

Translation of low-risk dementia-associated interventions into practice - a call to action

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Abstract

Aging is a central part of life. The insults we place on our bodies during the first 60 years of life eventually overload the system. Unfortunately, this occurs around the same time as when cellular processes that are capable of repairing the human body begin to slow down; another central process associated with an aging system. However, research informs us that interventions are capable of decelerating the aging process. Why then are we not slowing down aging? Regulatory bodies advise us that research-derived interventions must pass through rigorous testing prior to being prescribed. Have we taken this advice too far? This Perspective article outlines interventions that are perceived as being low-risk, which are undertaken daily by millions of people and have been “proven” to have a beneficial effect on an aging body. Furthermore, a challenge is issued to healthcare providers to adopt some of the highlighted suggestions.

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Introduction

With a burgeoning global population currently estimated at 7.2 billion and at least 8% of this population being over the age of 65 [1], multiple diseases, including dementia are unfortunately becoming common vocabulary. Developed nations spend significant proportions of their budgetary funding trying to identify ‘silver bullets’ that may combat diseases of a sedentary lifestyle.

The dawn of the electronic era has brought with it unfathomable technology as well as devastating diseases. The ease with which the “push of a button” has changed lives was inconceivable a few decades ago, as was the prevalence of age-related diseases. Could this be because the electronic era has led to a sedentary lifestyle? One could argue that the prevalence of age-related diseases is a result of an increased understanding of disease and detection

mechanisms and a longer lifespan. However, we cannot refute what we see: obese individuals, increased admissions to hospitals, smoking, sedentary lifestyles and increased consultations for depression and mental illness. These are modifiable risk factors for both the disease state (cardiovascular, hypertension, diabetes mellitus, arteriosclerosis) as well as dementia, a complex, multifactorial disease that has reached pandemic proportions. The most prevalent of the dementias is Alzheimer’s disease (AD), a disease of unknown etiology accounting for 60-80% of all dementias. Current estimates suggest that around 33.9 million individuals over the age of 65 have AD. Incidence of the disease doubles every five years thereafter, with 40-50% of the population over the age of 85 living with the disease. Current estimates, based on the assumption that 60% of dementia patients have AD, indicate that by 2050, 106.2 million individuals will be afflicted with the

disease [2]. It is hopeful that by 2050 we will have a treatment or a cure for AD. However, the question remains whether we will be able to reduce the prevalence of the disease before it reaches catastrophic proportions. A projection model developed by Brookmeyer and colleagues suggests that delaying the onset of AD by a single year would lower the prevalence of the disease in 2050 by 11% [2]. Although this may not appear to be significant when comparing numbers (90 million vs. 106.2 million), the effect of this decrease is staggering when considering that in 2010, an estimated 35.6 million individuals were living with dementia and the estimated worldwide cost of dementia was US\$604 billion [3].

Risk factors linked to Alzheimer's disease

The diagnosis of AD, made on the basis of a battery of tests including those for memory, is often difficult and is generally believed to occur 7-10 years following initial disease onset. Age is the strongest risk factor associated with the sporadic form of the disease, with most individuals being diagnosed after the age of 65. The next strongest risk factor for developing sporadic AD is the presence of the apolipoprotein E (ApoE) gene variant $\epsilon 4/\epsilon 4$ [4, 5]. Numerous other risk factors have been proposed by various studies, but the lack of a consistent and uniformly applied definition of AD makes it difficult to interpret these results [6]. In April 2010 the National Institute on Aging and the Office of Medical Applications of Research of the National Institutes of Health convened a State-of-the-Science Conference to assess the available scientific evidence on the relationship between mild cognitive impairment or Alzheimer's disease, and factors such as nutrition, medical history, socioeconomic, psychological and emotional health, environment and genetics [6]. The panel was charged with the task of addressing six specific questions related to the prevention of AD and cognitive decline. The concluding remarks from the panel stated that firm correlations could not be drawn regarding the association of any modifiable risk factors and cognitive decline or AD [6]. It was suggested that large-scale population-based studies and randomized clinical trials (RCTs) were urgently needed to investigate strategies that could prevent cognitive

decline or AD [6]. However, based on the level of potential risk, some of these recommendations do not require large-scale population-based studies or RCTs in order to be implemented.

