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Aging with HIV-1 Infection: Motor Functions, Cognition, and Attention – A Comparison with Parkinson’s Disease

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Abstract

Recent advances in highly active anti-retroviral therapy (HAART) in their various combinations have dramatically increased the life expectancies of HIV-infected persons. People diagnosed with HIV are living beyond the age of 50 but are experiencing the cumulative effects of HIV infection and aging on brain function. In HIV-infected aging individuals, the potential synergy between immunosenescence and HIV viral loads increases susceptibility to HIV-related brain injury and functional brain network degradation similar to that seen in Parkinson’s disease (PD), the second most common neurodegenerative disorder in the aging population. Although there are clear diagnostic differences in the primary pathology of both diseases, i.e., death of dopamine-generating cells in the substantia nigra in PD and neuroinflammation in HIV, neurotoxicity to dopaminergic terminals in the basal ganglia (BG) has been implied in the pathogenesis of HIV and neuroinflammation in the pathogenesis of PD. Similar to PD, HIV infection affects structures of the BG, which are part of interconnected circuits including mesocorticolimbic pathways linking brainstem nuclei to BG and cortices subserving attention, cognitive control, and motor functions. The present review discusses the combined effects of aging and neuroinflammation in HIV individuals on cognition and motor function in comparison with age-related neurodegenerative processes in PD. Despite the many challenges, some HIV patients manage to age successfully, most likely by redistribution of neural network resources to enhance function, as occurs in healthy elderly; such compensation could be curtailed by emerging PD.

Keywords

HIV infection; Aging; Functional brain network degradation; Parkinson’s disease (PD); Basal ganglia (BG); Cognition; Motor functions

Since the discovery of the Human Immunodeficiency Virus (HIV) in the 1980s and its common sequelae with infection, the progression to Acquired Immune Deficiency Syndrome (AIDS), characterized by a CD4+ T cell count below 200 per mm³, a vast amount of knowledge of the virus has been accrued with major implications for the management of the disease. Today, HIV is no longer a terminal illness due to the introduction of highly active antiretroviral therapy (HAART), which has allowed individuals with HIV to regain near average life expectancy (Crum et al. 2006; Di Carlo et al. 2014; Hunt 2014; van Sighem et al. 2010). It is projected that by 2015, more than 50 % of individuals infected with HIV will have reached the age of 50 (Greene et al. 2013). In May 2015, the National Institute of Allergy and Infectious Diseases (NIAID) released new evidence from the Strategic Timing of AntiRetroviral Treatment (START) study emphasizing the beneficial effects of early HAART treatment to all HIV-infected individuals irrespective of CD4+ T-cell count (www.nih.gov/news/health/may2015/niaid-27.htm). With HAART, the replication of the virus is suppressed, allowing the immune system to function longer, but despite these advancements in the treatment and management of the disease, HIV-infected individuals are at high risk for cognitive impairment (Heaton et al. 2010; Chow 2014) and motor disturbance (Bhidayariri and Tarsy 2012; Mirsattari et al. 1998; Tse et al. 2004).

As a normal consequence of aging and as a risk factor with HAART therapy (Antinori et al. 2007), hypertension, diabetes, and vascular disease are comorbidities in older HIV-infected patients (Arruda et al. 2010; Mateen et al. 2013), potentially affecting brain structure and function (Becker and Snitz 2013). With the increase in life expectancy, neurodegenerative diseases are becoming more common in the HIV population as advancing age itself is a risk factor associated with functional decline, disability, and disease (Farooqui and Farooqui 2009).

Despite improved immune status with effective HAART by increasing CD4+ T-cells and decreasing plasma viral loads, HIV-associated neurocognitive disorders (HAND), particularly mild forms, occur in upwards of 50 % of treated HIV-infected patients (Dore et al. 2003; Heaton et al. 2010, 2015; Nightingale et al. 2014). Although less common, motor disorders, mainly Parkinsonian symptoms, occur in about 5 % of HIV-infected patients (Bhidayariri and Tarsy 2012). In the pre-ART era (1984–1999), motor disorders were more commonly observed in up to 5–10 % of HIV-infected individuals (Arendt et al. 1990; Mirsattari et al. 1998; Itoh et al. 2000), and extrapyramidal signs were criteria for the diagnosis of minor cognitive motor disorder (MCMD) and HIV-associated dementia (HAD) (American Academy of Neurology AIDS Task Force 1991; see also Brew and Perdice 1992; Cysique et al. 2006; Antinori et al. 2007; Valcour et al. 2008). With the advent of HAART, motor symptoms became less common (Heaton et al. 2011). In the now aging HIV population on HAART, an increased incidence of extrapyramidal motor signs or Parkinsonian symptoms was noted (Hettige et al. 2009; Tisch and Brew 2009, 2010; Valcour et al. 2008) and regarded as the combined effects from aging and HIV/AIDS on neurofunctional compromise. This is critical, considering that older age itself is associated with immune senescence, an age-associated dysregulation and dysfunction of the immune system (Mekker et al. 2012) that may add to HIV/AIDS-related vulnerability in organs and the brain.

