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Cognitive Consequences of Aging with HIV: Implications for Neuroplasticity and Rehabilitation

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Abstract

Combination active antiretroviral therapy prevents HIV from replicating and ravaging the immune system, thus allowing people to age with this disease. Unfortunately, the synergistic effects of HIV and aging can predispose many to become more at-risk of developing cognitive deficits which can interfere with medical management, everyday functioning, and quality of life. The purpose of this article is to describe the role of cognitive reserve and neuroplasticity on cognitive functioning in those aging with this disease. Specifically, the role of environment and the health of these individuals can compromise cognitive functioning. Fortunately, some cognitive interventions such as prevention and management of co-morbidities, cognitive remediation therapy, and neurotropic medications may be of value in preventing and rehabilitating the cognitive consequences of aging with HIV. Novel approaches such as cognitive prescriptions, transcranial direct stimulation, and binaural beat therapy may also be considered as possible techniques for cognitive rehabilitation.

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Keywords

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Fifty-two percent of adults with HIV experience some measurable cognitive deficit according to Heaton and colleagues.¹ In deriving this percentage, they conducted neuropsychological evaluations with 1,555 adults with HIV from 6 sites across the United States. They categorized 33% with asymptomatic impairment, 12% with mild impairment, 5% with confounded impairment, and 2% with dementia. These cognitive deficits are observed across multiple cognitive domains including attention, memory, speed of processing, executive functioning, and psychomotor ability.^{2–10}

These cognitive deficits can create a poor person-environment fit, thus creating problems with everyday functioning such as with employment, financial management,¹¹ driving,^{12–15} remembering medical appointments, and medication adherence.^{16,17} For example, in a sample of adults with ($n = 42$) and without HIV ($n = 21$), Marcotte and colleagues found that those with HIV performed more poorly on a cognitive measure of visual attention and visual speed of processing (i.e., the Useful Field of View test) than those without HIV. Furthermore, they found that those classified with poor visual attention and speed of processing experienced a higher rate of automobile crashes compared to those classified with normal visual attention and speed of processing. As people age normally, cognitive loss in visual attention and speed of processing commonly occur which also affects driving safety;¹⁸ thus, there is concern that those aging with HIV may experience even more problems with driving.

As people age with HIV, the synergistic effects of aging and HIV may translate into more vulnerability of developing such cognitive deficits that impact everyday functioning.^{9,19–24} This phenomenon is of concern given that by 2015 half of those living with HIV in the United States will be 50 and older.²⁵ Therefore, this percentage of 52% with cognitive deficits is likely to rise, thus representing a public health problem. Understanding this problem and developing appropriate and affordable solutions for preventing and rehabilitating for such cognitive deficits is imperative.

The purpose of this article is to review the cognitive consequences of aging with HIV within the framework of cognitive reserve and neuroplasticity. From this framework, the role of environment and health on cognition is reviewed as it pertains to HIV. Following this, novel cognitive interventions are presented that may theoretically prevent cognitive loss or rehabilitate such cognitive functioning. Finally, although not exhaustive, novel cognitive interventions are examined as potential interventions worthy of future study.

Principles of Cognitive Reserve and Neuroplasticity

As mentioned, as people age with HIV, they will be more vulnerable of developing cognitive deficits. In a cross-sectional study with 161 older (50+) and younger (<50) adults with and without HIV, Vance and colleagues administered seven neuropsychological and

two laboratory-based everyday functioning tests to these participants.²⁶ They found that, as a group, older adults with HIV performed the worst on all of these tests; this was followed by younger adults with HIV and older adults without HIV, and then with younger adults without HIV performing the best. This and other studies support similar findings.^{9,19–22,27}

One reason for these cognitive deficits may be due to the depletion of cognitive reserve. Cognitive reserve refers to the amount of damage the brain can absorb and yet maintain functioning. Cognitive reserve has become a theoretical explanation for describing the differences observed in brain pathology and the clinical or observed manifestation of the physiological damage on individuals who are diagnosed with Alzheimer's disease.^{28,29} In fact, cognitive reserve may explain why individuals experience differential rates of change in cognitive function, and that such cognitive reserve capacity may provide a buffer to cognitive decline.³⁰ Recent evidence demonstrates that cognitive reserve offers protection from neuronal damage.³¹ Unfortunately, once the damage accumulates to a certain threshold, cognitive deficits begin to emerge.^{32–34}

