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Author(s)	Olsen, Laura K.; Dowd, Eilís; McKernan, Declan P.
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Review Article

A role for viral infections in Parkinson's etiology?

Laura K. Olsen, Eilis Dowd and Declan P. McKernan

Pharmacology and Therapeutics, National University of Ireland, Galway, Ireland

Correspondence: Declan P. McKernan (declan.mckernan@nuigalway.ie)

Despite over 200 years since its first description by James Parkinson, the cause(s) of most cases of Parkinson's disease (PD) are yet to be elucidated. The disparity between the current understanding of PD symptomology and pathology has led to numerous symptomatic therapies, but no strategy for prevention or disease cure. An association between certain viral infections and neurodegenerative diseases has been recognized, but largely ignored or dismissed as controversial, for decades. Recent epidemiological studies have renewed scientific interest in investigating microbial interactions with the central nervous system (CNS). This review examines past and current clinical findings and overviews the potential molecular implications of viruses in PD pathology.

Introduction

Parkinson's disease (PD), the most common neurodegenerative motor disorder, is generally characterized by the selective degeneration of dopaminergic neurones in the substantia nigra pars compacta (SN) of the midbrain, resulting in decreased dopamine (DA) transmission throughout the nigrostriatal pathway [1]. PD symptoms include resting tremors, unstable posture, bradykinesia, rigidity, and non-motor symptoms (such as dysphagia, olfactory impairment, sleep disturbances, dementia, and constipation) [2-4]. This progressive neurodegenerative disease can be familial (associated with early onset) or sporadic [5-8]. Hallmark pathological features of both familial and sporadic PD include uncontrolled protein aggregation (primarily α-synuclein fibrils forming Lewy bodies), oxidative stress (OS), mitochondrial dysfunction, chronic neuroinflammation (including microglia activation and astrogliosis), and autophagy disruption [5,9-11].

Despite over two centuries of investigation, the cause(s) of most cases of PD are still unknown. Epidemiological studies suggest there is a gene–environment interaction involved in the development of sporadic/idiopathic PD (iPD). Previous studies suggest a correlation between iPD development and exposure to pesticides or heavy metals, traumatic brain injury, and viral/bacterial infection [12-14]. Although multiple reviews describe the association between pesticides and PD (most notable rotenone and paraquat) [15,16], there are few reviews detailing all the epidemiological, *post-mortem*, and preclinical evidence surrounding the association between viral infections and PD. As urgently expressed by both scientists and clinicians in a recent article by Itzhaki et al. [17], previous studies identifying microbial associations with Alzheimer's disease (AD) (the most common neurodegenerative disorder) [18,19,20,21,22] have largely been ignored or dismissed as controversial despite the current lack of progress for understanding or curing this disease. Similarly, the same lack of progress and dismissal of previous epidemiological findings regarding viral infections can be said for PD. The purpose of this review is to revisit historical conclusions, provide a comprehensive update on recent clinical findings, and overview the potential molecular and cellular implications of neurotropic viruses in PD pathology.

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Viruses as a risk factor for PD: sifting through historical and clinical evidence

The first suggestion of a relationship between viral infections and PD was the 1920–1930s influenza epidemic, which was associated with encephalitis lethargica (EL) [23]. Although EL patients exhibited

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Table 1 Viral infection associations with PD

Viral infection	Relation to PD	Study
HSV	↑ incidence (HSV-I)	[49-51,55]
-Enveloped, linear dsDNA genome (152–154 kb)	↑ incidence	[53]
-Causes blistering of mouth/genitals, latency in neurones	↑ incidence (HSV-I)	[54]
	No association	[52]
Influenza virus A	↑ incidence	[53]
-Enveloped, linear ssRNA(–) genome (13.5 kb)	↑ incidence	[52]
-Causes fever, cough, runny nose, malaise	No association	[49]
Measles virus	↓ incidence	[52]
-Enveloped, linear ssRNA(–) genome (15–16 kb)	No association	[53]
-Causes rash, white spots, cough, red eyes	No association	[55]
Cytomegalovirus	↓ incidence	[52]
-Enveloped, linear dsDNA genome (∼200 kb)	No association	[51]
-May cause mononucleosis, pnuemonia	No association	[54]
Coronavirus	No association	[56]
-Enveloped, linear ssRNA(+) genome (27–32 kb)		
-Causes upper/lower respiratory infection, sometimes gastroenteritis		
Mumps	↑ incidence	[53]
-Enveloped, linear ssRNA(–) genome (15 kb)		
-Causes parotid gland swelling, malaise		

drastic irregularities in disease progression and displayed 'symptomatological polymorphisms,' EL has been described as a type of 'sleeping sickness' which can include headache, nausea, fever, uncontrollable sleepiness, catatonia, and sometimes coma [24]. The EL epidemic coincided with an equally significant influenza pandemic (the Spanish influenza), leading many clinicians and other prominent scientists from that time to believe there was a causal relationship (or at least an epidemiological association) between these conditions [25]. Multiple studies investigating the preserved brain samples of EL patients from the epidemic years (1918–1930) found no evidence of the 1918 influenza virus in these tissues [26-28]. Also, 1918 influenza-derived sequences revealed mutations in two surface protein-encoding genes that suggest this viral strain was incapable of replicating outside of the respiratory system [29,30]. Reports from more current cases of EL suggest that EL may be an auto-antibody disorder [23,31-37].

Since the EL epidemic, numerous cases of post-encephalitic Parkinsonism (PEP) after certain viral infections (H5N1, coxsackie virus, Japanese encephalitis B., St. Louis viral encephalopathy, and HIV) have been reported, but these cases of Parkinsonism often do not exhibit the same cellular or molecular pathologies as seen in PD and are suggested to be 'phenocopies' of PD [38-44]. Although these acute cases of viral infection did not present with classical PD, these findings (along with the believed EL association with PD) led to multiple clinical studies in the late 1970s and early 1980s investigating the relationship between viral infections and PD.

Studies examining the relationship between viruses and PD are detailed in Table 1. A study by Elizan et al. [45] found a significant relationship between viruses (herpes simplex virus (HSV), measles, and influenza A) and iPD, but these findings may be confounded since their control group included amyotrophic lateral sclerosis and AD patients (conditions which have since been suggested to be associated with certain viral infections themselves). Another set of studies found an increased incidence of PD amongst those chronically infected with hepatitis C virus (HCV), but these studies are confounded by the fact that some HCV patients received interferon (IFN) treatments; with a follow-up investigation finding a much stronger relationship between IFN-treated groups and PD (249 PD incidents/100000 person-years) than non-IFN-treated groups (30 PD incidents/100000 person-years) [46-48]. Multiple studies by Marttila and colleagues, using a variety of antibody detection techniques (complement fixation, RIA, indirect immunofluorescent assay, microindirect hemagglutination), found a significant increase in HSV antibody titers and mean HSV titer in iPD patient serum [49-51]. A study using the microindirect hemagglutination test was able to differentiate between HSV-I and HSV-II; finding that increases in antibody titers and mean titer amongst iPD patients was specific to HSV-I only (not HSV-II) [51]. Other studies have questioned iPD patients for their history of HSV, measles, and influenza A infection with conflicting results (see Table 1). Although a significant association was found between severity and frequency of influenza A infection and PD incidence (with no association for HSV), the conclusions based on these studies are limited in that they rely on accurate patient memory and interpretation of their condition (patients cannot be expected to correctly diagnose their previous exposure or infection with viruses)

[52,53]. A more recent study that examined PD patient serum found a more frequent incidence of HSV-I infections amongst iPD patients [54], further supporting the findings of the Marttila studies. Based on the aforementioned clinical evidence, HSV-I and strains of influenza A will be reviewed for their neurovirulence and association with PD-like pathology in the central nervous system (CNS). Molecular and cellular events associated with HSV-I/influenza A infection will be discussed for their potential implications in PD.

CNS viral entry: HSV-I and influenza A

Since the primary disease pathology characteristics of PD exist in the CNS, it may be relevant (but possibly not crucial) to study the neurovirulence of viruses associated with PD. HSV-I and influenza A have very different life cycles, resulting in different strategies for survival/replication within the host. Influenza A is generally a transient infection, lasting only a few weeks inside the host [57]. On the other hand, an acute infection of HSV-I (presented as epithelial blistering in the mouth or genitalia) is followed by viral latency, which is generally established in the trigeminal ganglia (TG) [58]. Although dormant, HSV-I is a chronic infection that maintains latency in sensory ganglia that innervate the brainstem and cerebellum of the CNS [59,60]. Primarily residing in the respiratory system during acute infection, influenza A can enter the CNS through the olfactory nerve [61]. Found to be axonally transported via cytoskeleton intermediate filaments, influenza A can follow olfactory neurone projections through the cribiform plate in the nasal cavity into the olfactory bulbs and olfactory tracts of the CNS [62,63].

Previously, viral entry of either HSV-I or influenza A into the CNS was considered fatal (or nearly fatal) via the rare condition of herpes simplex encephalitis (HSE) or acute encephalitis, respectively [38,64,65]. More recent findings now suggest that viral entry into the CNS does not necessarily result in a drastic, usually fatal, immune response. Although many studies have not found the existence of HSV-I DNA or antigens in *post-mortem* PD patient brains [66,67]; multiple studies have found HSV-I DNA in the brains of normal aged humans and AD patients [22,66,68-70]. The presence of HSV-I DNA was associated with increased age and the characteristic amyloid-β plaques found in AD [70,22]. Determining the neurovirulence and brain cell localization of influenza A in the CNS of PD patients is far more difficult since it is a transient infection. Although partially determined by the route of infection, preclinical mouse models of neurovirulent strains of influenza A have found this infection to successfully enter the CNS and localize in the SN, thalamus, hippocampus, locus coeruleus, ganglia (trigeminal, vagal, spinal, and sympathetic trunk ganglia), olfactory bulbs, and thoracic spinal cord around day 10 post-infection [39,71-73]. Influenza A antigens were also found to preferentially exist in catecholaminergic neurones, meninges, and ependymal areas [74]. Despite influenza A entry into the CNS in these mouse models, viral replication and maintenance in the CNS did not extend past 2 weeks, and was generally non-existent in the CNS by day 21 post-infection. More relevant to PD pathology, the neurotropic H5N1 influenza virus was found to induce long lasting microglia activation and α-synuclein phosphorylation and aggregation in the mouse SN post-infection [39,75].

An increased incidence of HSV-I DNA in the CNS and increased sensitivity to respiratory infections amongst the elderly [76,77] is worth noting since the greatest risk factor for PD is old age [78]. With age, the blood–brain barrier (BBB) becomes more permeable, resulting in more fluid entry of peripheral proteins into the CNS (including neurotoxic peripheral pro-inflammatory mediators) [79]. The immune system is also compromised in the elderly, with increases in pro-inflammatory cytokines and decreases in lymphocytes [80]. Disruptions to the BBB and normal immune processes amongst the aged population could also result in increased entry of HSV-I and influenza A into the CNS during infection/HSV-I reactivation. Since HSV-I and some strains of influenza A have demonstrated their ability to infect the CNS (especially amongst the elderly) without immediately fatal consequences, the effects of these viral infections in host neurones in the CNS will be reviewed, with a focus on PD-related pathology.