The occurrence of Parkinsonian symptoms, or even Parkinson's disease (PD) (Gaig and Tolosa 2009), in aging HIV-infected individuals may be considered coincidental (Hettige et al. 2009; Moulignier et al. 2015) or based on a pathogenetic link (Tisch and Brew 2009, 2010). As the HIV-infected population treated with HAART is now aging, HIV-Parkinsonism may become more frequent (Valcour et al. 2008).

A few clinical case studies have linked the initiation and time on HAART in HIV-1 infected individuals who already exhibit extrapyramidal motor signs with changes to symptoms and the course of PD (Hettige et al. 2009; Gago et al. 2011; Kobylecki et al. 2009; Poletti et al. 2009; Tisch and Brew 2009, 2010). After the initiation of HAART, a reversal of HIV patients' Parkinsonism was observed and associated with normalization of CD4+ T-cell counts (Hersh et al. 2001; Shimohata et al. 2006; Cheng et al. 2014); yet, Parkinsonian symptoms and dementia then still progressed over the course of HAART (Shimohata et al. 2006). It has been speculated that over time HAART exacerbates the aging process related to oxidative stress, telomere shortening (Torres and Lewis 2014), and mitochondrial dysfunction (Chiappini et al. 2004; Tisch and Brew 2010; Torres and Lewis 2014). At the cellular level, the enzyme mixed lineage kinase type 3 (MLK3), indicative of metabolic stress, is highly activated in HIV-infected individuals with cognitive deficits (Gelbard et al. 2010), which has also been observed in other degenerative diseases such as Alzheimer's Disease (Johnson and Bailey 2003) and PD (Harper and Wilkie 2003). In summary, these studies provide some initial insight toward a possible link between HIV disease, HAART, aging, and PD symptoms (Smith et al. 2013). The view is that an earlier start of HAART in the course of the disease can ameliorate symptoms from viral burden and prevent mortality, but it may also increase the risk for long-term detrimental effects on the brain that are similar to those seen in neurodegenerative diseases.

Cognitive Reserve in Aging and HIV Infection

As individuals with HIV achieve longer life expectancy, the interaction between HIV and the effects of normal aging poses concerns in managing disability especially in the public health domain (Cohen et al. 2015). It is well known that there is a general loss of cortical volume associated with normal aging (Raz et al. 2010) and that aging itself can be considered as an independent risk factor for HIV-associated dementia (McArthur and Brew 2010). However, older adults may benefit from "cognitive reserve," an efficient utilization of brain networks or a helpful mechanism to recruit alternate brain networks (Stern 2002) that serves as a buffer against the age-related functional decline (Satz et al. 2011). The observation that in some older adults cognitive performance is better than expected despite changes in brain morphology implies a neural substrate such as the efficiency of neural networks that can protect against the functional consequences of neuropathology (Richards and Deary 2005). In healthy aging, the ability to compensate for functional decline has been associated with recruitment of additional brain regions that are not activated in younger adults performing the same task (Cabeza et al. 2002; Martins et al. 2015; Stern et al. 2005). Only few studies examined behavioral factors that might be related to cognitive reserve in the HIV population in general, and specifically in HIV-associated neurocognitive disorder (HAND).

In the pre-HAART era, Satz et al. (1993) suggested that lower cognitive reserve capacity might be a risk factor for neuropsychological abnormalities in early HIV, based on their findings from a large epidemiological study during the years 1984 and 1985 showing a 38 % prevalence of cognitive abnormality in 888 seropositive (in contrast to 17 % in 885 seronegative subjects) that was strongly associated with lower education levels. Morgan et al. (2012) also demonstrated that severity of cognitive symptoms in HIV was related to lower cognitive reserve with cognitive reserve consisting of multiple factors such as verbal IQ, years of education, and highest occupation (for a review on cognitive reserve in PD see Hindle et al. 2014). In addition, older HIV patients with normal cognition showed a task demand-dependent increase in the activation from posterior to anterior attention network regions, whereas those with HAND exhibited a reduced capacity to recruit such alternative networks (Chang et al. 2013). Thus, as the HIV population is aging and consequently needing to manage chronic disability, understanding cognitive reserve (Richards and Deary 2005; Stern et al. 2005), and compensatory neurofunctional mechanisms (Chang et al. 2013) will be of high importance in managing the deficits associated with the negative sequelae of HIV.

Aging, HIV, and Risk for Neurodegenerative Disease

Yet, it is unclear how common neurodegenerative disorders manifest in the aging HIV population. Recent studies suggest that exposure to the HIV virus may indeed increase the risk for developing neurodegenerative diseases (Bhaskaran et al. 2008; Cohen et al. 2015; Sheppard et al. 2015). Genes associated with increased risk of developing cognitive deficits for older adults may account for more severe cognitive deficits in this population (De Chiara et al. 2012). For example, the presence of the apolipoprotein E4 allele (ApoE4) is considered a risk factor in the development of dementia among all ethnic groups irrespective of gender (Farrer et al. 1997; Sadigh-Eteghad et al. 2012); but it is unclear whether HIV-individuals with the same gene are at a greater risk for neurodegeneration than carriers without HIV (Burt et al. 2008; Morgan et al. 2013). When taking age into consideration, the Hawaii Aging with HIV cohort study found that older HIV-1 infected individuals with an apoE4 genotype are at greater risk of developing dementia in comparison to younger individuals with HIV (Valcour et al. 2004; Kuhlmann et al. 2010). In addition, a recent neuroimaging study measuring white matter fiber tract integrity in older HIV-seropositive patients (60–80 years old) found greater network structure deficits in ApoE4 genotype carriers than non-carriers, and specifically in those with longer illness duration (Jahanshad et al. 2012). Further, individuals with HIV and the ApoE gene demonstrated greater cognitive deficits in tests measuring executive function, attention, and working memory than HIV-infected individuals lacking the ApoE gene (Chang et al. 2014).

