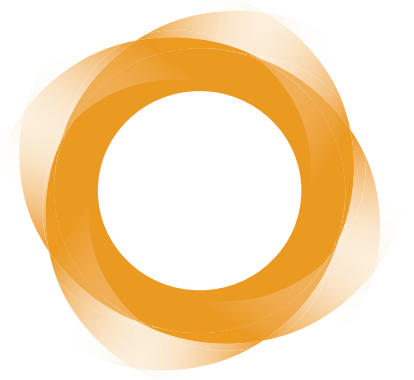

SYRACUSE UNIVERSITY
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Policy Brief

The Challenge of Optimal Brain Health Throughout Life

Mark P. Mattson, Ph.D.

March 6, 2014

Mark P. Mattson, Ph.D. is Chief of the Laboratory of Neurosciences at the National Institute on Aging Intramural Research Program in Baltimore, and a Professor in the Department of Neuroscience at Johns Hopkins University School of Medicine. His research has elucidated how the brain responds adaptively to challenges such as fasting and exercise, and he has used that information to develop novel interventions to promote optimal brain function throughout life. He has published more than 800 articles and is one of the most highly cited neuroscientists in the world with an 'h' index of over 170. He has received many awards including the Metropolitan Life Foundation Medical Research Award and the Alzheimer's Association Zenith Award, and he was elected an AAAS Fellow in 2011.

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The Problem

Most, if not all, Americans have witnessed the devastating impact of one or more of the three major age-related brain disorders - Alzheimer's disease (AD), stroke, and Parkinson's disease (PD) - on family members and friends. Each of these three disorders typically involves long-term morbidity and constant care for many years. Currently there are no effective treatments for AD and stroke, although treatments that temporarily improve the symptoms of PD are available. Based upon data from the Alzheimer's Association (www.alz.org), the Parkinson's Disease Foundation (www.pdf.org) and the American Heart Association (www.heart.org), the burden of AD, PD, and stroke on the patients, family/caregivers, and the health care system is currently more than 300 billion dollars per year, and is expected to double within the next 20 years.

Because the brain has a highly complex cellular structure involving billions of neurons and trillions of synaptic connections between those neurons, and because AD, PD, and stroke involve the degeneration and death of neuronal networks, it is unlikely that it will be possible to repair the neuronal circuits in patients who already suffer from these disorders. However, emerging scientific evidence described herein suggests that it may be possible to forestall each of

these age-related brain disorders by implementing dietary and lifestyle interventions throughout adult life.

The number of Americans with age-related brain disorders is rapidly increasing. For example, AD currently afflicts approximately 5 million Americans and this number will triple by 2050 (Thies and Bleiler, 2013). There has been an increase in the number of people living into their seventh and eighth decades of life, the 'danger zone' age range for AD, PD and stroke (Figure 1). There are several reasons including:

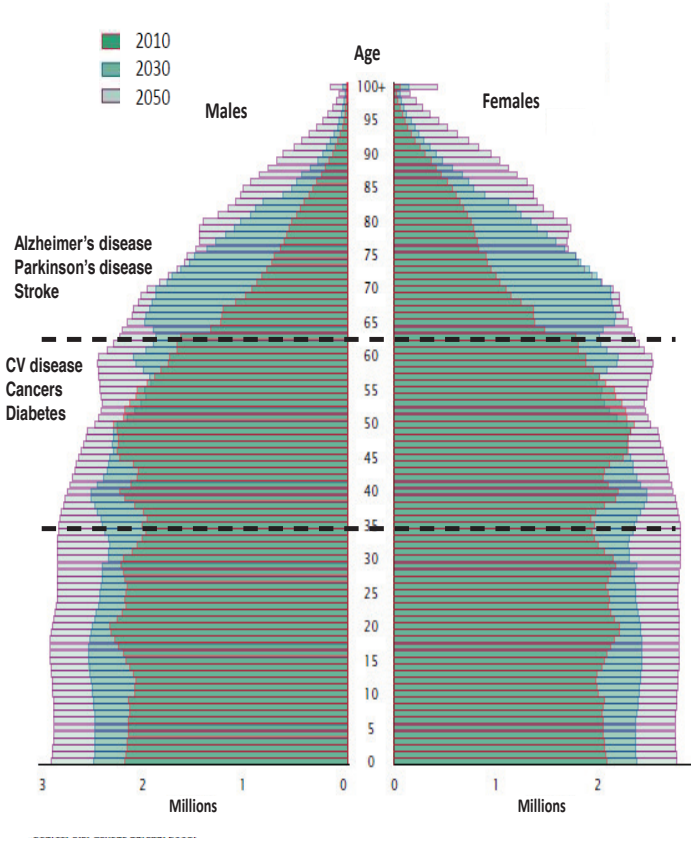
1) The 'baby boomer' generation of people born in the two decades after World War II are now elderly;