Viral infection in the CNS: inflammation, synaptic dysfunction, and autophagy disruption

Upon viral infection, the host immune system usually becomes activated and attempts to remove or destroy the invading pathogen via inflammatory mediators, autophagy degradation, or sometimes controlled cell death of infected cells [81]. Although viral pathogens have evolved multiple ways of evading the host immune response (and so host clearance of viral pathogens), host immune circumvention is dependent on virus strain, evasion strategy, and host cell type. Of relevance to PD, the viral evasion of the host immune response may be modulated by BBB integrity, CNS immune cell sensitivity, and duration/severity of infection. The next few sections review viral modulation of the host immune/autophagy response due to HSV-I or influenza A infection. Virus mediated inflammation, synaptic dysfunction, and autophagy disruption in the CNS will be discussed.

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Neuroinflammation

The human immune system is divided into the adaptive (memory-based specific response) and innate (genetically conserved, non-specific response) immune systems [82]. Macrophages are able to attack pathogens due to pattern-recognition receptors (PRRs) that have evolved to recognize pathogen-associated molecular patterns (PAMPs) [83,84]. Meanwhile, the adaptive immune response uses lymphocytes (B and T cells) to 'remember' and attack the pathogen more efficiently [85,86]. This immune response sometimes includes cytotoxic lymphocytes, which kill and destroy infected host cells.

Of importance to HSV-I, cluster of differentiation 8 ($CD8^+$) T cells have been found to have HSV-I epitopes and block reactivation [87,88]. Although involved in hindering HSV-I reactivation, there are suggestions that these T cells lead to chronic inflammation. Residual lymphocytes were found to recognize HSV-I during latency in the TG, resulting in cytokine release, T-cell exhaustion, and eventual allowing of viral reactivation [89-91]. The H5N1 influenza A strain was also found to induce excessive peripheral T-cell activation [92]. There is evidence of T-cell population modulation in PD as well. T-cell population increase/decrease and impairment in PD depends on T-cell type, and more recently T cells have been found to recognize α-synuclein epitopes [93,94]. Interestingly, recent studies identified homologous cross-reactivity between HSV-I and α-synuclein, suggesting that HSV-I may induce an autoimmune response [95]. Indeed, auto-antibodies against HSV-I peptide were cross-reactive with an α-synuclein epitope [95].

While lymphocytes are involved in the adaptive immune response, the innate immune system also initiates an immediate response due to PAMPs. A key set of PRRs regulating the innate immune system are the Toll-like receptors (TLRs). TLRs are glycoprotein transmembrane receptors that recognize PAMPs (such as lipopolysaccharides, dsDNA/RNA, ssRNA) [96]. Of significance to HSV-I and influenza A, TLR3 is known to recognize viral dsRNA that is present during the viral life cycle within infected host cells [97,98]. TLR3 activation leads to pro-inflammatory cytokine and type I IFN-α/β production, and regulation of DNA expression through nuclear factor κ-light-chain-enhancer of activated B (NF-κB) and IFN regulatory factor (IRF) activation [99].

Neuroinflammation in PD patients has previously been investigated to characterize potential biomarkers. Genetic mutations in PD-related genes (*lrrk2* and *parkin*) have been found to regulate the immune system response [100-104]. Also, single nucleotide polymorphisms in the MHC-II (an antigen-presenting component of specific adaptive immune cells) locus were associated with an increased incidence of PD [105-108]. *Post-mortem* studies have found increased levels of pro-inflammatory cytokines [109]. They also found increased levels of IFNs and p65 subunits of NF-κB [110]. Cerebrospinal fluid (CSF) and peripheral levels of cytokines are also elevated in PD [110,111]. Although the role of these cytokines/IFNs in PD is unknown, animal models have demonstrated that increases in pro-inflammatory mediators results in dopaminergic neurodegeneration [112,113]. Examination of the TLR profile in animal models found increases in TLR3/4 expression in the striatum in response to OS and the pesticide rotenone, possibly leaving these cell populations/brain regions more sensitive to an infection [114]. Interestingly, certain viral infections have found ways to circumvent IFN-stimulated pathways, possibly allowing them to enter and remain dormant in the CNS.

Although the host immune system is well evolved to combat viral infections through type 1 IFNs and IFN-stimulated genes (ISGs), HSV-I and influenza A have also evolved ways to evade this host immune response. HSV-I proteins inhibit NF-κB and IRF3 (a TLR3 downstream regulator of IFNs) activation [115-117]. The influenza A non-structural protein 1 (NS1) prevents the host innate immune response and cellular apoptosis of infected cells by suppressing IFN activation through multiple routes [118]. Also, NS1 regulates IFN-α/β receptor subunit 1 (IFNAR1) surface expression [119]. Due to suppression of the innate immune system, influenza A infection of neurones only leads to increases in tumor necrosis factor-α (TNF-α) release, not interleukin-6 (IL-6) or IFNs [120].

Despite multiple HSV-I proteins working to dampen IFN signaling, still there has been clear evidence of IFN signaling and regulation of viral replication in HSV-I infected cells. This is not surprising since HSV-I inhibition or activation of IRF3 appears to be cell-type dependent [117]. Sensory neurones, where HSV-I latency is generally maintained, are innately unable to mount a large IFN response [121,122,123]. This may be why sensory neurones are ideal for HSV-I to maintain latency, but even so, some level of IFN signaling may be required for HSV-I reactivation. Latency-associated transcripts (LATs) have not been found to produce an inflammatory cytokine/IFN response themselves, but instead may require some cytokines/IFNs to initiate reactivation [124,125]. One study suggested that IFNs regulate LAT expression in a way that benefits HSV-I infection; by promoting neurone cell survival throughout latency, HSV-I is provided an opportunity for reactivation and viral spread [125]. Interestingly, neuronal IFN-β suppression was associated with α-synuclein accumulation and PD-like neurodegeneration [126].

Although HSV-I and influenza A viruses have evolved ways to circumvent neuronal innate immune sensing of infection, other CNS cells can still sense and defend against pathogens (see Table 2). Glial cells in the CNS mainly

Table 2 Viral induced molecular/cellular changes related to PD pathology

Theme	Condition		
	PD	**HSV-I**	**Influenza A**
Inflammation			
Glial cells	Activated microglia and astrogliosis in PD midbrain [130,131]	↑ microglia in HSV-I infected ependymal [132]	H1N1 ↑ astrogliosis and activated microglia in SN and VTA [133]
T cells	T-cell modulation and recognition of α-synuclein epitopes in PD [93,134]	Exhausted T cells in HSV-I infected brain stem and TG express HSV-I epitope [87,89,132]	H5N1 causes excessive peripheral T-cell activation [92]
Cytokines	↑ CSF and peripheral cytokines in PD [110,111]	T-cell associated cytokines ↑ in HSV-infected TG [88,90,91]	H5N1 ↑ astrocyte/neuronal cytokines [135,136]
Autophagy			
Disruption	Autophagic and lysosomal defects in PD neurones [137,138]	PKR inhibition disrupts autophagy/autophagosome formation [139,140,141]	PKR inhibition and autophagosome/lysosome fusion blocked [142,143]
Synapse			
Proteins	Redistribution of synaptic proteins in PD models [144,145]	↓ synapsin-1 and synaptophysin in murine cortical neurones [146,147]	H5N1 inhibits PSD-95; SNAP25 differentially expressed in neonatal infection [148,149]
Activity	↓ synaptic connectivity and glutamatergic synapse loss in PD models [150,151]	Reduced NMDAR and synaptic activity in HSE patients [146,152]	↓ neuronal excitatory synaptic activity and amplitude [153]

As detailed above, multiple parallels can be drawn between PD pathology and the potential molecular and cellular consequences of HSV-I/influenza A infection. Abbreviations: NMDAR, N-methyl-d-aspartate receptor; PKR, protein kinase R; PSD-95, post-synaptic density protein-95; SNAP25, synaptosomal-associated protein 25; VTA, ventral tegmental area.

function as regulators of the cellular environment to promote healthy neuronal cell function. Astrocytes (the most abundant cell type in the CNS) support neurone homeostasis by regulating synaptic activity, assisting in BBB formation, and interacting with immune cells. They regulate neurotransmission and metabolism by controlling extracellular potassium levels, uptake of neurotransmitters (such as glutamate), and storing glycogen/exporting lactate [127]. Microglia cells act as resident immune cells in the CNS, with the capability of sensing, engulfing, and degrading invading pathogens [128]. The activation of microglia can have neuroprotective or neurotoxic effects depending on their microenvironment. When activated, some microglia release reactive oxygen species (ROS), inducible nitric oxide synthase (iNOS), and cytokines [129]. These oxidative species and cytokines interact with dopaminergic neurones to regulate cell fate during stress [129].

Astrocytes and microglia participate in the defense against viral spread throughout the CNS [154]. Although HSV-I may find a safe haven in sensory neurones, replication in these neurones for reactivation may alert neighboring astrocytes. These cells recognize extracellular dsRNA since they can express cell surface TLR3 [155]. Indeed, previous studies have found astrocytes to be reactive to a synthetic mimetic of dsRNA, albeit with conflicting conclusions [155-160]. One study found synthetic dsRNA to produce an anti-inflammatory response in astrocytes [156], while others found a pro-inflammatory response [157,160]. The reasons for these differences may be due to astrocyte source (fetal or adult). Overall, synthetic dsRNA treatment in human astrocytes *in vitro* was found to cause increases in IFNs, IL-6, and a down-regulation in connexin 43 (a crucial protein for intercellular gap junctions between astrocytes and maintaining BBB integrity) [157,160,161]. Interestingly, a rat study also found synthetic dsRNA to attenuate astrocytic L-glutamate uptake by inhibiting EAAT1/GLAST transporter gene transcription [162]. Studies examining HSV-I infection in the mouse CNS found increased inflammation and ROS [163,164]. These studies suggest viral infection and replication in neurones near astrocytes could cause an inflammatory response and disrupt healthy astrocyte function, possibly leading to neuronal signaling dysfunction and cell death.

Of relevance to HSV-I and glia activity, a study describing a mouse model of HSE found lytic genes (*ICP0* and *ICP27*) to sustain their expression long into 'latency' within the brain ependymal after HSE recovery [132]. This HSV-I gene expression profile differs from its life in the TG and was associated with a loss of effector T-cell function and an increase in microglia in the region. Although most humans infected with HSV-I never experience an episode of HSE during their lifetime, the present study not only further demonstrates that not all cell types respond in the same way to HSV-I, but that HSV-I can infect regions of the CNS without lethal consequences.