The potential synergy between immunosenescence and HIV viral loads increases susceptibility to HIV-related brain injury (Jahanshad et al. 2012; Pfefferbaum et al. 2009, 2012, 2014; Schulte et al. 2008; Schulte et al. 2012), functional brain network degradation (Thomas et al. 2013), and alteration in the nigrostriatal dopaminergic system (Koutsilieri et al. 2002; Kumar et al. 2009, 2011) similar to that seen in PD, the second most common neurodegenerative disorder in the aging population (de Lau and Breteler 2006). As in HIV-associated dementia, a major independent risk factor to develop PD is age (Collier et al.

2011), and approximately two-thirds of cases have an onset of the disease in their 50s (Hoehn and Yahr 1998).

Dopamine-rich brain regions, particularly the basal ganglia, are highly vulnerable to HIV-related neuropathological processes (Navia et al. 1986; Aylward et al. 1993) with 25% neuronal loss in the substantia nigra in AIDS (Berger and Arendt 2000). HIV neurotoxic proteins Tat and gp120 can lead to apoptosis of striatal neurons (Jones et al. 1998; see also Berger and Nath 1997; Hayman et al. 1993) and were detected in the basal ganglia of patients with HIV encephalitis (Hofman et al. 1994; Kruman et al. 1999; Nath et al. 2000). Compared to healthy subjects, dopamine levels in the cerebrovascular fluid in HIV-1 individuals were reported to be on average 60 % less in those without neurological disease and 80 % less in those with evidence of neurological disease (Berger et al. 1994). Postmortem examination of HIV patients on HAART revealed a significant decrease in dopamine in the caudate nucleus, putamen, globus pallidus, and substantia nigra, with similar structures affected by PD (Kumar et al. 2009). In PD, degeneration of dopaminergic cells in the pars compacta of the substantia nigra results in disruption of basal ganglia-thalamocortical connections (Damier et al. 1999), similar circuits to those compromised in individuals with HIV (Granziera et al. 2013). Another postmortem study of HIV-infected brains indicated increased α -synuclein expression in the substantia nigra (SN) (Khanlou et al. 2009), a protein that, if accumulated, is hypothesized to play a role in the apoptosis of dopaminergic cells in the SN (Xu et al. 2002; see also Louboutin et al. 2009). This has advanced the idea that aging HIV-infected individuals may be at risk to develop neurodegenerative disease such as PD (Brew et al. 2009).

Since the partially overlapping pathogenetic mechanisms of HIV (Berger and Arendt 2000) and PD (Hirsch and Hunot 2009) affect nigrostriatal structures with resulting dopaminergic dysfunction, neurodegenerative processes in the aging HIV brain may involve the same basal ganglia-thalamocortical networks. Taken together, these findings point to a possible pathogenic link between HIV infection and PD. Likewise, similarities in cognitive deficits and motor functioning exist between PD (Muslimovi et al. 2005) and HIV patients (Brew 2004; Castellon et al. 2000; Woods et al. 2009).

Neural Mechanisms of Functional Compromise in HIV Infection and PD

Although there are clear diagnostic differences in the primary pathology of both diseases, e.g., death of dopamine-generating cells in the substantia nigra in PD and neuroinflammation in HIV, neurotoxicity to dopaminergic terminals in the basal ganglia (BG) has been implied in the pathogenesis of HIV (Wang et al. 2004) and neuroinflammation to play a role in the pathogenesis and course of PD (Chung et al. 2010; Collins et al. 2012; Mosley et al. 2012). Similar to PD, HIV infection affects structures of the BG (Woods et al. 2009), which are part of interconnected circuits including mesocorticolimbic pathways linking brainstem nuclei to the BG and cortices. Connected via the thalamus, the BG are linked to the various cortical circuits (McFarland and Haber 2002; Haber and Calzavara 2009), with several projections to frontal areas of the brain. This complex system of interaction between the BG, thalamus, and frontal cortical areas is displayed in Fig. 1.

The BG are part of diverse cortico-subcortical loops that subserve attention, emotion, cognitive processes, and motor functions (Alexander et al. 1986; Parent and Hazrati 1995; Tommasi et al. 2015). A complex system of pathways of BG and thalamus plays a role in the facilitation of movement and the execution of purposeful behavior, although the exact mechanisms remain poorly understood (Yin and Knowlton 2006). Rather than directly initiating motor movement, the BG play a role in selectively gating certain motor plans to the motor cortex while simultaneously inhibiting competing plans and updating task rule-relevant representations in the prefrontal cortex (Mink 1996). As the BG are associated with learning motor sequences, specifically, during initial learning stages, the dorsal putamen, rostral striatal areas, the anterodorsal globus pallidus, and the nuclei of the thalamus, which constitute the associated areas of the BG circuit, are active (Lehéricy et al. 2005). Once the sequence of motor movements becomes habitual, activity in sensorimotor areas of the caudoventral regions of the putamen increases. With its rich connection to other cortical areas, particularly the frontal cortex, the disruption in the functional network integrity in HIV-infected individuals and PD can result in cognitive deficits spanning emotional changes, attention, executive dysfunction, and memory problems (Watkins and Treisman 2015).