This process of cognitive reserve can be exemplified in the following manner. Imagine neurons are avenues (left panel of Figure 1), which is an apt analogy since electrical impulses travel from synapse to cell body to dendrites to the terminal buttons where neurotransmitters are released into the synaptic cleft. In this analogy, the synaptic clefts can be likened to the intersections. As electrical impulses (i.e., traffic) travel from neuron to neuron, cognition emerges. Cognition can continue to emerge as long as the avenues are open and the intersections are clear. But as seen in the right panel of Figure 1, as the intersections (i.e., synaptic clefts) are clogged by amyloid plaques or the avenues (i.e., neurons) are less viable because of oxidative stress, neurofibrillary tangles, or cortisol toxicity, the electrical impulses are no longer as free to travel. These hindrances result in traffic being slower even though it may be bypassed onto other avenues. But eventually, if the intersections and avenues become too clogged, traffic comes to a standstill; likewise, in the brain, if the neurons and their connections become too damaged, electrical impulses cannot travel and cognition becomes slowed or does not even emerge.

For those aging, those with HIV, and especially those aging with HIV, there are several mechanisms that can deplete cognitive reserve. Some of these mechanisms can be encapsulated under two processes: oxidative stress and neuroinflammation. Oxidative stress refers to the process whereby tissues of the body react to oxygen molecules. Although oxygen is needed by the body to convert food into energy, particular oxygen molecules, referred to as reactive oxygen species, is actually corrosive and damages tissues. Fortunately, the body possesses a complex system of enzymes that absorbs these damaging molecules and makes them inert; in fact, certain foods such as green tea and red wine contain polyphenols (an antioxidant) that render these reactive oxygen species inert. But with age, the body becomes less able to defend itself against these damaging molecules. Likewise, when tissues are damaged, the body produces an inflammatory response.³⁵ Inflammation is a complex biochemical protective response of the endocrine system that aids in repairing tissues. Specialized proteins called cytokines and leukocytes (white blood cells) eradicate pathogens and molecularly rebuild tissue. But inflammation over prolonged periods of time can actually damage tissue as well. Brain tissue is also vulnerable to these

effects, thus giving rise to neuroinflammation. Several studies show that prolonged neuroinflammation is associated with increased risk of cognitive impairment, stroke, and dementia.^{35–37}

Neuroinflammation is of particular concern for those aging with HIV. HIV is considered a slow burner “inflammation” disease; some may even remark that AIDS stands for Acquired Inflammation Disease Syndrome instead of Acquired Immunodeficiency Syndrome. For many reasons (and several have been considered), HIV produces neuroinflammation. In fact, cognitive deficits and changes in brain metabolism have been detected as early as one year post HIV diagnosis.^{38,39}

As HIV crosses the blood brain barrier, although it generally does not infect neurons per se, it is able to enter glial cells (i.e., microglia, macrophages) and replicate, thus killing these cells.^{40,41} Given that glial cells facilitate neuronal health and contribute to neuronal modulation, this is of concern. Continuing with the neuron-avenue cognitive reserve analogy (Figure 1), glial cells help keep the avenues clear so that electrical impulses can continue to travel. But as glial cells become damaged or die (i.e., astrogliosis), neurotoxic byproducts are produced such as cytokines and quinolic acid. These byproducts: 1) compromise the functioning of other glial cells, 2) elevate oxidative stress and neuroinflammation, and 3) compromise or kill neurons.^{41,42} As a result, this reduces cognitive reserve, rendering people more susceptible of developing cognitive deficits.

