid space to the cervical lymph system. In mice, lymph vessels were associated with cranial nerves (particularly cranial nerves II, V, IX, X and XI) as they exited the brain. Lymph vessels are also observed in the dura lining the cribriform plate [160]. Lymph vessels were also associated with the middle cerebral artery, an artery serving the dura mater. If the exit of fluids at the cribriform plate was blocked, the additional connections between CSF and the lymphatic system associated with the dura mater could account for a means of regularly moving excess Ab from the subarachnoid space to the cervical lymphatics. Nevertheless, the reduction of flow from brain to the lymphatic system due to disease at the B-NC interface might result in a slow accumulation of Ab in the distal olfactory brain, and a slow accumulation of Ab is a hallmark of the beginnings of AD.

Positing that disease at the B-NC interface disrupts fluid flow which ordinarily removes excess Ab by itself does not specify how excess Ab leads to death of neurons and glia. Given the susceptibility of neurons to disruption of blood flow at the capillary beds, it is likely that excess Ab, Ab-plaques and an inducement of immune processes somehow, together, block the regular flow of blood through the capillary beds [6,87], hence starving neurons to death. Treating multiple risk factors associated with AD, including hyposmia and anosmia, are likely to sustain healthy bulk flow of fluids throughout the brain.

Positing that interference with circulation of blood to distal portions of the olfactory brain does not, by itself, explain how the damage to the distal portions of the olfactory brain slowly, but insidiously, causes cell death in adjacent tissue. It is posited that cell-death at a focal area incites cell-death in adjacent areas. Cell-death spreads from one damaged area to the next and so on until there is dementia. The critical event may be the accumulation of proteins that are not cleared sufficiently. There is recent research

indicating that excess Ab might be toxic itself. He et al. injected human Ab1-42 into the mouse olfactory bulb and then tracked the spread of the injected material [163]. They found that the injected Ab spread to areas adjacent to the injected area and induced neuronal apoptosis in the adjacent areas. They concluded that Ab peptides could readily move via neural connections and that excess Ab is toxic.

5.5. Summary on the olfactory brain and AD

Treating lost olfactory perception and strengthening ordinary olfaction might further reduce the risks of AD when engaged along with the risks treated in the FINGER study. Further, the treatment of olfactory deficits is easy to implement; and evidently readily engaged. Further, the recognition that olfactory training might reduce the risk of AD is apt to sustain olfactory training. With the goal of preventing AD, it seems rational to add testing for olfactory deficits. If olfactory deficits should be present (and not due to features such as physical blockage of the nasal passages), then it just seems reasonable to engage the simple treatment of briefly, but regularly, practicing sniffing and attempting to smell a variety of scents for many days. Further, it appears to be best to engage the treatments of practicing sniffing as soon as a deficit in olfaction is recognized. Daily exercise is apt to further the effects of olfactory training because both would induce more fluid flow at the B-NC interface leading to less accumulation of Ab, hence no excess of Ab.

We believe that behavioral treatment for hyposmia and anosmia has yet to be tried as a part of a comprehensive program designed to prevent AD. There is another risk factor that also seems particularly salient to the development of AD that has not been a part of a program to prevent AD; i.e., treating the risk factor of disturbed sleep. Along with hyposmia, disturbances of healthy sleep are signs of imminent AD [116,164–167].

6.0. Recent studies of sleep add to the theory on ordinary, regular fluid flow in the brain.

Prof. Nedergaard and colleagues [22,168–170] and others [171,172] studying the brain during the circadian cycle have made observations germane to the maintenance of homeostasis of the

brain's fluids. Total volume of fluids in the healthy brain remains nearly constant, but the proportion of fluid might vary among the various fluid compartments of the brain, i.e., varies among the ventricles and subarachnoid spaces, the extracellular space, the intracellular space and the fluids associated with arteries and veins. Interestingly, it is posited [170] that the fraction of extracellular volume is about 14% during the awake state compared to about 23% during the sleep state (data from mice), i.e., about 60% from awake to sleep. It is posited that the greater volume of extracellular fluid during sleep facilitates the removal of metabolic products, notably accumulation of Ab. Such a proposition is supported by data indicating that Ab is probably cleared twice as fast during sleep compared to being awake [170]. Interestingly, a single night of sleep deprivation led to elevated levels of Ab-42 in healthy middle-aged men [173].