2) advances in the early diagnosis and treatment of cardiovascular disease and some cancers has allowed extended survival of many people who would have previously died when they were in their 50s and 60s;

3) as a result of sedentary overindulgent lifestyles there has been a rapid increase in the number of Americans who are overweight/obese and/or have diabetes; obesity and diabetes are risk factors for AD and stroke (Goldstein et al., 2011; Lee and Mattson, 2014).

In this policy brief, I first summarize what is known about the mechanisms underlying the pathogenesis of AD, PD, and stroke, and the evidence from studies of human populations and animal models supporting the effectiveness of dietary energy restriction, exercise, and intellectually challenging endeavors in promoting optimal brain health and forestalling age-related brain disorders. I then suggest that a multi-pronged society-wide strategy will be required to reduce the number of individuals affected by AD, PD, and stroke during the coming decades and in future generations. Development and implementation of such a strategy will require coordinated

Figure 1. Age distribution of the US population in 2010, 2030 and 2050. Note that the number of men and women in the age range of 65-80 years will approximately double in the period from 2010 to 2030.



Source: U. S. Census Bureau, 2009

efforts of governments (federal, state, and local) and education systems, major revisions to medical training and the health care system, and the commitment of families and communities.

The Aging Brain is Vulnerable to Dysfunction and Neurodegeneration

Age is the major risk factor for AD, PD, and stroke. There are several changes that occur in the brain during normal aging that are believed to 'set the stage' for neurodegenerative disorders including: increased oxidative damage to proteins DNA and lipids; impaired cellular bioenergetics, particularly problems with mitochondria not generating enough ATP (adenosine triphosphate); accumulation of certain proteins and lipids within and outside of brain cells; and an impaired ability of neurons to control their excitability (Mattson and Magnus, 2006).

All of these age-related changes in the brain are amplified by disease-specific abnormalities that occur in AD, PD, and stroke. In AD, altered proteolytic processing of the amyloid precursor protein results in increased production of amyloid β-peptide (Aβ) which accumulates inside neurons, and outside of neurons, where it forms the classic amyloid plaques that typify AD. The increased oxidative stress and reduced ability of neurons to sustain energy levels that occurs during aging is believed to promote increased production of Aβ. As Aβ aggregates in and on neurons it causes oxidative stress and impairs the ability of the neuron to maintain ion (Na^+ and Ca^{2+}) gradients across the cell membrane, which can result in the dysfunction and degeneration of synapses, and the death of the neurons. These neurodegenerative processes typically occur most in brain regions such as the hippocampus and frontal

cortex that play critical roles in learning and memory. In PD, a protein called α-synuclein accumulates inside vulnerable populations of neurons including those involved in control of body movements (dopamine-producing neurons in the substantia nigra) and bodily functions such as gut motility and regulation of heart rate (autonomic neurons in the brainstem).

