*Archives of Assessment Psychology,* Vol. 12, No. 1, (43-64)
Printed in U.S.A. 


# Psychiatric and Neuropsychological Sequelae of Herpes Simplex Encephalitis

***Carla Cabrera, M.S. and Charles Golden, Ph.D.***

**Abstract**

*Herpes simplex encephalitis (HSE) is caused by the herpes simplex virus (HSV), often from the Type 1 (HSV-1) viral infection. This neurotropic double-stranded DNA virus impairs the integrity and permeability of the blood-brain barrier, allowing the virus to enter the brain. In several studies, HSV-1 impacts the temporal lobe, frontal lobe, and limbic system, leading to brain damage. While significant progress has occurred in understanding this infection, clinicians should be vigilant for acute and chronic complications associated with HSE, such as autoimmune encephalitis, differential diagnoses, and psychological disorders. A growing body of literature focuses on the evidence of an association between HSE and neuropsychological effects discussed in this review. Current research limitations and future research directions are discussed to highlight the need for further research efforts to improve the understanding of the long-term sequelae caused by HSE.*

## Introduction

Encephalitis is an inflammation of the brain caused by viral infection, or less commonly by bacteria, fungi, or autoimmune reaction. From 2000 to 2010, there were 7.3 encephalitis hospitalizations per 100,000 population in the U.S. alone (George et al., 2014). Research reveals that encephalitis is a substantial burden with considerable mortality (Vora et al., 2014). Moreover, infants, older adults, and those with weakened immune systems are at higher risks of hospitalization (U.S. Department of Health and Human Services, 2018). Viral causes (e.g., HSV, West Nile virus, and rabies lyssavirus) are frequent, and one of the most common is HSV: More than 60% of the world's population is positive for HSV-1 (Menendez & Carr, 2017). However, data suggest that outcomes in encephalitis are not well characterized.

HSE critically impacts psychological, neurological, and neuropsychological functioning. Additionally, stress systems can negatively affect neurobiological regulation and psychiatric states, including schizophrenia and bipolar disorders (Dickerson et al., 2008; Glaser et al., 1987). Knowing HSE's neurological, neurovascular, and neuropsychological effects enables psychologists and related professionals to recognize etiological contributions and complex clinical sequelae. Associated neurological and neurovascular changes include changes to the blood-brain barrier, gray matter loss, and effects on the parietal lobe and limbic system (Tucker & Bertke, 2019). Several neuropsychological domains are also impacted by HSE, including executive functioning, motor skills, language, attention, and working memory (Tucker & Bertke, 2019).

The purpose of this review is to demonstrate recent findings of neuropsychological sequelae and to discuss emerging research into pervasive outcomes of HSE. In addition, there is increasing scrutiny of HSE patient outcomes to determine the contribution of misleading initial symptoms and late-appearing HSV antibodies.

## Virology, Transmission, and Pathology of HSV

HSV-1 is one of several simplexes of herpesvirus. It is a human-specific double-stranded-DNA virus in which the prevalence of the virus increases with age. Before reaching the blood-brain barrier, the virus inoculates through a primary or secondary transmission type. Primary is through direct contact with the viral-infected host, while the secondary onset is via the immune system. Once the virus infects an individual, it may take days to weeks to show symptoms (Cleator & Klapper, 2004). Moreover, symptomatology progression may be sudden or gradual. Onset varies due to individual differences (e.g., medical history) and risk factors (e.g., age or weak immune system; Gluska et al., 2014; Meyding-Lamadé & Strank, 2012; Winkelmann et al., 2016). In 2016, an estimated 3.7 billion people under the age of 50 (67% of the population) had HSV-1 infections, while the U.S. seroprevalence of HSV-1 was 53.9% between 2005 and 2010 (Bradley et al., 2013; World Health Organization, 2020). According to the National Health and Nutrition Examination Survey (NHANES), 30% of these individuals demonstrated clinical outbreaks (Bradley et al., 2013).

These viral infections were of the primary transmission type. In the primary form, HSV enters via the cutaneous or mucosal surface (leading to herpes labialis and possibly genital herpes by contact with oral lesions) and begins infecting sensory or autonomic nerve endings. Next, the virus is transported to cell bodies in the ganglia, where it spreads through the blood-brain barrier to the temporal lobe via the meningeal branches of Cranial Nerve IV. HSV may remain latent for the lifespan in the trigeminal ganglia and olfactory bulbs (Liu et al., 2019) in a non-infectious state until reactivation (Cruz et al., 2018). The latency phase is thought to be harmless, but during the reactivation phase, viral particles replicate and travel across the sensory nerves, causing lesions in the mucosal membrane or skin (e.g., recurrent cold sores; Steiner et al., 2007). Hence, the viral genome is present even when no virus is present.

## Impairment of the Blood-Brain Barrier

The permeability and integrity of the blood-brain barrier, where the trigeminal ganglia are located, is compromised in HSE, leading to edema (i.e., excessive watery fluid in the intra- and extracellular space of the brain), hemorrhage (i.e., bleeding in the brain that can reduce oxygen delivery to the brain, create extra pressure, and kill brain cells), leukocyte infiltration (i.e., cells that are involved in counter tracing foreign substances), and progressive inflammation-inducing damage (Baringer & Pisani, 1994). This issue is further accompanied by cerebral microcirculation and metabolic disturbances (Liu et al., 2019).

The blood-brain barrier is comprised of several components that become disrupted in HSE. Endothelial cells, the layer that lines blood vessels, do not limit the entry of immune cells into the central nervous system, a prerequisite for the protection of the central nervous system from harm. Likewise, tight junctions, localized between endothelial cells in a series of multiple barriers, help seal the interendothelial cleft. When disrupted, the adhesion junction proteins undergo degradation, preventing the regulation of interactions between cells, phosphorylation, and redistribution. Other components such as astrocytes can undergo apoptosis due to mitochondrial dysfunction in HSE, while microglia become unable to sense changes in the surrounding environment (disrupts homeostasis; Liu et al., 2019).

**Structural Brain Changes**

Few studies have examined the neuroanatomical changes that can occur as a result of HSE. Those who have investigated report abnormal gray matter density in the limbic and paralimbic cortices in patients recovering from HSE. For individuals positive for HSV-1 without encephalitis, the reduced prefrontal gray matter was observed in a sample of psychiatric patients (Prasad et al., 2006). Computer tomography has revealed hypodense regions, edema, or arias of increased contrast even shortly after admission (Raschilas et al., 2002). Moreover, perivascular lymphocytic cuffing has been identified in areas such as the pons, midbrain, and temporal lobe, along with hemorrhages, ecchymosis, and thalamic, brain stem, and cerebellar involvement in HSE (Garg, Kulkarni & Udwadia Hegde, 2018).