It remains to be learned whether subcortico-cortical structural and functional neural circuits in older HIV patients are distinct from those seen in normal aging, yet parallel to those seen in PD (Wang et al. 2004). Dopaminergic dysfunction (Lee et al. 2009) and loss of midbrain dopaminergic projections to the BG (Beste et al. 2010), in turn, affect motor functions and cognition via interconnected striatocortical and corticostriatal networks (Albin et al. 1989; Betchen and Kaplitt 2003; Damier et al. 1999). Because HIV, like PD, affects striatal structures (caudate nucleus, putamen), neurodegenerative processes in the aging HIV brain may be related to the same striatal-thalamo-cortical networks and dopaminergic abnormalities as in PD (Ipser et al. 2015). Thus, neuronal degradation in dopaminergic midbrain structures and the BG have the potential to impede effective communication between subcortico-cortical network nodes, with consequences for attention, emotion, cognition, and motor control (Fig. 2).

We will next review the combined effects of aging and HIV-infection on cognition and motor function and compare these with PD and healthy aging.

Motor Deficits in HIV Infection and PD

HIV-infected individuals exhibit deficits in motor functioning, particularly on tasks requiring fine motor movement (Wilson et al. 2013), gait (Robertson et al. 2006), and postural stability (Bernard et al. 2013; Sullivan et al. 2011). Impaired motor functioning in HIV-infected individuals was a prominent symptom before the introduction of HAART and comprised a unique diagnostic category before the revision of neurocognitive disorders criteria in 2007 (Antinori et al. 2007). Although the prevalence of motor deficits has not been sufficiently examined in the era of HAART, Valcour et al. (2008) quantified motor deficits in HIV-infected individuals on HAART using the Unified Parkinson's Disease Rating Scale (UPDRS). Compared to a seronegative control group, HIV-infected individuals exhibited signs of bradykinesia, hypomimia, action or postural tremor, and poor hand agility and further results indicated that age and HIV status exacerbate these motor deficits. Of the HIV

participants in the Richert et al. (2014) study, 12 % reported falls at the two-year follow-up assessment, and these falls were associated with poorer performance on the 5-sit-to-stand test (Csuka and McCarty 1985). Extrapyramidal signs are less likely to occur in patients on HAART treatment (Woods et al. 2009); however, individuals with HIV, in general, are more likely to develop motor abnormalities as they age. In a study by von Giesen et al. (2000), it was found that in the initial stages of HIV, minor motor movement remains intact and hypermetabolism is present as evidenced by performance on attention challenging tasks. However, hypometabolism of the BG was found through fMRI scans of older adults with advanced stages of HIV. Hypometabolism was associated with motor slowing and poor performance on a range of fine-finger movement tasks. Recently, Bernard et al. (2013) used diffusion tensor imaging (DTI) and the 5-sit-to-stand test to assess HIV-infected individuals' motor functioning at a central and peripheral level. Nearly half (40 out of 86) of the participants produced 5-sit-to-stand test scores that were more than 2 standard deviations below normative scores, indicating motor impairment and greater risk for falls. In addition, the HIV patients with motor impairments had lower fractional anisotropy in cortico-motor tracts, as well as low axial diffusivity in the left cortico-spinal tract suggesting microstructural white matter fiber compromise as an underlying correlate for motor deficits. Thorough assessment of motor functioning holds importance due to its implications on the safety of HIV infected individuals, especially with regard to falls and driving ability (Marcotte et al. 1999).

Parkinsonian symptoms in HIV typically have a bilateral onset, more rapid progression, abnormal eye movements, and no resting tremor (Bhidayariri and Tarsy 2012). In PD, typical symptoms are mental slowing (Cooper et al. 1991, 1994; Jokinen et al. 2013) and motor deficits; resting tremor that usually emerges unilaterally before affecting other limbs, bradykinesia, rigidity, and loss of posture are common features (Jankovic 2008). A recent fMRI study examining BG functional networks in PD found decreased connectivity to several brain regions including supplementary motor area and dorsolateral prefrontal cortex (DLPFC) (Wu et al. 2012). Not only is the execution of voluntary movement compromised, PD patients have difficulty in perception particularly with proprioception, which is necessary for correct execution of movement (Konczak et al. 2009). Moreover, PD patients have great difficulty in the initiation and inhibition of motor movements. In an fMRI study using the stop-signal task, PD had lower inferior frontal gyrus activity during the inhibition of motor movements than controls (Vriend et al. 2015). Treatment with Levodopa (L-Dopa) restores the loss of dopamine and improves difficulties in motor functions, and certain cognitive functions such as working memory (Lewis et al. 2005). However, the benefits of L-Dopa wear off over time and motor symptoms reemerge (Pahwa and Lyons 2009). A recent longitudinal study comparing 15 PD patients with HIV-1 infection to 30 PD without HIV over a 12-year period (2002–2013) found that clinical characteristics and treatment of PD symptoms did not differ between patients with and without HIV-1; in addition, HIV-PD patients showed good responses to dopamine replacement therapy that was well tolerated in combination with HAART (Moullignier et al. 2015). A comparison between older HIV-infected individuals and patients with PD might identify structural and functional connectivity patterns that can serve as potential biomarkers for incipient PD in HIV-infected individuals (Schulte et al. 2013).