Increasing Cognitive Reserve

Fortunately, cognitive reserve can be increased; this is a useful fact should one be interested in preventing cognitive loss in later life.³³ Continuing with the neuron-avenue cognitive reserve analogy (Figure 1), new avenues (i.e., neuronal pathways) can be created; this process is referred to as positive neuroplasticity. Simply stated, positive neuroplasticity is a complex biochemical process whereby new connections (i.e., avenues) are created between neurons. In contrast, negative neuroplasticity is a complex biochemical process whereby connections are pruned, atrophied, or destroyed. These processes are affected by inflammation, disease and pathogens, insults to the body and brain, and the environment. In fact, the enriched environment paradigm (below) poignantly epitomizes these processes of neuroplasticity.

In this classic enriched environment paradigm, animals (usually rats or mice) are randomly selected to live in one of three environments – an enriched, a standard, or an impoverished environment.³³ Animals in the enriched environment live with other animals of their kind and have toys with which they can interact. Animals in the standard environment are grouped in threes and placed in a cage with no toys. Animals in the impoverished environment are placed in isolation with no toys. Otherwise, the environmental conditions (e.g., lighting, temperature, food) are kept constant across the three environments. Researchers have found that those animals placed in the enriched environment have more brain-derived neurotropic factors that favor positive neuroplasticity along with larger brains and more dense dendritic connections compared to animals placed in the other two conditions. Similarly, animals placed in the impoverished environment have less brain-derived neurotropic factors indicative of negative neuroplasticity along with smaller brains

and less dense dendritic connections compared to animals placed in the other two conditions. Likewise, these physiological differences translate into maze performance tests in that animals placed in the enriched environment negotiate such mazes faster and more efficiently than animals placed in the other two conditions; the same comparison can be observed between animals in the standard environment compared to those in the impoverished environment.^{33,34} These effects are also observed in human studies whereby exposure to leisurely, intellectual, physical, and occupational activities has been shown to change the morphology of the brain and delay the onset of cognitive aging and dementia.^{33,43}

In the classic London Taxi Driver Study, Maguire and colleagues used MRI scans to examine neuroplasticity in taxi drivers and bus drivers.⁴⁴ They exploited a naturalistic opportunity whereby taxi drivers and bus drivers learned and practiced their profession. Typically, London taxi drivers have to train for 2 to 4 years to learn to effectively traverse the many streets of London and learn various points of interest along the way. In contrast, London bus drivers do not have to undergo such a vigorous training program; instead, they drive in set routes while the taxi drivers do not have any set route. Similar to the enriched environmental paradigm above, the taxi drivers represent the enriched environment and the bus drivers represent the standard environment. These researchers found that the taxi drivers had larger mid-posterior hippocampi than the bus drivers; furthermore, the size of the hippocampi was associated with the years of driving. Clearly environment plays a crucial role in neuroplasticity. Likewise, learning new information has been shown in other studies to develop brain regions and even perhaps slow the progression of dementia.^{33,45,46}

Decreasing Cognitive Reserve

Just as there are factors that increase cognitive reserve, there are also factors that decrease cognitive reserve, thus creating cognitive deficits. As already mentioned, oxidative stress and neuroinflammation are contributing factors. However, the medications used to treat HIV can also produce metabolic syndromes that can result in diabetes, hypercholesterolemia, hypertension, and heart disease.⁴⁷ As people age with HIV, they will be more vulnerable of developing such co-morbidities. Thus, there is concern that these co-morbidities will indirectly deplete cognitive reserve in these adults. Numerous studies show that such co-morbidities can increase oxidative stress, cortisol levels, and neuroinflammation, all of which decrease cognitive reserve.^{35,48} Additionally, combined antiretroviral therapy (cART)-related mitochondrial damage also contributes to this process of decreasing cognitive reserve.⁴⁹

In addition to the physical factors that can contribute to a decrease in cognitive reserve in those aging with HIV, psychological and social factors are also involved. First of all, across age groups, ~50% and ~20% of adults with HIV experience depression and anxiety, respectively.⁴⁷ Likewise, a significant number of adults with HIV suffer from concomitant psychiatric co-morbidities such as bipolar disorder (~2%) and substance use/abuse (~25%).⁴⁷ Such psychiatric conditions create a stress response within the hypothalamus-adrenal-pituitary axis resulting in the release of cortisol; sustained release of cortisol causes neuroinflammation.³⁵