A call to action

It is logical to think that factors labeled as 'health-promoting' are beneficial. However, we would rather "pop pills" than take a brisk daily walk, read an engaging book, eat a balanced meal, focus positively on our daily interactions with others or, in fact, communicate. A search of the scientific literature on the term "physical activity and cognition" renders over 1000 articles in PubMed. However, we still claim that large-scale "clinical trials" are warranted in order to associate these entities - the issue being that not all studies report a positive correlation. Additionally, the physiological benefits of regular exercise or mental activity on the prevention of AD are not completely understood.

The important question to be asked is whether we need scientific investigations in order to sustain life. Understanding the molecular events and interactions resulting in beneficial effects is an important endeavor. However, understanding these molecular events will not improve an individual's health. Therefore, clinical practice should focus on simple strategies aimed at mobilizing both mind and body.

Blood flow and neurons

Neurons require a constant supply of oxygen and nutrients in order to maintain functionality. The paths by which these essential components can reach the brain are via the blood and cerebrospinal fluid, with the former being the most critical. By-products of neuronal metabolism must be cleared from the brain or else the toxic build up can be catastrophic. Activity in neurons results in local increases in cerebral blood flow. Therefore, active neurons are healthier since these cells receive a continuous supply of oxygen and nutrients, as well as removal of waste products. Maintaining healthy neurons therefore requires them to be active. Physical activity improves oxygen circulation throughout the body and also causes the release of hormones and neurochemicals that are

beneficial to the mind and body. On the other hand, mental activity results in focal increases in blood flow to areas of the brain that are involved in the activity, as well as other areas of the cortex referred to as association areas. These effects have been displayed using the technique of functional magnetic resonance imaging (fMRI) by Meister and colleagues [7], who demonstrated that mental imagery of piano playing results in an increase in cerebral blood flow to frontoparietal areas of the cortex, including pre-motor areas overlapping with areas in the group that physically played the piano. Pascual-Leone and colleagues [8] demonstrated that such mental rehearsal was accompanied by transient increases in the cortical representation of the fingers associated with the mental activity. This increase in cortical grey matter representation, termed plasticity, is now a well-accepted phenomenon and is the basis for learning and memory. Decreased cortical activity results in the loss of synapses - neuronal connections that are the foundations of neural communication. The loss of these synapses, referred to as synaptic pruning, can lead to further downstream events including neuronal atrophy.

The sections below discuss two modifiable risk factors that have been shown to have beneficial effects on cognitive decline and AD. The attempt here is to highlight how simple modifications to everyday tasks could have a largely beneficial effect on both the individual and society. This Perspective is not intended to be an exhaustive review of the literature, and as such a very limited number of studies are used to communicate the author's view.

Factors intimately associated with reducing the risk of cognitive decline in older adults

Physical activity

Physical activity is one of the most easily modifiable risk factors associated with cognitive decline. The Centers for Disease Control and Prevention (CDC) stipulate that adults should be involved in two forms of physical activity on a weekly basis, aimed at improving cardiovascular (CV) function and muscle strength [9]. A weekly regimen of 150 minutes of moderate intensity aerobic activity, as well as muscle-

strengthening activities on two or more days per week is recommended as a minimum. A brisk walk, bike riding, mowing the lawn, jogging, swimming and playing tennis or basketball are among the recommended activities that could improve CV health, whereas working with resistance bands, push-ups, sit-ups, heavy gardening and yoga are recommended as muscle-strengthening activities [9]. A 150-minute aerobic workout per week appears a daunting task but this can be achieved in 10-minute blocks of moderate to vigorous activity spread over the week.