To summarize, HIV-infected individuals and PD patients share similarities in that both patient groups display motor, cognitive, and functional brain network deficits characteristic of subcortical dementias (Ances et al. 2012), wherein deficits in attention, executive functions, and abnormalities in motor control functions are the predominant features (Salmon and Filoteo 2007; Turner et al. 2002).

The rise in life expectancy for individuals with HIV in the older adult years has allowed for an examination on the effect of aging processes on the HIV-infected brain. Likewise, an understanding of the similarities and differences may inform unique cognitive, biological, and neurological profiles of HIV-related disorders and neurodegenerative disorders and would allow for the development of specific interventions in terms of neurorehabilitation and management of disability. Next, cognitive profiles of PD patients and HIV-individuals are reviewed to determine similarities and unique aspects of each population with implications that could lead to better optimizing diagnostics. Neurological characteristics of each disorder may shed more light on mechanisms in cognitive assets and deficits. However, this necessitates a discussion on the challenges in the determination of cognitive deficits in HIV-infected individuals and PD patients.

Cognitive Deficits in HIV Infection and PD

Cognitive deficits are common among HIV-infected individuals and patients with PD irrespective of age, education, and other factors affecting performance on cognitive tests (Aarsland et al. 2003a; Harezlak et al. 2011). Deficits in cognitive domains are similar among HIV-infected individuals and PD, most notably in tasks measuring attention and executive functions. Both groups demonstrate difficulties on tasks measuring visuospatial functioning (Olesen et al. 2007; Galtier et al. 2014), which is a predominant sign in Parkinson's disease, yet not of HIV/AIDS-associated cognitive impairment (Maruff et al. 1994). Similarly, memory deficits are a prominent feature in the cognitive profile of individuals with HIV, especially deficits in episodic memory and prospective memory (Woods et al. 2009), and are also present among Parkinson's patients although less pronounced (Pahwa et al. 1998).

A number of challenges arise when determining the presence and extent of cognitive deficits in HIV-infected individuals (Antinori et al. 2007; Watkins and Treisman 2015) and PD (Geurtsen et al. 2014; Hobson and Meara 2015; Litvan et al. 2012). Cognitive deficits in individuals with HIV are commonly referred to as HIV-associated neurocognitive disorders (HAND) with estimates in prevalence varying from approximately 26% (Robertson et al. 2007) to 48% (Harezlak et al. 2011). The introduction of HAART has not only resulted in a higher life expectancy for HIV-infected individuals, but also changed the rates for severe forms of AIDS-related dementia. The prevalence of dementia due to AIDS significantly decreased in the past two decades, although a greater number of individuals experience milder neurocognitive deficits (Woods et al. 2009). Additionally, there has been a shift pertaining to types of cognitive domains that appear to be impaired (Heaton et al. 2011). In the pre-HAART era, HIV-infected individuals were more likely to demonstrate impairment in motor skills, processing speed, and verbal fluency, whereas patients receiving HAART are more likely to exhibit difficulties with memory and executive functioning (Heaton et al.

2011). These quantitative and qualitative changes were taken into account when the criteria for diagnostic classification were revised (Antinori et al. 2007). Also known as the “Frascati” criteria, the new classification system aims to identify at risk individuals by differentiating between milder forms of neurocognitive impairment with moderate to severe forms, hence it is a more refined classification system. Although those with asymptomatic impairment (ANI) and mild neurocognitive impairment (MNCI) demonstrate mild deficits on neuropsychological tests, only for the latter group do these impairments interfere with everyday functioning. HIV-infected individuals demonstrating moderate impairment on neuropsychological tests with major functional impairment in everyday life are classified as having HIV-associated dementia (HAD). In general, low CD4+ T-cell count is a predictor of neurocognitive impairment for HIV-infected individuals on HAART (Ellis et al. 2011). However, those showing severe neurocognitive impairment early in the course of the disease often experience significant impacts on daily living functioning, everyday cognitive complaints, employment status, and clinician-rated performance independent of HIV severity, i.e., functional impairment was unrelated to markers of HIV status such as CD4+ T-cell count, an indicator of immune functioning (Doyle et al. 2013). A recent cross-sectional study estimated the prevalence of ANI to be 33 %, 12 % for MNCI, and only 2 % for HAD (Heaton et al. 2010), reflecting the shift in the distribution of types of cognitive deficits (Heaton et al. 2011).