6.1. Some caveats

There have been serious questions (e.g., [23,174]) raised concerning the generalization that there are marked changes in extracellular volume as a function of being asleep or being awake. The questions revolve around the idea that the observations may be peculiar to the preparation used to measure changes (e.g., using barbiturate anesthesia); and the impossibility that such volume changes might not occur ordinarily because it would involve nearly pathological changes in osmotic balances between fluid compartments [174].

We note that the procedures used by Nedergaard and colleagues [22,168–170] did not allow for measures associated with a full cycle of healthy sleep, i.e., a periodic shift from non-REM sleep to REM sleep that characterizes healthy sleep. Consequently, the shifting levels of brain activity (measured by EEG activity) from non-REM sleep to REM sleep (paradoxically awake-like brain activity while asleep involving dreaming) was not considered in their formulations. Extending our extrapolations from (a) understanding of the essentiality of neuro-vascular coupling, (b) the requirement that all areas of the brain cannot simultaneously have high levels of vascular input, and (c) that efficient waste management of the brain demands that all areas of the brain have substantial activity periodically, but regularly, thereby having

substantial fluid flow, it is speculated that: as Nedergaard and colleagues posit [22,168–170], during sleep there might be systematic changes in fluid flow that might contribute to better "waste" management. Also, potentially relevant, there is more production of CSF during sleep-time [23]. We posit that the shifting levels of activity among brain areas during sleep (cycles of REM and non-REM sleep) might be a mechanism for areas that might not have been particularly active while awake to be active during a period of sleep. It might be therapeutic with respect to AD to attend to the risk of sleep disturbances.

6.2. Treatment of sleep disorders will improve CSF flow, hence treat AD.

There are recent reviews [164,175] on sleep and AD. Sleep disruption is a prodromal sign of AD [115,116,163]. Also, the consequences of sleep disruption might contribute to the progression of AD. As symptoms of AD progresses in severity, so does severity of sleep disruption. The sleep disturbances common to AD include increased sleep in daytime, increase frequency of nocturnal awakenings and a net decrease in both slow wave and REM sleep. Also, confusion and agitation are worse later in the day among those with clear signs of AD. There is a possibility that commonly prescribed hypnotics may contribute to sleep problems (and their correlates) rather than treating them, except in the very short-term (most widely used hypnotics interfere with REM sleep and memory consolidation).

Fortunately, there are effective treatments for common problems of sleep. Extensive, well-done research indicates that CBT for insomnia (CBT-I) was and is likely to be effective [176]. Studies of comparative effectiveness confirm that sleep problems should be attended to by CBT-I rather than by hypnotics [176–178]. These studies led American College of Physicians to recommend CBT-I in their new clinical practice guide for management of chronic insomnia [177,179]. Pharmacological treatments for insomnia can be effective, but risk adverse side-effects which are problematic for people at risk for AD, e.g., memory-problems [180]. If drugs are used to treat insomnia, they should be used under the general rubric of "psychopharmacology is merely a setting condition for psychotherapy."

There is counseling usually embodied with CBT-I called sleep hygiene. Sleep hygiene is rather common sense advice on how to treat insomnia. Often sleep hygiene is the provision of a checklist of activities that a patient might engage, including such things as do not drink coffee close to bedtime and establish a regular time to go to bed and when to get out of bed. Those who comply with the advice often have a better quality of sleep. Further, sleep-hygiene-advice can be effectively delivered over the internet, hence be cost-effective [181]. A treatment program designed to treat the first signs of AD [175] would attend to sleep problems beginning with sleep-hygiene-advice; and if that does not succeed, a referral to someone who can deliver more comprehensive CBT-I.