Many lines of evidence indicate that aerobic exercise decreases brain atrophy in humans, while some suggest that it increases the size of certain structures including the hippocampus, a structure intimately linked to memory consolidation and which is often the earliest and most severely affected structure in dementia. Colcombe and colleagues [10] mapped the brains of 59 individuals aged 60-79, randomly assigning them to either an aerobic or a non-aerobic exercise group. Following six months of participation in the program the investigators used MRI to analyze brain volume in the two groups [10]. The study revealed that participation in an aerobic exercise program resulted in increased volume in both grey and white matter areas of the brain, primarily prefrontal and temporal cortices [10]; areas that often show substantial age-related atrophy. Similar results were recently reported in a group of females who had mild cognitive impairment (MCI) [11]. Participants were subjected to twice-weekly sessions of aerobic exercise, or resistance training and muscle toning, for one hour per session for six months; 29 of these subjects underwent MRI scans performed both before and after the trial period. Regular aerobic exercise was found to significantly increase the size of the hippocampus in this group of females, who were aged between 70 and 80 [11]. These results provide further evidence that regular aerobic exercise is associated with volume increases in the brain and are promising in terms of neurodegenerative diseases where we often see both the loss of neurons and brain volume.

Further compelling evidence for the benefit of exercise, and in fact, general overall activity, was reported in a recent study by Buchman and colleagues who measured all physical activity for a period of ten days (with a follow-up of 3.5 years) in a large cohort

of individuals ($n=716$) with an average age of 82 [12]. The investigators discovered that high levels of activity were associated with a decrease in incidence of AD. Individuals with the lowest 10% of daily activity were reported to have a two-fold higher risk of developing AD compared to individuals in the top 10% of activity levels. The interesting feature of this investigation was the activity measured. Generally, physical activity is measured by the amount of exercise performed over a given period of time. The investigators of this study reasoned that the elderly might be unable to keep accurate records of personal training and daily activity, and therefore recorded all activity, using an actigraph (a device that records all movements) worn on the subjects' non-dominant hand [12]. Measurements made in this manner would encompass all movements, both exercise and non-exercise physical activity, throughout the day and would therefore provide a more global measurement of activity as opposed to a more circumscribed "snapshot" of physical exercise. There are arguments for and against this approach of activity measurement that will not be discussed here, but the interesting finding of this study was that individuals who were generally more active were less likely to develop AD [12]. Furthermore, a positive correlation between activity and cognitive function was also reported in this group of subjects. These are intriguing findings with widespread ramifications since they suggest that a generally more active lifestyle may prevent the development of AD and dementia.

Regular aerobic exercise has also been shown to preserve the structural integrity of the brain - in particular the white matter tracts - of endurance athletes late in life. Tseng and colleagues [13] compared the integrity of white matter in the brains of "Masters athletes" to individuals living a sedentary lifestyle (defined as not engaging in moderate or high intensity aerobic exercise for more than 30 minutes, three times/week over the past two years). "Masters" athletes were defined as a group of older adults who had participated in life-long, high volume and high intensity exercise training. These individuals were still engaged in endurance exercise at the time of the study. White matter, generally referring to the myelination state of axons and tracts, are important in the conduction of neural impulses. Demyelination, as seen in diseases such as multiple sclerosis and

dysmyelination, slow down and impair the conduction of neural messages. This in turn impairs sensory and motor function, coordination and information processing. Tseng and colleagues discovered an 83% reduction in deep white matter hyperintensities and a 44% reduction in total white matter hyperintensities in the "Masters" group, indicating that regular aerobic exercise preserves the integrity of white matter [13]. The team also investigated the microstructural integrity of deep white matter tracts carrying sensory and motor information to and from the cerebral cortex, as well as tracts carrying information within the brain. They discovered that the overall integrity of these tracts was significantly superior in the "Masters" subjects compared to sedentary individuals [13]. It is important to note that this investigation was performed in individuals with an average age of 72, and that the "Masters" subjects were still actively involved in endurance activities, supporting earlier studies describing preserved cortical integrity and brain volume in older active adults [10, 11].