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Synaptic dysfunction

Previous models of PD have suggested that synaptic dysfunction (such as alterations to long-term potentiation/depression, changes in synaptic proteins, and N-methyl-D-aspartate receptor (NMDAR) subunit composition) in nigrostriatal and corticostriatal pathways could be responsible for the physical manifestations of DA loss in the SN [165-167]. *Post-mortem* studies have found decreases in glutamatergic synapses and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) GluR1 in the striatal regions of PD patients [168,150]. Also, human-induced pluripotent stem cell derived neurones from familial PD patients demonstrated reduced synaptic connectivity and hindered neurite outgrowth [151]. Although more research needs to be conducted to better understand synaptic dysfunction in PD, HSV-I and influenza A associated modifications to normal synaptic function are worth review (see Table 2).

Influenza A infection has been found to disrupt synaptic activity through modulation of host gene expression and interaction with synaptic related proteins. Pandemic and seasonal influenza A infections were examined for their modulation of genes in the CNS [169]. Pandemic influenza strains were associated with down-regulation of 'neuron projection,' 'synapse assembly,' and 'calcium channel activity' related genes [169]. Genes that were down-regulated compared with the seasonal flu strain included glycoprotein M6A, protocadherin α-subfamily C2, and cAMP-regulated phosphoprotein. Influenza A NS1 and nucleoprotein (NP) were also found to modify the host synapse. The influenza A NP was found to localize within dendritic spine-like structures of hippocampal neurones, resulting in reduced spontaneous excitatory synaptic frequency and decreased amplitude of excitatory post-synaptic currents [153]. Also in hippocampal neurones, the post-synaptic density protein-95 (PSD-95)/discs-large/ZO-1 (PDZ) motif of the C-terminus of H5N1 influenza A NS1 (not H1N1 influenza A NS1) was found to bind to PSD-95 [148]. NS1 binding to PSD-95 was suggested to prevent normal post-synaptic processes.

Although there is no evidence of direct inhibition of synaptic proteins, HSV-I infection is associated with changes in the host synapse. HSE patients are often found to have NMDAR antibodies, with a reduction in NMDAR and synapsin protein in murine hippocampal neurones after treatment with HSE patient serum [146]. In an animal model, HSV-I infection of murine cortical neurones resulted in reduction in synapsin-1 and synaptophysin proteins, and disrupted synaptic transmission [147]. Although synaptic dysfunction in PD may be a result of other features of PD pathology (such as α-synuclein aggregation or DA striatal denervation), it is worth noting viral induced changes in synaptic function. HSV-I or influenza A infection may exacerbate already stressed synaptic connections or weaken synaptic activity before other PD pathological features have fully manifested.

Autophagy

The autophagy process is fundamental for cellular homeostasis. Briefly, unwanted components (misfolded proteins, foreign structures, dysfunctional proteins etc.) are engulfed in double-membraned vesicles (autophagosomes) for digestion and substrate recycling [170]. Autophagy pathways have been suggested to be very important for amounting an antiviral defense in non-replicating cells [171]. Epithelial cells infected with HSV-I can produce pro-inflammatory cytokines and undergo cell death to prevent viral spread without permanent tissue damage because they can be replaced afterward. Non-replicating cells, such as neurones, may be more reliant on autophagy processes to limit viral replication and viral spread without undergoing cell death [172]. Similar to IFN signaling evasion, HSV-I and influenza A proteins have evolved ways to disrupt autophagy events to prevent clearance of viral components from host cells during latency and replication.

Previous studies have identified ICP34.5 as a crucial HSV-I protein for inhibiting autophagic degradation of virion structures [173,139]. Multiple HSV-I and influenza A proteins are able to disrupt autophagy. HSV-I ICP34.5 is able to indirectly inhibit protein kinase RNA-activated (PKR), while HSV-I US11 directly binds to PKR to prevent activation [174-176]. Influenza A NS1 and NP also inhibit PKR [142]. This PKR activation inhibition prevents PKR-mediated autophagy activation [139,142]. Also, HSV-I ICP34.5 has been found to bind directly to Beclin-1 [140]. Beclin-1 binds with other autophagy components to promote the formation of autophagosomes [141]. The amino acid region 68–87 of ICP34.5 binds to Beclin-1, leaving the section that functions to inhibit PKR signaling to remain open [140]. HSV-I ICP34.5 inhibition of autophagy through Beclin-1 binding also prevents antigen presentation and cluster of differentiation 4 ($CD4^+$) T-cell response [177]. Further investigation into the consequences of ICP34.5-mediated autophagy disruption needs to be done to understand the effects on host neurone homeostasis beyond increased neurovirulence of HSV-I.

Viral mediated autophagy disruption or suppression could lead to a decrease in clearance of misfolded/aggregated proteins. Studies examining *post-mortem* AD brains found HSV-I DNA to be associated with amyloid-β plaques [70,22,178]. Although a majority of HSV-I DNA positive CNS neurones were found to have amyloid-β plaques, there

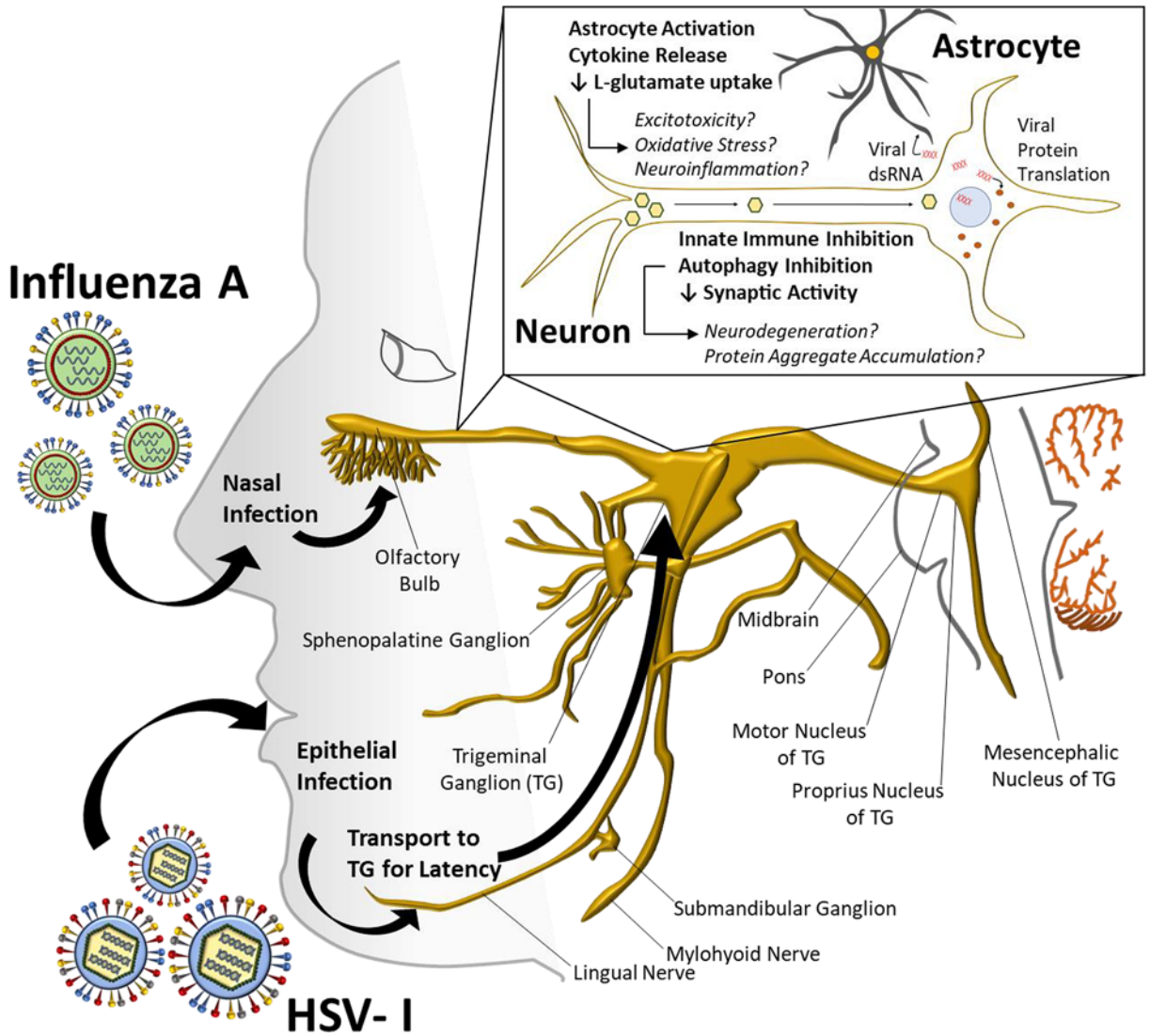

Figure 1. HSV-I and Influenza A viral infections may lead to PD-like pathology

HSV-I and influenza A viral infections have the potential to cause molecular and cellular changes that can alter healthy neuron function within the CNS. Viral transcripts/proteins due to HSV-I/influenza A infection may cause inflammation, autophagy disruption, and synapse dysfunction, possibly contributing to a PD-like pathology.

was no correlation between amyloid-β plaque containing neurones and presence of HSV-I DNA [70]. These findings suggest that HSV-I infection may cause an increase in amyloid protein aggregation. Further investigation should be conducted to determine if there may also be an association between HSV-I DNA positive neurones and α-synuclein aggregation. A study by Santana et al. [179] found HSV-I infection in neuronal cell cultures to cause an increase in amyloid-β aggregation accumulation, along with an increase in microtubule-associated protein 1A/1B-light chain (LC3-II). This study further supports the theory that HSV-I may contribute to amyloid protein aggregation, but does not refute the possibility that this is related to HSV-I mediated autophagy disruption since ICP34.5 disrupts autophagy through Beclin-1 binding, not LC3-II. Also, the lack of correlation between amyloid-β plaque containing neurones and HSV-I DNA positivity may be due to cross-seeding. HSV-I may cause autophagy disruption in innervating neurones (possibly latent sensory neurones), leading to amyloid fibril accumulations that may have the capability of spreading to other non-HSV-I DNA positive neurones. These protein aggregates may then be transported to innervating neurones or be exocytosed for extracellular cross-seeding. In general, autophagy disruption has been previously found to cause an increase in neurodegeneration, presynaptic α-synuclein accumulation, neuronal inclusions, and dopaminergic axon and dendritic degeneration [137,180].

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Conclusion

The purpose of this review was to demonstrate the need to revisit the association between viral infections and PD. It is clear that parallels can be drawn between viral-induced changes in the CNS (ranging from chronic inflammation to synaptic dysfunction) and PD pathology (Figure 1). Further investigation of viral infections (specifically HSV-I and influenza A) should be conducted to determine if intervention can suppress the long-term consequences in the CNS and possibly mitigate the association between viral infections and incidence of PD.

Competing interests

The authors declare that there are no competing interests associated with the manuscript.

Abbreviations

AD, Alzheimer's disease; BBB, blood–brain barrier; CNS, central nervous system; DA, dopamine; EL, encephalitis lethargica; HCV, hepatitis C virus; HSE, herpes simplex encephalitis; HSV, herpes simplex virus; IFN, interferon; IL-6, interleukin-6; iPD, idiopathic Parkinson's disease; IRF, IFN regulatory factor; LAT, latency-associated transcript; LC3-II, microtubule-associated protein 1A/1B-light chain 3; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cell; NMDAR, N-methyl-D-aspartate receptor; NP, nucleoprotein; NS1, non-structural protein 1; OS, oxidative stress; PAMP, pathogen-associated molecular pattern; PD, Parkinson's disease; PKR, protein kinase R; PRR, pathogen-recognition receptor; PSD-95, post-synaptic density protein-95; ROS, reactive oxygen species; SN, substantia nigra pars compacta; TG, trigeminal ganglia; TLR, toll-like receptor.