7.0. Treating multiple risk factors might be particularly effective in sustaining cognitive health.

Imagine a brain fitness center associated with places where elders congregate such as retirement communities, assisted living facilities, and senior citizen centers. Also, there could be places specifically established to engage retirees in activities that will reduce the risk of AD. There may be opportunities to cooperate with those working to prevent diabetes. Such centers would collect information germane to testing the general concept that treating multiple risk factors for AD would delay the onset of AD.

The centers would be places for obtaining baseline data, such as results of tests of cognitive ability and information on general health. There would be testing for hyposmia and anosmia and cognitive abilities, thereby, having the means of advising participants to engage a regimen of brain fitness designed to prevent AD. Many with reduced olfactory perception and mild cognitive decline may not be particularly aware of the extent of their losses or more likely attribute them to the inevitability of aging. Making elders aware (a) of their potential losses (b) the good possibility that relevant practices might restore losses, and (c) that restoration to a normal level of functioning might delay onset or even prevent AD may persuade elders to commit to engaging in activities to prevent AD.

The beneficial results of the FINGER study [51] encourage attempts to improve on treatments they designed to halt the development of AD. For example, making use of modern

technology (e.g., exergaming programs and using best learning theory practices that would more fully reward the relevant activity). Also, we posit that there can be substantial improvements in the treatment by adding to the risks that they treated. In addition to treatments used in the FINGER study, considerable attention might be directed toward treating hyposmia and anosmia. There would be available treatments for sleep disorders.

There would be stations with computers for the systematic collection of data as well as a place to introduce and encourage practicing cognitive tasks designed to strengthen cognition such as those commercially- available [11,164]. Even ordinary daily computer use has been proposed to facilitate cognitive functioning and enhancing hippocampal volume in older individuals [182]. That center might be equipped with a few modern, treadmills or stationary bikes to encourage physical exercise (i.e., exergaming) [68,69,75,155,158,159,175,176,183–185], thereby, improving CSF flow [21]. For those who can afford computers and exercise equipment at home, there will be encouragement to engage cognitive training as well as exercise at home.

The centers would be a place for giving advice on sleep hygiene. As indicated above, CBT-I might be indicated for those for whom advice on sleep hygiene was not helpful. Also, new research has indicated that skillful adjustment of the lighting of the places where retirees live would nudge toward healthier sleep [186], which, in turn, is germane to the prevention and treatment of AD.

It seems obvious that better nutrition, better sleep, better exercise, and cognitive engagement will reduce the risk of diseases of the brain; nevertheless, little is done to encourage and sustain healthy lifestyles among those at retirement-age and particularly those who might need special support for engaging health-sustaining activities (e.g., very gradual introduction to an exercise program or attention to lost olfaction). We promote the idea that treatment of hyposmia and anosmia should be routine, rather than ignored. Even marginal enhancement of treatment of problems of olfaction and sleep will reduce the risk of lethargy and depression which, in turn, will facilitate general activity and, thereby, reduce the risk of AD.

The earlier prognostic signs of advancing AD including lost olfaction, sleep disturbance, chronic inactivity, and mild cognitive decline need not be merely signs of unremitting accumulation of Ab plaques, but rather conditions that can be remedied. If these prognostic signs are remedied, they will most likely prevent what has seemed to be the inevitable slow erosion of the brain that is AD. Treating selected risk factors will very likely sustain the ordinary, regular healthy removal of excess Ab as occurs during pre-retirement years and in about half of those reaching the age of 85 years.