The final study used to support this "push" for increasing physical activity and aerobic exercise in older adults is evidence provided by Erickson and colleagues [14]. Hypothesizing that moderate intensity exercise would increase hippocampal volume, Erickson and coworkers undertook a single-blind, randomized controlled trial in which adults were assigned to receive either moderate intensity aerobic exercise ($n=60$; mean age 67.6) three days per week, or stretching and toning exercises ($n=60$; mean age 65.5) that served as controls. MRIs were obtained for all participants prior to intervention, as well as at six and 12 months. Hippocampal volume increased by ~2% in the aerobic exercise group over the 12-month period, whereas in the control group a ~1.40% decline in volume was observed over this same period [14]. This decrease in hippocampal volume is within the average for this age group of normal healthy, non-demented individuals [15]. These results demonstrate the unique capability of the brain to maintain and in fact modify its size and connections into late adulthood; the phenomenon referred to as plasticity. An interesting discovery in the Erickson study was the selective expansion of the anterior hippocampus following aerobic exercise. The anterior hippocampus is generally associated with spatial memory acquisition and undergoes significant age-related

decreases in volume (as observed in the control group) [14]. These results demonstrate the rather selective maintenance of structures, which are based on usage patterns and may represent underlying molecular mechanisms associated with the growth and maintenance of neurons (cell bodies and axons) and synapses.

Mental activity

This section of the Perspective will highlight studies that have demonstrated benefits of daily mental activity on “cognitive aging”. Just as was described previously, the term “mental activity and cognition” renders over 250 articles in PubMed.

Mental activity is defined as endeavors that require thought, stimulate cognitive processes and increase brain activity. Evidence suggests that these activities stave off, or at least delay, the onset of dementia and cognitive decline. In a recent study, Wilson and colleagues investigated the temporal relationship between changes in cognitive activity and its effects on function in 1,076 non-demented individuals (at study inception) over the age of 65 [16]. Subjects were asked to annually self-report their frequency of participation in seven activities that included reading, writing, visits to a library and playing mentally challenging games during the previous year. The cognitive function of subjects was assessed annually for an average of five visits per subject with a battery of 20 individual tests that evaluated episodic, semantic, perceptual and working memories. The authors discovered that a higher level of cognitive activity in the preceding year was positively correlated with performance on global cognitive function and domain-specific measures [16]. Although self-reporting justifiably has its critiques, the association that Wilson and colleagues describe between clinically validated performance tests and activity reporting cannot be refuted.

As with studies reported in the section on physical activity, associations between cognitive/mental activity and structural/morphometric changes have also confirmed a strong association between both life-long and late-life cognitive activity and resilience to dementia and AD. Fjell and colleagues [17] demonstrated this phenomenon by relating executive

and fluid functions to cortical thickness. Executive function is a commonly used term for functions that relate to and require cognitive processes for the execution of tasks, such as those required for working memory, problem solving, decision-making and reasoning. These tasks have been associated with structures located within the frontal lobes and other areas of the brain. “Fluid” function, on the other hand, has been described as a type of intelligence that is applied to novel problems and is relatively independent of educational and cultural influences [17]. In the study, which involved 74 subjects aged 20-88, both fluid and executive functioning was measured in young ($n=35$; mean age =35.5) and old ($n=39$; mean age =70.7) groups of individuals, and results were correlated to MRI volumetric measurements of the cortical mantle. Subjects in each age category were further divided into either average or high, executive and fluid functioning groups. Interestingly, no association was discovered between executive function and cortical thickness in either group; however, a highly significant correlation was found between cortical thickness and high fluid functioning in the “old” group [17]. In particular, increased thickness was observed in the posterior cingulate gyrus of the right hemisphere, frontal and prefrontal areas of both hemispheres, and the cingulate isthmus - the area of cortex in the anterior-most region of the cingulate that connects this structure to the parahippocampal gyrus. The cingulate has been variably associated as a link between the neocortex and several brain areas, including the hippocampus (discussed in [17]). This regional thickening of the cortex was specific to the “old high fluid function” group and was independent of the generalized overall “thinning” of the cortex observed with age. Fjell and colleagues have discussed in depth the neuroanatomical and functional relevance of these findings [17], but it suffices to state that plasticity associated with active cognitive functioning persists into advanced age. The result of a lack of association between cortical thickening and executive function in old age is somewhat plausible given that one would probably not require “extra” executive functioning in old age, as would be required for “novel problems” that may be encountered on a relatively more frequent basis.