A number of screening instruments for the detection of cognitive impairment in HIV-infected individuals are available, although with limitations. For example, although the HIV Dementia Scale (HDS) and its international version were specifically developed to assess cognitive deficits associated with subcortical abnormalities in HIV, sensitivity and specificity are drastically reduced for milder forms of cognitive deficits compared to HAD (Haddow et al. 2013). Therefore, screening utility of these instruments may not generalize to the current presentation of cognitive deficits in the HIV population where milder forms are more common. According to Koski et al. (2011), the Montreal Cognitive Assessment (MoCA) screening instrument may be a useful tool for detecting milder forms of HAND, rather than simply detecting HAD. Further, it has been observed that over time, great fluctuation of cognitive deficits exists within the same individuals, particularly for those with milder deficits (Antinori et al. 2007), adding to the challenge of classifying these deficits. Such forms of “cognitive dispersion,” i.e., when individuals demonstrate great variability in performance on neuropsychological tests, is a challenge to the classification of HAND as HIV-infected individuals can experience impairment in everyday functioning, but show cognitive performance within the normal age range on tests (Morgan et al. 2012). In conclusion, classifying cognitive deficits in HIV-infected individuals remains a challenge.

Although motor symptoms are considered a distinctive characteristic of PD, cognitive deficits among Parkinson’s patients are common (Dubois and Pillon 1997; Gasca-Salas et al. 2014). Cognitive deficits, particularly those involving attention, mental flexibility, conflict resolution, and executive functions (e.g., planning, initiation and monitoring of actions) (Aarsland et al. 2003b; Caballol et al. 2007; Dubois and Pillon 1997; Muslimovi et al. 2005), are frequently observed, even at the early stage of the disease (Aarsland et al. 2010) and before treatment commences (Cooper et al. 1992). Using metabolic positron emission tomography (PET), Spetsieris et al. (2015) found reductions in the metabolic resting-state

networks in PD that were parallel with the development of mild cognitive impairment in PD and in part reversible with dopamine treatment. Cognitive deficits are common even in patients without formal diagnosis of dementia (Kim et al. 2009; McKinlay et al. 2010). The prevalence of mild cognitive impairment (MCI) in patients with Parkinson's disease was estimated to be 25.8 % (Aarsland et al. 2010) and efforts have been made to develop uniform diagnostic criteria for MCI specific to PD to reduce methodological variability in research (Litvan et al. 2012). According to these criteria, PD-MCI must involve either global functioning or impairment in at least two cognitive domains as evidenced by performance of 1 to 2 standard deviations below the normative population. For MCI, these cognitive deficits cannot interfere with daily functioning.

However, prevalence rates between studies vary widely, possibly due to the heterogeneity of disease presentation and its aspects, such as medications or severity (Lewis et al. 2003) and also because of methodological differences (Aarsland et al. 2005), posing a major challenge for research on cognitive deficits in PD similar to research examining those deficits in the HIV population.

Attention Deficits in HIV Infection and PD

Attention deficits observed among HIV-infected individuals have been found to increase with the severity of the disease, and are more prominent when individuals with HAND have CD4+ T-cell counts below 200 (Reger et al., 2002). Impairments are also more likely when HIV-infected individuals attempt attentional tasks that are complex (Chang et al. 2013). Especially, HIV-infected individuals may have more difficulties with tasks that require orienting, divided attention, and response inhibition (Martin et al. 1995; Hinkin et al. 1999, 2000).

Previous research has produced inconsistent findings on the presence of attentional deficits with PD. Kingstone and colleagues (2002) proposed that past studies did not discriminate between different types of attention, specifically overt and covert attention. Overt attention is observable to others, as it requires rapid eye movement, referred to as "saccades," through which an individual extracts information from his or her environment; alternatively, covert attention is not outwardly observable, as it takes place without saccadic eye movement. With overt orienting, attention deficits in PD patients may be indistinguishable from the motor movements that are involved, highlighting the importance of measuring different types of attention. Furthermore, PD patients may benefit from external visual cues when experiencing difficulties on tasks that require attention. For example, many PD patients experience micrographia, meaning their handwriting becomes smaller in size as they write at length. Healthy people usually do not have to attend to whether their handwriting is large enough to be legible, but this automatic process is often impaired with PD patients (Oliveira et al. 1997) and external cues that guide attention to the size of one's handwriting may help to overcome such difficulties in daily life.

Executive Function Deficits in HIV Infection and PD

Executive functions constitute a range of abilities such as problem solving, emotion regulation, and attention, and can therefore be considered as a form of metacognition (Groome and Baker 2005). Recent studies found that HIV-infected individuals exhibited deficits in executive functions similar to those in PD, and also had problems with response inhibition that was accompanied by reduced brain activity in the striatal, prefrontal, parietal, and cingulate areas (Chang et al. 2001, 2002; du Plessis et al. 2015). Previous research has shown that HIV-infected individuals had more difficulties with inhibitory processes in comparison to controls, as evidenced by performance on a Stroop task (Hinkin et al. 1999). HIV-infected individuals made more errors and had increased reaction times on trials that presented incongruent stimuli (Hinkin et al. 1999). They may also experience declines in their levels of ability related to planning and adherence to rules, as measured by their performance on a Tower of London test (Cattie et al. 2012), as well as abstraction and problem solving, as assessed by the Halstead Category Test and Wisconsin Card Sorting Test (Grant et al. 1987; Heaton et al. 1995). Performance deficits likely have neurofunctional correlates.

