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Review article

The impact of aging on HIV-1-related neurocognitive impairment

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ABSTRACT

Depending on the population studied, HIV-1-related neurocognitive impairment is estimated to impact up to half the population of people living with HIV (PLWH) despite the availability of combination antiretroviral therapy (cART). Various factors contribute to this neurocognitive impairment, which complicates our understanding of the molecular mechanisms involved. Biological aging has been implicated as one factor possibly impacting the development and progression of HIV-1-related neurocognitive impairment. This is increasingly important as the life expectancy of PLWH with virologic suppression on cART is currently projected to be similar to that of individuals not living with HIV. Based on our increasing understanding of the biological aging process on a cellular level, we aim to dissect possible interactions of aging- and HIV-1 infection-induced effects and their role in neurocognitive decline. Thus, we begin by providing a brief overview of the clinical aspects of HIV-1-related neurocognitive impairment and review the accumulating evidence implicating aging in its development (*Part I*). We then discuss potential interactions between aging-associated pathways and HIV-1-induced effects at the molecular level (*Part II*).

1. Introduction

HIV-1 is the causative agent of acquired immunodeficiency syndrome (AIDS), a devastating disease characterized by $CD4^+$ T-cell depletion and immune dysregulation (Douek et al., 2002; Levy, 1993; McCune, 2001; Veazey et al., 1998). Despite barriers to cure, the introduction of combination antiretroviral therapy (cART) in the mid-1990s transformed HIV-1 infection from a lethal condition into a manageable chronic disease (Gulick et al., 1997; Hammer et al., 1997; Marcus et al., 2020; Nakagawa et al., 2013). As a result, successfully treated people living with HIV-1 (PLWH) are now expected to live a normal lifespan (Marcus et al., 2020; Nakagawa et al., 2013). It is estimated that twenty years after the introduction of cART 50 % of PLWH in the USA are now above the age of 50 (Wing, 2016). Further, a model based on the Dutch ATHENA cohort predicts that from 2010 to 2030, the proportion of PLWH aged 50 or older will have increased from 28 % to 73 % (Smit et al., 2015). Importantly, cART has also reduced the rates of the most severe forms of HIV-1-related neurocognitive impairment, but its overall prevalence remains comparable to the pre-cART era (Bhaskaran et al., 2008; Heaton et al., 2010; Robertson et al., 2007; Sacktor et al., 2016; Tozzi et al., 2007; Xia et al., 2011). This is due to still obscure molecular mechanisms. Given the regained life expectancy of PLWH, it remains therefore critical to elucidate the exact role of aging in HIV-1-induced brain disease onset and progression.

1.1. The role of aging in HIV-1-related neurocognitive impairment is not clear

The cognitive decline observed in the general population that is thought to be age-related seems to progress faster in PLWH. Aung et al. recently reviewed 37 studies that have performed neurocognitive performance testing to describe a potential premature, accentuated or accelerated brain aging in PLWH (Aung et al., 2021). The authors found evidence for premature neurocognitive aging in 45 % of studies.

Abbreviations: AAN, American Academy of Neurology; AIDS, Acquired immunodeficiency syndrome; ANI, Asymptomatic neurocognitive impairment; BBB, Blood-Brain-Barrier; BMVEC, Blood microvascular endothelial cell; CART, combined antiretroviral therapy; CNS, Central nervous system; CSF, Cerebrospinal fluid; EV, Extracellular vesicle; HABI, HIV-associated brain injury; HAD, HIV-associated dementia; HAND, HIV-associated neurocognitive disorders; HIV-1, Human immunodeficiency virus type 1; MND, Mild neurocognitive disorder; NPC, Neural progenitor cell; NVU, Neurovascular unit; PLWH, People living with HIV; ROS, Reactive oxygen species.

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Accelerated neurocognitive aging, as defined by a significant interaction effect of HIV status and age on longitudinal neurocognitive test performance or incidence of neurocognitive impairment, was found in 75 % of the longitudinal studies that were analyzed (Aung et al., 2021). Overall, the authors concluded that there is some evidence supporting premature and accelerated brain aging in PLWH, but that more harmonized assessment methods and larger samples sizes are needed (Aung et al., 2021). Of note, the presumed accelerated aging of PWLH is not restricted to the brain. Epigenetic clock analysis and higher rates for additional age-related conditions (e.g., cardiovascular disease, chronic renal disease or stroke) substantiate the accelerated aging of PWLH in general (Aung et al., 2021; Gross et al., 2016; Guaraldi et al., 2015; Horvath and Levine, 2015; Negredo et al., 2017; Shiau et al., 2021; Stoff et al., 2017; Van Epps and Kalaylian, 2017).

There are two major hypotheses that try to explain the phenomenon of accelerated brain aging in PLWH. One hypothesis argues that HIV-1 and aging have synergistic deleterious effects on cognitive performance (Cañizares et al., 2014). Following this *synergy* hypothesis, the pathomechanisms associated with aging and HIV-1 may amplify each other's impact on cognitive performance. In this context, aging processes lead to cognitive decline independently as observed in the general population but may also be considered risk factors that enhance HIV-1-related neurocognitive impairment via aging-associated molecular pathways that promote HIV-1-induced CNS effects.

There is, however, evidence contradicting this hypothesis. As discussed below, not all studies have found evidence for interactions between age and HIV-1. It is therefore also possible that HIV-1 and aging affect the brain independently. Associated pathomechanisms may exist in parallel but there is no synergy that might amplify the exerted deleterious effects. Nonetheless, it is assumed that the sum of the additive effects of age and HIV-1 leads to a higher rate of cognitive impairment in aging PLWH, which explains the steeper progression of cognitive impairment among PLWH.

Overall, there is still uncertainty in the field, and it remains unclear whether HIV-1 and aging both affect neurocognitive decline independently, or whether there are interactions between HIV-1-induced and aging-associated mechanisms that promote HIV-1-related neurocognitive impairment in the elderly.

1.2. History and classifications

The first findings that HIV-1 can be directly responsible for neurocognitive impairment, and dementia in particular, were obtained in the mid-1980s (Navia et al., 1986). First, evidence for HIV-1 neuroinvasion in patients suffering from AIDS encephalopathy and dementia began to accumulate, e.g. by southern blot analysis, and RNA-hybridization (Shaw et al., 1985), or by electron microscopy (Epstein et al., 1984). Next, Navia et al. found a correlation between the frequency and severity of brain abnormalities and the degree and duration of clinical dementia by studying the brains of 70 autopsied AIDS patients (Navia et al., 1986). These results led to the introduction of the *AIDS dementia complex* as a distinct clinical and pathological condition (Fig. 1).

The nature of HIV-1-related neurocognitive impairment changed after the introduction of cART (reviewed in (Sacktor, 2018)). To better classify neurocognitive impairment that is caused by HIV-1 and not by potential co-morbidities, an updated nosology was published in 2007 (Antinori et al., 2007). This nosology makes use of the term *HIV-associated neurocognitive disorders* (HAND), and the underlying criteria are often referred to as the *Frascati criteria*. Briefly summarized, HAND was categorized into (i) HIV-associated asymptomatic neurocognitive impairment (ANI), (ii) HIV-associated mild neurocognitive disorder (MND) and (iii) HIV-associated dementia (HAD) (Antinori et al., 2007). This divides HIV-associated neurocognitive impairment into (i) cognitive impairment that *does not interfere with everyday functioning* (ANI), (ii) cognitive impairment that *produces at least mild interference in daily functioning* (MND) or (iii) cognitive impairment that *produces marked interference with day-to-day functioning* (HAD) (Antinori et al., 2007). To determine the state of HAND according to the Frascati criteria, comprehensive neuropsychological evaluation is necessary (Antinori et al., 2007).

Although the HAND nomenclature has been widely applied to date, the classification and diagnosis on which it is based has been the subject

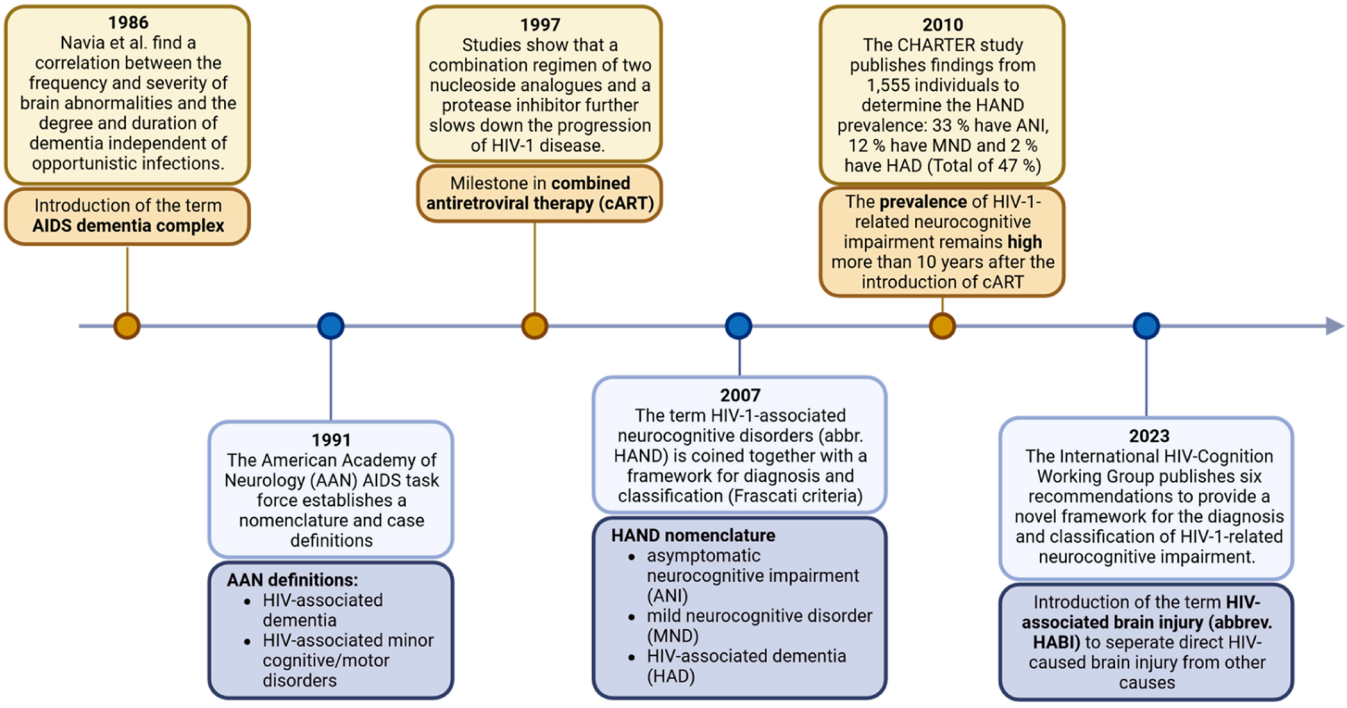

Fig. 1. Timeline illustrating the history of clinical recognition of HIV-1-related neurocognitive impairment and its classification. This figure summarizes the different diagnosis and classification frameworks for HIV-1-related neurocognitive impairment (blue) in the context of hallmark studies (yellow) that shaped the HIV-1/AIDS field since neurological manifestations were associated with HIV-1 infection.

of debate (Nightingale et al., 2021). For instance, PLWH cannot be diagnosed with HAND according to these criteria when the presented neurocognitive impairment can be explained by existing comorbidities, which are then referred to as confounding (Antinori et al., 2007; Hellmuth et al., 2018; Nightingale et al., 2014). In addition, broad neurocognitive performance testing but not the history of clinical symptoms or standard neurological investigations is used to diagnose HAND.

