# Virus and Accelerated Brain Aging

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Contributor: Alexey LARIONOV

Accelerated brain aging is often related to enhanced neurodegeneration, which includes loss of neuronal cell structure and function due to (1) metabolic changes, (2) neuronal cell death (3) decline in the neuronal network, (4) neuronal functional deficiency, (5) decline in neuronal regeneration, or (6) a combination of the mentioned reasons. It also includes functional and structural changes of the glial cells, resulting in demyelination and gliosis. Neurodegeneration is aggravated by neuroinflammation, which contributes substantially to accelerated brain aging. Neuroinflammation usually correlates with the activation of microglia, the resident macrophages and innate immune cells of the brain.

Keywords: brain aging ; microglia ; neuroinflammation ; neurotropic virus ; HIV ; flavivirus ; SARS-CoV-2 ; human herpes virus

## 1. Overview

Microglia are the resident immune cells of the central nervous system contributing substantially to health and disease. There is increasing evidence that inflammatory microglia may induce or accelerate brain aging, by interfering with physiological repair and remodeling processes. Many viral infections affect the brain and interfere with microglia functions, including human immune deficiency virus, flaviviruses, SARS-CoV-2, influenza, and human herpes viruses. Especially chronic viral infections causing low-grade neuroinflammation may contribute to brain aging. This review elucidates the potential role of various neurotropic viruses in microglia-driven neurocognitive deficiencies and possibly accelerated brain aging.

## 2. Brain Aging

Aging is a programmed biological process, affecting all biological systems, controlled by genetic [1] and epigenetic mechanisms [2], and influenced by environmental factors [3][4]. The principles of aging apply also to humans [5], to all organ systems and to the brain [6]. Physiological aging of the healthy brain is an age-dependent biological process and consists of deterioration of structure and function [7][8][9][10][11][12]. However, brain aging can be accelerated by multiple factors, due to traumatic events [13][14], following neurovascular conditions [15][16][17], or related to specific brain diseases, including Alzheimer's and Parkinson's disease. Accelerated brain aging is often related to enhanced neurodegeneration, which includes loss of neuronal cell structure and function due to (1) metabolic changes [18], (2) neuronal cell death [19] (3) decline in the neuronal network [20], (4) neuronal functional deficiency [21], (5) decline in neuronal regeneration [22][23][24], or (6) a combination of the mentioned reasons. It also includes functional and structural changes of the glial cells, resulting in demyelination and gliosis [25][26][27]. Neurodegeneration is aggravated by neuroinflammation, which contributes substantially to accelerated brain aging. Neuroinflammation usually correlates with the activation of microglia, the resident macrophages and innate immune cells of the brain [28][29]. Thus, the role of microglia in neuroinflammation and brain aging will be explored. Neuroinflammation is often induced by viral infections culminating in encephalitis, which is an inflammatory process of the brain that usually involves the microcirculation, neurons and glia cells, including microglia, as well as infiltration of brain tissue by other cells of the innate and acquired immune system like monocytes, dendritic cells, granulocytes and various subpopulations of T lymphocytes [30][31][32][33]. Encephalitis can be mild, with reversible functional deficiencies, but it can also result in severe structural damage with corresponding functional defects and sequelae [34]. Viruses that affect the brain and may contribute to accelerated brain aging will be reviewed. Finally, the role of microglia in viral brain infections and corresponding accelerated aging of the brain will be unfolded [35].

## 3. Neuroinflammation in Brain Aging

Neuroinflammation relates to a pathological immune response in the brain. It can be sudden and excessive, or subliminal, as well as short-lived or chronic. It may include a cellular immune response of the innate [36] and/or the acquired immune system [37], as well as humoral (antibodies) [38] and soluble factors (chemokines, cytokines) [39][40][41]. It certainly includes

general basic cellular responses to inflammatory inducers and mediators (toxins, microbial products, metabolic or other damage-related cellular molecules), recognized by corresponding receptors, i.e., Pattern Recognition Receptors (PRRs) for Pathogen-Associated Molecular Patterns (PAMP) and/or Damage-Associated Molecular Patterns (DAMP) [42][43][44][45][46]. In that respect, all cells of the brain may respond to inflammatory signals, including neurons, astrocytes, oligodendrocytes, microglia, and the cells of the blood vessels (endothelial cells, pericytes, myofibroblasts, vascular dendritic cells, etc.) and the meninges.

There is increasing evidence that the aging immune system is skewed towards a more inflammatory status, increasing the probability and intensity of neuroinflammation [47][48][49]. In addition, a strong systemic inflammatory immune response may influence the brain function and cause corresponding syndromes and disease, as well as induce or aggravate neuroinflammation [50][51][52].

Neuroinflammation interferes with the brain function, may cause structural damage, influence regeneration, and modulate remodeling. It may induce neuronal cell death directly by acting on neurons, or indirectly through actions via astrocytes, oligodendrocytes and microglia, mediated by various neural and inflammatory factors [25][53]. Neuroinflammation and its consequences contribute to physiological brain aging and certainly enhances and accelerates the aging process [19][54]. Neuroinflammation has been shown to contribute to Alzheimer's and Parkinson's disease [29][55][56]. It may also play a role in certain psychiatric diseases, including depression, schizophrenia, autism spectrum disorders, etc., some with increasing incidence in aged individuals [57][58][59][60][61].

A plenitude of inflammatory cytokines may contribute to neuroinflammation and its pathological consequences in the brain, including interferons, interleukin-1, 6, 17, 23, and 34, tumor necrosis factor and related cytokines and receptors [62][63][64][65][66][67][68][69][70]. Interestingly, there is evidence that certain cytokines may affect specific brain regions or functional structures. For example, interferon-gamma has been correlated with effects in the hippocampus, where decreased neurogenesis and neuronal apoptosis has been shown in a mouse model [71], whereas interleukin-6 has been shown to disrupt synaptic plasticity [72]. The inflammatory cytokines may enter the brain from the blood circulation through the disrupted blood–brain barrier, or may be produced by infiltrating immune cells, as well as by the local immune cells, i.e., the microglia.

## 4. Conclusions

The more we age, the more our immune system gets toward a more inflammatory status. The increased systemic inflammatory immune status also affects microglia, resulting in decreased physiological neuroregeneration and remodeling [49][73]. The inflammatory status is certainly enhanced and accelerated through frequent or chronic viral infections. The increased and chronic inflammatory status in the brain may contribute to neurodegeneration due to increased neuronal cell death and reduced neurogenesis, reduced remodeling and irreparable damage to the neuronal network, resulting in an enhanced or accelerated brain aging process. In the context of microglia and viral infection, most research has been done in HIV, where the association has been shown for neurocognitive decline [74][75][76][77]. However, there is little information available about the cellular and molecular mechanisms that contribute to or influence the chronic HIV infection and corresponding involvement of microglia, which requires more future research. The same accounts for other viruses, including flaviviruses, human herpes viruses and SARS-CoV-2.

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