The Theory that Alzheimer's Disease is a Product of Disrupted Cerebrospinal Fluid Flow has Interesting Implications

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Abstract

The hypothesis is that Alzheimer disease (AD) is (a) a reduction in the efficiency of the regular clearance of excess amyloid beta (Aβ) which sets the initial stages of the progressive disease that is AD; (b) further, that the initial events of many instances of AD begin with ill-health at the brain-nasal cavity (B-NC) interface; (c) disease of the B-NC interface hinders olfactory perception and disrupts the flow of fluids from the medial temporal pole to the cervical lymphatics; (d) that flow of fluids sustains the homeostasis of the anterior olfactory nucleus, piriform and entorhinal cortices, and eventually, the hippocampus and related areas, areas that are progressively unhealthy during the initial and middle stages of AD; (e) therefore, preventing and treating any dysfunction of fluid flow from the medial temporal pole at the B-NC interface will prevent and treat early stages of AD; (f) treating lost olfactory perception and disturbances of sleep will improve fluids flowing from the brain at the B-NC interface, thereby restoring homeostasis in the limbic system, and thereby treating early stages of AD; and (g) the most efficient way of treating lost olfaction and sleep disturbances is by way of behavioral therapy. In this review with hypotheses, these points will be addressed leading to implications of how behavioral therapies, or training, aimed at olfaction, sleep, exercise and practicing specially designed computer-assisted game-like programs may be a feasible avenue toward reducing Alzheimer's disease risk and morbidity.

Keywords: olfaction, behavior, plasticity, neurodegeneration, exercise, sleep, Alzheimer disease

This article is germane to Prof. Ethell's article titled "Disruption of Cerebrospinal Fluid Flow through the Olfactory System May Contribute to Alzheimer's Disease Pathogenesis," a well-developed hypothesis appearing in this journal [1]. Ethell posits that the essence of Alzheimer disease (AD) is an inability of cerebrospinal fluid flow (CSFF) to regularly clear waste, and particularly excess amyloid beta (Aβ), from the interstitial fluid of the brain [1]. It is estimated that over 80% of the bulk flow exiting the cranium is by way of the functionalities of the brain-nasal cavity (B-NC) interconnection [2]. Even partial impairment of this exit would degrade the steady removal of proteins which can accumulate in interstitial fluid. The accumulated proteins tend to combine with each other to form large proteins whose effects induce toxicities [3]. Consequently, it is posited [1] that any event that might disrupt CSFF at the B-NC interface may be a causal link in the development of AD, or, at least, a major contributing factor to the development of AD. Here, we review this hypothesis and related evidence, concluding with suggestions of behavioral interventions to remedy ill-health at the B-NC interface.

Authors of articles on correlates of AD often conclude that neuro-degenerative diseases *cause* loss of olfactory perception. For example, Mackeay-Sim et al. [4, p 763] said, "…many neurodegenerative diseases also induce loss of olfactory function." However, it is equally plausible that a feature of olfactory dysfunction may induce neurodegeneration. The idea of a causal link between the blocking of CSFF associated with the olfactory brain and AD is made considerably more plausible by Ethell's scholarship [1].

It is known that other animals show cognitive decline with aging, but not the extensive, progressive neuronal death characteristic of AD [1, 5]. From a phylogenetic perspective, it is posited [1] that humans' large increase in frontal cortex was at the expense of a vulnerability of their medial temporal lobe's way of clearing metabolic products such as Aβ as well as Aβ-plaques and other debris that might ordinarily be taken away from the fluids next to neurons and glia. This vulnerability is made manifest by the weathering of aging and is concordant with the common observation that AD is more common as one ages [6, 7]. Ethell's reasoning [1] is congruent with the modern amyloid hypothesis of AD [3], but his hypothesis focuses on the CSFF associated with the medial temporal lobe; here, we will examine implications of this to behavioral training.

The tissues of the nasal cavity are essential to olfaction and a way for fluids of the brain to flow into the peripheral lymphatic system. The tissues of the nasal cavity are vulnerable.