The dysfunction of mitochondria, the 'energy factory' of cells, is believed to be a major abnormality underlying PD because certain toxins that specifically impair mitochondrial energy production can cause PD-like neuropathology and symptoms in humans and animal models, and because genetic mutations that cause rare inherited early-onset PD occur in genes involved in mitochondrial function. In both AD and PD, neurons also have difficulty removing damaged proteins and mitochondria, which therefore accumulate inside of neurons.

Stroke most commonly results from the formation of a blood clot in an artery in the brain that has been narrowed by atherosclerosis. Just as a myocardial infarction causes damage to heart muscle cells, a stroke causes damage to neurons in the brain. The location and amount of brain tissue damage in a stroke depends upon the artery in which the clot occurs, and how long the blood flow to the tissue is reduced. There are certain arteries in the brain that are particularly prone to atherosclerosis and stroke. The symptoms of a stroke that commonly occur in patients include a sudden onset of numbness in one limb, slurred speech, confusion, and/or vision problems.

While being overweight and/or diabetic increases the risk of stroke by promoting atherosclerosis, a 'couch potato' lifestyle may also result in a greater amount of brain tissue damage and poorer recovery from a stroke (Kurukulasuriya et al., 2006). Numerous alterations occur in brain tissue affected by a stroke

that result in the degeneration of neurons including a dramatic reduction in energy (glucose) supply to the neurons, oxidative stress, and local inflammation involving activation of immune cells. All of these alterations are amplified during aging, which is one reason why the elderly are more likely to have a poorer outcome from a stroke compared to younger people.

The Brain Functions Best, and is Most Resilient, When Challenged Intermittently

A major take-home message of this brief is that it is important to challenge oneself intermittently with exercise, dietary energy restriction, and intellectual endeavors in order to optimize brain function and protect against AD, PD, and stroke. In addition to improving cardiovascular and metabolic health, regular exercise reduces anxiety, improves mood, and enhances learning and memory (Voss et al., 2013). Emerging evidence suggests that intermittent fasting (for example, eating only one modest size meal 2 or 3 days each week, while eating regular meals on the other 4 or 5 days) is also beneficial for overall health and brain function (Longo and Mattson, 2014).

Engaging in intellectually challenging occupations and leisure activities also bolsters brainpower and may protect against AD (Stern, 2006). Why, from an evolutionary perspective, would the brain function better and be more resilient when challenged intermittently? Simply put, the individual whose brain functions well during periods of hunger and when expending considerable physical effort is most likely to survive. As with other mammals, humans evolved as lean, mean, resource-acquiring machines. Even highly sophisticated capabilities of our brains likely evolved for the purpose of acquiring food, including the ability to invent and use tools

(e.g., a bow and arrow or gun), language, and cooperation among members of the community. A classic example is hunter-gatherers who typically hunt in small groups and implement sophisticated communication- and weapon-based hunting strategies. The success of such hunts requires that the brain function well in a hungry/fasted state while expending considerable physical effort (running). Consistent with this evolutionary perspective, research in laboratory animals has shown that intermittent fasting and running wheel exercise improve learning, memory ability, and sensory–motor function, and sustain brain function during aging (Mattson, 2012).

The changes that occur in the brain in response to exercise, fasting, and intellectual challenges are being elucidated (Mattson, 2012). Two adaptive responses to these challenges are increased formation of synapses and production of new neurons from stem cells (a process called neurogenesis) in the hippocampus; both of these effects of intermittent challenges can enhance learning and memory.

Another response to exercise, fasting, and intellectual challenges is increased production of neurotrophic factors, which are proteins that help neurons survive, grow, and form and maintain synapses; this may be particularly important for sustaining cognitive function during aging. Brain-derived neurotrophic factor (BDNF) is one such neurotrophic factor that is believed to play an important role in the beneficial effects of all three challenges on learning and memory. Recent studies have shown that BDNF can stimulate the production of new mitochondria in neurons and can enhance the ability of neurons to repair damaged DNA (Cheng et al., 2012; Yang et al., 2014). The latter findings suggest that intermittent energetic and intellectual challenges that increase BDNF production can bolster energy levels in neurons, and can

protect them against damage to DNA that occurs during aging and neurodegenerative disorders.