Several animal studies have been used to assess the neuroanatomical changes from HSE. Past studies have examined mice injected with HSV that developed encephalitis and found that if the disease is inoculated into the hippocampal area, it was yielding more severe disease than inoculation into the cerebellum (McFarland & Hotchin, 1987). Rabbits have also been studied in which it was reported that signs of neuronal and glial necrosis in the cerebral cortex were present (Grest et al., 2002). Current research aimed at investigating the link between HSV infection and multifocal central nervous system demyelination (Boukhvalova et al., 2019) found that HSV-1 infection in rats can cause multifocal central nervous system demyelination and inflammation. Moreover, they discovered that remyelination occurred after demyelination in HSV-1 infected rats but was possibly structurally and functionally incomplete, resulting in scars forming in the nervous system. This further supported the hypothesis of there being an association between the two. Subsequently, brain pathology developed mostly on the ipsilateral side of the brain stem and cerebellum and the contralateral side of the forebrain/midbrain, suggesting brain changes may arise along the trigeminal lemniscus pathway (Boukhvalova et al., 2019).

**Diagnostic Criteria**

HSV-1 infection is frequently asymptomatic; however, there is a wide range of clinical presentations (Saleh et al., 2021). Individuals with HSV encephalitis usually undergo an altered mental status consisting of (1) an altered level of consciousness, (2) lethargy, (3) and personality change for 24 hours or more with no alternate cause identified. It has been suggested that in order to meet the minor criteria for HSE, two conditions must be met to be considered possible, while three or more conditions are required for a probable or confirmed case: (1) Fever of 100.4 degrees F or more, (2) New-onset seizures that are not attributed to a prior seizure disorder, (3) New onset of focal neurologic findings in the brain, spinal cord, or nerves, (4) Cerebrospinal fluid white blood cell count needs to be five cells per cubic millimeter or more, (5) Neuroimaging demonstrates brain parenchymal (brain tissue) abnormality suggestive of encephalitis, and (6) Electroencephalogram demonstrates abnormality consistent with encephalitis (Mayo Clinic, 2020; Venkatesan et al., 2013).

**Assessing for Encephalitis**

Medical facilities are the only settings where HSE can be assessed. The utilization of diagnostic instruments such as MRI, CT scan, and EEG are imperative for diagnosing encephalitis. Physicians also assess through blood, urine, and stool tests. Brain biopsies are rare; nonetheless, they are considered whenever necessary. One of the most common techniques is lumbar puncturing to obtain a sample of infection in the cerebral spinal fluid (CSF) (Bechter et al., 2019; U.S. Department of Health and Human Services, 2018). Neurological examinations further assess

the individual's level of consciousness, mental status, seizures, speech, raised intracranial pressure, cranial nerves, and limbs for focal neurological features. Additionally, physicians should be aware of differential or comorbid diagnoses such as meningitis, myelitis, radiculitis, or neuritis that may be present (Venkatesan et al., 2013).

**Psychiatric and Neuropsychological Findings**

Since HSV-1 can cause a lifelong infection in the central nervous system, it is a plausible risk factor for cognitive impairment. Infectious microorganisms such as HSV have been shown to be involved in neurological and psychiatric disorders. Antibodies found in HSV-1, the most common of the herpes viruses, have also demonstrated they can be an independent predictor of cognitive functioning. Moreover, the acute exacerbation of infection in carriers has been associated with elevated stress level and its immunosuppressive effect, which can possibly lead to a cycle of psychosocial stress resulting in manic or depressive episodes and can even exacerbate the HSV infection, contributing to an increase in functional impairment and poor quality of life (Dickerson et al., 2008; Glaser et al., 1987).

**Schizophrenia and Bipolar Disorder Studies**

Schizophrenia is a neuropsychiatric disorder where cognitive deficits are common features. Compared to the general population, individuals with schizophrenia perform poorly on a broad range of cognitive tasks (Heinrichs, 2005). Evidence suggests that areas that are usually impaired include episodic memory and processing speed but have also been observed in executive functioning (i.e., reasoning, abstraction, and fluency; Orellana and Slachevsky, 2013; Schaefer et al., 2013; Skelley et al., 2008; Weickert et al., 2000). Although the etiology is not known, exposure to HSV has been found to produce viral particles and subsequent infection of additional cells in the central nervous system (Arbusow et al., 1999; Quinn et al., 2000). Therefore, research on cognitive impairment in HSV-1 positive patients with schizophrenia or bipolar disorder has questioned whether HSV could potentially be associated with these disorders (Gerber et al., 2012; Lindgren et al., 2018; Suvisaari et al., 2017).

Previous studies have suggested that infectious pathogens, such as HSV, Toxoplasma gondii, or influenza could be associated with schizophrenia and bipolar disorder (Gerber et al., 2012). Each of these pathogens gains access to the brain during infection, contributing to psychotic symptoms, behavioral abnormalities, and cognitive impairment characterizing the disorders (Hannachi et al., 2014). According to Tucker and Bertke (2019), there is also evidence of neuroanatomical changes in the brain that may contribute to cognitive impairment.

For instance, gray matter density has been identified as one of the structures that change HSE, with the loss occurring within a year or longer. MRIs have demonstrated gray matter loss in Brodmann's areas 8, 9, and 32 in HSV-positive patients who have schizophrenia compared to HSV-negative patients (without a diagnosis of schizophrenia). Tucker and Bertke (2019) revealed gray matter loss in the posterior cingulate, declining executive functioning, and declining working memory in HSV-positive patients with schizophrenia and bipolar disorders. Similarly, volume loss on the cingulate gyrus, cerebellum, and hippocampal volume has also been conveyed. Tucker and Bertke analyzed neuropsychological testing data from various studies regarding the impact of HSV-1 on cognitive functioning in patients diagnosed with schizophrenia and bipolar disorder. They found that HSV-1 infection significantly impacts cognitive functioning with small to moderate effect sizes, particularly affecting memory and attention. In studies focusing on bipolar disorder, activations were found in the dorsolateral prefrontal cortex (Gerber et al., 2012).

Moreover, researchers found decreased glial and neuronal density in the prefrontal cortex and neurotransmitters that may be implicated in the development of bipolar disorder.

Gerber et al., (2012) examined the relation of infection, cognitive functioning, and demographic parameters to the prevalence of infectious agents in HSV-positive patients with bipolar disorder compared to healthy controls. They utilized the Positive and Negative Syndrome Scale, RBANS, Trail Making Test (TMT) A and B, Letter Number Sequencing (LNST), and Information subtest of the WAIS-III, and they were tested for HSV-1 antibodies (See Table 1).