Olfactory nerves extend through the cranium by way of the numerous foramina of the cribriform plate of ethmoid bone separating the nasal cavity from the olfactory bulb. At the nasal epithelium, bulk flow from the medial temporal pole merges into the cervical lymphatics [1, 8]. Any event disrupting the functionality of fluids exiting the cranium, olfactory nerves and their supporting tissues at the cribriform plate would have unhealthy consequences, including 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 bacteria, virus, fungi, 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 [9, 10]. Some commonly prescribed drugs may also affect olfaction [11]. Ethell [1] pointed out that physical trauma to the head can disrupt the fragile structures of the cribriform plate hence disrupting fluid flow. Physical trauma can also move the brain and olfactory nerves against the more stable skull shearing the neural extensions traversing the skull. Ethell [1] posited a potential causal link between such physical damage and AD, because it would disrupt fluid flow regulating the concentration of Aβ and removing other debris. The basic idea is that the vulnerability of the olfactory system to disease leads to disruption of CSFF associated with clearance of toxicities from the olfactory brain.

There is theory [8, 12-16] that flow of interstitial fluid and CSFF have separate mechanisms for exiting the cranium at the B-NC interface. Regardless of the particular mechanisms, the regular fluid flow from the medial temporal pole by way of the B-NC interface to the cervical lymphatics is critical to sustaining the homeostasis of the anterior olfactory nucleus, piriform and entorhinal cortices as well as the hippocampus, all areas involved in the early stages of AD [1]. Regular fluid flow clears the medial temporal pole of excess Aβ and cellular debris. The failure to regularly remove Aβ and other proteins from the fluid surrounding neurons and glia leads to an accumulation of those products which coalesce into larger products such as Aβ plagues. The larger plaques disrupt the processes sustaining the viability of neurons. One of those disruptive processes might be hindering the fluid transfer at the cerebral blood vessels [16]; stated differently, this may involve impaired paravascular glymphatic clearance [17].

Ethell's reasoning is supported by evidence that loss of olfactory perception is an early sign of impending, fully developed AD [e.g., 18-26]. 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. The limbic system has multiple roles including learning and spatial orientation (centered about the hippocampus) as well as emotional regulation. It is notable that changes in mood/depression may be a very early sign of AD [27]. Also, olfactory bulbectomy is an animal-model of depression [28].

Probably the first study [18] to compare the histology of the olfactory bulb of patients who had died with AD to the bulbs of those who died without evidencing AD found interesting differences. Those with AD had neurofibrillary tangles and reduced cell density in the anterior olfactory nucleus and those without AD had little or none, i.e., the distal portions of the olfactory system are clearly affected in those manifesting AD [18]. As mentioned by Ethell [1], AD is characterized by a progression of ill health from the olfactory bulb, anterior olfactory nucleus to other segments of the limbic brain and eventually to nearly the whole brain [29-32]. Also, it is noted that olfactory bulbectomy in mice leads to accumulation of metabolic and cellular debris in the entorhinal cortex [33].

Recent studies of sleep add to the theory of the role of faulty olfaction

Prof. Nedergaard and colleagues [17, 34-36] and others [37, 38] studying the brain during the circadian cycle have made discoveries germane to the maintenance of homeostasis of the brain's interstitial fluid. Total volume of fluids in the healthy brain remains nearly

constant but the proportion of fluid varies among the various fluid-compartments of the brain, i.e., varies among the ventricles and subarachnoid spaces, the interstitial space, the intracellular space and the fluids associated with arteries and veins. Interestingly, the fraction of interstitial 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 [36]. It is posited that the greater volume of interstitial fluid during sleep facilitates the removal of metabolic products, notably accumulation of Aβ. Such a proposition is supported by data indicating that Aβ is probably cleared twice as fast during sleep compared to being awake [36]. Interestingly, a single night of sleep deprivation led to elevated levels of Aβ-42 in healthy middle-aged men [39]. The results of the research demonstrating the dynamics of these sleep-accompanying changes in brain are concordant with Ethell's theory of AD [1]. Along with hyposmia, disturbances of healthy sleep are signs of imminent AD [40-44].

There are enzymatic processes helpful in removing metabolic products from interstitial fluids [16, 45]. There are alternate sites for drainage into the lymphatic system beside those at the B-NC interface, e.g., there are drainage sites at the 5th cranial nerve and spinal nerves [46]. However, it is posited that these alternatives to the bulk flow at B-NC interface are by themselves not efficient enough to routinely clear excess Aβ. When there is chronic disease at the brain-nasal cavity interface, manifest as hyposmia or anosmia, there is likely a slow accumulation of Aβ which, in turn, induces Aβ-plaques which, in turn, causes neural and glial damage and death in the distal portions of the olfactory brain which, in turn, leads to inflammatory processes. In addition, it is likely there will no longer be healthy neurogenesis characteristic of the distal portions of the olfactory brain. Remaining healthy neurons, in turn, continue the production of Aβ. The accumulation of Aβ and Aβ-plaques along with the debris of dying cells eventually affects the efficient transfer of fluids in and out of cerebral blood vessels [17]. This slow cumulative process is the essence of the Aβ cascade hypothesis [3] with a focus on the bulk flow of the medial temporal pole [1]. In brief, it is posited that AD is a two stage process, an early stage associated with ill-health of the distal portions of the olfactory brain and a later stage involving wide-spread vascular problems.