A functional magnetic resonance imaging (fMRI) study by Melrose et al. (2008) found that HIV-infected individuals performed worse in semantic event sequencing than controls, showed decreased activation in the left DLPFC, bilateral ventral prefrontal cortex, and the left caudate, and exhibited less frontostriatal functional connectivity. Although the severity of executive functioning deficits may vary across PD patients, even PD patients without dementia show declines in this cognitive domain (McKinlay et al. 2010). Findings indicate that PD patients without dementia exhibit difficulty with set-switching, as measured by the fluency task, planning and organization, as measured by the CLOX-I test (Royall et al. 1998), and inhibition, as measured by the Stroop test (McKinlay et al. 2010). An fMRI study with PD patients tested twice, during a relatively hypodopaminergic state and during a dopamine-replete state, indicated dopamine modulation of functional activity via two distinct mechanisms: nigrostriatal pathways facilitating motor function indirectly via thalamic connectivity to motor cortices, and the mesocortical pathways facilitating cognitive function via direct inputs to prefrontal cortex (Mattay et al. 2002). These two pathways appear to interact in a complex manner in order to accomplish tasks requiring executive performance. A study analyzing the activation of brain regions including nigrostriatal pathways and mesocortical pathways using a modified version of the Wisconsin-Card Sorting Task indicated different activation patterns depending on whether patients with PD off L-Dopa were required to “set shift,” i.e., demonstrate cognitive flexibility (Monchi et al. 2007), a condition in which young healthy adults engage the caudate nucleus (Monchi et al. 2004, 2006). Here, reduced involvement of the nigrostriatal pathway was apparent in PD with reduced dorso- and ventrolateral prefrontal cortical activation likely via striatal dopamine depletion that decreases cortical activity, i.e., through increased inhibitory output of the basal ganglia to the thalamus (Albin et al. 1989). Conversely, when the task required retrieval without shift, mesocortical pathway recruitment presented with increased activation in prefrontal, frontopolar, and premotor cortex in PD. Furthermore, patients demonstrated

greater activation in occipital and parietal areas of the brain compared to a healthy control group possibly indicating compensatory efforts (Monchi et al. 2007).

The Role of Compensatory Mechanisms

Despite the many challenges, some HIV-infected individuals manage to age successfully (Langford et al. 2011; Malaspina et al. 2011; Moore et al. 2013), most likely by redistribution of neural network resources to enhance function, as occurs in healthy elderly (Hakun et al. 2015; Schulte et al. 2011). The ability to compensate for loss of function by recruiting alternative networks in the brain of some HIV-infected individuals may be crucial in managing the effect of a deficient immune system and may also have implications for successful aging for the general population. Likewise, patients with PD, particularly those with later onset, with an average life expectancy of 20 years after diagnosis (Ishihara et al. 2007) will therefore need to manage emerging cognitive deficits in daily living.

In the initial stages of HIV, attention deficits are typically rare; however, as the virus progresses, impairments mild-to-moderate in severity may arise (Brew 2004; Woods et al. 2009). In principle, brain networks have the potential to enhance function with redistribution of resources (Schulte et al. 2011), but this likely comes at the expense of usurping functional reserve. Indeed, while HIV-infected individuals were able to maintain accurate performance on simple tasks, they required more time to perform (Chang et al. 2001). An fMRI study demonstrated this greater use of neuronal reserve by HIV-infected individuals utilizing higher blood-oxygen-level dependant (BOLD) signals compared to a control group while performing the same tasks with similar accuracy levels (Chang et al. 2001; for similar results with high-density magnetoencephalography (MEG), see Wilson et al. 2015). However, neuronal reserve may be depleted as tasks increase in complexity in which HIV-infected individuals make more errors (Chang et al. 2013). The asymptomatic (Antinori et al. 2007) aging HIV-infected brain likely manifests in functional neuroadaptation that results in altered functional network connectivity. For example, a recent study found that HIV status and cognitive impairment was related with less DLPFC–dorsal caudate connectivity, and that the dorsal caudate was less connected to the executive network in HIV-infected individuals than controls (Ipser et al. 2015). However, HIV patients diagnosed with more severe cognitive deficits, classified as HAND, performed poorly on visual attention tasks and did not show this compensatory increase in activation during task processing despite absence of structural brain compromise compared to HIV patients without evidence of cognitive decline. This implies that functional neuroadaptation occurs in HIV-infected individuals without cognitive deficits to compensate for a decrease in neural efficiency (Wilson et al. 2015). Cognitive reserve may be particularly relevant for attention and executive functions and enable the utilization of compensatory strategies to circumvent cognitive deficits in HIV-infected individuals.