Table 1
*Assessments and descriptions*

| Assessment | Description |
|---|---|
| Scale for the Assessment of Negative Symptoms (SANS) | Rating scale to measure negative symptoms in SZ |
| Scale for the Assessment of Positive Symptoms (SAPS) | Rating scale to measure positive symptoms in SZ |
| Trail Making Test- Part A (TMT A) | Attention and processing speed |
| Trail Making Test- Part B (TMT B) | Executive functioning |
| Brief Test of Attention (BTA) | Attention |
| Hopkins Verbal Learning Test (HVLT) | Test of verbal learning and memory; consist of 3 trials of free recall of a 12-item list, followed by yes/no recognition |
| Brief Visuospatial Memory Test (BVMT) | Test of visuospatial memory; consists of 6 geometric figures, with stimulus exposure for 10 seconds, followed by drawing figures accurately in the correct location |
| Wisconsin Card Sorting Test (WCST) | Executive functioning |
| Grooved Pegboard Test | Requires complex visual motor coordination; consists of 25 holes with randomly positioned slots |
| Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol | Similar to Coding on WAIS 4th edition; processing speed, attention |
| Controlled Oral Word Association Test (COWAT) | Verbal fluency test that uses letters C, F, and L to assess phonemic fluency |
| Letter-n-Back test | Measures working memory; presented with a sequence of stimuli (list of letters) and client indicates when current stimulus matches the one from n-steps in the sequence. |

*Note.* SZ = schizophrenia; BP = bipolar disorder.

They found that in a sample with no significant difference between age, gender, or education, depression and manic scores were low and that the controls did not evidence significant

difficulties on any of the measures. The bipolar group scored higher on positive symptoms and significantly lower on the RBANS, TMT A and B, and LNST. Thus, HSV-1 was found to be a predictor for neuropsychological impairment (See Table 2). Gerber et al. (2012), also found that within the RBANS, HSV-1 positive individuals with bipolar disorder had a significant decrease in total score compared to HSV-1 patients without bipolar disorder. It was determined that interaction between specific genetic polymorphisms, and the virus might negatively impact memory.

Table 2
*Findings on the Comparison Between Individuals with Schizophrenia versus Bipolar Disorder*

| Assessments | Domains | Group | Patients |
|---|---|---|---|
| Scale for the Assessment of Negative Symptoms (SANS) | | | |
| Scale for the Assessment of Positive Symptoms (SAPS) | | HSV positive | SZ |
| Trail Making Test- Part A (TMT A) | Processing speed and attention | HSV positive | BP |
| Trail Making Test- Part B (TMT B) | Executive functioning | HSV positive | SZ |
| Hopkins Verbal Learning Test (HVLT) | Verbal memory | HSV positive | SZ |
| Brief Visuospatial Memory Test (BVMT) | Visuospatial memory | | |
| Wisconsin Card Sorting Test (WCST) | Executive functioning | HSV positive | S.Z. |
| Grooved Pegboard Test | Motor functioning | | |
| Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol | Processing speed | HSV positive | SZ |
| Controlled Oral Word Association Test (COWAT) | Verbal fluency | | |
| RBANS total score | | HSV positive | BP & SZ |
| RBANS- Immediate memory | | HSV positive | BP & SZ |
| RBANS- Visuospatial construct | | HSV positive | SZ |
| RBANS- attention | | HSV positive | BP & SZ |
| RBANS- delayed memory | | HSV positive | BP & SZ |

| | | | |
|---|---|---|---|
| RBANS- verbal | | HSV positive | BP |
| Letter-N-Back test | | HSV positive | SZ |
| Brief Assessment of Cognition (BACS) in SZ | Multiple cognitive domains | HSV positive | BP & SZ |

*Note.* HSV = Herpes Simplex Virus; SZ = Schizophrenia; BP = Bipolar Disorder; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status.

An overview of research on psychiatric disorders and HSV-1 revealed that cognitive impairment is also correlated with social adjustment and quality of life. Individuals diagnosed with bipolar disorder have reported more dissatisfaction with their working situation, financial income, relationship with their family and friends, social interactions, and mental health. Moderate correlations were found between immediate memory and work situation, verbal ability, and long-term memory with social interactions and relationships with family and friends (Gerber et al., 2012; Tucker & Bertke, 2019).

These findings suggest that although schizophrenia and bipolar disorder impair functioning, HSV-1 infection further exacerbates cognitive impairment in patients with the same disorders (Tucker & Bertke, 2019). Moreover, the common denominator for HSV-positive patients with schizophrenia or bipolar disorder was memory impairments. According to Tucker and Bertke (2019), HSV-1 infection significantly impacts immediate memory and attention for individuals who have been diagnosed with schizophrenia. Immediate and delayed memory, working memory, and attention may be more susceptible to impairment. This is because HSV-1 infects the trigeminal and olfactory nerves and disseminates to the temporal lobes and limbic system, which are responsible for executive functioning and memory.

Dickerson et al. (2020) sought to determine the relationship between HSV-1 exposure and cognitive functioning (delayed memory, emotion, processing speed, reasoning, verbal learning, vigilance, visual learning, visual-spatial, and working memory) in individuals with schizophrenia. A systematic review found that HSV-1's role on cognitive functioning is independent of medication and that the infection contributed to the impairments in individuals with schizophrenia on all domains except emotions compared to a control group.

**HSV versus non-HSV samples**

Research has shown that individuals with HSV-1 have greater difficulty with verbal memory, semantic, and visuospatial tasks than other etiological groups. Pewter et al. (2007) compared HSV and non-HSV patients with infectious or autoimmune etiologies. They found significant and widespread cognitive deficits in HSV patients. Moreover, non-HSV patients showed more isolated disorders of executive functioning. Persisting hyperintensities on MRIs and substantial volume loss in the medial temporal lobes have been found in patients with HSV-1. Lateral temporal and widespread cortical damage is also common (Harris et al., 2020). The severity of anterograde amnesia after HSE appears to be correlated with the extent of pathology in the medial temporal regions, with bilateral damage predictive of severe amnesia.

***Neurocognitive Evaluations***

In order to understand the presence of distinct patterns of neuropsychological impairment across different subgroups of encephalitis, Harris and colleagues (2020) assessed patients' perceptions of the impact of encephalitis on their lives, changes in neuropsychological

performance across subgroups, and the relationship between clinical variables, neuroimaging, and neuropsychological/psychiatric outcomes. The results of this study are shown in Table 3.