Second, HIV is a stigmatizing disease which can result in social withdrawal and isolation.⁵⁰ In a study of 160 older (50+) adults with HIV in New York City, Shippy and Karpiak found that 71% lived alone, two-thirds were not in a significant intimate relationship, and 57% reported that their emotional needs were unmet.⁵¹ Thus, from this and other studies,^{52–54} it was shown these older adults have a fragile social network, and as a group, may not have the social and personal resources to help mitigate the physical and psychological stressors common with HIV. In fact, studies show that social isolation and social rejection in adolescents results in increased inflammatory biomarkers (i.e., interleukin-6, C-reactive protein).⁵⁵ Thus, it is likely that those aging with HIV who experience such social isolation and social rejection may also experience an increased stress response that may fuel inflammation and neuroinflammation.^{56,57}

Third, as observed in several studies, social interaction is helpful in promoting brain health and positive neuroplasticity; likewise, no or little social interaction can result in negative neuroplasticity and thus decrease cognitive reserve.^{43,56,58} For example, Wilson and colleagues followed 823 older adults without Alzheimer's disease for 4 years and examined their perceived loneliness.⁵⁹ When they compared the most lonely (above the 90th percentile) to the least lonely (below the 10th percentile), they found that those who were lonely experienced a two-fold increase in developing Alzheimer's disease compared to the non-lonely group. Other studies also suggest that social interaction is important for brain health and positive neuroplasticity.⁵⁸ This point is very important when one considers that many older adults with HIV may not work, and thus do not have that opportunity to interact socially with coworkers, an activity hypothesized to stimulate cognition.^{43,60}

Cognitive Interventions

Although there are several interventions for preventing and rehabilitating cognitive deficits in adults with HIV, a few of the more well-known and practical interventions are cART, co-morbidity prevention and management, neurotropic medications, and cognitive remediation therapy.

cART

Al-khindi, Zakzaic, and van Gorp reviewed 23 studies on the effects of cART on neurological functioning in those with HIV; they found that such antiretrovirals are effective in improving virological outcomes, functioning in a variety of cognitive domains including psychomotor, executive, and attention also occur.⁶¹ Most likely, cART-induced reduction of viral load also affects the brain, with consequent reductions in neuronal injury. Although there are probably many other mechanisms in which cART improve brain health (e.g., reducing neuroinflammation caused by HIV; improved immunological response and fewer opportunistic infections), there are still some concerns about a few cART medications (e.g., efavirenz) that may actually create mitochondrial toxicity, neurotoxic effects, and co-morbidities.⁴⁷ In fact, Giunta and colleagues studied the use of cART and the incidence of HIV-associated neurocognitive disorders (HAND).⁶² They found that cART inhibited microglial phagocytosis (i.e., devouring foreign particles) of amyloid beta protein known to accumulate in the brains of those with Alzheimer's disease, thus leading to neurotoxicity. Despite this finding, cART is by far the first line of defense against preventing cognitive

deficits by restoring and/or protecting overall health and preventing AIDS and opportunistic infections.

Physical and Psychiatric Co-morbidity Prevention and Management

As stated, physical and psychiatric co-morbidities have been shown to increase cortisol levels which can produce cytokines and neuroinflammation, resulting in poorer cognitive reserve and thus cognitive functioning.^{3,63–65} For those with HIV experiencing common physical co-morbidities such as diabetes, hypertension, hypercholesterolemia, microbial translocation (i.e., leaky gut syndrome), heart disease, liver disease, and renal disease, this represents added stress on the body and thus the brain.^{47,66–68} In fact, there are several mechanisms in which each of these co-morbidities can create problems in brain function. For example, in a study of 145 adults with HIV, Valcour and colleagues observed that greater levels of cognitive impairment were associated with greater levels of insulin resistance (the hallmark of diabetes).⁴⁸ In fact, in 22 older adults (50+) with HIV, irregular glucose metabolism is associated with abnormal microstructural changes in the hippocampus and caudate nucleus, brain structures responsible for memory formation and consolidation.⁶⁹ Fortunately, some studies show that diabetes management can reverse or prevent such cognitive deficits.⁷⁰ This prevention and reversal of cognitive deficits through effective medical management has also been observed in other co-morbid conditions.^{71,72}