References

1 Tanner, C.M. and Goldman, S.M. (1996) Epidemiology of Parkinson's disease. *Neurol. Clin.* **14**, 317–335, https://doi.org/10.1016/S0733-8619(05)70259-0
2 Hoehn, M.M. and Yahr, M.D. (1967) Parkinsonism onset, progression, and mortality. *Neurology* **17**, 427, https://doi.org/10.1212/WNL.17.5.427
3 Martinez-Martin, P., Chaudhuri, K.R., Rojo-Abuin, J.M., Rodriguez-Blazquez, C., Alvarez-Sanchez, M., Arakaki, T. et al. (2015) Assessing the non-motor symptoms of Parkinson's disease: MDS-UPDRS and NMS Scale. *Eur. J. Neurol.* **22**, 37–43, https://doi.org/10.1111/ene.12165
4 Pfeiffer, R.F. (2016) Non-motor symptoms in Parkinson's disease. *Parkinsonism Relat. Disord.* **22** (Suppl. 1), S119–S122, https://doi.org/10.1016/j.parkreldis.2015.09.004
5 Braak, H., Del Tredici, K., Rüb, U., De Vos, R.A., Steur, E.N.J. and Braak, E. (2003) Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol. Aging* **24**, 197–211, https://doi.org/10.1016/S0197-4580(02)00065-9
6 Klein, C. and Westenberger, A. (2012) Genetics of Parkinson's disease. *Cold Spring Harb. Perspect. Med.* **2**, a008888, https://doi.org/10.1101/cshperspect.a008888
7 Polymeropoulos, M.H., Lavedan, C., Leroy, E., Ide, S.E., Dehejia, A., Dutra, A. et al. (1997) Mutation in the α-synuclein gene identified in families with Parkinson's disease. *Science* **276**, 2045–2047, https://doi.org/10.1126/science.276.5321.2045
8 Zarranz, J.J., Alegre, J., Gómez-Esteban, J.C., Lezcano, E., Ros, R., Ampuero, I. et al. (2004) The new mutation, E46K, of α-synuclein causes parkinson and Lewy body dementia. *Ann. Neurol.* **55**, 164–173, https://doi.org/10.1002/ana.10795
9 Chung, K.K., Zhang, Y., Lim, K.L., Tanaka, Y., Huang, H., Gao, J. et al. (2001) Parkin ubiquitinates the α-synuclein–interacting protein, synphilin-1: implications for Lewy-body formation in Parkinson disease. *Nat. Med.* **7**, 1144–1150, https://doi.org/10.1038/nm1001-1144
10 Lynch-Day, M.A., Mao, K., Wang, K., Zhao, M. and Klionsky, D.J. (2012) The role of autophagy in Parkinson's disease. *Cold Spring Harb. Perspect. Med.* **2**, a009357, https://doi.org/10.1101/cshperspect.a009357
11 Taylor, J.M., Main, B.S. and Crack, P.J. (2013) Neuroinflammation and oxidative stress: co-conspirators in the pathology of Parkinson's disease. *Neurochem. Int.* **62**, 803–819, https://doi.org/10.1016/j.neuint.2012.12.016
12 Lai, B., Marion, S., Teschke, K. and Tsui, J. (2002) Occupational and environmental risk factors for Parkinson's disease. *Parkinsonism Relat. Disord.* **8**, 297–309, https://doi.org/10.1016/S1353-8020(01)00054-2
13 Liou, H., Tsai, M., Chen, C., Jeng, J., Chang, Y., Chen, S. et al. (1997) Environmental risk factors and Parkinson's disease: a case-control study in Taiwan. *Neurology* **48**, 1583–1588, https://doi.org/10.1212/WNL.48.6.1583
14 Seidler, A., Hellenbrand, W., Robra, B.-P., Vieregge, P., Nischan, P., Joerg, J. et al. (1996) Possible environmental, occupational, and other etiologic factors for Parkinson's disease A case-control study in Germany. *Neurology* **46**, 1275, https://doi.org/10.1212/WNL.46.5.1275
15 Breckenridge, C.B., Berry, C., Chang, E.T., Sielken Jr, R.L. and Mandel, J.S. (2016) Association between Parkinson's disease and cigarette smoking, rural living, well-water consumption, farming and pesticide use: systematic review and meta-analysis. *PLoS ONE* **11**, e0151841, https://doi.org/10.1371/journal.pone.0151841
16 Van Maele-Fabry, G., Hoet, P., Vilain, F. and Lison, D. (2012) Occupational exposure to pesticides and Parkinson's disease: a systematic review and meta-analysis of cohort studies. *Environ. Int.* **46**, 30–43, https://doi.org/10.1016/j.envint.2012.05.004
17 Itzhaki, R.F., Lathe, R., Balin, B.J., Ball, M.J., Bearer, E.L., Braak, H. et al. (2016) Microbes and Alzheimer's disease. *J. Alzheimers Dis.* **51**, 979, https://doi.org/10.3233/JAD-160152
18 Balin, B.J., Gérard, H.C., Arking, E.J., Appelt, D.M., Branigan, P.J., Abrams, J.T. et al. (1998) Identification and localization of Chlamydia pneumoniae in the Alzheimer's brain. *Med. Microbiol. Immunol.* **187**, 23–42
19 Letenneur , L., Pérès, K., Fleury, H., Garrigue, I., Barberger-Gateau, P., Helmer, C. et al. (2008) Seropositivity to herpes simplex virus antibodies and risk of Alzheimer's disease: a population-based cohort study. *PloS One* **11**, e3637, https://doi.org/10.1371/journal.pone.0003637

20 Lövheim, H., Gilthorpe, J., Adolfsson, R., Nilsson, L.G. and Elgh, F. (2015) Reactivated herpes simplex infection increases the risk of Alzheimer's disease. *Alzheimers Dement.* **11**, 593–599, https://doi.org/10.1016/j.jalz.2014.04.522
21 Miklossy, J., Khalili, K., Gern, L., Ericson, R.L, Darekar, P., Bolle, L. et al. (2004) Borrelia burgdorferi persists in the brain in chronic lyme neuroborreliosis and may be associated with Alzheimer disease. *J. Alzheimers Dis.* **6**, 639–649
22 Wozniak, M.A., Frost, A.L. and Itzhaki, R.F. (2009) Alzheimer's disease-specific tau phosphorylation is induced by herpes simplex virus type 1. *J. Alzheimers Dis.* **16**, 341–350, https://doi.org/10.3233/JAD-2009-0963
23 Von Economo, C. (1931) *Encephalitis Lethargica: Its Sequelae and Treatment*, Oxford University Press
24 Neal, J.B. and Bentley, I.A. (1932) Treatment of epidemic encephalitis: a review of the work of the Matheson Commission. *Arch. Neurol. Psychiatry* **28**, 897–907, https://doi.org/10.1001/archneurpsyc.1932.02240040142010
25 Ravenholt, R. and Foege, W. (1982) 1918 influenza, encephalitis lethargica, parkinsonism. *Lancet North Am. Ed.* **320**, 860–864, https://doi.org/10.1016/S0140-6736(82)90820-0
26 Lo, K., Geddes, J., Daniels, R. and Oxford, J. (2003) Lack of detection of influenza genes in archived formalin-fixed, paraffin wax-embedded brain samples of encephalitis lethargica patients from 1916 to 1920. *Virchows Arch.* **442**, 591–596
27 McCall, S., Henry, J.M., Reid, A.H. and Taubenberger, J.K. (2001) Influenza RNA not detected in archival brain tissues from acute encephalitis lethargica cases or in postencephalitic Parkinson cases. *J. Neuropathol. Exp. Neurol.* **60**, 696–704, https://doi.org/10.1093/jnen/60.7.696
28 Taubenberger, J.K., Reid, A.H., Krafft, A.E., Bijwaard, K.E. and Fanning, T.G. (1997) Initial genetic characterization of the 1918 "Spanish" influenza virus. *Science* **275**, 1793–1796, https://doi.org/10.1126/science.275.5307.1793
29 Reid, A.H., Fanning, T.G., Hultin, J.V. and Taubenberger, J.K. (1999) Origin and evolution of the 1918 "Spanish" influenza virus hemagglutinin gene. *Proc. Natl. Acad. Sci. U.S.A.* **96**, 1651–1656, https://doi.org/10.1073/pnas.96.4.1651
30 Reid, A.H., Fanning, T.G., Janczewski, T.A. and Taubenberger, J.K. (2000) Characterization of the 1918 "Spanish" influenza virus neuraminidase gene. *Proc. Natl. Acad. Sci. U.S.A.* **97**, 6785–6790, https://doi.org/10.1073/pnas.100140097
31 Anderson, L., Vilensky, J. and Duvoisin, R. (2009) Neuropathology of acute phase encephalitis lethargica: a review of cases from the epidemic period. *Neuropathol. Appl. Neurobiol.* **35**, 462–472, https://doi.org/10.1111/j.1365-2990.2009.01024.x
32 Dale, R.C., Church, A.J., Surtees, R.A., Lees, A.J., Adcock, J.E., Harding, B. et al. (2004) Encephalitis lethargica syndrome: 20 new cases and evidence of basal ganglia autoimmunity. *Brain* **127**, 21–33, https://doi.org/10.1093/brain/awh008
33 Dale, R.C., Irani, S.R., Brilot, F., Pillai, S., Webster, R., Gill, D. et al. (2009) N-methyl-D-aspartate receptor antibodies in pediatric dyskinetic encephalitis lethargica. *Ann. Neurol.* **66**, 704–709, https://doi.org/10.1002/ana.21807
34 Lopez-Alberola, R., Georgiou, M., Sfakianakis, G.N., Singer, C. and Papapetropoulos, S. (2009) Contemporary encephalitis lethargica: phenotype, laboratory findings and treatment outcomes. *J. Neurol.* **256**, 396–404, https://doi.org/10.1007/s00415-009-0074-4
35 Rail, D., Scholtz, C. and Swash, M. (1981) Post-encephalitic parkinsonism: current experience. *J. Neurol. Neurosurg. Psychiatry* **44**, 670–676, https://doi.org/10.1136/jnnp.44.8.670
36 Singer, H.S., Hong, J.J., Yoon, D.Y. and Williams, P.N. (2005) Serum autoantibodies do not differentiate PANDAS and Tourette syndrome from controls. *Neurology* **65**, 1701–1707, https://doi.org/10.1212/01.wnl.0000183223.69946.f1
37 Vincent, A., Buckley, C., Schott, J.M., Baker, I., Dewar, B.K., Detert, N. et al. (2004) Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. *Brain* **127**, 701–712, https://doi.org/10.1093/brain/awh077
38 de Jong, M.D., Cam, B.V., Qui, P.T., Hien, V.M., Thanh, T.T., Hue, N.B. et al. (2005) Fatal avian influenza A (H5N1) in a child presenting with diarrhea followed by coma. *N. Engl. J. Med.* **352**, 686–691, https://doi.org/10.1056/NEJMoa044307
39 Jang, H., Boltz, D., Sturm-Ramirez, K., Shepherd, K.R., Jiao, Y., Webster, R. et al. (2009) Highly pathogenic H5N1 influenza virus can enter the central nervous system and induce neuroinflammation and neurodegeneration. *Proc. Natl. Acad. Sci. U.S.A.* **106**, 14063–14068, https://doi.org/10.1073/pnas.0900096106
40 Mattos, J.P.d., Rosso, A.L.Z.d., Corrêa, R.B. and Novis, S.A. (2002) Movement disorders in 28 HIV-infected patients. *Arq. Neuropsiquiatr.* **60**, 525–530, https://doi.org/10.1590/S0004-282X2002000400002
41 Poser, C.M., Huntley, C.J. and Poland, J.D. (1969) Para-encephalitic parkinsonism. *Acta Neurol. Scand.* **45**, 199–215, https://doi.org/10.1111/j.1600-0404.1969.tb01232.x
42 Pranzatelli, M.R., Mott, S.H., Pavlakis, S.G., Conry, J.A. and Tate, E.D. (1994) Clinical spectrum of secondary parkinsonism in childhood: a reversible disorder. *Pediatr. Neurol.* **10**, 131–140, https://doi.org/10.1016/0887-8994(94)90045-0
43 Tse, W., Cersosimo, M.G., Gracies, J.-M., Morgello, S., Olanow, C.W. and Koller, W. (2004) Movement disorders and AIDS: a review. *Parkinsonism Relat. Disord.* **10**, 323–334, https://doi.org/10.1016/j.parkreldis.2004.03.001
44 Walters, J.H. (1960) Postencephalitic Parkinson syndrome after meningoencephalitis due to coxsackie virus group B, type 2. *N. Engl. J. Med.* **263**, 744–747, https://doi.org/10.1056/NEJM196010132631507
45 Elizan, T.S., Madden, D.L., Noble, G.R., Herrmann, K.L., Gardner, J., Schwartz, J. et al. (1979) Viral antibodies in serum and CSF of Parkinsonian patients and controls. *Arch. Neurol.* **36**, 529–534, https://doi.org/10.1001/archneur.1979.00500450023002
46 Chen, H.H., Liu, P.F.-C., Tsai, H.H., Yen, R.F. and Liou, H.H. (2016) Re: Wangensteen et al. of a letter on 'Hepatitis C virus infection: a risk factor for Parkinson's disease'. *J. Viral Hepat.* **23**, 560, https://doi.org/10.1111/jvh.12521
47 Tsai, H.-H., Liou, H.-H., Muo, C.-H., Lee, C.-Z., Yen, R.-F. and Kao, C.-H. (2016) Hepatitis C virus infection as a risk factor for Parkinson disease: a nationwide cohort study. *Neurology* **86**, 840–846, https://doi.org/10.1212/WNL.0000000000002307
48 Wu, W.Y.Y., Kang, K.H., Chen, S.L.S., Chiu, S.Y.H., Yen, A.M.F., Fann, J.C.Y. et al. (2015) Hepatitis C virus infection: a risk factor for Parkinson's disease. *J. Viral Hepatol.* **22**, 784–791, https://doi.org/10.1111/jvh.12392
49 Marttila, R., Arstila, P., Nikoskelainen, J., Halonen, P. and Rinne, U. (1977) Viral antibodies in the sera from patients with Parkinson disease. *Eur. Neurol.* **15**, 25–33, https://doi.org/10.1159/000114785