Likewise, patients with PD can utilize compensatory resources while completing tasks. Several studies have observed compensatory attempts in PD patients off levodopa medication. An fMRI study by Mallol et al. (2007) examined neuronal activation in PD patients while performing complex sequential movements and being off medications. As expected, compared with controls, PD demonstrated hypoactivation as indicated by fMRI

signals in the anterior supplementary motor area, thalamus, putamen, and globus pallidus. However, increased fMRI signals in PD were observed in the lateral premotor cortex and thalamus, as a possible attempt to compensate. Additionally, a negative relationship was observed between scores on the UPDRS scale and the magnitude of activation, indicating that those with greater motor difficulty needed to exert greater effort in compensating. Also Helmrich et al. (2010) used fMRI to assess BOLD pairings and reported a decrease in functional connectivity between the posterior putamen and cortical sensorimotor regions in PD. Interestingly, they also found increased functional connectivity of these regions with the anterior putamen, suggesting altered spatial segregation between different cortico-striatal loops. Helmrich et al. (2010) assumed that the remapping of cortico-striatal functional loops in PD was due to dopamine depletion in PD, i.e., functional network connectivity was redirected toward relatively unaffected parts of the striatum to serve functional compensation. In a recent task-activated fMRI study, we found that PD evoked stronger striatal–cortical connectivity, specifically between caudate–prefrontal, caudate–precuneus, and putamen–motor/premotor regions than age-matched controls. Greater functional connectivity strength correlated with less severe PD symptoms and better performance on the Stroop task performed during the scan (Müller-Oehring et al. 2014). These results are supportive of compensatory BG-cortical network enhancement to meet task demands and improve performance levels in PD. These and other findings of parallel functional network engagement suggest that remapping of cerebral connectivity can affect motor activity and cognitive behavior and may occur with normal aging, in HIV infection, and age-related neurodegenerative disease.

Conclusion

HAART has allowed aging with HIV with near normal life expectancy to become a possibility. People diagnosed with HIV are living longer with the infection and beyond the age of 50 years, but they are at risk for experiencing the cumulative effects of HIV infection and aging on brain functions. Additionally, negative side effects of HAART medication, such as hypertension and coronary heart disease, have been observed.

The potential combination of immunosenescence and HIV viral loads increases the likelihood of HIV-related brain injuries and functional brain network degradation, thereby increasing the risk for brain related injury and disability. As the population is aging, with the last cohorts of the baby-boomers reaching age 60, the management of chronic disability becomes a major public health concern (NIH, 2015; www.nia.nih.gov/newsroom/features/aging-hiv-respondingemerging-challenge). As individuals with HIV are exposed to the general effects of aging, while managing the adverse effects of the virus, with a greater risk for developing neurological impairment, they become a population distinguished amongst their peers for risk factors and increased healthcare costs. The HIV population over the age of 50 years has likely been infected for more than two or three decades, some with periods of uncontrolled viral replication, and many did not survive past 1990–1995 due to the significant physical consequences of HIV infection. In addition, prior the introduction of HAART, some HIV-1 infected individuals were identified who lacked the immunologic progression of the virus to AIDS despite seropositivity for 10–15 years (Buchbinder et al. 1994), with greater supply of CD4+ T-cells possibly allowing survival (Pereyra et al. 2008).

Today's aging HIV/AIDS survivors likely suffered HIV-related CNS structural and functional change, and this is difficult to discern from immunosence and side effects from long-term HAART. However, the increased life expectancy in individuals with HIV will allow future examination of similarities and differences with other neurodegenerative diseases in cognition and motor function as well as neuronal changes in the brain and potential for compensation, which will in turn deepen understanding of unique characteristics of each and improve diagnostic criteria. A limited number of studies have so far compared the characteristic cognitive deficits seen in advanced stages of HIV and AIDS-associated dementia with those in Alzheimer's Disease (AD) and other neurodegenerative diseases (Kernutt et al. 1993; Sadek et al. 2004). HIV-individuals who are also comorbid with substance abuse show deficits in dopaminergic transmission preceding neuron loss (Berger and Arendt 2000; Jacobs et al. 2013) that can increase the frequency to develop PD. However, with the introduction of HAART, the cognitive deficits associated with HIV have shifted to milder forms of cognitive decline, similar to those seen in mild PD. Studies have suggested that although the prevalence of PD in HIV is low, in about half the cases, the development of Parkinsonian symptoms in this population is associated with the HIV infection itself (e.g., Cardoso 2002). A comparison of future cohorts of older HIV-infected individuals with PD patients might identify patterns of structural and functional neural network degeneration that can serve as potential biomarkers for incipient PD in HIV-infected individuals. Structural and functional changes in the subcortical neural circuits in HIV are similar to those found in PD with decreased dopamine receptors and transporters in the putamen and caudate (Wang et al. 2004). Identifying and understanding the similarities and differences in cognitive and motor functioning in HIV and PD would refine diagnostic criteria. However, HIV-infected individuals and PD patients, who are able to compensate for cognitive and motor deficits, accomplish tasks demands through redistribution of resources in their neural networks. This achievement may have implications for managing the deficits in HIV and PD and to remain functionally independent in carrying out activities of daily living.

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Fig. 1. Interactive subcortico-cortical brain model: Subcortical nuclei, including thalamus (TH), basal ganglia (BG), and frontal cortical areas.
Abbreviations: Nucleus accumbens (*NAcc*)

Fig. 2.

Subcortico-cortical brain model: Subcortical nuclei (thalamus, TH; basal ganglia, BG), function as a switch to gate stimulus processing depending on task salience and emotion (amygdala, AMYG; hippocampus, HIP), attention and relevance (visual association areas, VAA; inferior parietal lobe, IPL) for flexible updating of cognitive sets (prefrontal cortex, FC) and motor plans (suppl. motor areas, SMA; cerebellum, CB)