To address the beforementioned issues regarding the Frascati criteria, the International HIV-Cognition Working Group published six recommendations in June 2023 that do not constitute a novel set of criteria, but instead reflect the consensus opinion of the group to develop a new system of diagnosis and classification (Nightingale et al., 2023). These recommendations offer a framework of classification for both clinical management and research studies that represents the evolving profile of HIV-1-induced CNS effects and address the inadequacies resulting from the HAND nomenclature.

An important point made is the introduction of the term HIV-associated brain injury (abbr. HABI), which is used to distinguish direct HIV-induced effects from other potential causes of brain injury (Nightingale et al., 2023). Since the additional content of the individual recommendations is beyond the scope of this review, the reader is referred to the original and related publications (Cysique et al., 2024; Nightingale et al., 2023, 2024).

As this review focuses on the underlying pathomechanisms of HIV-1-induced CNS injury, we will apply the term HIV-1-related neurocognitive impairment to include all HIV-1-associated CNS effects that may contribute to neurocognitive decline irrespective of any confounding or other co-existing conditions.

Part I: Evidence for the role of aging in HIV-1-related neurocognitive impairment

2. Evidence for the role of aging in HIV-1-related neurocognitive impairment

2.1. Prevalence of neurocognitive impairment in PLWH

The prevalence of the most severe forms of neurocognitive impairment in PLWH remarkably decreased after the introduction of cART in the mid-1990s (Hammer et al., 1997; Heaton et al., 2010, 1995). However, its overall prevalence has remained substantial (Heaton et al., 2010, 1995).

The CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study has been one of the largest studies on HAND prevalence with 1555 PLWH tested. The results were published in 2010 (Heaton et al., 2010): 33 % of study participants showed ANI, 12 % MND and 2 % showed signs of HAD (total of 47 %) (Heaton et al., 2010). The Multicenter AIDS Cohort Study (MACS), another large study setting, determined that among the 197 PLWH tested in 2011/12, 31 % were diagnosed with HAND (Sacktor et al., 2016). Of these individuals, 19 % had ANI, 10 % had MND and 2 % HAD (total of 31 %).

To account for different study populations, a recent meta-analysis tried to determine the global HAND prevalence based on 19 different studies from all over the world. The authors determined a likely global HAND prevalence of 43.9 %. Here, 26.2 % of PLWH showed ANI, 8.5 % MND and 2.1 % HAD (Wei et al., 2020). It is to note that this meta-analysis only included studies in which more than 200 individuals were tested and that adhered to the Frascati criteria.

2.2. The effect of aging on the prevalence of HIV-1-related neurocognitive impairment

Concerning the influence of aging on neurocognitive impairment in the time of cART, the Hawaii Aging with HIV-1 Cohort study of 2004 determined the odds of having HAD to be 3.26 times higher in older participants (> 50 years old) than in the younger group (20–39 years) (Valcour et al., 2004). Becker et al. likewise found a higher rate of dementia among PLWH that were above the age of 50 (22 %) compared to PLWH that were below 50 years of age (9 %) (Becker et al., 2004). While focusing on memory deficits rather than dementia, Tan and colleagues showed that old age (> 50 years) was associated with 4.8-fold higher odds of having memory impairment (Tan et al., 2013). The authors determined that every 1 year increase in age has been associated with 1.11-fold higher odds in their study cohort (Tan et al., 2013). In addition, a longitudinal study by Seider and colleagues showed that the interaction of HIV-1 and age significantly predicted the observed longitudinal change in verbal memory performance (Seider et al., 2014). In a study conducted with 133 older (> 50 years) and 121 younger PLWH (20–39 years) in 2007, age was further associated with lower performance tests in executive functioning, and motor performance (Sacktor, Skolasky, et al., 2007). The cross-sectional study conducted by Vance and colleagues substantiated that old age (>50 years) and HIV-1 are both independently associated with decreased neuropsychological measures and, moreover, showed that older PLWH have in total the worst cognitive test results (Vance et al., 2013). Despite the accumulating evidence for age as factor in the prevalence of HIV-1-related neurocognitive impairment, a twelve-year follow-up study based on the CHARTER cohort (402 PLWH) has recently revealed that neurocognitive decline was predicted by comorbidities including diabetes, hypertension, chronic pulmonary disease, frailty, and neuropathic pain but was not associated with chronological age (Heaton et al., 2023).

Notably, several studies did not include non-infected controls. Matching PLWH with non-infected individuals is, however, crucial for revealing the true impact of HIV-1, and cART on cognition. Moreover, when investigating the impact of aging on cognition in PLWH, it is of utmost importance to also control for co-morbidities. The caveat of not analyzing non-infected controls in these studies is therefore a methodological flaw that may prevent us from drawing any conclusions about whether the higher rate of neurocognitive decline in the elderly can be attributed to HIV-1-induced effects. Given the controversy about the over- or under-estimation of neurocognitive impairment in PLWH, in particular in the light of aging, we call for more inclusive study designs to better understand the impact of the aging process on cognition in PLWH.

Interestingly, this problem appears not to be restricted to prevalence studies. As recently reviewed by Ojeda-Juárez and Kaul (2021), many transcriptome studies on brain tissue from PLWH that attempt to analyze a potential dysregulated gene expression, which may underly cognitive decline in PLWH, lack non-infected controls as well (Ojeda-Juárez and Kaul, 2021). It has been pointed out that in comparison to studies on, for instance, Alzheimer's or multiple sclerosis, studies on HIV-1-related neurocognitive impairment are thus underpowered.

2.3. Clinical signs and symptoms of neurocognitive impairment in PLWH

HIV-1-induced CNS effects can affect cognition, behaviour and motor functions, although memory impairment often prevails (reviewed in (Chan and Valcour, 2022)) (Fig. 2).

These CNS manifestations can occur during the acute phase of HIV-1 infection (Braun et al., 2015). A study by Serena Spudich and others found that 73 of the 139 participants (53 %) had neurological symptoms within 12 weeks following primary HIV-1 infection (Hellmuth et al., 2016). The 245 individual neurological findings in these 73 participants included difficulties with memory, concentration, speech and upper extremity coordination (Hellmuth et al., 2016). Additionally, study participants experienced involuntary movements or slowed responses (Hellmuth et al., 2016). Yet, the majority of symptoms was classified as mild and more than 90 % of neurological findings resolved after 24 weeks (Hellmuth et al., 2016).

Neurocognitive impairment following HIV-1 infection may, however, also persist, progress or develop over time (Cysique et al., 2010; Heaton et al., 2008). In a set of studies performed in China, chronic

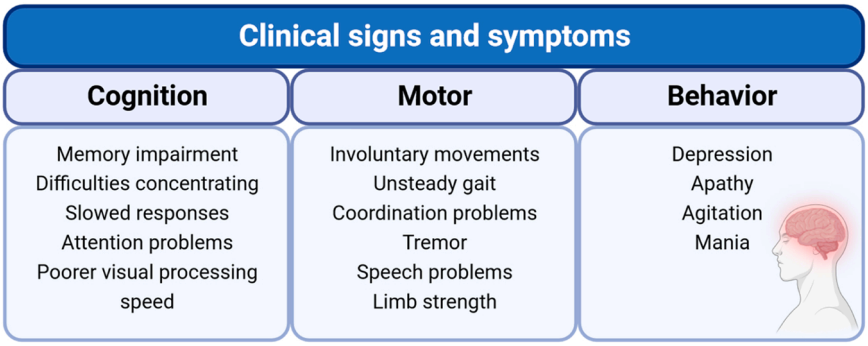

Fig. 2. Clinical signs and symptoms linked to HIV-1-related neurocognitive impairment that may exacerbate with age. This figure lists clinical signs and symptoms of HIV-1-related neurocognitive impairment. The purpose of this figure is to give the reader a compact overview of potential symptoms to better understand the observed disease patterns. This list is neither exhaustive nor does it reflect the different degrees of symptoms. Adapted from Chan and Valcour (2022) (Chan and Valcour, 2022).

HIV-1 infection was linked to problems with executive function, verbal fluency, attention, learning, memory, motor functions and depression (Cysique et al., 2010; Heaton et al., 2008). Most effect sizes were small at the baseline study (Heaton et al., 2008), but the 1-year follow-up study showed a decline in neurocognitive capacities in 27 % of PLWH compared to a decline only in 5 % of well-matched, HIV-1-negative individuals (Cysique et al., 2010). This decline of neurocognitive capacities occurred despite prescription of cART (Cysique et al., 2010). However, most study participants met criteria for AIDS at baseline and at the time of the follow-up study, only 61 % were receiving cART (Cysique et al., 2010). Hence, the study results may not be representative of PWLH that start treatment earlier in the disease course or those who maintain durable viral suppression on cART.

2.4. The impact of age on the severity of HIV-1-related neurocognitive impairment

With respect to age as potential risk factor for more severe symptoms, older PWLH (> 50 years) have been found to have greater memory deficits compared to younger PWLH (Tan et al., 2013). In one small study, old age was associated with poorer driving abilities in 26 PLWH that used a driving simulator to test cognitive functioning in a near to real-life setting (Vance et al., 2014). The observed poorer driving abilities were likely related to poorer visual speed of processing performance (Vance et al., 2014). In a larger cohort of 254 PLWH, old age (> 50 years) was associated with impaired visual memory, verbal memory, verbal fluency, and psychomotor speed (Sacktor, Skolasky, et al., 2007). Unfortunately, most study designs again lacked control groups of HIV-1-negative individuals (Vance et al., 2014). Conversely, Schantell and colleagues not only included non-infected control individuals but differentiated between the chronological and the biological age of their study participants by epigenetic clock analyses to account for the accelerated aging observed in PLWH (Schantell et al., 2022). This study has linked the biological age of PLWH to aberrant neural oscillatory dynamics potentially affecting visuospatial processing (Schantell et al., 2022).

2.5. Structural brain changes in PLWH

As early as 1986, an observed correlation between the frequency and severity of brain abnormalities with the degree and duration of clinical dementia following HIV- infection led to the definition of an AIDS dementia complex (Navia et al., 1986). Abnormalities were particularly found in the white matter and subcortical structures at this time (Navia et al., 1986).

In the era of cART, the main observation among PLWH is atrophy of the white, and gray matter both leading to a volumetric decrease that is observed either for the total brain, or sometimes specific brain regions (Alakkas et al., 2019; Aylward et al., 1995; Haziot et al., 2015; Heaps et al., 2015; Lew et al., 2021; Wade et al., 2015). McMahan et al. published an observational study this year showing that despite decade-long adherence to cART (> 15 years), MRI and CSF analysis can reveal reduced brain volumes and ongoing neuronal injury and neuroinflammation in PLWH when compared to non-infected controls (McMahan et al., 2023). The same study also reported a higher rate of cognitive difficulties, motor function impairment, lower information processing speed, depressive symptoms, and anxiety among PLWH, which substantiates a relation between HIV-1 infection-induced brain abnormalities and neurocognitive impairment (McMahan et al., 2023). In addition to tissue atrophy, arterial spin labeling revealed that the gray matter cerebral blood flow may be reduced in PLWH (Petersen et al., 2021). The continuous improvement of brain imaging techniques led to additional findings over the years, which are, however, beyond the scope of this review.