50 Marttila, R.J. and Rinne, U.K. (1978) Herpes simplex virus antibodies in patients with Parkinson's disease. *J. Neurol. Sci.* **35**, 375–379, https://doi.org/10.1016/0022-510X(78)90017-5
51 Marttila, R.J., Rinne, U.K., Halonen, P., Madden, D.L. and Sever, J.L. (1981) Herpes viruses and Parkinsonism: herpes simplex virus types 1 and 2, and cytomegalovirus antibodies in serum and CSF. *Arch. Neurol.* **38**, 19–21, https://doi.org/10.1001/archneur.1981.00510010045007
52 Harris, M.A., Tsui, J.K., Marion, S.A., Shen, H. and Teschke, K. (2012) Association of Parkinson's disease with infections and occupational exposure to possible vectors. *Mov. Disord.* **27**, 1111–1117, https://doi.org/10.1002/mds.25077
53 Vlajinac, H., Dzoljic, E., Maksimovic, J., Marinkovic, J., Sipetic, S. and Kostic, V. (2013) Infections as a risk factor for Parkinson's disease: a case–control study. *Int. J. Neurosci.* **123**, 329–332, https://doi.org/10.3109/00207454.2012.760560
54 Bu, X.L., Yao, X.Q., Jiao, S.S., Zeng, F., Liu, Y.H., Xiang, Y. et al. (2015) A study on the association between infectious burden and Alzheimer's disease. *Eur. J. Neurol.* **22**, 1519–1525, https://doi.org/10.1111/ene.12477
55 Marttila, R.J., Rinne, U.K. and Tiilikainen, A. (1982) Virus antibodies in Parkinson's disease: herpes simplex and measles virus antibodies in serum and CSF and their relation to HLA types. *J. Neurol. Sci.* **54**, 227–238, https://doi.org/10.1016/0022-510X(82)90184-8
56 Fazzini, E., Fleming, J. and Fahn, S. (1992) Cerebrospinal fluid antibodies to coronavirus in patients with Parkinson's disease. *Mov. Disord.* **7**, 153–158, https://doi.org/10.1002/mds.870070210
57 Samji, T. (2009) Influenza A: understanding the viral life cycle. *Yale J. Biol. Med.* **82**, 153–159
58 Kumar, S.P., Chandy, M.L., Shanavas, M., Khan, S. and Suresh, K. (2016) Pathogenesis and life cycle of herpes simplex virus infection-stages of primary, latency and recurrence. *J. Oral Maxillofac. Surg. Med. Pathol.* **28**, 350–353, https://doi.org/10.1016/j.ajoms.2016.01.006
59 Marfurt, C.F. and Rajchert, D.M. (1991) Trigeminal primary afferent projections to "non-trigeminal" areas of the rat central nervous system. *J. Comp. Neurol.* **303**, 489–511, https://doi.org/10.1002/cne.903030313
60 Miller, K.D., Schnell, M.J. and Rall, G.F. (2016) Keeping it in check: chronic viral infection and antiviral immunity in the brain. *Nat. Rev. Neurosci.* **17**, 766–776, https://doi.org/10.1038/nrn.2016.140
61 Kuiken, T. and Taubenberger, J.K. (2008) Pathology of human influenza revisited. *Vaccine* **26**, D59–D66, https://doi.org/10.1016/j.vaccine.2008.07.025
62 Matsuda, K., Shibata, T., Sakoda, Y., Kida, H., Kimura, T., Ochiai, K. et al. (2005) *In vitro* demonstration of neural transmission of avian influenza A virus. *J. Gen. Virol.* **86**, 1131–1139, https://doi.org/10.1099/vir.0.80704-0
63 van Riel, D., Verdijk, R. and Kuiken, T. (2015) The olfactory nerve: a shortcut for influenza and other viral diseases into the central nervous system. *J. Pathol.* **235**, 277–287, https://doi.org/10.1002/path.4461
64 Esiri, M.M. (1982) Herpes simplex encephalitis: an immunohistological study of the distribution of viral antigen within the brain. *J. Neurol. Sci.* **54**, 209–226, https://doi.org/10.1016/0022-510X(82)90183-6
65 Shoji, H., Koga, M., Kusuhara, T., Kaji, M., Ayabe, M., Hino, H. et al. (1994) Differentiation of herpes simplex virus 1 and 2 in cerebrospinal fluid of patients with HSV encephalitis and meningitis by stringent hybridization of PCR-amplified DNAs. *J. Neurol.* **241**, 526–530, https://doi.org/10.1007/BF00873514
66 Hemling, N., Röyttä, M., Rinne, J., Pöllänen, P., Broberg, E., Tapio, V. et al. (2003) Herpes viruses in brains in Alzheimer's and Parkinson's diseases. *Ann. Neurol.* **54**, 267–271, https://doi.org/10.1002/ana.10662
67 Wetmur, J.G., Schwartz, J. and Elizan, T.S. (1979) Nucleic acid homology studies of viral nucleic acids in idiopathic Parkinson's disease. *Arch. Neurol.* **36**, 462–464, https://doi.org/10.1001/archneur.1979.00500440032004
68 Fraser, N.W., Lawrence, W.C., Wroblewska, Z., Gilden, D.H. and Koprowski, H. (1981) Herpes simplex type 1 DNA in human brain tissue. *Proc. Natl. Acad. Sci. U.S.A.* **78**, 6461–6465, https://doi.org/10.1073/pnas.78.10.6461
69 Gordon, L., McQuaid, S. and Cosby, S. (1996) Detection of herpes simplex virus (types 1 and 2) and human herpesvirus 6 DNA in human brain tissue by polymerase chain reaction. *Clin. Diagn. Virol.* **6**, 33–40, https://doi.org/10.1016/0928-0197(95)00203-0
70 Olsson, J., Lövheim, H., Honkala, E., Karhunen, P.J., Elgh, F. and Kok, E.H. (2016) HSV presence in brains of individuals without dementia: the TASTY brain series. *Dis. Models Mech.* **9**, 1349–1355, https://doi.org/10.1242/dmm.026674
71 Park, C.H., Ishinaka, M., Takada, A., Kida, H., Kimura, T., Ochiai, K. et al. (2002) The invasion routes of neurovirulent A/Hong Kong/483/97 (H5N1) influenza virus into the central nervous system after respiratory infection in mice. *Arch. Virol* **147**, 1425–1436, https://doi.org/10.1007/s00705-001-0750-x
72 Reinacher, M., Bonin, J., Narayan, O. and Scholtissek, C. (1983) Pathogenesis of neurovirulent influenza A virus infection in mice. Route of entry of virus into brain determines infection of different populations of cells. *Lab. Invest.* **49**, 686–692
73 Takahashi, M., Yamada, T., Nakajima, S., Nakajima, K., Yamamoto, T. and Okada, H. (1995) The substantia nigra is a major target for neurovirulent influenza A virus. *J. Exp. Med.* **181**, 2161–2169, https://doi.org/10.1084/jem.181.6.2161
74 Yamada, T., Yamanaka, I., Takahashi, M. and Nakajima, S. (1996) Invasion of brain by neurovirulent influenza A virus after intranasal inoculation. *Parkinsonism Relat. Disord.* **2**, 187–193, https://doi.org/10.1016/S1353-8020(96)00024-7
75 Jang, H., Boltz, D., McClaren, J., Pani, A.K., Smeyne, M., Korff, A. et al. (2012) Inflammatory effects of highly pathogenic H5N1 influenza virus infection in the CNS of mice. *J. Neurosci.* **32**, 1545–1559, https://doi.org/10.1523/JNEUROSCI.5123-11.2012
76 Jamieson, G.A., Maitland, N.J., Wilcock, G.K., Yates, C.M. and Itzhaki, R.F. (1992) Herpes simplex virus type 1 DNA is present in specific regions of brain from aged people with and without senile dementia of the Alzheimer type. *J. Pathol.* **167**, 365–368, https://doi.org/10.1002/path.1711670403
77 Nicholson, K.G., Kent, J., Hammersley, V. and Cancio, E. (1997) Acute viral infections of upper respiratory tract in elderly people living in the community: comparative, prospective, population based study of disease burden. *BMJ* **315**, 1060–1064, https://doi.org/10.1136/bmj.315.7115.1060
78 De Lau, L.M. and Breteler, M.M. (2006) Epidemiology of Parkinson's disease. *Lancet Neurol.* **5**, 525–535, https://doi.org/10.1016/S1474-4422(06)70471-9