Likewise, psychiatric co-morbidities can negatively impact cognition through: 1) competing for cognitive resources through rumination (i.e., depressive or suicidal thoughts that prevent other thoughts from emerging),⁷³ 2) displaying different cognitive profile (e.g., executive dysfunction is common in schizophrenia), and 3) producing cytokines and neuroinflammation.⁶⁵ As with physical co-morbidities, some studies show that treating such psychiatric co-morbidities may help reverse or prevent some cognitive deficits from developing.^{65,74,75} For example, although hypertension can cause white matter lesions and result in poorer cognitive functioning, taking antihypertensive medications can prevent or even improve cognitive functioning in those with hypertension.⁷⁶

Furthermore, since HIV is considered an inflammation and neuroinflammation disease, proactively reducing such inflammation should be considered as a way to protect or improve cognition.⁷⁷ Becker and colleagues examined MRIs of 84 adults with HIV and 71 adults without HIV.⁷⁸ Compared to the HIV-negative sample, those with HIV had more cortical thinning, especially in the right and left putamen and caudate nucleus. Clearly, such thinning may be a result of such neuroinflammation. Therefore, in addition to treating both physical and psychiatric co-morbidities, addressing the underlying neuroinflammation caused by these co-morbidities, aging, and HIV represents a potential therapeutic approach.² One way to reduce such systemic inflammation as well as neuroinflammation may be to incorporate polyphenols and other antioxidants into the diet of those aging with HIV. For example, using HIV-Tat transgenic mice, Rrapo and colleagues found that by introducing green tea, a powerful polyphenol, into the diet of these mice actually reduced the death of glial cells (i.e., astrogliosis), cells that support neuronal functioning.⁷⁹ In fact, it has also been suggested that non-steroidal anti-inflammatory medicines such as ketorolac, aspirin, and ibuprofen may reduce inflammation and protect the brain by decreasing such neuroinflammation;^{80–82}

however, further research is recommended to determine the safety and efficacy of this approach in adults with HIV.

Cognitive Remediation Therapy

Cognitive remediation therapy refers to a variety of techniques that are designed to enhance existing cognitive functioning. Typically, the delivery mechanism for such therapies include computer programs via videogames, workshops and theatre groups, workbooks, and other modalities that exercise the mind.^{83,84} In a recent pre-post experimental study, Vance and colleagues randomized 46 middle-aged and older adults (40+ years) with HIV into two groups; one group played approximately 10 hours of a computerized game designed to improve their visual attention and speed of processing and the other group served as a no-contact control group.⁸⁵ Compared to the control group, those in the training group improved significantly on a cognitive measure of visual attention and speed of processing (i.e., Useful Field of View), which also translated into significant improvement in a measure of everyday functioning (i.e., Timed Instrumental Activities of Daily Living Test). These results are encouraging because this training is quite similar to another training program designed to improve visual speed of processing, which has been found to be related to lower depression and improve locus of control (i.e., sense of control over one's life) and health-related quality of life in normal community-dwelling older adults;^{86–89} obviously these are areas that must also be addressed in those aging with HIV.⁴⁷

Neurotropic Medications

Methylphenidate (Ritalin) and modafinil are neurotropic medications that have been shown to improve cognitive functioning in adults with HIV. Methylphenidate has been found to improve cognition in healthy adults and those with attention deficit hyperactivity disorder.⁹⁰ In a single-blind crossover study involving 16 adults with HIV, Hinkin and colleagues found that a daily dose of 30 mg of methylphenidate was effective in improving cognition.⁹¹ In fact, these researchers also found that those who displayed more depressive symptomatology and slower speed of processing improved the most. Other studies also show that methylphenidate is effective in reducing low density lipoprotein cholesterol, triglycerides, and total cholesterol as well as ameliorating the effects of fatigue.^{92,93} These added effects are particularly advantageous given that of those with HIV, 38% experience hypercholesterolemia and nearly 50% experience a range of depressive symptomatology.^{47,94}