Intermittent fasting and exercise can preserve neuronal function in animal models of AD and PD (for review see Mattson, 2012). For example, when maintained on an alternate day fasting diet, transgenic mice expressing mutated human genes that cause inherited AD exhibit preserved learning and memory ability compared to AD mice maintained on the usual ad libitum diet. Intermittent fasting can also protect neurons and improve motor function in a mitochondrial toxin-based PD mouse model, and can protect autonomic neurons against dysfunction in α-synuclein mutant mice (a model of inherited PD) (Duan and Mattson, 1999; Griffioen et al., 2013). Exercise has also been shown to ameliorate neuropathological alterations and improve cognition or motor function in animal models of AD and PD (Intlekofer and Cotman, 2013; Zigmond and Smeyne, 2014.)

Intermittent fasting has also proven beneficial in rodent models of stroke, and can lessen the amount of brain damage and improve functional outcomes in animal models of traumatic brain and spinal cord injury (Mattson, 2014). If similar effects of intermittent energetic challenges on the brain occur in humans, then individuals who exercise regularly and maintain intermittent fasting diets would be expected to have better outcomes should they suffer a stroke or traumatic brain injury.

In addition to stimulating the production of neurotrophic factors and bolstering neuronal bioenergetics, fasting and exercise may increase the ability of neurons to eliminate free radicals. For example, running wheel exercise resulted in increased levels of superoxide dismutase and glutathione peroxidase enzymes in rats (Marosi et al., 2012), and alternate day fasting increased levels of the antioxidant enzyme heme

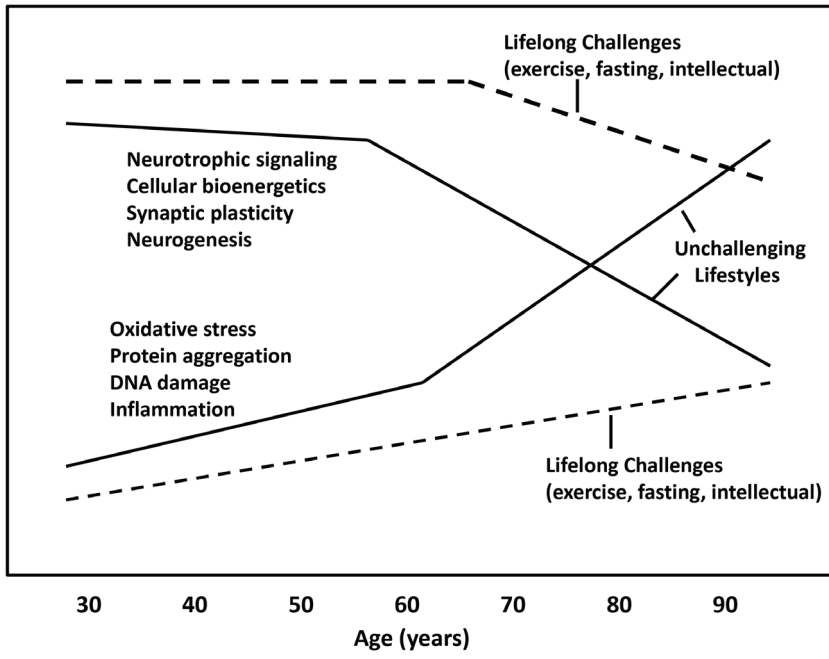
oxygenase 1 in the brains of mice (Arumugam et al., 2010). Changes that occur in the body in response to fasting and exercise may also benefit in the brain. For example, fasting and vigorous exercise can stimulate the mobilization of fatty acids from fat cells and the production of ketone bodies from those fatty acids. Ketone bodies provide an energy source for neurons and have been shown to be neuroprotective in an animal model of AD (Kashiwaya et al., 2013).