Systematic reviews of the cerebrovascular manifestations of HSV infection of the central nervous system have found these individuals undergo several complications, including reported intracranial hemorrhage and ischemic stroke (Pillai et al., 2015). Moreover, it was found that these complications occurred exclusively within the temporal lobe, consistent with previous findings. Hauser et al. (2017) found that cerebrovascular complications were independent of age and gender and were not associated with comorbidities. They found that HSE typically affects the cortex and underlying white matter of the temporal lobe, consistent with research on patients with schizophrenia (Gnann & Whitley, 2017). They also found that parts of the cerebral cortex such as the insula, cingulate gyrus, and posterior orbital frontal lobe are less frequently involved and suggested that HSV-related infarction is a rare but potentially treatable cause of stroke that may not even be considered a stroke.

Previous research studies as early as the 1970s have found that HSE lesions usually occur in the limbic and paralimbic regions, including the areas mentioned above (Adams & Miller, 1973; Damasio et al., 1985; Kennedy et al., 1988). Dickerson et al. (2008) found greater deficits in delayed memory and executive functioning among HSV-positive individuals than non-HSV individuals, but not for the HSV-2 virus. They suggested that cognitive impairments due to HSV-1 are more observable or prominent. Studies with older adults found that the viral burden of HSV-1 infection was associated with more cognitive impairments in those who also suffered from cardiovascular diseases, suggesting that the impact of HSV on cognitive impairment could be biological and psychological (Strandberg, 2003).

Table 3
*Comparison Between Different Viral Infections*

| Assessment | Domain | Short and Medium | Long-term | Explanation |
|---|---|---|---|---|
| Wechsler Test of Adult reading (WTAR) | Intelligence (Pre-morbid IQ) | HSV | | |
| Wechsler Abbreviated Scale Intelligence-Revised (WASI-II) | Intelligence (Current IQ) | HSV (FSIQ) and Other (FSIQ and VIQ) | | Hippocampal and T.L. damage found in MRI's |
| Doors and People Battery | memory (Anterograde) | HSV (visual recall and recognition) | HSV | Hippocampal and T.L. damage found in MRI's |
| Autobiographical memory interview | memory (Retrograde) | HSV and Other | HSV and Unknown | Hippocampal and T.L. damage found in MRI's |

| | | | | |
|---|---|---|---|---|
| Controlled Oral Word Association Test (COWAT) | Executive functioning (verbal fluency) | HSV | | |
| Trail Making Test-Part A (TMT A) | Executive functioning | | | |
| Hayling Test | Executive functioning | HSV | | Hippocampal and T.L. damage found in MRI's |
| Brixton Test | Visuospatial | | | |
| Graded Naming test | Word retrieval/object naming | HSV | | |
| Pyramids and Palm Trees Test | Language (Visual Semantics) | | | |
| Visual Object and Space Perception Battery | Perception | | | |
| Benton Facial Recognition test | Perception | | | |
| Beck's Depression Inventory (BDI) | Psychiatric-Depression | HSV and Other | HSV and Other | |
| Beck's Anxiety Inventory (BAI) | Psychiatric-Anxiety | Unknown | Unknown | Negative impact of receiving uncertain diagnosis |
| AB Neuropsychological Assessment Schedule (ABNAS) | Self-perception | HSV and Other | HSV more than Other and Unknown | Depression (tiredness, mental speed, memory, concentration, language) |

*Note.* HSV = Herpes Simplex Virus; IQ = Intelligence Quotient; FSIQ = Full-Scale Intelligence Quotient; VIQ = Verbal Intelligence Quotient; T.L. = Temporal Lobe.

Outcomes after encephalitis varied according to the etiology. Memory and naming impairments were most severely affected in the HSV group and were associated with more severe medial temporal lobe damage, as evidenced by the MRI results. Cognitive performance improved over time; however, cognitive complaints, depression, and anxiety were not. According to Harris et al. (2020), executive functioning, naming, and I.Q. impairments appeared to be resolved after the first year despite all groups continuing with high levels of depression and anxiety, suggesting psychiatric sequelae of encephalitis. Moreover, they found that tiredness was a significant

complaint, while anxiety was more significant in the Unknown group, suggesting a negative impact of receiving an uncertain diagnosis. Thus, the delayed time until appropriate treatment and prolonged hospital stay was correlated with poorer outcomes.

### *Depression*

Undoubtedly, healthy cognitive functioning is critical for physical and mental health. However, several risk factors can reactivate HSV-1, including psychosocial distress, which symptoms of depression can measure. On its own, depression is known to contribute to cognitive vulnerability in memory, psychomotor skills, executive functioning, and intelligence (Marazziti et al., 2010). When combined with HSV-1, it fosters early cognitive vulnerability in otherwise healthy middle-aged adults. Cassill et al. (2018) examined how psychosocial distress and HSV-1 foster early cognitive vulnerability. They found that subclinical depressive symptoms can exacerbate the negative effects of HSV-1 infection on global cognitive functioning. Moreover, it was suggested that HSV-1 positive individuals reporting some depressive symptomatology performed worse on the Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II) than HSV-1 positive individuals without depressive symptoms. However, the results conveyed no effect on memory or executive functioning, likely due to the large sample of younger adults participating in the study.

Other studies show that depression independently leads to cognitive decline and additive effects on HSV-1 positive individuals (Borrell-Carrio et al., 2004; Marazziti et al., 2010). Although the negative impact of depression on cognition has been demonstrated, some believe that the relationship between depression and cognitive decline is thought to be caused by a lack of motivation, or a response to decreased functionality, while others hypothesize that an underlying neuropathological factor may lead to depression and cognitive dysfunction (Panza et al., 2010; Yaffe et al., 1999). Regardless, research conveys that HSV-1 infection results in lower cognitive reserve that exacerbates the effects of depression on cognition.

### *Dementia*

Increasing evidence suggests a possible link between the infection and Alzheimer's Disease (A.D.), the most common neurodegenerative disease associated with dementia in older adults (Itzhaki, 2017). Previous studies have demonstrated the presence of the HSV-1 genome in patients with A.D., particularly those with the E3 allele of apolipoprotein E, a risk factor for A.D. (Itzhaki et al., 2004). In addition, other studies found HSV-1 infection affects the microtubule-associated protein tau, triggering its hyperphosphorylation and aggregation, possibly leading to its deposition in neurofibrillary tangles, another characteristic of A.D., supporting the hypothesis that the accumulation of A.D. biomarkers are triggered by HSE (Zambrano et al., 2008; Wozniak et al., 2009). Moreover, a study with HSE-infected mice found that the progressive accumulation of A.D. biomarkers in the neocortex and hippocampus, triggered by repeated virus reactivations, was associated with an increase in cognitive deficits that became irreversible after seven reactivations (De Chiara et al., 2019). This provided evidence that mild and recurrent HSV-1 infections in the bran produce an AD-like phenotype and increase A.D risk.