2.6. The role of aging in HIV-1 infection-associated structural brain changes

Importantly, HIV-1 infection-related brain abnormalities were only recently linked to the accelerated aging of PWLH as determined by conducting brain imaging and comparing the chronological with the biological age. The biological age was hereby studied based on epigenetic markers derived from blood samples (Hoare et al., 2022; Lew et al., 2021). Lew at al. compared 110 virally suppressed PLWH with 122 uninfected controls (age 22 – 72) and showed that the accelerated aging in PLWH is associated with total gray matter reductions (Lew et al., 2021). In an independent study, Hoare and co-workers tested adolescent PLWH from the Cape Town Adolescent Antiretroviral Cohort revealing that accelerated aging in the 180 individuals tested is likewise associated with alterations of brain volumes, cortical thickness, cortical surface areas, and neuronal microstructure (Hoare et al., 2022). These studies support the assertion that the systemic accelerated aging of PLWH is reflected in the brain.

A deep learning algorithm-based brain age estimation following MRI analysis supported the idea that PLWH suffer from accelerated brain aging (Petersen et al., 2021). The authors of this study showed that PLWH had a structurally predicted brain age that was significantly older than that of the matched HIV-1-negative controls, regardless of viral load (Petersen et al., 2021). While analyzing a potential correlation of brain age and neurocognitive performance, the authors further found an association between predicted brain age and reduced psychomotor speed (Petersen et al., 2021).

Altogether, the different studies on the prevalence of neurocognitive impairment, the severity of symptoms, and structural brain changes suggest that biological age is somewhat linked to HIV-1-related neurocognitive impairment. Yet, the question remains whether (i) biological

aging promotes HIV-1-induced effects on the CNS, (ii) infection-mediated accelerated aging is responsible for the neurocognitive decline, or (iii) whether both are true. For this, understanding the interaction of HIV-1-induced and aging-related pathways is key. Hence, cellular and molecular studies are necessary. Few studies have specifically investigated mechanisms associated with aging in the context of HIV-1-related neurocognitive impairment. This is most likely due to a lack of human-relevant model systems to study aging-related effects in neuronal, and other brain-derived cells. To nevertheless dissect a potential interaction, we will summarize the molecular pathways that are suggested to cause HIV-1-related neurocognitive impairment and discuss them in light of aging-related findings in the second part below.

Part II: Cellular and molecular mechanisms associated with biological aging and their role in HIV-1-related neurocognitive impairment

3. The hallmarks of aging and physiological brain aging

Biological aging is considered the time-dependent accumulation of cellular damage and research made considerable progress in understanding the different cellular and molecular pathways involved. In 2013, López-Otín et al. published nine *hallmarks of aging*, which represent aging-associated mechanisms and that provided a basic framework to guide research in the aging field (López-Otín et al., 2013). Over the years, these hallmarks were a matter of debate and the Copenhagen aging meeting of 2022 proposed additional hallmarks based on our increased understanding of the underlying mechanisms (Gems and de Magalhães, 2021; Schmauck-Medina et al., 2022). Recently, the authors of the original hallmarks have published an updated version of their scheme that better reflects the latest research (López-Otín et al., 2023). Altogether, suggested hallmarks of aging are altered intercellular communication, deregulated nutrient-sensing, chronic inflammation, senescence, epigenetic alterations, telomere attrition, compromised macro-autophagy, loss of proteostasis, genomic instability, splicing deregulation, microbiome disturbance, altered mechanical properties, stem cell exhaustion, and mitochondrial dysfunction. These hallmarks are conserved in neural cells and contribute to the physiological and pathophysiological aging of the brain (Jin and Cai, 2022; Lee and Kim, 2022).

Brain aging has been extensively reviewed recently (for recent reviews see (Blinkouskaya et al., 2021; Jin and Cai, 2022; Lee and Kim, 2022; Zia et al., 2021)). Overall, the sum of aging-associated molecular mechanisms lead to changes on a single cell level (e.g., demyelination, decrease in neuronal size, de-arborization of the dendritic network, synaptic loss) and eventually drive morphological changes (e.g., volume loss, cortical thinning, white matter degradation, ventricular enlargement), which are associated with neurocognitive decline in healthy and more pronounced in diseased brains (Blinkouskaya et al., 2021; Jin and Cai, 2022; Pini et al., 2016)

Notably, some mechanisms that may be irrelevant to other tissues are suggested to have more pronounced effects on the brain. For instance, neuronal functions highly depend on proper regulation of ion homeostasis. Therefore, the calcium (Ca^{2+})-dysregulation hypothesis of brain aging, and Alzheimer's disease proposes that the age-related disruption of Ca^{2+} regulation in neurons plays a significant role in age-related neuronal dysfunction (Thibault et al., 2001).

Hou and colleagues have previously discussed the original hallmarks of aging and their contribution to the most common neurodegenerative diseases including Alzheimer's, and Parkinson's Disease (Hou et al., 2019). Their work showed that each of these aging-associated mechanisms can be linked to the development of neurodegenerative disease, which has further underlined that age is the number one risk factor for neurodegenerative disease (Hou et al., 2019).

In line with the neurodegenerative component of HIV-1-related neurocognitive impairment, we discuss possible interactions between HIV-1-induced CNS effects and aging-associated pathways in the following. This may help us understand the complex role of biological aging in HIV-1-related neurocognitive impairment and thus, help further research to find potential novel therapeutics (Ostermann and Evering, 2023).

4. The role of aging in HIV-1 neuroinvasion

Viruses cause neurological symptoms in different ways. HIV-1 is known to directly infect brain and invading immune cells leading to cytopathic effects in infected and bystander cells. A prerequisite for the infection of brain cells is *viral neuroinvasion*. Viral neuroinvasion is the infiltration of the central nervous system (CNS) by a virus and presumably occurs within two weeks after infection in the context of HIV-1 (Valcour et al., 2012). Although the human brain may be considered a dead-end for viral pathogens from an evolutionary perspective, viruses may follow different strategies to overcome the biological barriers that protect the CNS.

There are two major routes for viruses to infiltrate the CNS (reviewed in (Koyuncu et al., 2013; McGavern and Kang, 2011; Swanson and McGavern, 2015)). The first is via the peripheral nervous system (Schnell et al., 2010). The second is via the blood stream. While taking this route, viruses enter the CNS via the blood-brain barrier (BBB) or the blood-cerebrospinal fluid (CSF) barrier (McGavern and Kang, 2011). The BBB is typically depicted as the main entry site for HIV-1 (McGavern and Kang, 2011).

Notably, lymphatic vessels have also been proposed as a route for HIV-1 neuroinvasion after the identification of a meningeal lymphatic system in the last decade (Lamers et al., 2016). This idea is plausible given the trafficking of immune cells susceptible to HIV-1 via these anatomical sites (Lamers et al., 2016). However, experimental studies that demonstrate a link between these newly identified structures and HIV-1-related neurocognitive impairment are lacking.

The BBB is a multi-layered structure whose purpose is to prevent pathogens and toxins access to the brain. This is achieved by separate mechanisms. Tight junctions connect the brain microvascular endothelial cells (BMVECs) (Koyuncu et al., 2013; McGavern and Kang, 2011). These BMVECs generate a basement membrane (Koyuncu et al., 2013; McGavern and Kang, 2011). Third, nearby astrocytes form the so-called glial limitans, which is composed of laminin and cellular extensions (astrocyte endfeet) (Koyuncu et al., 2013; McGavern and Kang, 2011). In addition, brain pericytes, perivascular macrophages, and microglia participate in regulating BBB integrity and provide immune surveillance (McGavern and Kang, 2011). These mechanisms are the major components of the BBB, but further mechanisms are involved that may be more subtle. The entirety of different cell types that are involved in BBB function is termed the neurovascular unit (NVU).

HIV-1 particles are described to cross the BBB in distinct pathways. It is likely that all of these contribute to HIV-1 neuroinvasion. These pathways include (i) the "Trojan-Horse" mechanism, (ii) paracellular migration through a leaky BBB, (iii) productive infection of BMVSCs and (iv) transcytosis (Fig. 3).

4.1. The Trojan-Horse mechanism – Crossing the BBB within infected cells

The most well-studied pathway is (i) the "Trojan-Horse" mechanism (Fig. 3). This term describes the viral infiltration of the CNS by infection of immune cells that cross the BBB or Blood-CSF barrier. Based on its receptor tropism, HIV-1 primarily infects $CD4^+$ T-cells and cells of the monocyte/macrophage lineage. Both cell types naturally enter the CNS and hence can be detected in the CSF under physiological conditions (Burdo et al., 2013; Ransohoff et al., 2003; Strazielle et al., 2016): Leukocytes present in the CSF are foremost T-cells, with a higher ratio of $CD4^+$ to $CD8^+$ T-cells than in the blood (Ransohoff et al., 2003; Svenningsson et al., 1995). Monocytes are found in the CSF as well and make

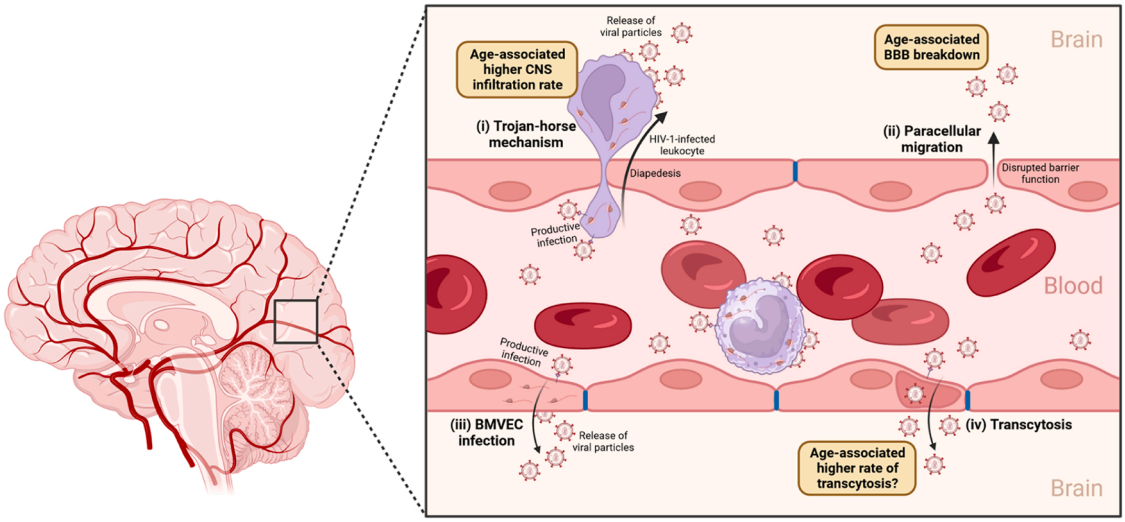

Fig. 3. Routes of HIV-1 neuroinvasion potentially impacted by age. There are four routes described that allow HIV-1 entry into the CNS. The Trojan-Horse mechanism (i) involves passage of HIV-1-infected monocytes/macrophages or $CD4^+$ T-cells across the blood-brain barrier. This migration of leukocytes is called diapedesis. HIV-1 virions may also enter the CNS by paracellular migration (ii) through a disrupted blood-brain barrier. Productive infection (iii) of blood microvascular endothelial cells (BMVECs) or transcytosis (iv) mediated by BMVECs are also considered routes for HIV-1 neuroinvasion.

up about 5 % of the total CSF leukocytes (Ransohoff et al., 2003).