Similar to methylphenidate, modafinil has also been shown to ameliorate the symptoms of fatigue as well as improve cognitive functioning in those with attention deficit hyperactivity disorder.⁹⁵ As such, this has also been used effectively in adults with HIV. In a sample of 103 adults with HIV, McElhiney and colleagues randomized participants into two groups, modafinil or placebo, and followed them over a 4-week period.⁹⁶ Those who were prescribed modafinil improved on global cognition and experienced fewer cognitive complaints compared to those who received the placebo. Although no large randomized clinical studies have been conducted on the effects of methylphenidate and modafinil on cognition in adults with HIV, these results are encouraging, especially since these are

medications that have been studied well in other populations and have been shown to be well tolerated and generally safe.⁹¹

Unfortunately, other neurotropic medications such as memantine and donepezil, which improve cognition in those with Alzheimer's disease, are not recommended at this time. Memantine has been shown to be tolerated well in adults with HIV; but improvement on cognitive functioning has not been found at this time.⁹⁷ Furthermore, based on a recent search in PubMed (April 4, 2013), there are no studies that have examined the use of donepezil in adults with HIV.

Future Consideration

Several novel approaches may be considered for preventing or rehabilitating cognitive deficits in adults aging with HIV. These include cognitive prescriptions, addressing microbial translocation, lithium, transcranial direct current stimulation, vagus nerve stimulation, and binaural beat therapy. Although innovative, these approaches require additional research before being used as a part of standard of care.

Cognitive prescriptions are individually written behavioral programs designed to improve several areas that support overall cognitive functioning.⁹⁸ This holistic approach targets behavioral improvements in sleep hygiene, physical exercise, intellectual activity, mood, social interaction, and nutrition; all of which have been shown to be related to positive neuroplasticity, cognitive reserve, and cognitive functioning.^{99–110} For example, in generating a behavioral goal for physical activity, the patient may enjoy swimming but has not done so for years; therefore the goal may be to “Go to the pool and swim 10 laps twice a week”; as a result, this may improve cardiovascular functioning and mood, both of which support brain health. In the area of nutrition, the behavioral goal may be to “Eat salmon once a week” given that this is a rich source of omega-3-fatty acid which is also linked to brain health. All of the behavioral goals are either: 1) geared to improve body health and thus brain health, or 2) facilitate positive neuroplasticity (i.e., intellectual activity, social interaction) and increase cognitive reserve. Practical implementation of this has not been tested yet; however, several intervention studies that have targeted individual areas have been shown to support cognitive functioning. For example, targeting nutritional needs in adult 50 to 70 years, Durga and colleagues conducted a 3-year randomized controlled study and found that those assigned to take folic acid supplementation experienced lower homocysteine levels and better cognitive functioning compared to those assigned to the control group.¹¹¹ Therefore, this holistic approach with cognitive prescriptions may provide even more cognitive support and assist with successful cognitive aging.

Addressing microbial translocation (i.e., leaky gut syndrome) is another novel area that needs to be addressed in those aging with HIV.^{112,113} The prevalence of cognitive deficits is present despite virologic suppression from cART suggesting independence of this decline from viral replication.^{114,115} Instead, cognitive deficits have been linked to inflammatory responses to microbial products (i.e., lipopolysaccharide) leaked into and circulating within the bloodstream.¹¹⁶ As a result of inflammatory cytokines and depletion of key immune cells in the gut associated lymph tissue, the effects of microbial translocation are increased