Implications of modern theory of AD for prevention, hence treatment of AD

Ethell's [1] and Nedergaard's [17] research plus two additional advances in understanding of the functional organization of the brain have interesting implications germane to prevention and treatment of AD. The two additional advances are (a) the understanding that the brain is considerably more plastic than previously recognized and that plasticity extends even to advanced ages [47], and (b) there is neurogenesis in the adult brain, even aged brains [48]. 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.

Despite knowledge that the brain is more plastic than previously thought and there is the possibility for neurogenesis, it is seemingly impossible to replace the extensive loss of neural and glial tissue suffered by a person with advanced AD. That reality implies that the only treatment possible for AD is preventing the conditions causing the losses.

Selective behavioral treatments of early signs of AD will reduce incidence of AD

With respect to prevention and treatment of AD, Ethell drew an implication. He suggested that because intracranial pressure forces the flow of fluids through the cribriform-foramina, any event that might enhance relevant intracranial pressure would aid CSFF's ability to remove debris. Citing research [49-51] showing that sedentary lifestyles risk the progression of AD, Ethell [1] implied that healthy exercise might facilitate healthy CSFF, hence be therapeutic. A meta-analytic study involving 42 studies and 3,781 older adults [52] supports the conclusion that aerobic fitness training enhanced or sustained cognitive ability with small to moderate effect sizes. Also, reviews [53-56] of preventable risks indicate that regular exercise will likely delay the onset of full blown dementia.

There is an extensive longitudinal study done in Finland (the CAIDE study) studying potential risk factors for age-related dementia, including AD. That assessment [57] indicates that obesity at midlife, plus vascular risk factors (high systolic blood pressure and high total cholesterol level) were significant risks for later dementia. With recognition of the results of the CAIDE study, the medical records and survey data of participants in a large health care system were assembled. Data on midlife health and subsequent signs of dementia including AD were available [58]. 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 at post-retirement ages. Interestingly, adding new measures to a 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 [58].

Within the context of the CAIDE program, there is the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) [59]. That study [59] 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, a preeminent sign of advancing AD. All subjects were judged to be at risk for AD. In the intervention group, the risk factors attended to were diet, exercise, cognitive training and vascular risk monitoring. 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. Notably missing were the potentially modifiable risk factors of olfactory loss and sleep disturbances.

A comment [60] on the results of the FINGER study pointed out that the extensive involvement of the treated elders yielded rather small results as indexed by effect sizes. They

posited that it might be difficult, on a large scale, to implement what they perceived to be the extensive commitment necessary to correct many risks for advanced AD. They suggested that merely focusing on cognitive training might be a better approach and easier to implement [60, 61].

Barnes and Yaffe [62] assembled considerable data on risk factors that have been associated with AD. Using that data, they calculated a statistic call the *population attributable risk*, an estimate of proportion of cases of AD in a population attributed to a given risk provided there is a causal relationship. Using this information, they then estimated what would be the long-term consequence of reducing the risk of factors similar to those in the Finnish study. They [62, p 9] concluded that "…half of AD cases may be attributable to modifiable risk factors." Notably, their calculations did not include the potentially modifiable risks of lost olfaction and sleep disturbances, both of which may have a more direct causal relationship to AD.

Although the perspective and conclusion of Barnes and Yaffe [62] are interesting, it may not reflect what is salient. An alternative perspective can be derived from Ethell's hypothesis [1] and is associated with this question: What are the chances that an individual who has sustained, as they age, healthy bulk flow at the B-NC interface will develop advanced AD? A perspective derivable from Ethell's hypothesis [1] is that sustained, healthy bulk flow at B-NC would reduce the risk of AD to near zero. The issue then becomes what can be done to sustain the health of the tissues of the B-NC.