Joan Berman and co-workers have previously demonstrated that HIV-1-infected monocytes cross a blood-brain-barrier cell culture model at a higher rate than uninfected cells (Eugenin et al., 2006). This was suggested to be caused by an infection-dependent upregulation of the CCL2 receptor CCR2, because CCR2 interaction with CCL2 mediates transmigration (Eugenin et al., 2006). This suggests that HIV-1 infection may actively promote neuroinvasion via the trojan-horse mechanism. Interestingly, in a different study, monocytes from older individuals were found to infiltrate the brain at a higher rate than monocytes from younger individuals by using an advanced microfluid-based brain organoid platform (Ao et al., 2022). This finding may support a higher CNS infiltration rate by HIV-1 in older individuals via the trojan-horse mechanism.

4.2. Paracellular migration of HIV-1 through a leaky BBB

HIV-1 may also enter the CNS trough (ii) a leaky BBB (reviewed in (Zhang et al., 2015)). In this case, HIV-1 enters the CNS as free virions by paracellular migration through a disrupted BBB (Fig. 3).

BBB integrity can be disturbed during viral infection by different factors including proinflammatory signals or viral proteins, particularly HIV-1 gene products Tat, Vpr, Nef and gp120 (Atluri et al., 2015; Kim et al., 2003; Spindler and Hsu, 2012; Toborek et al., 2005; Zhang et al., 2015). HIV-1 Tat was recently shown to decrease expression of the tight junction protein ZO-1 by inducing the autophagy pathway in BMVECs (Liao et al., 2020). A breakdown of the BBB is also associated with biological aging. It is caused by various aging-related effects on each of the cell types (e.g., oxidative stress, accumulated DNA damage, and impaired DNA repair capacities) that make up the NVU as recently reviewed by Li et al. (Li et al., 2019). The chances of paracellular migration for neuroinvasion are therefore likely increased with age.

Importantly, virus-induced breakdown of the BBB probably exacerbates aging-related pathways that are associated with other neurodegenerative diseases or the general age-related neurocognitive decline in addition to increasing the chances of HIV-1 neuroinvasion. It has been shown that the breakdown of the BBB is an early event in the aging brain that may begin in the hippocampus and that this can serve as an early biomarker of cognitive dysfunction in humans (Montagne et al., 2015; Nation et al., 2019). In this regard, strategies were suggested that target the underlying detrimental effects on the BBB to slow down cognitive decline (Li et al., 2019). Hence, it would be interesting to specifically focus on the interaction of HIV-1- and aging-associated effects on the BBB in future studies for the analysis of possible synergistic effects that aggravate neurocognitive decline in PLWH.

4.3. Productive infection of blood microvascular endothelial cells

A third route of HIV-1 neuroinvasion (iii) is productive infection of BMVSCs (Fig. 3). Productive infection is the term used to indicate that infection results in the generation of infectious progeny virus, which sets it apart from abortive infection. In 1993, Moses and co-workers showed that human brain capillary endothelial cells are permissive to HIV-1 infection, i.e. they can be productively infected (Moses et al., 1993). However, this route of HIV-1 neuroinvasion is often excluded from the literature due to a lack of additional studies that support productive BMVSC infection. Cafaro et al. have recently showed that cytokine activation in addition to HIV-1 Tat protein pre-treatment rendered primary endothelial cells permissive to HIV-1 (Cafaro et al., 2020). It was suggested that uptake of secreted Tat by activated endothelial cells may provide a beneficial environment for HIV-1 replication (Cafaro et al., 2020). Hence, it remains debatable to which extent productive BMVSC infection contributes to HIV-1 neuroinvasion.

4.4. Transcytosis of HIV-1 particles across the BBB

The fourth mechanism by which HIV-1 is suggested to cross the BBB is (iv) transcytosis (Fig. 3) (Bobardt et al., 2004). Transcytosis is a mechanism by which cargo is transported through the endosomal compartment of epithelial and endothelial cells from one side to the other (Preston et al., 2014). It is based on endocytic uptake, coordinated intracellular traffic within the endosomal pathway during which lysosomal degradation is prevented, and exocytosis (Preston et al., 2014). Although another important mean to reduce BBB permeability is the downregulation of transcytosis in BMVECs, BMVECs make use of transcytosis to transport macromolecules such as insulin or transferrin across the BBB (Ayloo and Gu, 2019). In 2001, Gujuluva et al. found that BMVECs may also endocytose HIV-1 particles (Gujuluva et al., 2001). Electron microscopic analysis indicated that cultured BMVECs exposed to HIV-1 harbor vacuoles that contain viral particles (Gujuluva et al., 2001). Later, the mannose-6 phosphate receptor (M6PR) was suggested as a key player in BMVEC-mediated transcytosis of HIV-1 by

internalizing viral particles upon binding glycolyzed residues of the HIV-1 envelope (Dohgu et al., 2012). It is assumed that during transcytosis, HIV-1 virions are bound by nonspecific receptors including M6PR, which leads to endocytosis of intact viral particles without triggering conformational changes within the viral envelope protein that would induce membrane fusion. A recent study on HIV-1 transcytosis-mediated crossing of the BBB found that after exposing CMEC/D3 cells seeded on a transwell (a BBB cell culture model), 17 % of HIV-1 particles crossed the CMEC/D3 monolayer within 4 hours (Lorin et al., 2020). This model does not reconstitute the BBB in its entirety, but this observation substantiated that BMVECs transcytose HIV-1 virions. Interestingly, lipopolysaccharide (LPS) was shown to act on BMVECs to facilitate HIV-1 transcytosis (Dohgu and Banks, 2008). Moreover, high plasma LPS levels were recently linked to cognitive difficulties in PLWH (Isnard et al., 2023). In this regard, evidence from mouse experiments indicates that the aging-related shift in the microbiome is associated with increased LPS production and higher blood LPS levels (Kim et al., 2016). Hence, transcytosis of HIV-1 across the BBB may be increased with age due to the effects of LPS. On the other hand, a study by Yan et al. has shown that the overall rate of receptor-mediated transcytosis is reduced with age (Yang et al., 2020). Hence, it is not clear whether age-associated higher rates of LPS translocation affect HIV-1 transcytosis.

4.5. The role of brain pericytes in HIV-1 neuroinvasion

With respect to additional components of the NVU, productive infection of brain pericytes, which coat a large fraction of the brain microvasculature, might facilitate HIV-1 neuroinvasion (Bertrand et al., 2019; Nakagawa et al., 2012; Sá-Pereira et al., 2012). Pericytes promote BBB integrity by regulating tight junction protein expression in BMVECs. Upon infection of pericytes by HIV-1 in pericyte-BMVEC co-culture, BMVSC tight junction proteins occludin and ZO-1 were shown to be downregulated (Nakagawa et al., 2012; Sweeney et al., 2016). This infection of pericytes hence may promote the aging-, and infection-associated leakiness of the BBB.

Overall, HIV-1 is suggested to invade the CNS in distinct ways. Limited evidence in the literature suggests some aging-related effects that may promote HIV-1 neuroinvasion in the elderly. However, more targeted experimental studies are needed.

4.6. The formation of the HIV-1 CNS reservoir

After neuroinvasion, HIV-1 establishes a heterogenous viral reservoir in the brain that cannot be eradicated by cART, as recently highlighted by Riggs and colleagues based on the first results from the Last Gift Program – a unique venture that performs autopsies within six hours after death of PLWH that have donated their bodies to science (Riggs et al., 2022). Numerous studies analyzing viral sequences derived from CSF or brain tissue have identified compartmentalized infection with evidence for neuro-adapted virus in a subset of PLWH (Evering et al., 2014; Oliveira et al., 2023; Riggs et al., 2022). Mathias Lichterfeld and his group have recently performed HIV-1 single-genome sequencing with tissue from multiple CNS sites that indicates clonal proliferation also of HIV-1-infected cells particularly in the basal ganglia, frontal lobe, thalamus, and the periventricular white matter during antiretroviral therapy (Sun et al., 2023). In addition to clonal amplification of virus and clonal proliferation of infected cells, a recent single-cell analysis of blood, and CSF cells has shown a compartmentalized immune response in the form of abnormal $CD8^+$ T-cell activation inside the CNS despite cART-mediated viral suppression (Farhadian et al., 2022).

In conclusion, current therapy approaches cannot completely prevent, or eliminate viral CNS reservoir formation and neuro-adaption, together with the associated neuropathology. To our knowledge, an effect of aging-related mechanisms on viral compartmentalization has not been described thus far. As a result, the question of whether the increased leakiness of the BBB, or the suggested higher CNS infiltration rate of leukocytes affect the integrity of the viral CNS compartment with age remains unanswered.

5. HIV-1 target cells in the CNS

In line with other neurodegenerative diseases, HIV-1-related neurocognitive impairment is caused by the accumulation of neuronal injury. Interestingly, HIV-1 does not infect neurons (Joseph et al., 2015). However, several mechanisms have been described that damage neurons by infection of other neural and non-neural cells. The role of these target cells is briefly summarized in the following before we discuss the probable interactions of aging-associated mechanisms with HIV-1-induced effects on the CNS.

5.1. Microglia

Among the glial cells, microglia are the main target of HIV-1 (Donoso et al., 2022). Microglia are neural cells that function as tissue-resident macrophages throughout the brain parenchyma (Kierdorf and Prinz, 2017). The brain is composed of 5 – 15 % microglia (Allen and Lyons, 2018). Sampling the brain parenchyma by phagocytosis with their motile processes allows efficient immune surveillance in the CNS (Kierdorf and Prinz, 2017). In addition to their role in immune surveillance, microglia are important for physiological brain function by modulating synaptic plasticity and regulating neurogenesis in the adult brain (Kierdorf and Prinz, 2017). Microglia have also been found to be crucial for developing and maintaining healthy myelin growth, this way ensuring physiological neuronal signaling (McNamara et al., 2022). Microglial activation leads to large-scale cytokine production and recruitment of peripheral immune cells (reviewed in (Woodburn et al., 2021)). Although activation is necessary to overcome acute CNS injury, chronic activation during HIV-1 infection may contribute to disease progression.

Many studies have demonstrated productive HIV-1 infection of microglia (Albright et al., 2000; Cenker et al., 2017; Cosenza et al., 2002; Lee et al., 1993; Rawat and Spector, 2017; Watkins et al., 1990). Important for persistence is that microglial infection does not always induce cell death (Castellano et al., 2017; Wallet et al., 2019). On the contrary, it is assumed that HIV-1 infection induces pro-survival pathways to prevent apoptosis (Castellano et al., 2017). In this way, microglia may become latently infected and constitute a potential viral reservoir (Wallet et al., 2019). Latently infected microglia may exhibit low levels of viral gene expression leading to the accumulation of HIV-1 gene products inside the CNS (e.g., Tat, gp120, Vpr or Nef), which can lead to neuronal injury (Fig. 4) (Borrajo et al., 2021; Wallet et al., 2019).

In addition to the secretion of viral neurotoxic proteins as well as proinflammatory signals and reactive oxygen species (ROS), there are additional often-less recognized mechanisms of microglia-induced neural injury (Ojeda-Juárez et al., 2020; Yuan et al., 2024). For instance, HIV-1 was shown to induce a higher secretion of protease cathepsin B from microglia (Zenón et al., 2015). Treatment with supernatant from HIV-1-infected microglia containing these elevated levels of cathepsin B resulted in increased rates of neuronal apoptosis (Zenón et al., 2015). Neuronal apoptosis was inhibited by supplementing the supernatant with a cathepsin inhibitor or anti-cathepsin B antibody, which adds cathepsin B clearly to the list of microglia-secreted neurotoxic factors (Zenón et al., 2015).