The technologies of modern video games can be applied to make cognitive training and exercise more rewarding, hence reducing the "work" necessary to effect plasticity. Also, treating the risk factors of lost olfaction and disturbed sleep involve little time-consuming "work" (but sustained attention) and when successful have enduring effects that will be sustained without further attention to the problems. The idea is that it is surely possible to improve on treating known risk factors and provide a potentially larger benefit than what was demonstrated in the FINGER research [51] and further the improvements can be made in a cost-effective way.

7.1. Some caveats

The belief that one feature of a healthy lifestyle is sufficient may be a limited perspective. Attention to inactivity by prescribing exercise has been shown to be helpful in preventing cognitive decline and hence may be helpful in preventing AD. However, it is unlikely that a program of exercise by itself will prevent the high prevalence of AD among retirees. Studies addressing this issue show that the variable of exercise accounts for only a percent of the variance in measures indexing progression toward AD. We are focused on treating lost olfaction as being an important feature of a program designed to prevent AD. It is likely that treating lost olfaction may be helpful in preventing advancement of AD, but may not be sufficient by itself to end the high prevalence of developing AD among retirees. We posit that CBT for AD which addresses multiple risk factors associated with the development of AD will have a much better chance of markedly reducing the prevalence of AD then alternatives that address only one aspect of the problem.

8.0. Differing Perspectives

There is the question of whether Ab is similar to carbon dioxide, i.e., metabolic “waste” with little if any utility and needs to be removed; or similar to glutamate, a necessary product whose accumulation beyond its utility is problematic. There is support for the concept that Ab is more similar to glutamate. The genes producing Ab are phylogenetically conserved [187], Ab is nearly constantly produced [188], and Ab has functionalities [141,189]. More telling, however, is the fact that putative therapies based on the notion that Ab is garbage, waste, debris or like a microbe have failed to prevent the cognitive decline characteristic of AD (e.g., [190–194]).

Notice the difference between what is current (find the elusive medicine) compared to what is proposed. The extant perspective tends almost to ask retirees to be passive and to hope that the experts on molecular biology will find a cure for AD, just in case they are among the unlucky ones who will “catch” AD. What is really quite different is that CBT for AD asks retirees to be active participants in sustaining their brain-health. CBT-AD prescribes activities which in turn have a chance of sustaining the molecular biology of the brain typical of their younger, healthier, productive years. Also, the prescription of the activities of CBT-AD has a reasonable chance of halting the early stages of developing AD. The beneficial changes in the brain can come about by way of persistent activities because persistent activities engage the complex physiology of the brain (e.g., modifying fluid flow) consequently more likely to make system-wide changes (e.g., within the olfactory brain). The brain of a sedentary, intellectually inactive individual who has sleep problems is organized by those activities, and that organization has unhealthy consequences (e.g., an accumulation of Ab, leading to excess Ab, and toxicity). We posit, following others, that consistent physical exercise, specific kinds of cognitive exercise, activity toward healthy olfaction and efficient sleep will also organize the brain, but for the better (with reference to AD, no or limited excess Ab throughout the olfactory brain).

Prescribing drugs or vaccinations are not likely to correct a sedentary lifestyle and induce a more active lifestyle with cognitive challenges (e.g., such as learning to dance and then regularly

dancing often and getting better at it [195]). We can, however, prescribe activities that support healthy fluid flow in the brain and skillfully nudge retirees to engage activities that replace unhealthy patterns of behavior. This generalization does not obviate the possibility that a drug or a nutritional intervention might not be useful in helping retirees to *actively* sustain the health of their brains.

Note that the combination of successively treating hyposmia and anosmia (practice at sniffing), improving patterns of sleep (CBT-I), inducing a healthy level of daily activity (try exergaming), encouraging healthy eating habits (e.g., the MIND plan), and practice at tasks involving working memory and attention (selected computer-assisted game-like programs), might each and all, facilitate clearing the brain of excess proteins. Further, treatments for these lifestyle variables are well within our technology to do so beneficially and to do so in a cost-effective manner.