Somewhat related to the results of the investigation by Fjell and colleagues was a longitudinal study undertaken by Schooler and Mulato [18] who observed a sample of more than 600 individuals over a period of 20 years. As part of this investigation they discovered that the complexity of leisure activities of middle aged and older adults affected their intellectual functioning, where high levels of cognitive complexity in activities led to a high level of intellectual functioning and vice versa. There is debate over whether reduced engagement in cognitively stimulating activity in advanced age is due to prodromal disease that makes these tasks more challenging and less attractive and is therefore a function of intellectual capacity. The answer to this question may be difficult to decipher but, once again, the outcome is of little consequence, especially to individuals of advancing age, since we should engage in and prescribe cognitively stimulating activity as part of a daily routine. Questions regarding mental and physical activities should be incorporated into a patient's general history-taking and specific non-pharmaceutical interventional strategies should be prescribed. These prescriptions could be personalized, based on motivational and/or disease stage, but would require the physician and/or caregiver (in more advanced stages) to have a good working knowledge of the prescribed tasks. Part of this "personalization" would require a gradual evolution of the tasks in order to maintain the individual's interest, and provide the intellectual challenge and stimulation required to preserve the integrity of neural circuits.

Numerous studies have documented evidence showing highly beneficial effects of memory training programs. A large randomized controlled trial on the effects of cognitive training on non-demented older individuals was the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study [19]. The investigation consisted of 2,802 individuals aged 65-94 (mean = 73 years), who were recruited across six states in the USA and were randomized into four groups comprising a no-contact control group, and three interventional groups consisting of memory training, reasoning training and a group trained for speed-of-processing. The study's hypothesis was that each training group would perform better in their daily activities based on their primary training area. Ten 60-75-minute training sessions were delivered over a 5-6-

week period, and subjects were tested at baseline, post-test and at annual post-tests for two years [19], and a follow-up at five years [20]. The main outcomes were self-reported and performance-based measures of daily function and cognitive abilities. At baseline, all subjects had a mini mental state examination (MMSE) score of 23 or higher. A random subsample (60%) were given four sessions of booster training at 11 and 35 months into the trial, with the hypothesis that individuals receiving booster training would perform better than those who did not receive such training. Of this large original group, 89% of the participants completed eight or more of the ten training sessions, and 80% were retested at the two-year follow-up. Of the speed-trained individuals, 87% demonstrated immediate improvement on the pertinent cognitive composite following intervention, while 74% of the reasoning-trained, and 26% of the memory-trained individuals showed benefits of their training-associated tasks [19]. Importantly, these effects were maintained over a two-year period, especially in the speed-trained individuals, demonstrating that even a short period of specific activity (8-10 one-hour sessions delivered over 5-6 weeks) has a strong effect on neural plasticity that persists into advanced age. Booster training enhanced gains in both the speed and reasoning-trained groups, and these results were maintained at the two-year post-test. In the follow up investigation, Willis and colleagues [20] examined 67% of the original sample and discovered that the effects of cognitive training, especially for those who received the booster training, were maintained for five years. The most pronounced effects were observed in the speed-training cohort. Overall, the trained groups self-reported an improved quality of life compared to the no-contact control group. The finding that the speed-of-processing-trained cohort showed the most significant improvements at all time points tested demonstrates the more global nature of neuronal circuit recruitment and activation in the brain, whereas the memory and reasoning-trained cohort most likely had more circumscribed, task-specific cortical activation. A limitation to this type of training was that the benefits were "task-specific" and were not observed to extend to similar tasks involving day-to-day activity. However, these results demonstrate that well-designed, targeted and global cognitive training

interventions could have significant benefits for important aspects of everyday life.