5.2. CNS-associated macrophages

Microglia are the major immune cells within the brain, but there are additional brain-resident macrophages. These are the perivascular macrophages, choroid plexus macrophages and meningeal macrophages. These immune cells ward the borders of the CNS and are sometimes referred to as CNS-associated macrophages (CAMs) (Prinz

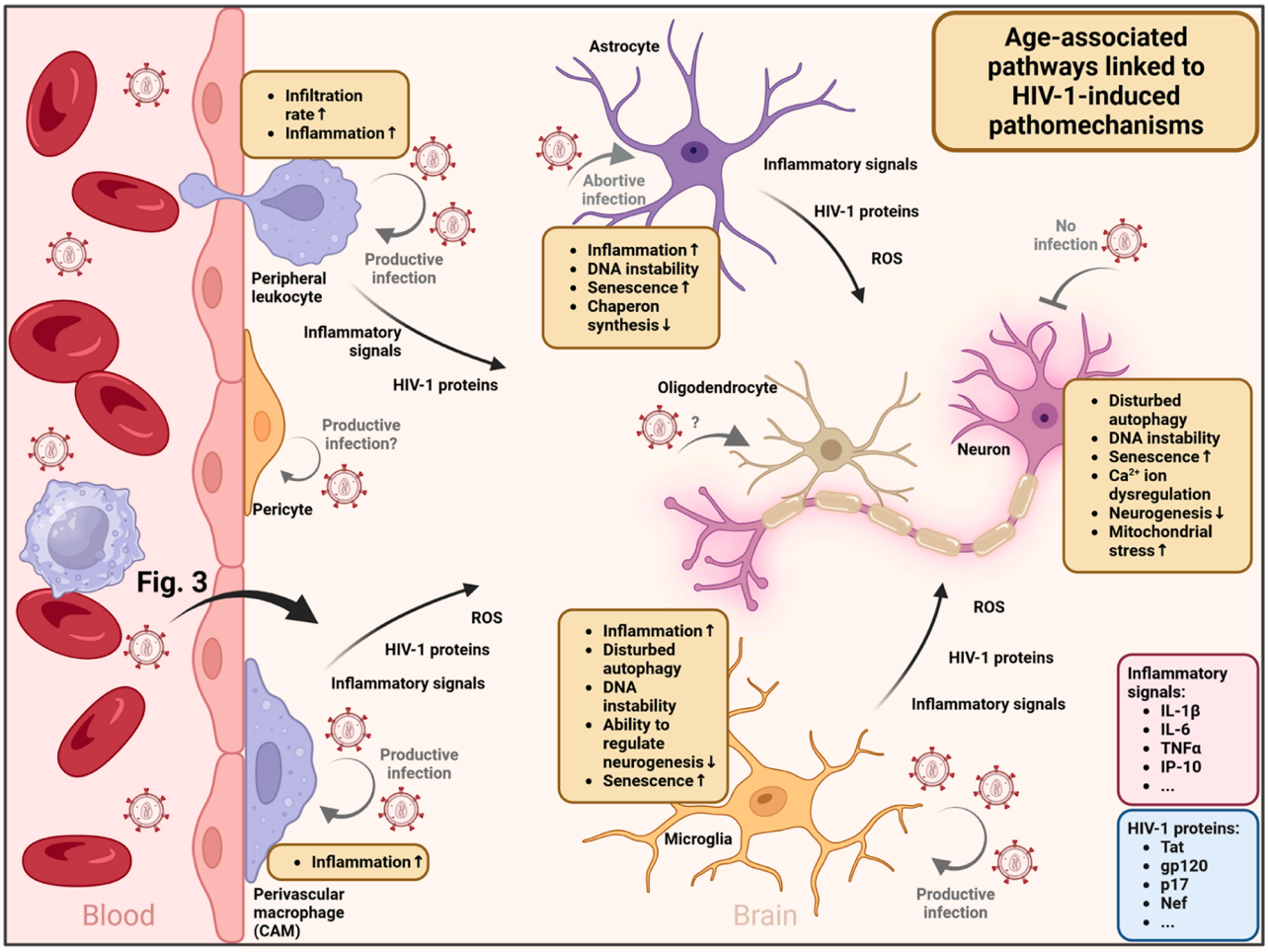

Fig. 4. Age-associated pathways with potential links to the central nervous system pathogenesis underlying HIV-1-related neurocognitive impairment. The schematic summarizes the general mechanisms that lead to neuronal dysfunction and death. Emphasis is on the different possible replication sites for HIV-1 within the central nervous system. Secreted neurotoxic factors include cellular (e.g., proinflammatory signals, reactive oxygen species (ROS), nitric oxide, lysosomal protein, etc.) and viral components (HIV-1 Tat, gp120, Nef, Vpr, etc.) (see text). The different pathways of HIV-1 neuroinvasion are shown in (Fig. 3).

and Priller, 2014; Rose et al., 2022). They also targeted by HIV-1 (Lamers et al., 2011; Rose et al., 2022; Thompson et al., 2011). Although microglia share functions with CAMs and constitute brain-resident macrophages as well, they have a different ontogeny and importance for physiological brain function (Kierdorf and Prinz, 2017; Prinz and Priller, 2014). Further, microglia are susceptible to HIV-1 infection despite the expression of SAMHD1, a known restriction factor of HIV-1 that limits infection of other macrophage populations (Cenker et al., 2017; Koppensteiner et al., 2012). Finally, microglia are a self-replenishing cell population with turnover rates of several years, whereas CAMs may be replaced by hematogenous cells and are suggested to exhibit turnover rates of few months (Lassmann et al., 1993; Le Douce et al., 2010; Williams et al., 2001). Hence, both cell types may be differently affected by aging-related effects.

Despite this, microglia and CAMs alike have been shown to constitute HIV-1 reservoirs, although there are ongoing debates on which cell type is HIV-1's primary target site in the brain (Donoso et al., 2022; Rose et al., 2022; Thompson et al., 2011; Williams et al., 2001). Because CAMs line the outer borders of the brain, like the perivascular macrophages that are part of the BBB, these cells may present the first anchor point for HIV-1 after neuroinvasion.

5.3. Astrocytes

Astrocytes are a type of glial cell within the CNS (Allen and Lyons, 2018). Their portion of the total glial cell number varies depending on the brain region analyzed but may be as high as 40 % (von Bartheld et al., 2016). Astrocytes are important for synapse formation and functioning. Their myriad functions include the recycling of neurotransmitters that have been secreted into synaptic clefts and supplying neurons with nutrients (Allen and Eroglu, 2017; Allen and Lyons, 2018; Nortley and Attwell, 2017). As a result, astrocytes and their dysfunctions have also been linked to neurodegenerative disease (reviewed in (Brandebura et al., 2022)). Activation of astrocytes by proinflammatory signals leads to the state of *reactive astrogliosis* (Pekny and Pekna, 2014). Reactive astrogliosis is considered an essential defense mechanism against CNS injury, but it has considerable negative effects (reviewed in (Pekny and Pekna, 2014)). It limits synaptic regeneration as well as the regeneration of axons (Pekny and Pekna, 2014). Prolonged activation during chronic neuroinflammation is suggested to be an additional driver of HIV-1-related neurocognitive impairment.

After HIV-1 neuroinvasion occurs, astrocytes are targeted by the virus (Donoso et al., 2022; Thompson et al., 2011). Hence, viral components and sometimes viral gene expression can be observed in astrocytes (Donoso et al., 2022; Watkins et al., 1990). Cell culture experiments and recently also a xenograft mouse model containing human astrocytes may even show viral replication, and egress (Berman et al., 2016; Lutgen et al., 2020). Notably, the xenograft mouse model showed HIV-1 reseeding from the infected astrocytes to peripheral organs after injection into the mouse brain (Lutgen et al., 2020). However,

replication in astrocytes is restricted at different levels (e.g., entry or nuclear RNA export), and there is ongoing debate on whether astrocytes support productive HIV-1 infection in the human brain (Fang et al., 2005; G. H. Li et al., 2020; Russell et al., 2017; Valdebenito et al., 2021; Vincendeau et al., 2010). Nevertheless, infection or exposure to viral proteins induce certain pathways associated with astrocyte dysfunction and neuronal injury (Berman et al., 2016; El-Hage et al., 2005; Jadhav et al., 2022; Kramer-Hämmerle et al., 2005; Köller et al., 2001, 2002; G. Li et al., 2020; Li et al., 2007; Liu and Kumar, 2015; Nookala and Kumar, 2014; Speth et al., 2000; Tewari et al., 2015; van Marle et al., 2004).

5.4. Additional HIV-1 CNS target cells

The glial cells of the CNS also include oligodendrocytes (Allen and Lyons, 2018). Oligodendrocytes are essential for brain functioning, because they form the myelin sheath that surrounds axons to ensure rapid neuronal signaling (Liu et al., 2016). In a comparative study, a 29 % loss of oligodendrocytes was observed in the brains of deceased AIDS patients compared to the brains of healthy controls (Kaalund et al., 2019). This rate was even higher than the loss of neocortical neurons, which was 19 % in the same study (Kaalund et al., 2019). Interestingly, primary human oligodendrocytes isolated from adult brain tissue were found to support productive infection by HIV-1 (Albright et al., 1996). Although further studies substantiating viral replication in oligodendrocytes are lacking, exposure to HIV-1 proteins is sufficient to cause oligodendrocyte dysfunction (reviewed in (Liu et al., 2016)). For instance, HIV-1 Tat was found to induce death of immature oligodendrocytes and reduced myelin-like membranes in mature oligodendrocytes (Zou et al., 2019, 2015). In addition, exposure to increased extracellular glutamate levels, as observed after microglia or astrocyte infection, inhibited oligodendrocyte maturation (Roth et al., 2021).

HIV-1 replication has also been observed in neural progenitor cells (Lawrence et al., 2004; Rothenaigner et al., 2007). Neural progenitor cells (NPCs) are the precursor cells of most neural cell types (Martínez-Cerdeño and Noctor, 2018). Hence, they play an important role in maintaining physiological brain functions. Importantly, HIV-1 replication in NPCs was found to be low (Lawrence et al., 2004; Rothenaigner et al., 2007), and additional studies confirming NPC infection are lacking.

Brain pericytes are another target for HIV-1 in the CNS and there is evidence that brain-pericyte infection affects BBB integrity (see above) (Nakagawa et al., 2012). Moreover, pericytes have been suggested to support latent HIV-1 infection, and therefore constitute an additional potential viral reservoir in the CNS (reviewed in (Naranjo et al., 2022)). Hence, more studies are warranted to evaluate their role in HIV-1-related neurocognitive impairment.

Of note, another way that neurons may be affected during HIV-1 infection is by blood-borne viral proteins that enter the CNS irrespective of HIV-1 neuroinvasion. Caccuri et. al. recently demonstrated that HIV-1 p17 protein enters the CNS via transcytosis across BMVECs (Caccuri et al., 2022). Free p17 can bind to different cell types, like monocytes, and induces multiple pathways that have been associated with neurocognitive impairment (Caccuri et al., 2016; Giagulli et al., 2012; Marini et al., 2008; Zeinolabediny et al., 2017).

At present, we lack a comprehensive understanding of the impact of these additional pathways on HIV-1-related neurocognitive impairment and future studies are warranted.