Collectively, the results from studies of animal models and human subjects suggest that a lifestyle that includes regular exercise, intermittent energy restriction, and intellectual challenges affords the brain protection against dysfunction and degeneration resulting from aging, injury, and neurodegenerative disorders. A model for changes that occur in the brain during aging in individuals who lead relatively unchallenging ('couch potato') lifestyles, and the effect of engaging in intermittent challenges on those age-related brain changes is shown in Figure 2. The model depicts increases in oxidative stress, protein aggregation, DNA damage and inflammation, and decreases in neurotrophic factors, cellular energy levels, synaptic plasticity, and neurogenesis in brain cells during aging. The dashed lines show that lifestyles that include exercise, intermittent energy restriction, and intellectual challenges can shift the trajectories of the detrimental age-related alterations in brain cells to improve brain function and forestall neurodegenerative disorders.

Implementation of Challenge-Based Lifestyles in Our Society

The past half-century has been troubling from a public health perspective. Technological advances, the proliferation of

Figure 2. Impact of lifestyles that incorporate intermittent challenges on age-related changes that increase the vulnerability of neurons to dysfunction and degeneration.



Source: Modified from Mattson (2014)

high-calorie processed foods replete with simple sugars and unhealthy fats, and an overemphasis on the development of drugs to treat extant diseases have all encouraged unchallenging, overindulgent, and sedentary lifestyles. This has occurred coincidently with an increase in the number of aging Americans, resulting in what is tantamount to an epidemic of elderly suffering from a brain disorder, with AD being the most prominent. It is now clear that a 'couch potato' lifestyle increases the risk of stroke, AD, and PD, and it is therefore likely that current predictions underestimate the rate of increase in prevalence of these age-related brain disorders in the coming decades.

Everyone has a stake in this emerging crisis. Unfortunately, there has not yet been a major effort to develop a society-wide strategy to reduce the number of Americans who are overweight and unfit, even as the epidemic of metabolic morbidity increasingly affects children. The longer we as a society wait to act, the bigger the problem will become.

***Some of the major barriers to implementing intermittent challenge-based diets and lifestyles include*:**

1) technological advances in mechanization and transportation have largely eliminated the need for physical exertion in daily activities;

2) the most common eating pattern of 3 meals plus snacks every day has become the cultural norm;

3) the agriculture and processed food industries have worked together to produce and market inexpensive, calorie-dense foods and drinks with addictive chemical properties;

4) the medical community has de-emphasized, and in some respects even suppressed, diet and lifestyle interventions for disease risk reduction. For example, medical training and practice emphasize treating the symptoms of diseases with drugs and surgical procedures, instead of more cost-effective disease prevention approaches;

5) drug companies (and the doctors they prod) encourage patients to depend upon drugs.

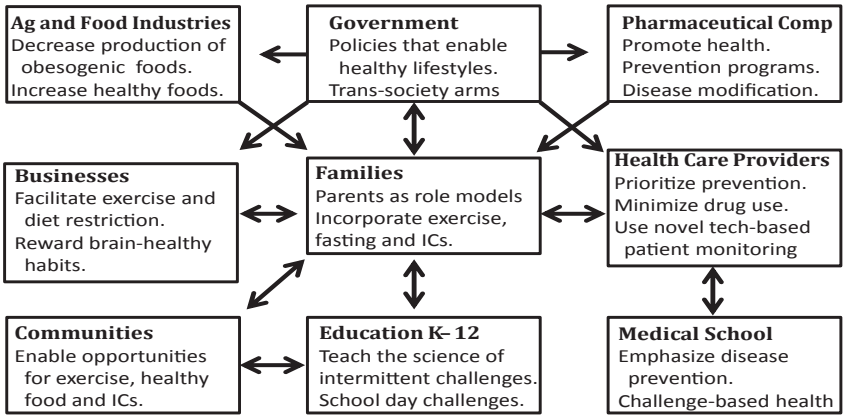
Each of these five barriers is formidable for one or more reasons. Lobbyists for the agriculture, processed food, and pharmaceutical industries lead policy makers to believe that jobs would be lost and the economy would suffer should restrictions that enable healthy diets and lifestyles be implemented. Being successful in getting individuals to change their eating patterns (e.g., to eliminate 'fast foods' and adopt an intermittent fasting diet) and to exercise regularly requires effort by health care providers and communities.