which amplify the immune response to these products and result in chronic inflammation.^{112,113,117} Even despite higher CD4 levels, the amplification of immune activation leads to early aging in people living with HIV and has been linked with HIV-associated dementia in which higher levels of microbial products were associated with higher levels of inflammatory immune response.¹¹³ Studies show that even in those with well controlled HIV, microbial translocation is common and may contribute to neuroinflammation. In a study with 97 adults with HIV, Lyons and colleagues found that soluble CD14 (an indicator of microbial translocation), was associated with poorer cognitive functioning; this could increase neuroinflammation.¹¹⁸ Studies have suggested that a healthy intestinal flora reduces microbial translocation, thereby subsequent immune activation evidenced by reduced levels of soluble CD14. One way to cultivate healthy intestinal flora is through regular consumption of yogurt and/or supplementation of over the counter probiotics at recommended doses. Therefore, in line with the cognitive prescription focus on nutrition, a dietary intervention with probiotic supplementation may produce cognitive benefits as well.¹¹⁹

Lithium has been used since the 1940s to treat mood disorders but recent evidence also suggests that lithium may be used to protect against decreases in cognitive reserve and improve cognitive functioning.¹²⁰ Lithium inhibits the glycogen synthase kinase-3 β enzyme and other enzymes that downstream reduce amyloid- β_{42} and tau protein phosphorylation, proteins associated with Mild Cognitive Impairment and Alzheimer's disease. Also, lithium has been found to stimulate the production of vascular endothelial growth factor and brain-derived neurotrophic factor. These particular factors protect against the neurotoxic effects of amyloid- β_{42} and promote hippocampal neurogenesis. Furthermore, lithium helps decrease oxidative stress and inflammation. For these reasons, this may be why neuroprotective effects are observed in adults with bipolar disorder who have been prescribed lithium for years. In fact, case registry studies indicate that such adults with bipolar disorder taking lithium long-term experience a lower incidence for dementia.^{18,121} Furthermore, structural imaging studies have found that both short-term and long-term lithium use are associated with increased cortical thickening as well as increased amygdala and hippocampal volume.¹²⁰

In a 12-month double-blind study of 45 adults with amnesic Mild Cognitive Impairment, Forlenza and colleagues found that those assigned to lithium had lower conversion rates to Alzheimer's disease compared to those assigned to a placebo.¹²² Based on these and other studies, subtherapeutic doses of lithium (0.2 – 0.4 mmol/L) may be used to protect cognitive reserve and cognitive functioning in normal adults¹²⁰ – and perhaps adults aging with HIV. Albeit, lithium use is not without risks (e.g., gastrointestinal disturbances, tremor, hypothyroidism, renal dysfunction) and can adversely interact with other medications (e.g., nonsteroidal anti-inflammatories, thiazide diuretics).¹²⁰ Yet, more research is needed to examine whether using lithium would be an effective neuroprotective agent in adults aging with HIV.

Transcranial direct current stimulation represents another novel area whereby low voltage current is applied to the scalp via electrodes. In doing so, this procedure produces changes in the cerebral cortex and influences cognition.^{123,124} For example, in a study involving 96

healthy adults, Clark and colleagues placed 10 cm² sponge electrodes directly over the right inferior frontal cortex above the sphenoid bone (an area referred to as F10) as participants played a virtual reality game whereby they received feedback as to where deadly objects (i.e., bombs) were concealed.¹²⁵ Electrical current was applied 5 minutes before playing the game and continued during the first 30 minutes of playing the game. These researchers found that those who received 2 milliamps compared to those who received 0.1 milliamps learned the game much better. Although it is not clear how this technology stimulates the brain or why different amperages produce varying effects, direct current stimulation has the potential to induce positive neuroplasticity. Unfortunately, no large randomized clinical trials have been conducted; however, smaller studies have shown that it can improve cognitive functioning in normal healthy adults as well as those with stroke and Parkinson's disease.¹²⁶ Thus, this technology may also be effective in those aging with HIV who suffer from cognitive deficits; albeit, studies must be conducted to examine its effectiveness in this clinical population.