5.5. Neurons

Neurons are the most essential components of the CNS. The formation of neural circuits is crucial for the fundamental brain functions like memory formation, sensory perception, and motor function (Abraira and Ginty, 2013; Azarfar et al., 2018; Bonanomi, 2019; Kagan et al., 2022; Magee and Grienberger, 2020; Opitz, 2014; Šimić et al., 2021). HIV-1 does not infect neurons, but numerous effects have been described by which the release of inflammatory signals and viral proteins by non-neuronal cells lead to neuronal injury. This eventually causes neuronal dysfunction and is thought to be responsible for neurocognitive decline in PLWH. The effects on neurons have been well-reviewed previously, and include synaptic degradation, dendritic injury, impaired autophagy, or cell death (Ajasin and Eugenin, 2020; D et al., 2016; Ellis et al., 2023; González-Scarano and Martín-García, 2005; Kaul et al., 2001; Kaul and Lipton, 2006; Nardacci et al., 2005) As a result, we will limit the following discussion to those mechanisms with direct interactions with aging-related pathways.

6. Conserved molecular and cellular mechanisms associated with biological aging that are relevant for the study of HIV-1-related neurocognitive impairment

6.1. Chronic inflammation

Biological aging is associated with a *chronic inflammation*, which involves enhanced activation of the NLRP3 pathway (López-Otín et al., 2013). The term “inflammaging” describes the increased production of proinflammatory signals due to aging-related processes like *cellular senescence* or *compromised autophagy*, which are discussed below (López-Otín et al., 2013).

Importantly, it is generally accepted that chronic inflammation is a key driver of HIV-1 infection-induced neuronal injury. Infection of susceptible cells leads to an inflammatory response that induces neuronal injury by secretion of proinflammatory signals.

For instance, infection of primary human microglia with HIV-1 was shown to result in IL-1β expression and release (Walsh et al., 2014). IL-1β expression is associated with a reduced neuronal density in the cortex in a feline immunodeficiency virus-based animal model (Walsh et al., 2014). Exposure to HIV-1 gp120 alone can induce the NLRP3 inflammasome pathway suggesting that infection is not even necessary to trigger an inflammatory response in microglia (He et al., 2020; Walsh et al., 2014). Exposure of microglia to HIV-1 Tat protein induces NLRP3 and IL-1β expression as well (Chivero et al., 2017). Blocking NLRP3 with the pharmacological inhibitor glyburide and silencing its expression by siRNA resulted in decreased IL-1β secretion (Chivero et al., 2017). In addition to gp120 and Tat, HIV-1 Vpr and single-stranded RNA from the HIV long terminal repeat region (ssRNA40) trigger the NLRP3 inflammasome pathway, which was also shown to result in expression and secretion of neurotoxic factors, among them IL-1β (Mamik et al., 2017; Rawat et al., 2019). In astrocytes, for instance, HIV-1 Nef protein expression after transfection with expression plasmids has been shown to result in increased mRNA levels of the proinflammatory cytokines IL-6, IP-10 and TNFα (Jadhav et al., 2022).

Together, this suggests a pivotal role for the inflammatory response following microglial and astrocyte infection in HIV-1-induced neuronal injury. As biological aging is likewise linked to enhanced inflammatory processes, HIV-1-induced and aging-associated mechanisms combined may exacerbate neuroinflammation this way leading to the observed higher degree of neurocognitive impairment in older PLWH compared to age-matched non-infected individuals and younger PLWH (Vance et al., 2013).

Inflammation also drives the invasion of inflammatory peripheral macrophages into the CNS (Burdo et al., 2010, 2015). Interestingly, the higher CNS infiltration rate of monocytes from older individuals as previously described, has been associated with apoptotic morphology in nearby neurons (Ao et al., 2022). This apoptotic morphology was accompanied by an increase in neuronal gene expression of aging-related genes, evidence for astrocyte activation and expression of proinflammatory signals IL-1β and TNF-α (Ao et al., 2022). Another group found that the number of circulating brain-derived extracellular vesicles (EVs) that express monocyte activation markers was significantly higher in PLWH showing cognitive impairment compared to PLWH without cognitive impairment (de Menezes et al., 2022).

Increased CNS invasion of peripheral monocytes upon inflammation associated with age and HIV-1 infection may advance neuronal injury in older PLWH by contributing to immune-mediated neuropathogenesis and providing additional replication sites for HIV-1 (Koppensteiner et al., 2012).

Interestingly, a recent review on innate immune sensing of viruses and its impact on the CNS has put HIV-1 neuroinvasion and reservoir formation into the larger context of viral infection-mediated innate immune responses as cause for CNS pathologies (Singh et al., 2021). It is suggested that many effects observed for HIV-1 are not necessarily specific to the virus but may be due to the innate immune sensing of viral components by CNS-resident cells or their interaction with peripheral immune cells trafficking into the CNS upon inflammation (Singh et al., 2021). Therefore, irrespective of any direct HIV-1-induced effects on neural cells, the mere course of neuroinvasion and presence of HIV-1 antigens within the CNS may cause pathologies that are likewise mediated by other viruses and enhanced with age (reviewed in (Singh et al., 2021).

6.2. Compromised (macro)-autophagy

Compromised (macro)-autophagy is not only associated with neurodegenerative disease in general, but is suggested to be a driver of biological aging (Nixon, 2013; Schmauck-Medina et al., 2022). Since cellular autophagy has important recycling functions, a malfunctioning regulation of autophagy pathways might have tremendous impact on long-lived cells like microglia that exhibit turnover rates of several years, and of course of neurons (Lassmann et al., 1993).

HIV-1 Tat is involved in microglia activation by induced gene expression of autophagy-related proteins LC3-II, Beclin-1, ATG5 and ATG7 (Yang et al., 2022). In line with this, the mere addition of supernatant from HIV-1-infected microglia to neuronal cultures has been shown to inhibit neuronal (macro-)autophagy (Alirezaei, Kiosses, Flynn, et al., 2008). Impaired autophagy in the context of HIV-1 infection has been further associated with neuronal dysfunction and cell death (Alirezaei, Kiosses, and Fox, 2008). Moreover, different antiretrovirals of current cART regimens exert neurotoxicity by likewise dysregulating energy homeostasis, and autophagy, which is a virus-independent mechanism of induced CNS pathology in virologically supressed PLWH (Sanchez et al., 2016). Aged cells already show signs of compromised (macro)-autophagy with consequences on different cellular functions (López-Otín et al., 2013). HIV-1 infection, viral proteins, and cART may therefore contribute to the disturbed cellular autophagy which is already driven by biological aging.

6.3. Genomic instability

During the lifetime of a cell, ROS are known to occur naturally within cells and induce age-related DNA damage. This damage is typically repaired by cellular repair mechanisms (Evans et al., 1997). Nevertheless, DNA mutations accumulate over time (Evans et al., 1997). These aging-related mutations lead to a genomic instability that can cause aberrant gene expression and differential use of transcriptional pathways ultimately resulting in cellular dysfunction, senescence, or apoptosis (Barascu et al., 2012; López-Otín et al., 2013). Excess ROS production as in the context of disease accelerates the accumulation of DNA damage, and long-lived cells like microglia and neurons seem particular vulnerable (Evans et al., 1997; Mattson and Arumugam, 2018). In addition to direct effects on DNA molecules, ROS causes altered nuclear morphologies by a dysregulation of laminins (Barascu et al., 2012). This dysregulation of laminins contributes to the aging-related genomic instability (López-Otín et al., 2013).

Increased ROS levels are also associated with HIV-1 infection as, for instance, an important aspect of microglial response to HIV-1 infection or proteins is the increased production and release of ROS including nitric oxide (Borrajo et al., 2021). Since HIV-1 infection and biological aging are therefore both associated with ROS-induced genomic instability, PLWH may experience an accelerated form of associated cellular, and tissue damage.

Notably, HIV-1 infection also hampers the cellular repair mechanisms that are responsible for withstanding ROS-related DNA damage (Aukrust et al., 2005). HIV-1 Vpr in particular is implicated in reducing DNA repair mechanisms (Hrecka et al., 2016). Hence, HIV-1 seems to promote genomic instability in neural cells by elevating ROS levels as well as a by hampering the activity of DNA repair mechanisms, together potentially accelerating aging-related neurocognitive decline.

6.4. Telomere attrition

Telomere attrition is a hallmark of aging closely related to *genomic instability* (López-Otín et al., 2013). During normal aging, telomere attrition is a specific form of DNA damage mainly caused by the lack of telomerase activity and corresponding shortening of telomeres in most mammalian somatic cells. This can lead to senescence or apoptosis (López-Otín et al., 2013). HIV-1 and cART have been associated with an accelerated shortening of telomeres in PBMCs as well as in microglia (Breen et al., 2022; Hsiao et al., 2021). Interestingly, NPC-derived neurons are particularly sensitive to apoptosis by telomere damage during neurogenesis (Cheng et al., 2007). Hence, a potential effect on neurons exerted by HIV-1 or cART may have a lasting impact on neurogenesis.

6.5. Stem cell exhaustion

The hallmark of *stem cell exhaustion* may play a role in HIV-1-related neurocognitive impairment as well (López-Otín et al., 2013). Not only are stem cell functions reduced, but the ability of microglia to regulate adult neurogenesis declines with age (Vukovic et al., 2012). Although not analysed in this specific study, it is conceivable that the different HIV-1-induced effects on microglia affect this regulation. In addition, intrinsic interferon signalling has recently been shown to be beneficial for neural stem cell function in young mice, but detrimental in older mice (Carvajal Ibañez et al., 2023). Hence, HIV-1-induced activation of the interferon pathway as suggested in the context of HIV-1-related neurocognitive impairment (Singh et al., 2020), may impact neurogenesis particularly in older individuals. Importantly, adult neurogenesis is implicated in memory formation in the hippocampus (Lazarov and Hollands, 2016). This might contribute to the memory impairment observed in PLWH that suffer from neurocognitive impairment.

6.6. Epigenetic alterations

Epigenetic alterations comprise changes in DNA methylation patterns and chromatin remodelling, which are associated with aberrant transcriptional activity (Hannum et al., 2013; Wang et al., 2022). Interestingly, DNA methylation analysis of brain tissue samples from deceased PLWH showed that the epigenetic age of neural cells is increased by 7.4 years, whereas the epigenetic age of the respective blood cell samples was only increased by 5.2 years (Horvath and Levine, 2015). Clearly, the mechanism underlying this higher rate of epigenetic aging of neural cells remains to be elucidated, but these HIV-1-induced effects on DNA methylation patterns might aggravate aging-related aberrant transcriptional activity. In addition to DNA methylation patterns, chromatin remodeling is involved in aging-related aberrant transcriptional activity (López-Otín et al., 2013). Very recently, studying microglia in frontal cortex samples from PLWH linked proviral integration to chromatin remodeling, which was associated with activation of interferon signaling and cell migratory pathways while neuronal health gene expression was downregulated (Plaza-Jennings et al., 2022). Hence, biological aging as well as HIV-1 infection of neural cells induces changes in DNA methylation patterns and chromatin remodelling, both of which are associated with aberrant transcription.