Consistent with the findings above related to risk factors, Tzeng et al. (2018) suggested that the risk of dementia was increased in persons with multiple outpatient visits due to HSV-1. However, they indicated that antiviral medication treatment decreased the risk of dementia in older adults. Similarly, a few longitudinal studies have examined the association between HSV-1 and dementia risks due to cognitive decline. For example, Lövheim and colleagues (2014) found that

individuals who tested positive for HSV almost doubled their risk for A.D. since it is believed that a weakened immune system later in life contributes to the HSV spreading while establishing a low grade of infection in the brain. This leads to inflammation and cellular changes, promoting amyloid-beta production and other components that cause A.D.

In a cross-sectional study, Tarter et al. (2014) found a relationship between HSV-1 infection and impaired reading and spatial reasoning in children, low coding speed in adults, and impaired immediate memory in older adults. However, other studies did not find any association on cognitive decline in older adults or on those with a risk of dementia, consistent with mixed findings on HSV encephalitis (Aiello et al., 2006; Barnes et al., 2015; Nimgaonkar et al., 2016; Torniainen-Holm et al., 2019). According to Torniainen-Holm et al. (2019), inconsistent results could imply the lack of knowledge of the timing of infection, or the type of cognitive batteries used for the investigation.

**Normal EEG**

HSE survival has been associated with normal EEG characteristics. In their study, Sutter et al. (2015) confirmed previously identified EEG features (i.e., uni- or bilateral periodic discharges, focal or generalized slow waves, and electrical seizures) to determine the further diagnostic and predictive value of EEG in acute encephalitis. The EEG interpretations revealed significantly higher proportions with periodic discharge and focal slowing in the frontotemporal and occipital regions for individuals with HSE. Additionally, they reported several clinical predictors in mortality, including coma at admission to a medical facility, edema, or the use of a mechanical ventilator. Thus, they concluded that a normal EEG is significantly associated with survival in HSE, despite an abnormal conscious state. This indicates that EEGs can be important for prognosis beyond cognitive conditions (Sutter et al., 2015).

**Autoimmune Encephalitis**

***Diagnostic Assessments***

Relapse symptoms post HSV encephalitis have been found in patients who have shown to be cleared from the virus in their CSF. Researchers imply that it may be caused by autoimmune mechanisms such as the post-HSE development of N-methyl-D-aspartate receptor (NMDAR) antibodies resulting in autoimmune encephalitis (Wang & Xiao, 2020). This occurrence is believed to be associated with the formation of antibodies against a subunit of NMDAR. In 2012, Pruss et al. reported that 30% of patients with HSE developed NMDAR antibodies in their serum. MRIs may also be helpful in the etiologic diagnosis because they may show a pattern characteristic of certain infections or a pattern commonly seen with autoimmune encephalitis, such as bilateral medial temporal lobe involvement.

Similarly, EEGs frequently show nonspecific features of encephalopathy and epileptiform activity. However, certain EEG patterns may have diagnostic utility, such as extreme delta brush (i.e., diffuse slow waves and rapid activity), which is seen in various cases of NMDAR encephalitis. In addition, since Pruss et al.'s (2012) findings, NMDAR antibodies have been identified in many patients with relapsing symptoms post-HSE (Sahar, Nurre, & Simon, 2019; Venkatesan & Murphy, 2018).

***Identifying Autoimmune Encephalitis***

Studies have indicated that relapsing symptoms are experienced following treatment of HSE. Moreover, CSF tests are repeated for HSV polymerase chain reactions when detectable HSV

suggests an ongoing infection. Undetectable HSV with a CSF pleocytosis supports an autoimmune mechanism; in these cases, NMDAR antibodies should be tested in the CSF and serum. Regardless of whether antibodies are actually detected at this stage, if a patient has a cleared HSV test result, an autoimmune mechanism should be suspected, and immunotherapy should be strongly considered (Venkatesan & Murphy, 2018).

Autoimmune encephalitis is recognized to cause diverse psychiatric symptoms, and several patients can go misdiagnosed with a primary psychiatric disorder. Thus, there is minimal consensus on which signs exhibited by psychiatric patients should prompt further antineuronal antibody investigation. Herken and Pruss (2017) analyzed symptoms of autoimmune encephalitis and the time between symptoms onset and initiation of antibodies. They found that the period between the occurrence of the first symptoms and the time antibody testing was conducted was prolonged. Seizures, catatonia, autonomic instability, or hyperkinesia were clinical signs determined to assist earlier diagnosis. It was further conveyed that CSF abnormalities, including the detection of anti-neural autoantibodies, were observed in over 50% of psychotic patients, suggesting a link between autoantibodies and psychotic disorders (Herken & Pruss, 2017). In addition, they reported that CSF-derived human monoclonal NMDAR antibodies alone represented a risk factor for neuropsychiatric symptoms. The prognosis of the disease largely depends on the rapid initiation of immunotherapy. Herken and Pruss (2017) also found that symptoms overlapped with viral encephalitis in that there are neurological and psychiatric changes, suggesting that the presence of antibodies should always be evaluated even when the virus diagnostic remains negative.

### *Case Study*

Case studies are relevant to understand the variability of autoimmune encephalitis and infectious triggers. One case constitutes a 61-year-old male who presented with agitation, behavioral changes, and confusion eight months after being treated for HSE. His physical examination was significant for difficulties with delayed recall and poor concentration. Moreover, diagnostic instruments conveyed edema, CSF revealed no organisms, and an MRI showed edema in the right frontotemporal lobe and left frontal lobe. Furthermore, the CSF HSV-1 polymerase chain reaction (PCR) test results were positive, confirming the diagnosis of HSE. The individual was further treated for 21 days with acyclovir (i.e., antiviral drug) and transferred to a rehabilitation unit. Studies have reported that acyclovir limits the course of HSV infection (Rechenchoski et al., 2017). Upon discharge, he demonstrated severe cognitive and linguistic deficits that caused him to be readmitted and receive lumbar puncturing. His results were negative for HSV PCR; however, the paraneoplastic CSF panel revealed anti-NMDAR antibodies, suggesting post-HSV autoimmune encephalitis. Sahar et al. (2019) believe that age and preceding HSE triggered the autoimmune response.