It is easy to imagine a relatively brief questionnaire asking about the presence of preventable risk factors. The typical individual at or near retirement-age could be asked about their height and weight, their olfactory ability, whether they are tired after a night of sleep, whether they might meet standards for daily exercise and the medicines they are taking. Responses indicating lost olfaction, poor sleep, being overweight and generally inactive (each of which contribute to ill health of the B-NC) could be used to prescribe activities that stand a good chance of avoiding AD.

Treating the risk factor of lost olfaction may also treat poor CSFF associated with the medial temporal pole

There have been extensive reviews on the topic of addressing potentially preventable risks for developing AD [53-56]. Notably, none have addressed the possibility that treating hyposmia and anosmia might be a way of preventing risk for AD. Perhaps, that is the case because until recently there was not sufficient recognition that AD was causally related to malfunction at B-NC interface, but now there is the work of Ethell [1]. Also, until recently there were only a few studies indicating that hyposmia and anosmia were easily treatable.

Disease at B-NC interface, of course, will likely be manifest as a loss of olfactory perception. Anosmia and hyposmia are associated with early signs of AD, and, therefore can be considered risk factors for AD [e.g., 19-26]. Also, anosmia and hyposmia are associated with a number of problems, e.g., reduced ability to sense spoiled foods and smoke [63]. The loss of pleasures from eating seem to be particularly problematic for the elderly [64]. Also, loss of olfactory perception is associated with clinical depression [64] which in turn is a risk factor for AD [62]. Olfactory bulbectomies are animal-models of clinical depression [28]. Also, it has been

posited that olfactory bulbectomies might also be a model of AD because of the extensive dysfunctions that resemble AD [65].

A study [4] of a relatively large group of adults of various ages confirmed that the quality of olfactory perception tends to decrease with age. However, a different perspective emerged when the tested participants were segregated 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 has 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 which were shown to be associated with reduced olfactory ability [11]. 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 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 [66] was sustained sufficiently to maintain olfactory perception. The conclusion: Degradation of olfactory perception is not an inevitable consequence of aging.

It is not known whether the prescription of antihypertensive and antihyperlipidemic medications reflect cardiovascular problems needing corrections or whether the chronic intake of such medication has adverse side-effects at the B-NC interface. Given that the USA has 5% of the World's population but purchases 50% of the World's available medicines [67] does give rise to the idea that there might be an over-prescription of medicines with side-effects that outweigh possible therapeutic effects. Medicines for hypertension have a mixed effect on cognitive decline characteristic of AD [53].

When hyposmia or anosmia occurs, there is sometimes slow recovery of olfactory perception with the passage of time and sometimes not [68]. Recently, it has been shown that sustained practice at sniffing and attempting to identify strong scents can induce restoration of lost olfaction, even in persons experiencing anosmia and whose recovery was deemed unlikely [68-78].

Sustained practice at attempting to smell can restore lost olfactory perception

Computer-assisted game-like programs have been used to enhance the peripheral vision among the elderly and others (thereby reducing auto accidents) and in enhancing auditory perception of words (thereby enhancing communication)[47]. These improvements are possible because brain plasticity is engendered by sustained behavior. Relevant visual and auditory stimuli can be presented using computers. Further, modern computing allows sophisticated programing and data-collection as manifest in commercial video games.

To provide practice with olfactory stimuli, it is necessary to present scents, something usual computers cannot do. The few studies demonstrating that daily training with scents have improved olfaction have done so by merely directing participants, every morning and evening, to sniff, for 10 seconds or so, each of four scents [68-78]. By doing so for months, about 30% of those presenting with hyposmia or anosmia recovered some of their lost olfaction [77] a much larger percent than those who did not practice. Recently the training regimen has been

modified [77]. 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 [77]. 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 [68, 77]. 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 finding are germane. Sniffing among those with anosmia enhances activity in olfactory cortical areas [78] as well as other areas of the brain [79] that might be critical to olfaction. For example, sniffing is critical to perception of the source of a scent. The control of sniffing might, in turn, control the amount of the potentially toxic chemicals or germs at the olfactory epithelium. In brief, sniffing is an integral component of olfactory perception [80]. Sniffing, therefore, might enhance relevant CSFF and, perhaps, neuropoiesis in portions of the olfactory brain [81].