The vagus cranial nerve is mixed in nature, capable of afferent (sensory) and efferent (motor) responses. Traditionally, this nerve has been associated with efferent parasympathetic responses in visceral organs, whereas vagus afferent fibers and their many projections in the forebrain and brain stem (thalamus, cerebellum, orbitofrontal cortex, limbic system, hypothalamus, and medulla) modulate cortical synchrony of electrical impulses, as well as cognition and memory-related functions.^{127–129} Neurostimulation of the vagus nerve can be achieved through implanted devices connected to electrodes near the left cervical branch of the vagus nerve, or transcutaneously at the level of the left auricular portion of the vagus nerve.¹³⁰ Indeed, vagus nerve stimulation by electric currents has been demonstrated to decrease the frequency and duration of seizures in epileptic individuals,^{131–134} being now an approved adjunct method of treatment of refractory epilepsies and depression. Incidentally, it was also noted that a significant portion of treated cohorts had improvements in cognition, particularly with respect to attention and memory recall.^{135–141} These observations lead to the establishment of several studies investigating the potential of vagus nerve stimulation as treatment for various mood and cognitive disorders, including anxiety, depression, and Alzheimer disease.¹⁴¹ To date, vagus nerve stimulation has proved effective in enhancing memory recall of conditioned behaviors in animal models.¹⁰⁰ Even though improved attention and memory recall have been described in some studies involving human participants,^{95, 97, 98} other studies suggested no cognitive improvements with vagus nerve stimulation.^{103–105} Still, the physiological associations of afferent fibers of the vagus nerve with various cognitive-related aspects of the brain, coupled with evidence suggesting that vagus nerve stimulation might increase cognitive reserve in humans, warrant further exploration of this therapy for persons experiencing chronic cognitive deficits, including older adults with HIV who often sustain cognitive deficits as an intrinsic aspect of their disease course.

Binaural beat therapy is designed to change brain waves in people to a more meditative state. It does this by separately presenting sounds with similar frequencies to each ear (e.g., 345 hertz to the left ear, 355 hertz to the right ear). The brain registers these differences and processes them through the superior olivary nucleus and the reticular activating system which stimulates the cerebral cortex and the thalamus which then produces theta waves.¹⁴²

Theta waves, which correspond to being in a relaxed meditative state, have been shown to facilitate executive functioning, promote reasoning, and help reduce anxiety.¹⁴³ For example, in a group of 15 people with anxiety, LaScouarnec and colleagues gave these participants music tapes with binaural beats embedded in the background sounds.¹⁴⁴ Participants were instructed to listen to the tapes five times a week for a month. These researchers found that anxiety was reduced after a month. Others studies have found similar effects of binaural beats on anxiety.¹⁴⁵ Given the high levels of anxiety and mood problems experienced by many with HIV, and given that such mood problems can interfere with cognitive functioning, binaural beat technology represents a potential solution for augmenting cognition in those aging with HIV.

Conclusion

As the graying of the HIV epidemic continues, healthcare providers will struggle with ways to improve the quality of life of their patients as they age. To facilitate such successful aging, Rowe and Kahn suggested that three things are needed: 1) prevention of disease and/or disability, 2) meaningful social engagement, and 3) maximization of physical and cognitive functioning.¹⁴⁶ Clearly, as adults age with HIV, they are vulnerable to developing other co-morbidities such as heart disease and diabetes which can be debilitating,⁴⁷ may encounter HIV-related stigma that can result in fragile and unsupportive social networks,⁵¹ and may experience cognitive deficits. As presented in this article, such cognitive deficits can negatively impact the other two areas needed for successful aging. Poor cognitive functioning can lead to poor medication adherence which can result in even more disease and disability. Reduced cognitive functioning can also lead to poor driving and perhaps reduced driving which in turn may result in less social contact.¹⁴⁷ Therefore, addressing the cognitive consequences of aging with HIV cannot be underscored enough given that it is so important for other components of life and successful aging. Unfortunately, sometimes other health concerns seem to take priority over addressing cognitive health, at least until one's cognitive abilities begin to deteriorate. Thus, it is important to proactively address cognitive health as well as physical health in routine clinic visits. This point is important because cognitive deficits may be avoided or mitigated.

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Figure 1.

Neuron-Avenue Analogy of Cognitive Reserve. Left panel demonstrates healthy cognitive reserve. Right panel demonstrates a depleted cognitive reserve.