How might we overcome the barriers that obstruct a clear, intermittent challenge-based path to lifelong brain health (Figure 3)?

Federal, state and local governments should develop and implement policies and programs that enable and empower individuals to incorporate brain-healthy intermittent challenges into their daily routines. Such policies and programs would include:

1) **reducing the availability of processed/fast food and increase the availability of vegetables, fruits, nuts and whole grains.** One example would be regulations that

Figure 3. Implementation of intermittent challenge-based brain-healthy lifestyles will require changes at all levels of society.



Source: Modified from Mattson (2012)

encourage the diversification of crops on large farms so as to provide fresh vegetables at low cost.

2) **limiting the influence of the processed food industries on dietary habits.** Examples are restrictions on advertisement (particularly to children), on the availability of 'fast food' restaurants, and on the amounts of simple sugars and unhealthy fats in processed foods;

3) **emphasizing challenge-based daily routines** should be emphasized in primary and secondary education, as well as in families.

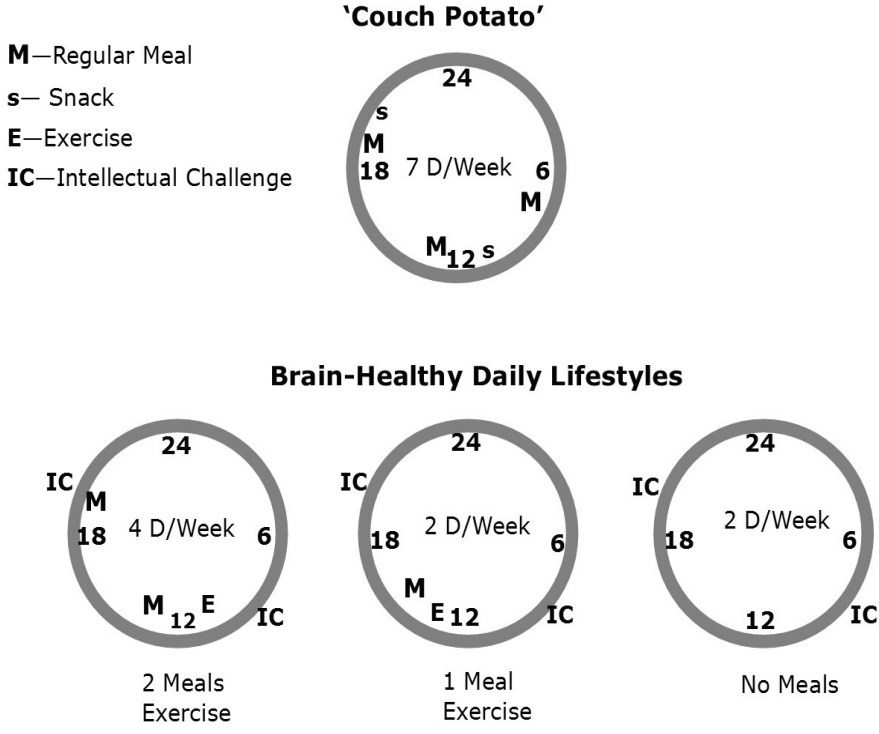
4) **facilitating and encouraging opportunities for daily exercise and intermittent energy restriction** in communities and businesses in designing and/or retrofitting buildings to create exercise opportunities for employees, such as building bicycle paths.

5) **requiring businesses to provide opportunities and facilities for exercise during the workday**, which would encourage employees to increase their exercise levels during normal routines, such as using the stairs.