The conclusion is that regular, sustained practice at attempting olfactory discrimination can facilitate recovery from hyposmia and anosmia. Toward that end, we have developed an automated way of presenting differing scents, one at a time to a participant. The participant then choses which of the just sniffed scents is one of four choices displayed on a computer screen. Then, another scent is presented and so on until there is daily practice at olfactory discrimination. The automation of training for olfactory discrimination has many advantages. First, it is possible to schedule the presentation of scents for optimal learning, i.e., gradually increasing the difficulty of discriminations so that the participant has some practice at previously successful discriminations while also presenting slightly more challenging discriminations. Second, because the training involves computers, there is a markedly increased ability to motivate users using the technology of video gaming, which is well-known to sustain practice on demanding tasks. Third, the system can be easily adapted to measure degree of olfactory loss, if any, and to measure threshold for detecting a standard set of scents. Fourth, there is enhanced capability of monitoring the effects of training and keeping track of the progress of a large number of participants for large scale data-collection and data-mining. Lastly, the regular automated training can be combined with the daily exposure to four scents at home as done in the studies showing that daily sniffing of presented scents is effective in treatment of even anosmia in some participants [68-78]. The conclusion is drawn that attention to olfaction can be germane to the restoration of CSFF at the B-NC interface.

The basis of fMRIs to index neural activity is that neural activity induces fluid flow and associated oxygenated blood, which can be indexed by magnetic resonance imaging. Consequently, when there is recovery of lost olfactory perception, it is surmised that there is increased bulk flow from the brain, by way of the cribriform plate to the lymphatic system, thereby, washing away potential debris. 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. Also, healthy olfaction is only possible with healthier neurogenesis [1]. Increasing the functionalities at the B-NC surely cannot be bad. Also, regardless of whether correcting hyposmia or anosmia by way of training procedures

enhances removal of sufficient debris from the medial temporal lobe to slow the advance of AD, it will assuredly enhance the mood of the participants.

Treatment of sleep disorders will improve CSFF, hence treat AD

Fortunately, there are effective treatments for some common problems of sleep. Extensive, well-done research indicates that cognitive behavioral therapy for insomnia (CBT-I) was and is likely to be effective [82]. Studies of comparative effectiveness [82-84] confirm that sleep problems should be attended to by CBT-I rather than by hypnotics which can interfere with memory and healthy sleep. These studies led American College of Physicians to recommend CBT-I in their new clinical practice guide for management of chronic insomnia [84, 85]. 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 [86]. 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 usually manifest as rather common sense advice on how to treat insomnia. Often sleep hygiene is the provision of a check list of activities that a patient might engage, including such things as do not drink coffee close to bed-time 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 cost-effective [87]. A treatment program designed to treat the first signs of AD [88] would attend to sleep problems beginning with sleep-hygiene-advice; and if that does not succeed, a referral to someone who can deliver more compressive CBT-I.

Exercise is likely to be helpful in sustaining healthy fluid flow at the B-NC interface

As mentioned, Ethell [1] posited that sustained exercise can benefit bulk-flow at the B-NC interface [49-51]. Also, multiple meta-analysis [53-56], assessing the effectiveness of treating modifiable risks associated with AD, indicated that regular exercise is beneficial. Exercise is helpful in controlling hypertension and hyperlipidemia; risks attended to in the FINGER study [58]. It has been posited [89, 90] that inactivity is a transdiagnositic condition of ill health. Such a proposition is similar to Selye's theory [91] that stress is a common factor of many different kinds of ill health, sufficient to be a disease in and of itself. The obvious implication is that regular exercise is the remedy for inactivity and a treatment salient to AD. Brain-scan technology has provided evidence that lack of activity reduces signs of health in areas know to be salient to AD, for example, the hippocampus [92-94].

Advising, counseling or 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 also be the end of the program. Rather than a "no pain, no gain" perspective, an alternative approach is more likely to succeed. The better approach might be to encourage less intense activity, but more regular daily activity which might be more compatible with the elderly, inactive citizen. Walking has been suggested with the goal of attaining 10,000 steps a day. Further, the general approach

should be to start with more modest goals and slowly increase the number of steps regularly, in small achievable increments. 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 [95]. Modern tread mills and stationary bikes can be used to increment the number of "steps" taken while making the walking or biking interesting [96]. In addition to these effects of physical activity for cognitive function [97-100], there is interest in the role of cognitive activity/training.

Can therapeutic computer games can be a stand-in for the protective factors of regularly engaging in taxing cognitive tasks and having received higher education? Probably.