## Differential Diagnosis

### *Distinguishable characteristics*

HSE is the most frequently identified cause of sporadic focal encephalitis and has been associated with temporal lobe abnormalities on neuroimaging tests. There are mimics, other infections that resemble HSE, that have resulted in the misdiagnosis of HSE. Chow et al. (2015) examined cases with temporal lobe abnormalities, investigated the spectrum of etiologies associated with temporal lobe encephalitis, and identified specific clinical and radiologic features associated with HSE. They found that HSE cases were most likely to present acutely and with

fever; less likely to present with rash or ataxia. Compared to autoimmune cases, seizures and upper respiratory symptoms were more frequent among HSE cases.
Additionally, HSE cases presented less commonly with cranial nerve deficits compared with autoimmune cases. Regarding neuroanatomical changes, bilateral temporal lobe involvement and lesions outside the temporal lobe, insula, or cingulate gyrus were less common in HSE cases (Chow et al., 2015). Therefore, although bilateral temporal lobe abnormalities were once thought to be virtually pathognomonic for HSE, such findings can occur in the setting of numerous other diseases, which is why using clinical and imaging characteristics is highly relevant to patient care.

***Case Study***

An example of a mimic case involves a 51-year-old female admitted to the hospital for acute disorientation and amnesia. After a neurological examination, it was confirmed that she had verbal memory impairment (Denays et al., 1999). EEG findings demonstrated discontinuous pseudo periodic discharge affecting mainly the left temporal lobe and considered the possibility of epileptic seizures due to HSE. The HSE diagnosis was reinforced by her MRI indicating bilateral mesiotemporal lesions, predominantly on the left side, and SPECT results indicating the left temporal lobe increased uptake on Tc-99m HMPAO, an agent used to assess regional blood flow (specific for HSE). However, the results were negative when tested for HSV DNA through CSF testing by PCR, prompting consideration for neurosyphilis. This was further strengthened by the finding of DNA antibodies against Treponema Pallidum. It is worth noting that the preparalytic phase of neurosyphilis usually involves the frontal and temporal parenchyma, producing impairment of intellect, memory, personality change, and possible seizures. Before being discharged, this individual demonstrated marked improvement of memory, a partial return to normal CSF, resolution of EEG and SPECT anomalies, and regression of MRI lesions (Denays et al., 1999).

Another case study involves a 6-year-old female admitted for right-sided upper and lower limb clonic movements, fever, high white blood cell count, and an E. coli urinary tract infection. She was given medication and discharged home the next day, only to be readmitted 12 hours later for several complex partial seizures. EEG results indicated left frontal and temporal sharp waves. After 10 days, she became ill and had to be given another MRI, indicating a left frontal lobe lesion of an unknown etiology. Her CSF showed no abnormality related to cells and was negative for HSV. After further deterioration, a repeated MRI conveyed extensions to her lesions with edema and a midline shift. She underwent a brain biopsy (usually rare) where they found diffuse mononuclear leptomeningeal (abnormality leading to/or associated with meningitis) and perivascular infiltrate (inflammatory cells infiltrating around her blood vessels) from bacteria. Hence, she was treated for a bacterial infection, and HSV was ruled out.

**Discussion**

There are many causes of encephalitis with various courses of entry. The most likely routes are via the olfactory or trigeminal nerve fibers into the central nervous system, occasionally leading to HSE (Liu et al., 2019). The integrity of the blood-brain barrier can become dysfunctional or compromised from HSV, affecting the permeability and hindering the functioning of various components working together to protect against circulating toxins or pathogens (Baringer & Pisani, 1994; Liu et al., 2019). Compromising the blood-brain barrier leads to edema, hemorrhage, leukocyte infiltration, and progressive inflammation-inducing damage (Baringer & Pisani, 1994).

HSV is the most common and latent from the various etiologies, leading to possible autoimmune encephalitis, even after improvements or discharges from a medical facility (Sahar et al., 2019; Venkatesan & Murphy, 2018; Wang & Xiao, 2020). In addition, neurological morphology and neuropsychological effects have been detected in those with HSE, specifically, in those who have comorbid psychiatric diagnoses (Dickerson et al., 2008; Glaser et al., 1987; Tucker & Bertke, 2019). Research has indicated alterations such as neuroimaging intensities, neuroanatomical morphology, or volume loss of grey matter in areas regulating motor, language, executive functioning, memory, and attention process. In addition, the temporal lobe, limbic system, hippocampus, thalamus, and pons have been shown to be affected by HSE (Tucker & Bertke, 2019). Additional neurocognitive domains affected by HSE include I.Q. and retrograde and anterograde memory (Harris et al., 2020). Hence, early detection and prolonged hospitalization upon identifying the virus can aid treatment and improve presenting difficulties, including impairment in various neurocognitive domains.

This relates to the field of neuropsychology in various ways. First, HSE is very likely to be misdiagnosed, so ruling out other diagnoses that mimic HSE is important (i.e., anxiety, depression, psychotic disorders). Although researchers have found that psychological effects include more reported depression and anxiety cases among positive HSV individuals, it does not eliminate the possibility of being misdiagnosed with a primary psychiatric disorder. Based on previous studies, many individuals have reported tiredness and perceive their cognitive functioning negatively despite signs of improvement (Harris et al., 2020). Moreover, professionals must pay attention to medical components when assessing patients because of their connection to psychiatric illnesses. Lastly, every mental health disorder has its own set of treatment protocols, and diagnosis directs the course of treatment. Comprehensively assessing patients is crucial in determining accurate diagnoses, and neuropsychological and personality measures are beneficial. As previously mentioned, medications are commonly prescribed and can cause side effects that are important to consider when evaluating the individual.

**Limitations**

This literature review revealed several limitations that should be considered when interpreting the findings. First, most research does not examine the level of psychosocial stress that may vary between cultures and populations who have HSE. Thus, the largely White sample precludes generalization of the results to other ethnic groups. Additionally, the studies mentioned in this review had small sample sizes, reducing the power of the studies and increasing their margin of error. Another limitation is that neither the time of exposure or the manifestation of HSV was determined in some studies, therefore it is unknown whether they played a role in the results.

**Future Research Directions**

Future studies should look at neuroanatomical changes in individuals with HSE with larger sample sizes and longitudinally to determine patterns over time and developmental trends. In addition, future studies should examine a more representative sample in terms of ethnicity, educational attainment, and I.Q. More studies should also investigate the differentiation between type 1 and type 2 of HSV, taking the factors above into account and assessing their impact on the risk for A.D. and psychological disorders. However, most studies likely research HSV-1 because it is more prevalent. Neuroimaging methods have enabled possible prognosis and pathogenesis due to HSV-1. However, trajectories still require further investigation to confirm the impact of the disease on various cognitive paths. As previously mentioned, longitudinal studies will be necessary

to fully elucidate the role of HSV-1 on the structure and functioning of the brain in those with encephalitis. Identifying HSV-1 as a contributor to cognitive neuropsychological dysfunction reinforces the need to suppress HSV-1 early to prevent further cognitive decline, neuroanatomical alterations, and psychological effects.