Modern research has discovered there are potentially multiple ways for clearing the brain of excess Ab (and potentially other proteins) including bulk flow at the B-NC interface [21], via other dura mater lymphatics [160,161], via glymphatic clearance [22] or by way of facilitated transport at the blood-brain barrier [196]. We posit that this redundancy, along with immune processes [4], usually prevents an accumulation of proteins in interstitial fluid thereby sustaining the homeostasis characteristic of a healthy, youthful brain. Presumably, these various processes are responsive in varying degrees depending on the changing status of the constituents of fluids reaching the brain (e.g., due to what has been eaten recently) and what an individual is doing (e.g., sleeping or dancing). When one means of clearing excess protein from the brain is sluggish, overwhelmed or otherwise inoperative, the other ways would become more salient to health. However, reduction in efficiency of one means of clearing the brain of excess protein (e.g., disease at the B-NC) puts the individual at great risk when another means of clearing excess protein is not functioning optimally (e.g., poor sleep habits). The implication is clear: to develop some insurance toward having a healthy brain throughout retirement age, it seems rational to engage activities that reduce multiple risks for developing AD. That is: maintain what is currently

extant as a healthy lifestyle (features of gross activity and diet) and also attend to risks that may not usually be considered as critical such as practicing olfactory perception, attending to habits of sleep, and practicing brain training.

It is known that senior citizens with the genetic profile of ApoE4 are at risk for AD; however, a goodly number of the healthy oldest old (older than 85 years and cognitively fit, i.e., super-seniors) also have the ApoE4 variant [15]. It appears that super-seniors with a potentially deleterious genetic profile (e.g., ApoE4) yet sustain their health (i.e., no AD) may also have a genetic profile that buffers the consequences of having the known deleterious profile (i.e., have epistatic variants) [15]. Further study indicated that there is a network of candidate epistatic longevity genes buffering the effects of having what is thought to be genes with deleterious effects. With respect to AD, the proteins produced by the network of genes germane to AD involve the regulation of cholesterol and lipid metabolism and immune and inflammatory responses with the adaptation of reducing the risk of adversity. This genetic complexity demonstrates that there is plenty opportunities to avoid the slow accumulation of Ab by way of activities such as by what is eaten and other lifestyle variables (e.g., variables affecting fluid flow throughout the brain).

Although we surely do not know all there is to know about the physiology of the CNS and further research may lead to a discovery of a medicine helpful in sustaining the health of the brain as we age; currently, AD is incurable. Currently, however, we do have sufficient information to conclude that CBT designed to prevent AD is apt to be effective, for a number of those at retirement age, in preventing the development of AD.

9.0. Conclusion

The proposition is that (a) lost olfaction, (b) consistently being tired after nightly sleep, and (c) an indication of some loss of skillful cognition are indications that fluid flow throughout the brain, and particularly at the B-NC interface, is sluggish [21]. Therefore, fluid flow at the B-NC interface probably needs rehabilitation. Further, we posit that each of the listed symptoms can be rectified by engaging some time-consuming, but rather simple, activities. Cognitive behavioral treatment for AD would involve the following:

training for better olfaction, engaging the already well-developed CBT-I, engaging the already well-developed computer-assisted game-like programs to sustain cognitive skills, using exergaming to enhance activity which, in turn will stimulate CSF flow throughout the brain. Also, providing advice on nutrition and drug-use is apt to be helpful. Further, much of this therapy can be engaged by the elderly without much professional help (much of it is already automated). Even further, the advocacy of these practices is supported by considerable research that supports the idea that *early stages* of AD are fundamentally a failure to sustain homeostasis of the interstitial fluid of the medial temporal pole [21]. CBT-AD as advocated here is different than what is currently practiced; now, we mostly render palliative care for those with advanced AD. Thus, behavioral therapies, or training, aimed at olfaction, sleep, exercise, attention to diet and/or practicing specially designed computer-assisted game-like programs may be a feasible avenue toward reducing the risk and morbidity of Alzheimer's disease.

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11.0. References

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