6.7. Loss of proteostasis

HIV-1-infection can also be linked to the hallmark *loss of proteostasis*. Proteostasis, or protein homeostasis, is assured by cellular quality control mechanisms with roles for chaperons in protein folding and proteolytic systems (López-Otín et al., 2013). Hence, a compromised chaperon synthesis as observed with age leads to a loss of proteostasis (López-Otín et al., 2013). The co-chaperone host heat shock protein 70 (HSP70) binding protein (HSPBP1) inhibits viral replication (Chaudhary et al., 2016). HSPBP1 also participates in maintaining protein homeostasis by regulating protein degradation (Alberti et al., 2004). Since viruses evolved to overcome such restriction factors, HIV-1 Tat binds the HSPB1 promoter region to inhibit its activity and hence transcription of HSPB1 at least partly by interfering with Sp1 binding (Iyer et al., 2022). This does not only allow viral replication, but likely affects protein homeostasis. Another important player involved in protein homeostasis is mortalin. Mortalin is a chaperon involved in cellular stress responses and mitochondrial function, among other cellular pathways (Londono et al., 2012). Its expression is downregulated in Alzheimer's, Parkinson's disease, and also HIV-1-related neurocognitive impairment, which substantiates the importance of protein homeostasis to prevent neurodegenerative disease (Priyanka and Seth, 2022). Hence, its specific role in normal brain functioning and its association with disease is widely investigated. With respect to HIV-1, mortalin expression was specifically investigated in astrocytes, where HIV-1 Tat was shown to downregulate its expression (Priyanka et al., 2020). Overall, such effects on individual chaperone proteins by HIV-1 could promote the aging-related loss of proteostasis, together accelerating the accumulation of defective proteins. HIV-1 infection is also associated with an activation of the unfolded protein response (UPR) in astrocytes (Proulx et al., 2022). In this context, HIV-1 Tat induces overexpression of UPR markers ER chaperone BiP, ER stress sensors ATF6, PERK and IRE1 on its own (Campestrini et al., 2018). Hence, the mere secretion of Tat by other neural cells may disturb protein homeostasis in neurons.

6.8. Deregulated nutrient-sensing

HIV-1 infection can be linked to *deregulated nutrient-sensing*, a hallmark of aging based on the observation that calorie restriction or rather a decreased nutrient signalling slows the aging process (López-Otín et al., 2013). Insulin-like growth factor (IGF-1) produced mainly by the liver upon growth hormone (GH) secretion by the brain is a key player in this context. IGF-1 signalling declines during brain aging, and its role in the aging process is substantiated by mutagenesis of IGF-1 signalling participating proteins, namely GH, IGF-1 receptor, AKT, FOXO transcription factors and mTOR that have been linked to long life (López-Otín et al., 2013; Mattson and Arumugam, 2018). Interestingly, different HIV-1 proteins have been shown to affect these factors (Cui et al., 2009; Kino et al., 2005). Further, HIV-1 Tat was found to inhibit secretory activity of neuroendocrine cells as measured by GH release assay (Tryoen-Tóth et al., 2013). Besides IGF-1 signalling, the mTORC1 and mTORC2 complexes are important master regulators in nutrient-sensing (López-Otín et al., 2013). HIV-1 interferes with mTORC signalling throughout its entire infection cycle (reviewed in (Akbay et al., 2020)).

6.9. Mitochondrial dysfunction

Mitochondrial DNA is damaged by ROS in the same way as nuclear DNA (Mattson and Arumugam, 2018). Consequently, age has been found to affect the quality as well as the quantity of mitochondrial DNA (Zhang et al., 2017). The elevated ROS levels induced by HIV-1 CNS infection, therefore likely also contribute to the aging-related *mitochondrial dysfunction*. Additionally, HIV-1 Tat was found to inhibit sirtuins SIRT1 and SIRT3, which play a role in mitochondrial biogenesis and are associated with Alzheimer's and Parkinson's disease (Figarola-Centurión et al., 2022). HIV-1 Tat was furthermore shown to alter proteins in the mitochondrial-associated ER membranes in neurons, this way inducing mitochondrial stress (Arjona et al., 2023).

6.10. Cellular senescence

The increased accumulation of neural cells in the state of senescence, which is characterized by a proinflammatory and dysfunctional phenotype, is associated with neurodegenerative diseases (Baker and Petersen, 2018; Hou et al., 2019; López-Otín et al., 2013). The state of cellular senescence can be induced by several pathways including genomic instability as discussed before. This process is accompanied by cell cycle arrest and certain phenotypic changes, including a higher expression of proinflammatory signals (López-Otín et al., 2013). It is assumed that throughout a lifetime, the clearance and replacement of senescent cells is hampered, which leads to the accumulation of cells that are harmful to the surrounding tissue (López-Otín et al., 2013). Concerning the brain parenchyma, aged astrocytes exhibit lower waste collection activity, and neuronal and synaptic support (Casoli, 2022; Kress et al., 2014). They also secret increased levels of inflammatory signals IL-6 and IL-1β (Casoli, 2022). Aged microglia have been found to have lower surveillance capacities and likewise show increased secretion of inflammatory signals IL-6, IL-1β (Casoli, 2022).

In the context of HIV-1-related neurocognitive impairment, HIV-1 Tat was shown to induce senescence of neural cells as reviewed by Marino and colleagues (Marino et al., 2020). Moreover, cellular senescence can be induced by DNA damage. Hence, the elevated ROS levels produced by neural cells upon HIV-1 infection may advance the turnover rate of functioning into senescence cells in the brain. Indeed, ROS were shown to induce senescence in astrocytes, and in this stress-induced state, astrocytes downregulate genes involved in neuronal development and differentiation while upregulating pro-inflammatory genes (Crowe et al., 2016).

Notably, HIV-1 infection of brain cells can also be linked to the aging-related process of "senescence-induced-senescence". Increased expression of Connexin 43 was observed in astrocytes while studying human brain tissue sections derived from individuals suffering from HIV-1-related neurocognitive impairment (Berman et al., 2016). Astrocytes co-stained for HIV-1 p24 capsid protein, and therefore likely infected, showed higher levels of Connexin 43 (Berman et al., 2016). Treating cultured astrocytes with different HIV-1 proteins subsequently revealed that viral Tat is responsible for not only maintaining but increasing Connexin 43 expression, which is typically downregulated during inflammation (Berman et al., 2016). This Tat-induced increase led to increased gap junctional communication, which was suggested to contribute to the spread of neurotoxic signals (Berman et al., 2016). Of note, HIV-1 was shown to increase the gap junction-dependent communication in pericytes as well, indicating that this might be a common phenotype among some HIV-1-infected cell types (Cho et al., 2017). Interestingly, senescence-induced-senescence may be enhanced in this manner (Nelson et al., 2012). This phenomenon is based on the senescent cell-induced senescence in bystander cells by a gap junction-mediated cellular communication, which can also involve ROS (Nelson et al., 2012). Hence, HIV-1 infection might enhance this process in the brain by inducing elevated ROS levels as well as by counteracting the inflammation-mediated decrease in gap junctional communication (Berman et al., 2016; Cho et al., 2017).

6.11. Splicing dysregulation

Splicing dysregulation is yet another conserved aging-associated pathway suggested as a hallmark in 2022 (Schmauck-Medina et al., 2022). The aberrant splicing processes observed with age derive from changes in the expression of splicing regulatory proteins (SRPs) (Holly et al., 2013). This observation suggests that the use of small molecules to alter SRP expression could, for instance, rescue cells from some aspects

of aging-related cellular senescence (Latorre et al., 2017). Besides this role in cellular senescence, several SRPs and consequently aberrant alternative splicing are directly associated with neurodegenerative disease (reviewed (Latorre and Harries, 2017)). Importantly, HIV-1 replication is not only dependent on fine-tuned, alternative splicing, but HIV-1 infection affects the splicing of cellular pre-mRNAs (Brillen et al., 2017; Byun et al., 2020; Erkelenz et al., 2015; Sertznig et al., 2018; Stoltzfus, 2009; Widera et al., 2013, 2014). This was shown to be at least partially mediated by an infection-induced change in the expression of SRPs including those of the hnRNP and the SR family (Dowling et al., 2008).

6.12. Additional conserved aging-associated mechanisms

There are additional conserved aging-associated mechanisms that have been suggested as hallmarks of aging including m*icrobiome disturbance, altered mechanical properties, and altered intercellular communication*. As we have discussed them already in the context of the increased LPS production by the age-related shift in the microbiome and its possible effects on HIV-1 neuroinvasion, the HIV-1-induced leakiness of the BBB, and the important role of microglia, astrocytes and other neural cells in maintaining proper neuronal function, we limit this part to aging-associated mechanisms that have not been suggested as hallmarks before.

A feature of biological aging that is not separately listed as a hallmark of aging, but that we think is important to discuss is the deregulation of human endogenous retroviruses (HERVs) (Dopkins and Nixon, 2023). As a retrovirus, HIV-1 has been shown to affect HERV expression in different ways, including Tat-mediated upregulation of HERV-K RNA expression (Gonzalez-Hernandez et al., 2012), or Rev-mediated HERV-K nuclear RNA export (Dopkins and Nixon, 2023; O'Carroll et al., 2020). Deregulated HERV expression has been associated with neurodegenerative disease (reviewed in (Dopkins and Nixon, 2023)), as well as with the phenomenon of contagious cellular senescence by HERV-derived virus-like particles (Liu et al., 2023). Therefore, more research is warranted that deals with HIV-1-induced deregulation of HERVs in the context of aging and neurodegenerative disease.

Neuronal accumulation of hyperphosphorylated tau protein has been linked to memory impairment in PLWH (Gonzalez et al., 2023). In a cohort of 135 cognitively-assessed PLWH, immunohistochemistry of autopsy brain samples for neuronal hyperphosphorylated tau predicted worse memory encoding and retrieval (Gonzalez et al., 2023). Tau pathologies (a.k.a. tauopathies) are associated with neurodegenerative disease, Alzheimer's in particular, and strongly related to biological aging (reviewed in (Wang and Mandelkow, 2016)). Hence, a possible link between HIV-1-induced CNS injury and aging may occur at the level of aberrant tau phosphorylation.

Information is forwarded and processed between neurons via synaptic firing (Azarfar et al., 2018). The rate and timing of action potentials are the two determinants that encode the information (Azarfar et al., 2018). The generation of action potentials is dependent on ionic currents, which are mediated by voltage-dependent ion channels that are located throughout the neuronal membrane (Bean, 2007). A dysregulation of cellular ion homeostasis therefore affects neuronal signaling.

The calcium (Ca^{2+})-dysregulation hypothesis proposes that the age-related disruption of Ca^{2+} regulation plays a role in neuronal dysfunction (Thibault et al., 2001). Interestingly, exposure to HIV-1 proteins, Tat in particular, has been found to induce increased intracellular Ca^{2+} levels in neurons. This leads to functional disturbances which are considered to be drivers of HIV-1-related neurocognitive impairment (reviewed in (Hu, 2016)). A few studies have revealed important insights into the potential interaction of HIV-1-related and aging-related mechanisms on a molecular level.

In their focus on Ca^{2+} regulation, one study showed that age and HIV-1 proteins both independently reduce protein levels of the high-voltage activated Ca^{2+} channel $Ca_V1.2$ in rat medial prefrontal cortex pyramidal neurons (Khodr et al., 2018). $Ca_V1.2$ protein levels were lowest in old and HIV-1 protein expressing neurons (Khodr et al., 2018). Hence, the HIV-1 protein-mediated effects exacerbated the already existing aging-related effects on intracellular Ca^{2+}.

In another study, the K^+ ion channels of these pyramidal neurons were likewise found to be independently affected by age and HIV-1 (Chen et al., 2019). Interestingly, this study found that evoked firing was decreased with age but increased when comparing neurons from transgenic rats that served as model for HIV-1-related neurocognitive impairment to non-transgenic rats (Chen et al., 2019). This finding was linked to aberrant levels of K^+ ion channels (Chen et al., 2019). Despite those opposite effects mediated by aging and HIV-1 on the K^+ ion channels, the authors suggested that the observed hyperactivity by long-term exposure to HIV-1 may promote the aging-related decline (Chen et al., 2019).