79 Kleine, T., Hackler, R. and Zöfel, P. (1992) Age-related alterations of the blood-brain-barrier (bbb) permeability to protein molecules of different size. *Z. Gerontol.* **26**, 256–259
80 Valiathan, R., Ashman, M. and Asthana, D. (2016) Effects of ageing on the immune system: infants to elderly. *Scand. J. Immunol.* **83**, 255–266, https://doi.org/10.1111/sji.12413
81 Levine, B. (2005) Eating oneself and uninvited guests: autophagy-related pathways in cellular defense. *Cell* **120**, 159–162
82 Abbas, A.K., Lichtman, A.H. and Pillai, S. (2014) *Basic Immunology: Functions and Disorders of the Immune System*, Elsevier Health Sciences
83 Mosser, D.M. and Edwards, J.P. (2008) Exploring the full spectrum of macrophage activation. *Nat. Rev. Immunol.* **8**, 958–969, https://doi.org/10.1038/nri2448
84 Schroder, K., Sweet, M.J. and Hume, D.A. (2006) Signal integration between IFNγ and TLR signalling pathways in macrophages. *Immunobiology* **211**, 511–524, https://doi.org/10.1016/j.imbio.2006.05.007
85 Dutton, R., Bradley, L. and Swain, S. (1998) T cell memory. *Annu. Rev. Immunol.* **16**, 201–223, https://doi.org/10.1146/annurev.immunol.16.1.201
86 Rajewsky, K. and Schittek, B. (1990) Maintenance of B-cell memory by long-lived cells generated from proliferating precursors. *Nature* **346**, 749, https://doi.org/10.1038/346749a0
87 Khanna, K.M., Bonneau, R.H., Kinchington, P.R. and Hendricks, R.L. (2003) Herpes simplex virus-specific memory CD8+ T cells are selectively activated and retained in latently infected sensory ganglia. *Immunity* **18**, 593–603, https://doi.org/10.1016/S1074-7613(03)00112-2
88 Leger, A.J.S., Jeon, S. and Hendricks, R.L. (2013) Broadening the repertoire of functional herpes simplex virus type 1–specific CD8+ T cells reduces viral reactivation from latency in sensory ganglia. *J. Immunol.* **191**, 2258–2265, https://doi.org/10.4049/jimmunol.1300585
89 Benmohamed, L., Srivastava, R. and Khan, A.A. (2016) The herpes simplex virus LAT gene is associated with a broader repertoire of virus-specific exhausted CD8+ T cells retained within the trigeminal ganglia of latently infected HLA transgenic rabbits. *J. Immunol.* **196**, 79.14–79.14
90 Halford, W.P., Gebhardt, B.M. and Carr, D.J. (1996) Persistent cytokine expression in trigeminal ganglion latently infected with herpes simplex virus type 1. *J. Immunol.* **157**, 3542–3549
91 Theil, D., Derfuss, T., Paripovic, I., Herberger, S., Meinl, E., Schueler, O. et al. (2003) Latent herpesvirus infection in human trigeminal ganglia causes chronic immune response. *Am. J. Pathol.* **163**, 2179–2184, https://doi.org/10.1016/S0002-9440(10)63575-4
92 Perrone, L.A., Plowden, J.K., García-Sastre, A., Katz, J.M. and Tumpey, T.M. (2008) H5N1 and 1918 pandemic influenza virus infection results in early and excessive infiltration of macrophages and neutrophils in the lungs of mice. *PLoS Pathog.* **4**, e1000115, https://doi.org/10.1371/journal.ppat.1000115
93 Saunders, J.A.H., Estes, K.A., Kosloski, L.M., Allen, H.E., Dempsey, K.M., Torres-Russotto, D.R. et al. (2012) CD4+ regulatory and effector/memory T cell subsets profile motor dysfunction in Parkinson's disease. *J. Neuroimmune Pharmacol.* **7**, 927–938, https://doi.org/10.1007/s11481-012-9402-z
94 Sulzer, D., Alcalay, R.N., Garretti, F., Cote, L., Kanter, E., Agin-Liebes, J. et al. (2017) T cells from patients with Parkinson's disease recognize α-synuclein peptides. *Nature* **546**, 656, https://doi.org/10.1038/nature22815
95 Caggiu, E., Paulus, K., Arru, G., Piredda, R., Sechi, G.P. and Sechi, L.A. (2016) Humoral cross reactivity between α-synuclein and herpes simplex-1 epitope in Parkinson's disease, a triggering role in the disease? *J. Neuroimmunol.* **291**, 110–114, https://doi.org/10.1016/j.jneuroim.2016.01.007
96 Chang, Z. (2010) Important aspects of Toll-like receptors, ligands and their signaling pathways. *Inflamm. Res.* **59**, 791–808, https://doi.org/10.1007/s00011-010-0208-2
97 Alexopoulou, L., Holt, A.C., Medzhitov, R. and Flavell, R.A. (2001) Recognition of double-stranded RNA and activation of NF-κB by Toll-like receptor 3. *Nature* **413**, 732–738, https://doi.org/10.1038/35099560
98 Matsumoto, M., Kikkawa, S., Kohase, M., Miyake, K. and Seya, T. (2002) Establishment of a monoclonal antibody against human Toll-like receptor 3 that blocks double-stranded RNA-mediated signaling. *Biochem. Biophys. Res. Commun.* **293**, 1364–1369, https://doi.org/10.1016/S0006-291X(02)00380-7
99 O'Neill, L.A., Golenbock, D. and Bowie, A.G. (2013) The history of Toll-like receptors - redefining innate immunity. *Nat. Rev. Immunol.* **13**, 453–460, https://doi.org/10.1038/nri3446
100 Bonifati, V. (2012) Autosomal recessive parkinsonism. *Parkinsonism Relat. Disord.* **18** (Suppl. 1), S4–S6, https://doi.org/10.1016/S1353-8020(11)70004-9
101 Hakimi, M., Selvanantham, T., Swinton, E., Padmore, R.F., Tong, Y., Kabbach, G. et al. (2011) Parkinson's disease-linked LRRK2 is expressed in circulating and tissue immune cells and upregulated following recognition of microbial structures. *J. Neural Transm.* **118**, 795–808, https://doi.org/10.1007/s00702-011-0653-2
102 Manzanillo, P.S., Ayres, J.S., Watson, R.O., Collins, A.C., Souza, G., Rae, C.S. et al. (2013) The ubiquitin ligase parkin mediates resistance to intracellular pathogens. *Nature* **501**, 512, https://doi.org/10.1038/nature12566
103 Zimprich, A., Biskup, S., Leitner, P., Lichtner, P., Farrer, M., Lincoln, S. et al. (2004) Mutations in LRRK2 cause autosomal-dominant Parkinsonism with pleomorphic pathology. *Neuron* **44**, 601–607, https://doi.org/10.1016/j.neuron.2004.11.005
104 Satake, W., Nakabayashi, Y., Mizuta, I., Hirota, Y., Ito, C., Kubo, M. et al. (2009) Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease. *Nat. Genet.* **41**, 1303, https://doi.org/10.1038/ng.485
105 Guo, Y., Deng, X., Zheng, W., Xu, H., Song, Z., Liang, H. et al. (2011) HLA rs3129882 variant in Chinese Han patients with late-onset sporadic Parkinson disease. *Neurosci. Lett.* **501**, 185–187, https://doi.org/10.1016/j.neulet.2011.05.245
106 Hamza, T.H., Zabetian, C.P., Tenesa, A., Laederach, A., Montimurro, J., Yearout, D. et al. (2010) Common genetic variation in the HLA region is associated with late-onset sporadic Parkinson's disease. *Nat. Genet.* **42**, 781–785, https://doi.org/10.1038/ng.642
107 Ahmed, I., Tamouza, R., Delord, M., Krishnamoorthy, R., Tzourio, C., Mulot, C. et al. (2012) Association between Parkinson's disease and the HLA-DRB1 locus. *Mov. Disord.* **27**, 1104–1110, https://doi.org/10.1002/mds.25035
108 International Parkinson Disease Genomics Consortium (2011) Imputation of sequence variants for identification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies. *Lancet* **377**, 641–649, https://doi.org/10.1016/S0140-6736(10)62345-8