In a novel approach to cognitive training for the elderly, extending upon a program designed to improve the function of the auditory system through intensive brain plasticity-based learning [21, 22], Smith and colleagues [23] studied 487 community-dwelling adults aged over 65 who did not have clinically significant cognitive impairment at baseline. Subjects were randomized to receive a neuroplasticity-based computerized cognitive training program, or a novelty and intensity-matched general cognitive stimulation program (active control). Subjects received a total of 40 hours training, delivered in 60-minute sessions, five days per week for eight weeks. The training consisted of six computerized exercises designed to improve the speed and accuracy of auditory information processing. The level of difficulty was continuously adjusted based on user performance to maintain approximately 85% accuracy in the tests. In each training session, a participant worked with four of the six exercises for 15 minutes per exercise. The aim of the investigation was to evaluate the effect of training on more global, untrained measures of memory, attention and participant-reported outcomes. The primary outcome measure was assessed on six subsets of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), a standardized neuropsychological assessment battery that is sensitive to mild cognitive deficits. These subtests used speech as a stimulus and as such were appropriate since the experimental training focused on improving auditory processing. The overall results of the study showed that individuals in the brain plasticity-based learning arm of the trial showed significant improvement on performance measures directly related to the trained tasks as expected [23]. Additionally, performance improvements were generalized to untrained measures of memory and attention, implying that more global gains occurred across systems serving auditory-based cognitive measures. These results suggest a unique opportunity for computer-aided software to assist in the cognitive activity domain of the elderly. There are numerous web-based programs currently available for such use, particularly for mobile devices. There is scientific evidence that some of these web-based brain-training programs, such as the one used by

Smith and colleagues [23], do provide cognitive stimulation but unfortunately, most require a paid subscription for the more advanced and brain-stimulating aspects. The advantage of web-based cognitive-stimulating programs is that they provide a more broad-based approach to brain activity where training is based on multiple modalities, providing a more global activation. Examples of these are the programs providing daily modules covering multiple areas such as active reading, writing (grammar), listening, mathematics, problem solving and vocabulary, amongst others.

The onus is now on regulatory bodies and government agencies to fund these activities as part of “treatment” and/or prevention strategies as these will be significantly beneficial to both individuals and to governments. In the meantime the duty of care rests on primary caregivers, including physicians, to “prescribe” and follow up on both mental and physical “prescriptions”. A starting point for mental activity could include the freely available web-based cognitive training programs, which, although limited in content (unless paid for) do offer some stimulatory activity. Other training practices could include crosswords, Sudoku, brain-teasers, Scrabble, learning a new language, poetry, dance steps or learning to play a new instrument. Maintaining a diary may also be a useful way of remembering and recalling events, thereby activating circuits that may not otherwise be utilized. The key task is to maintain the activity of neuronal circuits and prevent the loss of synapses and neurons in the brain.

Conclusions

The concept of healthy aging appears to be a misnomer with many individuals associating aging with morbidity and mortality. This Perspective has outlined measures through which healthy aging can be achieved and calls upon healthcare providers to “prescribe” both physical and mental exercises to all patients irrespective of age. The key to this prescription will involve the healthcare provider understanding the benefits of these regimens and prescribing a variety of mental and physical “exercises” that are both beneficial as well as those that keep individuals engaged and continuously stimulated.

It is postulated that increased blood flow resulting from mental or physical activity is key to maintaining a healthy brain. Increased blood flow will provide the brain with much-needed nutrients and oxygen and will remove metabolic by-products generated by neurons. The long-lasting effects observed in the ACTIVE study were obtained following ten one-hour sessions provided over a 5-6 week period (with some cohorts receiving “boosting”) [19]. If individuals are prescribed well designed, cognitively stimulating daily tasks that last 20-30 minutes (140-210 minutes per week), it is proposed that this will be similar to the 150 minutes of physical activity endorsed by the CDC, but this time, for the brain instead of the body. Combined, one hour of activity spread over an entire day will stave off age-associated mental and physical decline and will substantially improve the health and quality of life of older individuals.

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