**About the Authors**

**Carla Cabrera, M.S., is a student at** the College of Psychology, Nova Southeastern University. Correspondence concerning this article should be addressed to carlacab(at)mynsu.nova.edu

**Charles J. Golden, Ph.D., ABPP, ABAP,** is with the College of Psychology, Nova Southeastern University, Florida

**References**

Adams, H., & Miller, D. (1973). Herpes simplex encephalitis: A clinical and pathological analysis of twenty-two cases. *Postgraduate Medical Journal, 49*(572), 393-397. https://doi.org/10.1136/pgmj.49.572.393

Aiello, A. E., Haan, M. N., Blythe, L., Moore, K., Gonzalez, J. M., & Jagust, W. (2006). The influence of latent viral infection on rate of cognitive decline over 4 years. *Journal of the American Geriatrics Society*, *54*(7), 1046–1054. https://doi.org/10.1111/j.1532-5415.2006.00796.x

Arbusow, V., Schulz, P., Strupp, M., Dieterich, M., Von Reinhardstoettner, A., Rauch, E., & Brandt, T. (1999). Distribution of Herpes Simplex Virus Type 1 in human geniculate and vestibular ganglia: Implications for vestibular neuritis. *Annals of Neurology, 46*(3), 416–419. https://doi.org/10.1002/1531-8249(199909)46:3<416::aid-ana20>3.0.co;2-w

Baringer, J. R., & Pisani, P. (1994). Herpes simplex virus genomes in human nervous system tissue analyzed by polymerase chain reaction. *Annals of Neurology, 36*(6), 823–829. https://doi.org/10.1002/ana.410360605

Barnes, L. L., Capuano, A. W., Aiello, A. E., Turner, A. D., Yolken, R. H., Torrey, E. F., & Bennett, D. A. (2015). Cytomegalovirus infection and risk of Alzheimer disease in older Black and White individuals. *Journal of Infectious Diseases, 211*(2), 230–237. https://doi.org/10.1093/infdis/jiu437

Bechter, K., Brown, D., & Najjar, S. (2019). Editorial: Recent advances in psychiatry from psycho-neuro-immunology research: Autoimmune encephalitis, autoimmune encephalopathy, and mild encephalitis. *Frontiers in Psychiatry, 10*. https://doi.org/10.3389/fpsyt.2019.00169

Borrell-Carrió, F., Suchman, A. L., & Epstein, R. M. (2004). The biopsychosocial model 25 years later: Principles, practice, and scientific inquiry. *The Annals of Family Medicine, 2*(6), 576–582. https://doi.org/10.1370/afm.245

Boukhvalova, M. S., Mortensen, E., Mbaye, A., Lopez, D., Kastrukoff, L., & Blanco, J. C. (2019). Herpes simplex virus 1 induces brain inflammation and multifocal demyelination

in the cotton rat sigmodon hispidus. *Journal of Virology*, *94*(1). https://doi.org/10.1128/jvi.01161-19

Bradley, H., Markowitz, L. E., Gibson, T., & McQuillan, G. M. (2013). Seroprevalence of Herpes Simplex Virus Types 1 and 2—United States, 1999–2010. *Journal of Infectious Diseases, 209*(3), 325–333. https://doi.org/10.1093/infdis/jit458

Cassill, C., Steward, K., Eagan, D., Kaur, S., Kruzliak, P., & Haley, A. P. (2018). Depressive symptoms exacerbate the effects of HSV-1 infection on cognitive functioning in middle age. *Journal of Clinical and Infectious Disease and Practice, 3*(1). https://doi.org/10.4172/2476-213X.1000122

Chow, F. C., Glaser, C. A., Sheriff, H., Xia, D., Messenger, S., Whitley, R., & Venkatesan, A. (2015). Use of clinical and neuroimaging characteristics to distinguish temporal lobe herpes simplex encephalitis from its mimics. *Clinical Infectious Diseases*. https://doi.org/10.1093/cid/civ051

Cleator, G. M., & Klapper, P. E. (2004). Herpes simplex. In A. J. Zuckerman, J. E. Banatvala, & R. Pattison (Eds.), *Principles and Practice of Clinical Virology* (pp. 27-51). John Wiley & Sons.

Cruz, A. T., Freedman, S. B., Kulik, D. M., Okada, P. J., Fleming, A. H., Mistry, R. D., Thomson, J. E., Schnadower, D., Arms, J. L., Mahajan, P., Garro, A. C., Pruitt, C. M., Balamuth, F., Uspal, N. G., Aronson, P. L., Lyons, T. W., Thompson, A. D., Curtis, S. J., Ishimine, P. T., … Nigrovic, L. E. (2018). Herpes simplex virus infection in infants undergoing meningitis evaluation. *Pediatrics, 141*(2). https://doi.org/10.1542/peds.2017-1688

Damasio, A. R., & Van Hoesen, G. W. (1985). The limbic system and the localisation of herpes simplex encephalitis. *Journal of Neurology, Neurosurgery & Psychiatry*, *48*(4), 297–301. https://doi.org/10.1136/jnnp.48.4.297

De Chiara, G., Piacentini, R., Fabiani, M., Mastrodonato, A., Marcocci, M. E., Limongi, D., Napoletani, G., Protto, V., Coluccio, P., Celestino, I., Li Puma, D. D., Grassi, C., & Palamara, A. T. (2019). Recurrent herpes simplex virus-1 infection induces hallmarks of neurodegeneration and cognitive deficits in mice. *PLOS Pathogens*, *15*(3). https://doi.org/10.1371/journal.ppat.1007617

Denays, R., Collier, A., Rubinstein, M., & Atsama, P. (1999). A 51-year-old woman with disorientation and amnesia. *The Lancet*, *354*(9192), 1786. https://doi.org/10.1016/s0140-6736(99)09151-5

Dickerson, F., Schroeder, J. R., Nimgaonkar, V., Gold, J., & Yolken, R. (2020). The association between exposure to Herpes Simplex Virus Type 1 (HSV-1) and cognitive functioning in schizophrenia: A meta-analysis. *Psychiatry Research*, *291*, 113157. https://doi.org/10.1016/j.psychres.2020.113157