Many individuals of retirement ages have a subtle loss of cognition, being noticeable with some forgetfulness. If the losses are not great and not sufficient to disrupt the routines of an earlier time, we label this mild loss of cognition: 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 labelled *mild cognitive impairment* (MCI). MCI can be readily measured by standard tests of cognition. Further loss of cognition manifest as profound loss of memory is labelled *dementia*, the most common of which is AD. The process from age-related cognitive decline to full-blown AD and eventually death is considered a continuous process that might take a decade or more [101].

The study of the anatomy of the brain, including modern brain-scan technology, allows us to track the progressive loss of cognitive ability as a progressive loss of neural and glial tissue beginning in the distal portions of the limbic system and progressing throughout the brain [1]. Progressive cognitive decline is not only a risk factor for AD but a major symptom of progression to full blown AD. The idea emerges: If we could prevent the steady loss of cognition that would be a sign that we are also correcting whatever else might be problematic in the progression to dementia. Consequently, sensitive tests of cognition can assess the value of prospective therapies for AD long before the ultimate consequence 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 [53-56, 58]. 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 encourages 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 engage such ordinarily. Further, when there is some progress at getting individuals to engage one or more of these activities more than usual, there is no evidence that it modified ability to deal with other cognitive challenges; that is, capacity for transfer of training is still under

investigation [102-107]. 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 TV and driving a car and our brain responds by facilitating such viewing at the expense of peripheral vision [108, 109]. If we spend hours listening to loud music, loud TV, we adapt to such and tend to lose ability to discriminate softer sounds. Further, high intensity sound often actually damages the sensitive peripheral organ of hearing and results in unwanted central neural activity such as tinnitus, producing something similar to static (i.e., noise in two senses of the term).

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 research program is associated with Michael Merzenich [47] and his colleagues, including a former student of his Henry Mahnche. They founded Posit Science, a company that currently markets programs designed to enhance “brain fitness.” The programs that they have developed are based in the theory of brain plasticity, a theory that emerged from basic research with laboratory animals much of which involved Merzenich and a wide array of colleagues [47]. Here, is one specific example in support of brain training. 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 [112]. 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 receive 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 were 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 than 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, many conclude, based on continuing research, that specially designed computer-assisted game-like programs are useful and it would benefit healthy aging if widely used [61, 101, 108-114].

Prior to the work described above, there is the research of Karlene K. Ball of the University of Alabama at Birmingham. She and her colleagues, across the years and with multiple studies [e.g., 108, 109], 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 [114]. 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 most 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 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 in networks that might be engendered by practice in networks involved in memory and attention. In other words, enhanced fluid flow may clear the accumulation of excess Aβ in anatomical areas salient to early stages of AD. Note that the combination of treating hyposmia and anosmia, improving patterns of sleep, inducing a healthy level of daily activity, and practice at tasks involving working memory and attention might each and all facilitative clearing the brain of excess proteins by way of better bulk flow at the B-NC interface [1]. It also follows from that perspective that inefficient bulk-flow at the B-NC interface may be an explanation for why attending to any one risk factor produces only slight improvements in cognition.

Treating multiple risk factors, either concurrently or sequentially, might be particularly effective in sustaining cognitive health.

The advances in understanding the functionalities sustaining homeostasis of the medial temporal pole [e.g, 1, 12, 17] have important implications for the prevention and treatment of

AD. It is posited that the treatments for lost olfactory perception by programming systematic attempts to recognize scents might successfully treat conditions ordinarily leading to advanced AD. However, more can and should be done.

Imagine a brain fitness center associated with places where elders congregate such as retirement communities, assisted living facilities, and senior citizen centers. That center would be a place for testing for hyposmia and anosmia and mild cognitive decline, 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 of (a) their potential losses (b) the good possibility that relevant practice 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 the relevant health-restoring practices.

For those presenting with hyposmia and anosmia, there would be special encouragement to engage training for recovery of olfaction. There would be stations with computers for general use as well as introducing and practicing cognitive tasks such as those commercially available [47]; even daily computer use has been proposed to facilitate cognitive functioning and hippocampus volume in older individuals [115]. That center might be equipped with a few modern, tread mills or stationary bikes to encourage physical exercise (i.e., exergaming) [95-100], thereby, improving CSFF [1].

At the proposed brain fitness center there would be nutritional advice to ensure that participants had adequate, but not excessive, intake of essential vitamins, particularly thiamine, Vitamin D, and essential fatty acids [116]. 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 [117]. Recently, a group of experts on nutrition compiled what they deemed to be best nutritional practices relevant to the prevention and treatment of AD [118]. Obviously, their advice should be widely available to the elderly and those preparing meals for the elderly.