6) **requiring challenge-based disease prevention training** for medical students and the health care systems.

7) **developing specific prescriptions for intermittent energy restriction, fasting, and exercise** that can be monitored in ways that encourage patients to comply with the prescription. For example, health care provider staff could communicate with patients on a daily basis using text messaging and social media.

Figure 4. Examples of challenge-based prescriptions for brain and general health.



Intermittent challenge-based prescriptions for brain-health lifestyles.

Recent clinical trials have shown that it is indeed feasible for patients to change their eating patterns. For example, women were able to adhere for at least 6 months to an intermittent energy restriction diet in which they consumed only one moderate size (500 calorie) meal two days each week, while eating three meals the other 5 days (Harvie et al., 2013).

The diagram in Figure 4 shows 24 hour clocks that illustrate four different daily patterns of eating, exercise, and intellectual challenges. The current daily and weekly routine for many Americans (upper clock) is such that they eat three meals plus snacks every day, are sedentary, and do not engage in substantive intellectual challenges ('couch potato' lifestyle). The lower three clocks show examples of daily and weekly routines that incorporate intermittent fasting (reduced meal frequency), exercise, and intellectual challenges.

Ultimately, a society-wide change towards brain-healthy lifestyles will require education of parents and children, who must embrace the challenge of changing their eating patterns and incorporating exercise, and intellectual challenges into their lifestyles.

Accordingly, the family is placed at the center of Figure 3, showing that it's reciprocal interactions with government, schools, community organizations, and the health care system. Parents should participate in community efforts to remove barriers to challenge-based lifestyles, and to implement the kinds of societal changes that will be required to eradicate the epidemics of obesity and diabetes, and thereby reduce the number of Americans who will otherwise suffer from AD, PD, and stroke.

Families operate within a complex web of external influence. Therefore, systemic, structural change will be neccessary to enact meaningful behavioral change among individuals and within families.

References

Arumugam, Thiruma V., Phillips, Terry M., Cheng, Aiwu, Morrell, Christopher H., Mattson, Mark P., and Wan, Ruiqian. 2010. "Age and energy intake interact to modify cell stress pathways and stroke outcome." Annals of Neurology. 67(1) (January):41-52.

Cheng, Aiwu, Wan, Ruiqian, Yang, Jeng-Lin, Kamimura, Naomi, Son, Tae Gen, Ouyang, Xin, Luo, Yongquan, Okun, Eitan, and Mattson, Mark P. 2012. "Involvement of PGC-1α in the formation and maintenance of neuronal dendritic spines." Nature Communications. 3 (December):1250.

Duan, Wenzhen and Mattson, Mark P. 1999. "Dietary restriction and 2-deoxyglucose administration improve behavioral outcome and reduce degeneration of dopaminergic neurons in models of Parkinson's disease." Journal of Neuroscience Research. 57:195-206.

Goldstein, Larry B., Bushnell, Cheryl D., Adams, Robert J., Appel, Lawrence J., Braun, Lynne T., Chaturvedi, Seemant, Creager, Mark A., Culebras, Antonio, Eckel, Robert H., Hart, Robert G., Hinchey, Judith A., Howard, Virginia J., Jauch, Edward C., Levine, Steven R., Meschia, James F., Moore, Wesley S., Nixon, J.V. (Ian) and Pearson, Thomas A. 2011. "Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/ American Stroke Association." Stroke. 42:517-584.

Griffioen Kathleen J., Rothman, Sarah M., Ladenheim, Bruce, Wan, Ruiqian, Vranis, Neil, Hutchison, Emmette, Okun, Eitan, Cadet, Jean Lud, Mattson, Mark P. 2013. "Dietary energy intake modifies brainstem autonomic dysfunction caused by mutant α-synuclein." Neurobiology of Aging. 34:928-935.