109 Nagatsu, T., Mogi, M., Ichinose, H. and Togari, A. (2000) Cytokines in Parkinson's disease. *J. Neural Transm. Suppl.* **58**, 143–152
110 Mogi, M., Harada, M., Narabayashi, H., Inagaki, H., Minami, M. and Nagatsu, T. (1996) Interleukin (IL)-1β, IL-2, IL-4, IL-6 and transforming growth factor-α levels are elevated in ventricular cerebrospinal fluid in juvenile parkinsonism and Parkinson's disease. *Neurosci. Lett.* **211**, 13–16, https://doi.org/10.1016/0304-3940(96)12706-3
111 Reale, M., Iarlori, C., Thomas, A., Gambi, D., Perfetti, B., Di Nicola, M. et al. (2009) Peripheral cytokines profile in Parkinson's disease. *Brain Behav. Immun.* **23**, 55–63, https://doi.org/10.1016/j.bbi.2008.07.003
112 Depino, A.M., Earl, C., Kaczmarczyk, E., Ferrari, C., Besedovsky, H., Del Rey, A. et al. (2003) Microglial activation with atypical proinflammatory cytokine expression in a rat model of Parkinson's disease. *Eur. J. Neurosci.* **18**, 2731–2742, https://doi.org/10.1111/j.1460-9568.2003.03014.x
113 Koprich, J.B., Reske-Nielsen, C., Mithal, P. and Isacson, O. (2008) Neuroinflammation mediated by IL-1β increases susceptibility of dopamine neurons to degeneration in an animal model of Parkinson's disease. *J. Neuroinflammation* **5**, 8, https://doi.org/10.1186/1742-2094-5-8
114 McCabe, K., Concannon, R.M., McKernan, D.P. and Dowd, E. (2017) Time-course of striatal Toll-like receptor expression in neurotoxic, environmental and inflammatory rat models of Parkinson's disease. *J. Neuroimmunol.* **310**, 103–106, https://doi.org/10.1016/j.jneuroim.2017.07.007
115 Antrobus, R. and Boutell, C. (2008) Identification of a novel higher molecular weight isoform of USP7/HAUSP that interacts with the Herpes simplex virus type-1 immediate early protein ICP0. *Virus Res.* **137**, 64–71, https://doi.org/10.1016/j.virusres.2008.05.017
116 Lin, R., Noyce, R.S., Collins, S.E., Everett, R.D. and Mossman, K.L. (2004) The herpes simplex virus ICP0 RING finger domain inhibits IRF3-and IRF7-mediated activation of interferon-stimulated genes. *J. Virol.* **78**, 1675–1684, https://doi.org/10.1128/JVI.78.4.1675-1684.2004
117 Preston, C.M., Harman, A.N. and Nicholl, M.J. (2001) Activation of interferon response factor-3 in human cells infected with herpes simplex virus type 1 or human cytomegalovirus. *J. Virol.* **75**, 8909–8916, https://doi.org/10.1128/JVI.75.19.8909-8916.2001
118 Thulasi Raman, S.N. and Zhou, Y. (2016) Networks of host factors that interact with NS1 protein of influenza A virus. *Front. Microbiol.* **7**, 654, https://doi.org/10.3389/fmicb.2016.00654
119 Wang, B.X., Wei, L., Kotra, L.P., Brown, E.G. and Fish, E.N. (2017) A conserved residue, tyrosine (Y) 84, in H5N1 influenza A virus NS1 regulates IFN signaling responses to enhance viral infection. *Viruses* **9**, 107, https://doi.org/10.3390/v9050107
120 Pringproa, K., Rungsiwiwut, R., Tantilertcharoen, R., Praphet, R., Pruksananonda, K., Baumgärtner, W. et al. (2015) Tropism and induction of cytokines in human embryonic-stem cells-derived neural progenitors upon inoculation with highly- pathogenic avian H5N1 influenza virus. *PLoS ONE* **10**, e0135850, https://doi.org/10.1371/journal.pone.0135850
121 Liu, T., Khanna, K.M., Carriere, B.N and Hendricks, R.L. (2001) Gamma interferon can prevent herpes simplex virus type 1 reactivation from latency in sensory neurons. *J. Virol.* **75**, 11178–11184, https://doi.org/11602757
122 Olsson, T., Bakhiet, M., H.öjeberg, B., Ljungdahl, Å., Kelic, S., Edlund, C. et al. (1994) Neuronal interferon-γ immunoreactive molecule: Bioactivities and purification. *Eur. J. Immunol.* **24**, 308–314, https://doi.org/10.1002/eji.1830240205
123 Peng, W., Henderson, G., Inman, M., BenMohamed, L., Perng, G-C., Wechsler, S.L. et al. (2005) The locus encompassing the latency-associated transcript of herpes simplex virus type 1 interferes with and delays interferon expression in productively infected neuroblastoma cells and trigeminal ganglia of acutely infected mice. *J. Virol.* **79**, 6162–6171, https://doi.org/10.1128/JVI.79.10.6162-6171.2005
124 Carr, D.J., Noisakran, S., Halford, W.P., Lukacs, N., Asensio, V. and Campbell, I.L. (1998) Cytokine and chemokine production in HSV-1 latently infected trigeminal ganglion cell cultures: effects of hyperthermic stress. *J. Neuroimmunol.* **85**, 111–121, https://doi.org/10.1016/S0165-5728(97)00206-3
125 Rosato, P.C., Katzenell, S., Pesola, J.M., North, B., Coen, D.M. and Leib, D.A. (2016) Neuronal IFN signaling is dispensable for the establishment of HSV-1 latency. *Virology* **497**, 323–327, https://doi.org/10.1016/j.virol.2016.06.016
126 Ejlerskov, P., Hultberg Jeanette, G., Wang, J., Carlsson, R., Ambjørn, M., Kuss, M. et al. (2015) Lack of neuronal IFN-β-IFNAR causes Lewy body- and Parkinson's disease-like dementia. *Cell* **163**, 324–339, https://doi.org/10.1016/j.cell.2015.08.069
127 Kandel, E.R., Schwartz, J.H., Jessell, T.M., Siegelbaum, S.A. and Hudspeth, A.J. (2000) *Principles of Neural Science*, McGraw-Hill, New York
128 Banati, R.B., Gehrmann, J., Schubert, P. and Kreutzberg, G.W. (1993) Cytotoxicity of microglia. *Glia* **7**, 111–118, https://doi.org/10.1002/glia.440070117
129 Zhang, J., Perry, G., Smith, M.A., Robertson, D., Olson, S.J., Graham, D.G. et al. (1999) Parkinson's disease is associated with oxidative damage to cytoplasmic DNA and RNA in substantia nigra neurons. *Am. J. Pathol.* **154**, 1423–1429, https://doi.org/10.1016/S0002-9440(10)65396-5
130 Gerhard, A., Pavese, N., Hotton, G., Turkheimer, F., Es, M., Hammers, A. et al. (2006) *In vivo* imaging of microglial activation with [11C](R)-PK11195 PET in idiopathic Parkinson's disease. *Neurobiol. Dis.* **21**, 404–412, https://doi.org/10.1016/j.nbd.2005.08.002
131 Miklossy, J., Doudet, D., Schwab, C., Yu, S., McGeer, E. and McGeer, P. (2006) Role of ICAM-1 in persisting inflammation in Parkinson disease and MPTP monkeys. *Exp. Neurol.* **197**, 275–283, https://doi.org/10.1016/j.expneurol.2005.10.034
132 Menendez, C.M., Jinkins, J.K. and Carr, D.J. (2016) Resident T cells are unable to control herpes simplex virus-1 activity in the brain ependymal region during latency. *J. Immunol.* **197**, 1262–1275, https://doi.org/10.4049/jimmunol.1600207
133 Tesoriero, C., Codita, A., Zhang, M.-D., Cherninsky, A., Karlsson, H., Grassi-Zucconi, G. et al. (2016) H1N1 influenza virus induces narcolepsy-like sleep disruption and targets sleep–wake regulatory neurons in mice. *Proc. Natl. Acad. Sci. U.S.A.* **113**, E368–E377, https://doi.org/10.1073/pnas.1521463112
134 Arlehamn, C.S.L., Alcalay, R.N., Garretti, F., Cote, L., Kanter, E., Agin-Liebes, J. et al. (2017) Immune response in Parkinson's disease driven by HLA display of α-synuclein peptides. *J. Immnol.* **198** (1 Supplement), 55.26
135 Ng, Y.P., Lee, S.M.Y., Cheung, T.K.W., Nicholls, J.M., Peiris, J.S.M. and Ip, N.Y. (2010) Avian influenza H5N1 virus induces cytopathy and proinflammatory cytokine responses in human astrocytic and neuronal cell lines. *Neuroscience* **168**, 613–623, https://doi.org/10.1016/j.neuroscience.2010.04.013
136 Takahashi, M., Yamada, T., Nakanishi, K., Fujita, K., Nakajima, K., Nobusawa, E. et al. (1997) Influenza a virus infection of primary cultured cells from rat fetal brain. *Parkinsonism Relat. Disord.* **3**, 97–102, https://doi.org/10.1016/S1353-8020(97)00010-2