There is research [119] indicating that many participants, particularly those who regularly use alcoholic beverages, might suffer from 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 have been liked to AD [120, 121]. 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 diet or supplements. However, it is anticipated that before complete loss of thiamine, there would also be debris needing to be cleared from the area. Sustained regular exercise will further such debris-removal. More difficult to treat is the alcoholism that interferes with thiamine homeostasis; however, there are a reasonable improvements that can be made in the treatment of alcoholism [122].

The centers would be a place for giving advice on sleep hygiene, i.e., common sense advice that seems to get individuals to improve the likelihood that they will have a night of

healthier sleep. 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 assisted living centers would nudge toward healthier sleep [123], 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 life-styles 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 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 Aβ-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, because they would restore healthy, bulk flow at the B-NC interface.

Drugs or procedures that might have the ability to modify Aβ and Aβ-plaques have been developed and tested. However, when tested in the elderly, they routinely fail in preventing the progression of AD [e.g., 124-127]. As Merzenich [47] pointed out, without attending to the daily activity of the brain, the likelihood of such medicines to succeed is slight. Theory of AD [e.g., 1] that focuses on the conditions of CSFF in sustaining homeostasis of the medial temporal pole might also account for why these new medicines were not and may not be effective, i.e., they may modify Aβ-plaques or tangles, but the products of that modification will still have to be cleared from the brain. Medicines focusing on the molecular biology of Aβ may be effective if, and only if, they are accompanied by treatments strengthening the functionalities of fluid flow at the B-NC interface.

Why have some AD therapies failed in clinical trials? Theorists have assumed that Aβ is waste, trash or debris. It follows from that assumption that eliminating Aβ would be a good thing. However, Aβ likely has adaptive functionalities. Among the roles that Aβ might play are (a) to aid in regulation of angiogenesis with the end result of adapting the vascular system for efficiency of neural activity [128] and (b) as an antimicrobial peptide [129]. Germane to the idea that Aβ has utility is the finding that the amyloid-β precursor protein gene family is highly conserved across our phylogenetic history [130]. It was noted [129] that although amyloid precursor protein-deficient mice are viable and fertile, they exhibit motor and behavioral problems that would hinder survival in the wild. Also, consider the possibility that if Aβ is not regularly infused into the olfactory epithelium there would be less antimicrobial activity at this place prone to infection [129]. Nevertheless, there is considerable evidence that the accumulation of Aβ is the setting condition that is AD [3, 125], particularly as it binds with itself and other proteins forming large plaques. The conclusion is that is a disruption of the ordinary physiology at the B-NC interface is the setting condition for AD [1].

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 at the B-NC integration is sluggish. Therefore, that fluid flow 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 (CBT-AD) would involve the following: training for better olfaction, engaging the already well-developed CBT-I (including attention to the lighting of places where elderly live), engaging the already well-developed computer-assisted game-like programs to sustain cognitive skills, using exergaming to stimulate CSFF and providing advice on nutrition and drug-use. These treatments together can be the focus of well-designed brain fitness centers accessible to the elderly. 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 is fundamentally a failure to sustain homeostasis of the interstitial fluid of the medial temporal pole by way of healthy fluid flow at the B-NC interface [1, 12, 17]. We realize that CBT-AD as advocated is different than what is currently practiced; now we mostly render palliative care for those with advanced AD.

Those who have developed modern video games have learned how to sustain activities in front of a computer. Those technologies 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 study. In particular, attending to the risks of lost olfaction by adding training in olfactory perception is apt to sustain health at the B-NC interface. Further, elders can engage some of their therapy at a center where they can be encouraged to sustain relevant activities and also at home.

A worthwhile approach to address AD, as outlined here, may be to focus on olfaction. That may be particularly salient because improving olfaction is also likely to improve bulk fluid flow at the B-NC interface. This focus can be coupled with treatment of other risk factors; each of which may also facilitate "cleansing" the brain of metabolic waste. Indeed, the establishment of centers whose mission it is to encourage activities that promote brain fitness is a cost-effective way of slowing and maybe even halting the progression of AD. As well, promotion of olfaction and brain fitness is useful outside of AD, e.g., treating depression.

If such centers attend to conditions resulting in unhealthy fluid flow at the B-NC, that may be the only way we have of making AD less prevalent.

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