Harvie, Michelle, Wright, Claire, Pegington, Mary, McMullan, Debbie, Mitchell, Ellen, Martin, Bronwen, Cutler, Roy G., Evans, Gareth, Whiteside, Sigrid, Maudsley, Stuart, Camandola, Simonetta, Wang, Rui, Carlson, Olga D., Egan, Josephine M., Mattson, Mark P., and Howell, Anthony. 2013. "The effect of intermittent energy and carbohydrate restriction v. daily energy restriction on weight loss

and metabolic disease risk markers in overweight women." British Journal of Nutrition. 110:1534-1547.

Intlekofer, Karlie A,, and Cotman, Carl W. 2013. "Exercise counteracts declining hippocampal function in aging and Alzheimer's disease." Neurobiol Dis. 57 (September):47-55.

Kashiwaya, Yoshihiro, Bergman, Christian, Lee, Jong-Hwan, Wan, Ruiqian, King, M. Todd, Mughal, Mohamed R., Okun, Eitan, Clarke, Kiernan, Mattson, Mark P., and Veech, Richard L. 2013. "A ketone ester diet exhibits anxiolytic and cognition-sparing properties, and lessens amyloid and tau pathologies in a mouse model of Alzheimer's disease." Neurobiology of Aging. 34(6) (June):1530-1539.

Kurukulasuriya, L. Romayne, Govindarajan, Gurushankar, and Sowers, James. 2006. "Stroke prevention in diabetes and obesity." Expert Review of Cardiovascular Therapy. 4(4) (July):487-502.

Lee, Edward B. and Mattson, Mark P. 2014. "The neuro-pathology of obesity: insights from human disease." Acta Neuropathologica. 127(1) (January):3-28.

Longo, Valter D. and Mattson, Mark P. 2014. "Fasting: molecular mechanisms and clinical applications." Cell Metabolism. 19(2) (February):181-192.

Marosi, Krisztina, Bori, Zoltan, Hart, Nikolett, Sárga, Linda, Koltai, Erika, Radák, Zsolt, and Nyakas, Csaba. 2012. "Long-term exercise treatment reduces oxidative stress in the hippocampus of aging rats." Neuroscience. 226(13) (December):21-28.

Mattson, Mark P. and Magnus, Tim. 2006. "Ageing and neuronal vulnerability." Nature Reviews Neuroscience. 7 (April):278-294.

Mattson, Mark P. 2012. "Energy intake and exercise as determinants of brain health and vulnerability to injury and disease." Cell Metabolism. 16(6) (December):706-722.

Mattson, Mark P. 2014. “Lifelong brain health is a lifelong challenge: from evolutionary principles to empirical evidence.” Ageing Research Reviews. In press.

Stern, Yaakov. 2006. "Cognitive reserve and Alzheimer disease." Alzheimer Disease and Associated Disorders. 20(2) (April):112-117.

Thies, Wolf-Gerolf and Bleiler, Laura. 2013. “Alzheimer’s disease facts and figures.” Alzheimer’s & Dementia. 9 (2013):208-245.

Vincent, Grayson K. and Velkoff, Victoria A. 2010. "The Next Four Decades - The Older Population in the United States: 2010 to 2050." U.S. Department of Commerce, U.S. Census Bureau. (May):1-14.

Voss, Michelle W., Vivar, Carmen, Kramer, Arthur F., and van Praag, Henriette. 2013.”Bridging animal and human models of exercise-induced brain plasticity.” Trends in Cognitive Sciences. 17(10) (October):525-544.

Yang, Jenq-Lin, Lin, Yu-Ting, Chuang, Pei-Chin, Bohr, Vilhelm A., Mattson, Mark P. 2014. “BDNF and exercise enhance neuronal DNA repair by stimulating CREB-mediated production of apurinic/apyrimidinic endonuclease 1.” NeuroMolecular Medicine. 16(1) (March):161-174.

Zigmond, Michael J., and Smeyne, Richard J. 2014. "Exercise: is it a neuroprotective and if so, how does it work?" Parkinsonism & Related Disorders. 20 Suppl 1 (January):S123-127.

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