Overall, HIV-1 infection has been associated with multiple cellular pathways involved in each of the hallmarks of aging (Fig. 5). Most of these associations are not exclusive to neural cells. However, long-lived cells like neurons or microglia may be particularly vulnerable to these interactions. Together, the depicted links substantiate a role for biological aging in the pathogenesis of HIV-1-related neurocognitive impairment, and hence warrant additional research.

7. Summary and outlook

Several studies focusing on the prevalence or severity of HIV-1-related neurocognitive impairment indicate that HIV-1-related neurocognitive impairment is more profound in the elderly. However, only few experimental studies actually deal with potential interactions between aging- and HIV-1-induced mechanisms in neural cells that may be responsible.

In an attempt to address the role that the biological age is playing, we have discussed the major pathways involved in HIV-1-related neurocognitive impairment with regard to potential interactions with conserved aging-related mechanisms.

Based on aging-related pathways like the BBB breakdown, limited neurogenesis, accumulation of senescent cells, and the higher CNS infiltration rate of monocytes, we think that biological aging likely constitutes a risk factor facilitating or driving HIV-1-induced CNS pathogenesis (Fig. 6, **i**).

On the other hand, HIV-1 is associated with mediating genomic instability, epigenetic changes, loss of proteostasis, mitochondrial dysfunction, splicing dysregulation and most of all, (brain) inflammation, all of which are also HIV-1-independent age-related mechanisms associated with neurodegenerative disease (Fig. 6, **ii**).

Importantly, individuals living with HIV-1 may also be subject to a host of health conditions (e.g., cardiovascular disease, chronic renal disease, or frailty) that can also impact neurocognitive decline (Van Epps and Kalayjian, 2017). In some reports, HIV-1 infection has been associated with higher levels of stress, depression, and anxiety compared to the general population (Chaponda et al., 2018; Ciesla and Roberts, 2001; Hémar et al., 2022; Morrison et al., 2002). Recent evidence suggests that such psychological conditions may accelerate biological aging (Poganik et al., 2023; Polsky et al., 2022)

We use the general term accelerated aging in our scheme to also include the potential of such co-morbidities and psychological conditions that are likewise attributed to HIV-1-induced accelerated aging (Guaraldi et al., 2015; Negredo et al., 2017; Wing, 2016), and that may impact neurocognitive decline in PLWH in a more indirect fashion.

Research on age-related mechanisms in neural cells has been hampered by a lack of human-relevant model systems in the past. Notably, there is a transgenic HIV-1 gp120 expressing mouse model, which shares key features and differential gene expression associated with HIV-1-induced neuropathology in humans and moreover, shows age-related behavioral deficits (D'hooge et al., 1999; Maung et al., 2014; Toggas et al., 1994). While findings in mice cannot always be easily

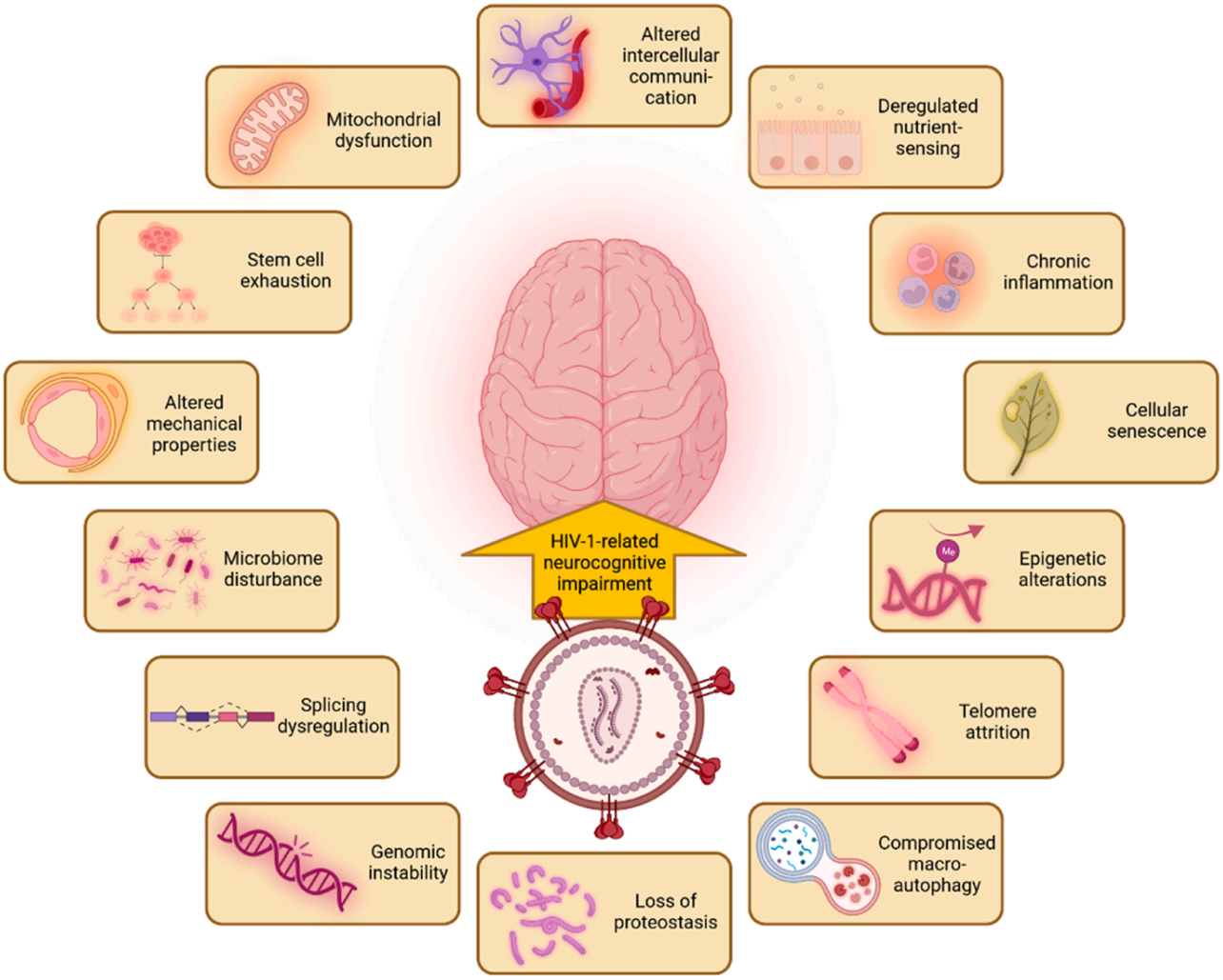

Fig. 5. Conserved molecular and cellular mechanisms associated with biological aging that are relevant for brain aging in people living with HIV. The probable interactions between aging-associated pathways and HIV-1 infection-induced effects on the CNS, which we have discussed here, suggest that the conserved molecular and cellular mechanisms associated with biological aging that are often summarized as the *hallmarks of aging* (see text) are relevant for brain aging in PLWH.

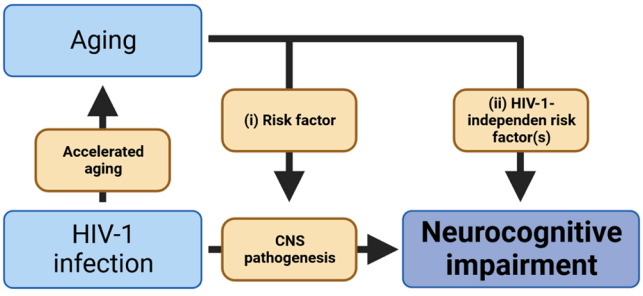

Fig. 6. Neurocognitive impairment trough biological aging as risk factor and consequence of HIV-1 infection. Biological aging affects HIV-1-related neurocognitive impairment likely in two ways. First, the biological age constitutes an intrinsic risk factor for the HIV-1-induced CNS pathogenesis. Secondly, biological age is an HIV-1-independent risk factor for neurocognitive impairment, and HIV-1 infection accelerates the cellular and molecular pathways underlying biological aging of PLWH, particularly in the brain.

extrapolated to humans and this transgenic mouse model relies solely on expression of the viral gp120 envelope protein, it may provide a starting point to investigate the impact of aging on some mechanisms associated with HIV-1-related neurocognitive impairment.

In this regard, the recent introduction of directly induced neurons (iNs) has paved the way for more elaborate studies on the effects of aging on neuronal function in healthy and diseased individuals (Church et al., 2021; Herdy et al., 2019; Zhou-Yang et al., 2021). These iNs are the product of transdifferentiated dermal fibroblasts, or other cell types and were shown to harbor aging-related defects that are deleted from induced pluripotent stem cell (iPSC)-derived neurons by the induction of the stem cell state prior to differentiation (Mertens et al., 2015). This neuronal cell culture model revealed not only a general age-dependent loss of nucleocytoplasmic compartmentalization but linked certain transcriptional pathways to Alzheimer's disease, which was not possible with iPSC-derived neurons (Mertens et al., 2021, 2015). Hence, these iNs might be key to study also aging-related mechanisms involved in HIV-1-related neurocognitive impairment.

Additional factors such as the viral genotype or genetic predisposition of the host, which are often not included in clinical research-based studies, can impact HIV-1-related neurocognitive impairment (Ogishi and Yotsuyanagi, 2018). There is evidence that HIV-1 subtypes exhibit different capacities to cause neurological disease (reviewed in (Sacktor, Nakasujja, et al., 2007)). HIV-1 subtype B Tat was shown to potentiate neuronal toxicity in the SK-N-MC cell line to a higher degree than subtype C Tat by differently affecting the expression of synaptic genes (Samikkannu et al., 2014). Different host genes are associated with the

progression of HIV-1-related neurocognitive impairment as well (Jia et al., 2017; Shapshak et al., 2011). A study by Victor Valcour and colleagues showed that carrying at least one allele of ApoE4, foremost known in the context of Alzheimer's disease, is associated with a decreased cognitive performance as well as brain atrophy in PLWH over 60 years of age (Wendelken et al., 2016). Tice et al. have further linked single nucleotide polymorphisms rs3875089 and rs3763040 in the aquaporin 4 gene, which is associated with waste clearance in the brain, to lower neuropsychological test scores in PLWH, but in non-infected controls (Tice et al., 2023). In addition to genetic factors, there is evidence that cART itself can affect cellular metabolisms in the brain (Kaur et al., 2023; X. Yang et al., 2023). Therefore, future clinical and basic research studies should address these aspects while investigating the role of aging in HIV-1-related neurocognitive impairment.

Concerning effective treatment of PLWH suffering from neurocognitive symptoms, cART initiation in treatment-naïve, or non-adherent PLWH has been shown in some studies to restore neurocognitive capacities to some extent (Becker et al., 2012; Dietrich et al., 2023). A recent randomized, double-blind, placebo-controlled, 96-week trial with 191 individuals, however, did not support intensification of cART as treatment for HIV-1-related neurocognitive impairment in PWLH strictly adhering to cART (Letendre et al., 2023). Hence, novel approaches must be considered to alleviate symptoms independent of cART. Given the suggested roles for biological aging outlined in this review, approaches that aim at cellular rejuvenation may be considered to further mitigate, or reverse HIV-1-induced CNS injury in the future (Macip et al., 2023; Ostermann and Evering, 2023; J. H. Yang et al., 2023).

In conclusion, HIV-1-related neurocognitive impairment is still of global concern in the era of effective antiretroviral therapy, and multiple pathways related to biological aging are involved in its underlying pathomechanisms.

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Declaration of Competing Interest

THE is a paid consultant for Tonix Pharmaceuticals. PNO declares no competing interests in relation to this work.

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Author contributions

PNO and THE discussed the scope of the review. PNO wrote the first draft. All authors agreed to the final version of the manuscript.

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