137 Friedman, L.G., Lachenmayer, M.L., Wang, J., He, L., Poulose, S.M., Komatsu, M. et al. (2012) Disrupted autophagy leads to dopaminergic axon and dendrite degeneration and promotes presynaptic accumulation of α-synuclein and LRRK2 in the brain. *J. Neurosci.* **32**, 7585–7593, https://doi.org/10.1523/JNEUROSCI.5809-11.2012
138 Schöndorf, D.C., Aureli, M., McAllister, F.E., Hindley, C.J., Mayer, F., Schmid, B. et al. (2014) iPSC-derived neurons from GBA1-associated Parkinson's disease patients show autophagic defects and impaired calcium homeostasis. *Nat. Commun.* **5**, 4028, https://doi.org/10.1038/ncomms5028
139 Tallóczy, Z., Virgin, I. and Herbert, L.B. (2006) PKR-dependent xenophagic degradation of herpes simplex virus type 1. *Autophagy* **2**, 24–29, https://doi.org/10.4161/auto.2176
140 Orvedahl, A., Alexander, D., Tallóczy, Z., Sun, Q., Wei, Y., Zhang, W. et al. (2007) HSV-1 ICP34. 5 confers neurovirulence by targeting the Beclin 1 autophagy protein. *Cell Host Microbe* **1**, 23–35, https://doi.org/10.1016/j.chom.2006.12.001
141 Kang, R., Zeh, H., Lotze, M. and Tang, D. (2011) The Beclin 1 network regulates autophagy and apoptosis. *Cell Death Differ.* **18**, 571–580, https://doi.org/10.1038/cdd.2010.191
142 Lussignol, M., Queval, C., Bernet-Camard, M.-F., Cotte-Laffitte, J., Beau, I., Codogno, P. et al. (2013) The herpes simplex virus 1 Us11 protein inhibits autophagy through its interaction with the protein kinase PKR. *J. Virol.* **87**, 859–871, https://doi.org/10.1128/JVI.01158-12
143 Gannagé, M., Dormann, D., Albrecht, R., Dengjel, J., Torossi, T., Rämer, P.C. et al. (2009) Matrix protein 2 of influenza A virus blocks autophagosome fusion with lysosomes. *Cell Host Microbe* **6**, 367–380, https://doi.org/10.1016/j.chom.2009.09.005
144 Garcia-Reitböck, P., Anichtchik, O., Bellucci, A., Iovino, M., Ballini, C., Fineberg, E. et al. (2010) SNARE protein redistribution and synaptic failure in a transgenic mouse model of Parkinson's disease. *Brain* **133**, 2032–2044, https://doi.org/10.1093/brain/awq132
145 Nash, J., Johnston, T., Collingridge, G., Garner, C. and Brotchie, J. (2005) Subcellular redistribution of the synapse-associated proteins PSD-95 and SAP97 in animal models of Parkinson's disease and L-DOPA-induced dyskinesia. *FASEB J.* **19**, 583–585, https://doi.org/10.1096/fj.04-1854fje
146 Prüss, H., Finke, C., Höltje, M., Hofmann, J., Klingbeil, C., Probst, C. et al. (2012) N-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis. *Ann. Neurol.* **72**, 902–911, https://doi.org/10.1002/ana.23689
147 Piacentini, R., Puma, D.D.L., Ripoli, C., Marcocci, M.E., De Chiara, G., Garaci, E. et al. (2015) Herpes Simplex Virus type-1 infection induces synaptic dysfunction in cultured cortical neurons via GSK-3 activation and intraneuronal amyloid-β protein accumulation. *Sci. Rep.* **5**, https://doi.org/10.1038/srep15444
148 Zhang, H., Li, W., Wang, G., Su, Y., Zhang, C., Chen, X. et al. (2011) The distinct binding properties between avian/human influenza A virus NS1 and Postsynaptic density protein-95 (PSD-95), and inhibition of nitric oxide production. *Virol. J.* **8**, 298, https://doi.org/10.1186/1743-422X-8-298
149 Fatemi, S.H., Sidwell, R., Kist, D., Akhter, P., Meltzer, H.Y., Bailey, K. et al. (1998) Differential expression of synaptosome-associated protein 25 kDa [SNAP-25] in hippocampi of neonatal mice following exposure to human influenza virus *in utero*. *Brain Res.* **800**, 1–9, https://doi.org/10.1016/S0006-8993(98)00450-8
150 Day, M., Wang, Z., Ding, J., An, X., Ingham, C.A., Shering, A.F. et al. (2006) Selective elimination of glutamatergic synapses on striatopallidal neurons in Parkinson disease models. *Nat. Neurosci.* **9**, 251, https://doi.org/10.1038/nn1632
151 Kouroupi, G., Taoufik, E., Vlachos, I.S., Tsioras, K., Antoniou, N., Papastefanaki, F. et al. (2017) Defective synaptic connectivity and axonal neuropathology in a human iPSC-based model of familial Parkinson's disease. *Proc. Natl. Acad. Sci. U.S.A.* **114**, E3679–E388, https://doi.org/10.1073/pnas.1617259114
152 Hacohen, Y., Deiva, K., Pettingill, P., Waters, P., Siddiqui, A., Chretien, P. et al. (2014) N-methyl-D-aspartate receptor antibodies in post–herpes simplex virus encephalitis neurological relapse. *Mov. Disord.* **29**, 90–96, https://doi.org/10.1002/mds.25626
153 Brask, J., Chauhan, A., Hill, R.H., Ljunggren, H.-G. and Kristensson, K. (2005) Effects on synaptic activity in cultured hippocampal neurons by influenza A viral proteins. *J. Neurovirol.* **11**, 395–402, https://doi.org/10.1080/13550280500186916
154 Hauwel, M., Furon, E., Canova, C., Griffiths, M., Neal, J. and Gasque, P. (2005) Innate (inherent) control of brain infection, brain inflammation and brain repair: the role of microglia, astrocytes, "protective" glial stem cells and stromal ependymal cells. *Brain Res. Rev.* **48**, 220–233, https://doi.org/10.1016/j.brainresrev.2004.12.012
155 Farina, C., Krumbholz, M., Giese, T., Hartmann, G., Aloisi, F. and Meinl, E. (2005) Preferential expression and function of Toll-like receptor 3 in human astrocytes. *J. Neuroimmunol.* **159**, 12–19, https://doi.org/10.1016/j.jneuroim.2004.09.009
156 Bsibsi, M., Persoon-Deen, C., Verwer, R.W., Meeuwsen, S., Ravid, R. and Van Noort, J.M. (2006) Toll-like receptor 3 on adult human astrocytes triggers production of neuroprotective mediators. *Glia* **53**, 688–695, https://doi.org/10.1002/glia.20328
157 Carpentier, P.A., Begolka, W.S., Olson, J.K., Elhofy, A., Karpus, W.J. and Miller, S.D. (2005) Differential activation of astrocytes by innate and adaptive immune stimuli. *Glia* **49**, 360–374, https://doi.org/10.1002/glia.20117
158 Jack, C.S., Arbour, N., Manusow, J., Montgrain, V., Blain, M., McCrea, E. et al. (2005) TLR signaling tailors innate immune responses in human microglia and astrocytes. *J. Immunol.* **175**, 4320–4330, https://doi.org/10.4049/jimmunol.175.7.4320
159 Park, C., Lee, S., Cho, I.H., Lee, H.K., Kim, D., Choi, S.Y. et al. (2006) TLR3-mediated signal induces proinflammatory cytokine and chemokine gene expression in astrocytes: differential signaling mechanisms of TLR3-induced IP-10 and IL-8 gene expression. *Glia* **53**, 248–256, https://doi.org/10.1002/glia.20278
160 Zhao, Y., Rivieccio, M.A., Lutz, S., Scemes, E. and Brosnan, C.F. (2006) The TLR3 ligand polyI: C downregulates connexin 43 expression and function in astrocytes by a mechanism involving the NF-κB and PI3 kinase pathways. *Glia* **54**, 775–785, https://doi.org/10.1002/glia.20418
161 Ezan, P., André, P., Cisternino, S., Saubaméa, B., Boulay, A.-C., Doutremer, S. et al. (2012) Deletion of astroglial connexins weakens the blood–brain barrier. *J. Cereb. Blood Flow Metab.* **32**, 1457–1467, https://doi.org/10.1038/jcbfm.2012.45
162 Scumpia, P.O., Kelly, K.M., Reeves, W.H. and Stevens, B.R. (2005) Double-stranded RNA signals antiviral and inflammatory programs and dysfunctional glutamate transport in TLR3-expressing astrocytes. *Glia* **52**, 153–162, https://doi.org/10.1002/glia.20234

163 Kavouras, J.H., Prandovszky, E., Valyi-Nagy, K., Kovacs, S.K., Tiwari, V., Kovacs, M. et al. (2007) Herpes simplex virus type 1 infection induces oxidative stress and the release of bioactive lipid peroxidation by-products in mouse P19N neural cell cultures. *J. Neurovirol.* **13**, 416–425, https://doi.org/10.1080/13550280701460573

164 Valyi-Nagy, T., Olson, S.J., Valyi-Nagy, K., Montine, T.J. and Dermody, T.S. (2000) Herpes simplex virus type 1 latency in the murine nervous system is associated with oxidative damage to neurons. *Virology* **278**, 309–321, https://doi.org/10.1006/viro.2000.0678

165 Picconi, B., Piccoli, G. and Calabresi, P. (2012) Synaptic dysfunction in Parkinson's disease. *Synaptic Plasticity* 553–572, https://doi.org/10.1007/978-3-7091-0932-8˙24

166 Scott, D.A., Tabarean, I., Tang, Y., Cartier, A., Masliah, E. and Roy, S. (2010) A pathologic cascade leading to synaptic dysfunction in α-synuclein-induced neurodegeneration. *J. Neurosci.* **30**, 8083–8095, https://doi.org/10.1523/JNEUROSCI.1091-10.2010

167 Volpicelli-Daley, L.A., Luk, K.C., Patel, T.P., Tanik, S.A., Riddle, D.M., Stieber, A. et al. (2011) Exogenous α-synuclein fibrils induce Lewy body pathology leading to synaptic dysfunction and neuron death. *Neuron* **72**, 57–71, https://doi.org/10.1016/j.neuron.2011.08.033

168 Bernard, V., Gardiol, A., Faucheux, B., Bloch, B., Agid, Y. and Hirsch, E.C. (1996) Expression of glutamate receptors in the human and rat basal ganglia: effect of the dopaminergic denervation on AMPA receptor gene expression in the striatopallidal complex in Parkinson's disease and rat with 6-OHDA lesion. *J. Comp. Neurol.* **368**, 553–568, https://doi.org/10.1002/(SICI)1096-9861(19960513)368:4%3c553::AID-CNE7%3e3.0.CO;2-3

169 Ebrahimie, E., Nurollah, Z., Ebrahimi, M., Hemmatzadeh, F. and Ignjatovic, J. (2015) Unique ability of pandemic influenza to downregulate the genes involved in neuronal disorders. *Mol. Biol. Rep.* **42**, 1377–1390, https://doi.org/10.1007/s11033-015-3916-4

170 Klionsky, D.J., Abdelmohsen, K., Abe, A., Abedin, M.J., Abeliovich, H., Acevedo Arozena, A. et al. (2016) Guidelines for the use and interpretation of assays for monitoring autophagy. *Autophagy* **12**, 1–222, https://doi.org/10.1080/15548627.2015.1100356

171 Shoji-Kawata, S. and Levine, B. (2009) Autophagy, antiviral immunity, and viral countermeasures. *Biochim. Biophys. Acta* **1793**, 1478–1484, https://doi.org/10.1016/j.bbamcr.2009.02.008

172 Yordy, B., Iijima, N., Huttner, A., Leib, D. and Iwasaki, A. (2012) A neuron-specific role for autophagy in antiviral defense against herpes simplex virus. *Cell Host Microbe* **12**, 334–345, https://doi.org/10.1016/j.chom.2012.07.013

173 Alexander, D.E., Ward, S.L., Mizushima, N., Levine, B. and Leib, D.A. (2007) Analysis of the role of autophagy in replication of herpes simplex virus in cell culture. *J. Virol.* **81**, 12128–12134, https://doi.org/10.1128/JVI.01356-07

174 He, B., Gross, M. and Roizman, B. (1997) The γ134. 5 protein of herpes simplex virus 1 complexes with protein phosphatase 1α to dephosphorylate the α subunit of the eukaryotic translation initiation factor 2 and preclude the shutoff of protein synthesis by double-stranded RNA-activated protein kinase. *Proc. Natl. Acad. Sci. U.S.A.* **94**, 843–848, https://doi.org/10.1073/pnas.94.3.843

175 Mulvey, M., Poppers, J., Ladd, A. and Mohr, I. (1999) A herpesvirus ribosome-associated, RNA-binding protein confers a growth advantage upon mutants deficient in a GADD34-related function. *J. Virol.* **73**, 3375–3385

176 Poppers, J., Mulvey, M., Khoo, D. and Mohr, I. (2000) Inhibition of PKR activation by the proline-rich RNA binding domain of the herpes simplex virus type 1 Us11 protein. *J. Virol.* **74**, 11215–11221, https://doi.org/10.1128/JVI.74.23.11215-11221.2000

177 Leib, D.A., Alexander, D.E., Cox, D., Yin, J. and Ferguson, T.A. (2009) Interaction of ICP34. 5 with Beclin 1 modulates herpes simplex virus type 1 pathogenesis through control of CD4+ T-cell responses. *J. Virol.* **83**, 12164–12171, https://doi.org/10.1128/JVI.01676-09

178 Mori, I., Goshima, F., Imai, Y., Kohsaka, S., Sugiyama, T., Yoshida, T. et al. (2002) Olfactory receptor neurons prevent dissemination of neurovirulent influenza A virus into the brain by undergoing virus-induced apoptosis. *J. Gen. Virol.* **83**, 2109–2116, https://doi.org/10.1099/0022-1317-83-9-2109

179 Santana, S., Recuero, M., Bullido, M.J., Valdivieso, F. and Aldudo, J. (2012) Herpes simplex virus type I induces the accumulation of intracellular β-amyloid in autophagic compartments and the inhibition of the non-amyloidogenic pathway in human neuroblastoma cells. *Neurobiol. Aging* **33**, 430.e19–430.e33, https://doi.org/10.1016/j.neurobiolaging.2010.12.010

180 Komatsu, M., Waguri, S., Chiba, T., Murata, S., Iwata, J., Tanida, I. et al. (2006) Loss of autophagy in the central nervous system causes neurodegeneration in mice. *Nature* **441**, 880–884, https://doi.org/10.1038/nature04723