Dickerson, F., Stallings, C., Sullens, A., Origoni, A., Leister, F., Krivogorsky, B., & Yolken, R. (2008). Association between cognitive functioning, exposure to Herpes Simplex Virus Type 1, and the COMT Val158Met genetic polymorphism in adults without a psychiatric disorder. *Brain, Behavior, and Immunity*, *22*(7), 1103–1107. https://doi.org/10.1016/j.bbi.2008.04.156

Garg, M., Kulkarni, S., & Udwadia Hegde, A. (2018). Herpes simplex encephalitis with thalamic, brainstem and cerebellar involvement. *The Neuroradiology Journal, 31*(2), 190–192. https://doi.org/10.1177/1971400917703990

George, B. P., Schneider, E. B., & Venkatesan, A. (2014). Encephalitis hospitalization rates and inpatient mortality in the United States, 2000-2010. *PLoS ONE, 9*(9). https://doi.org/10.1371/journal.pone.0104169

Gerber, S. I., Krienke, U. J., Biedermann, N. C., Grunze, H., Yolken, R. H., Dittmann, S., & Langosch, J. M. (2012). Impaired functioning in EUTHYMIC patients with bipolar disorder — HSV-1 as a predictor. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *36*(1), 110–116. https://doi.org/10.1016/j.pnpbp.2011.09.003

Glaser, R., Rice, J., Sheridan, J., Fertel, R., Stout, J., Speicher, C., Pinsky, D., Kotur, M., Post, A., Beck, M., & Kiecolt-Glaser, J. (1987). Stress-related immune suppression: Health implications. *Brain, Behavior, and Immunity, 1*(1), 7–20. https://doi.org/10.1016/0889-1591(87)90002-x

Gluska, S., Zahavi, E. E., Chein, M., Gradus, T., Bauer, A., Finke, S., & Perlson, E. (2014). Rabies virus hijacks and accelerates the p75NTR retrograde axonal transport machinery. *PLoS Pathogens*, *10*(8). https://doi.org/10.1371/journal.ppat.1004348

Gnann, J. W., & Whitley, R. J. (2017). Herpes simplex encephalitis: An update. *Current Infectious Disease Reports, 19*(3). https://doi.org/10.1007/s11908-017-0568-7

Grest, P., Albicker, P., Hoelzle, L., Wild, P., & Pospischil, A. (2002). Herpes simplex encephalitis in a domestic rabbit (oryctolagus cuniculus). *Journal of Comparative Pathology*, *126*(4), 308–311. https://doi.org/10.1053/jcpa.2002.0548

Hannachi, N., El Kissi, Y., Samoud, S., Nakhli, J., Letaief, L., Gaabout, S., Ben Hadj Ali, B., & Boukadida, J. (2014). High prevalence of human herpesvirus 8 in schizophrenic patients. *Psychiatry Research*, *216*(2), 192–197. https://doi.org/10.1016/j.psychres.2013.12.035

Harris, L., Griem, J., Gummery, A., Marsh, L., Defres, S., Bhojak, M., Das, K., Easton, A., Solomon, T., & Kopelman, M. (2020). Neuropsychological and psychiatric outcomes in encephalitis: A multi-centre case-control study. *PLOS ONE*, *15*(3). https://doi.org/10.1371/journal.pone.0230436

Hauser, R. G., Campbell, S. M., Brandt, C. A., & Wang, S. (2017). Cost-effectiveness study of criteria for screening cerebrospinal fluid to determine the need for herpes simplex virus

PCR testing. Journal of Clinical Microbiology, 55(5), 1566–1575. https://doi.org/10.1128/jcm.00119-17

Heinrichs, R. W. (2005). The primacy of cognition in schizophrenia. *American Psychologist*, *60*(3), 229–242. https://doi.org/10.1037/0003-066x.60.3.229

Herken, J., & Prüss, H. (2017). Red flags: Clinical signs for identifying autoimmune encephalitis in psychiatric patients. *Frontiers in Psychiatry*, *8*. https://doi.org/10.3389/fpsyt.2017.00025

Itzhaki, R. F. (2017). Herpes Simplex Virus Type 1 and Alzheimer's disease: Possible mechanisms and signposts. *The FASEB Journal*, *31*(8), 3216–3226. https://doi.org/10.1096/fj.201700360

Itzhaki, R. F., Dobson, C. B., Shipley, S. J., & Wozniak, M. A. (2004). The role of viruses and of APOE in dementia. *Annals of the New York Academy of Sciences*, *1019*(1), 15–18. https://doi.org/10.1196/annals.1297.003

Kennedy, P. G., Adams, J. H., Graham, D. I., & Clement, G. B. (1988). A clinical–pathological study of herpes simplex encephalitis. *Neuropathology and Applied Neurobiology*, *14*(5), 395–415. https://doi.org/10.1111/j.1365-2990.1988.tb01141.x

Lindgren, M., Torniainen-Holm, M., Härkänen, T., Dickerson, F., Yolken, R. H., & Suvisaari, J. (2018). The association between Toxoplasma and the psychosis continuum in a general population setting. *Schizophrenia Research*, *193*, 329–335. https://doi.org/10.1016/j.schres.2017.06.052

Liu, H., Qiu, K., He, Q., Lei, Q., Lu, W. (2019). Mechanisms of blood-brain barrier disruption in herpes simplex encephalitis. *Journal of Neuroimmune Pharmacology, 14*(2), 157–172. https://doi.org/10.1007/s11481-018-9821-6

Lövheim, H., Gilthorpe, J., Adolfsson, R., Nilsson, L.-G., & Elgh, F. (2014). Reactivated herpes simplex infection increases the risk of Alzheimer's disease. *Alzheimer's & Dementia*, *11*(6), 593–599. https://doi.org/10.1016/j.jalz.2014.04.522

Marazziti, D., Consoli, G., Picchetti, M., Carlini, M., & Faravelli, L. (2010). Cognitive impairment in major depression. *European Journal of Pharmacology*, *626*(1), 83–86. https://doi.org/10.1016/j.ejphar.2009.08.046

Mayo Foundation for Medical Education and Research. (2020, April 17). Encephalitis. Mayo Clinic. Retrieved October 4, 2021, from https://www.mayoclinic.org/diseases-conditions/encephalitis/symptoms-causes/syc-20356136

McFarland, D. J., & Hotchin, J. (1987). Contrasting patterns of virus spread and neuropathology following microinjection of herpes simplex virus into the hippocampus or cerebellum of mice. *Journal of the Neurological Sciences*, *79*(3), 255–265. https://doi.org/10.1016/0022-510x(87)90233-4

Menendez, C. M., & Carr, D. J. J. (2017). Defining nervous system susceptibility during acute and latent Herpes Simplex Virus-1 infection. *Journal of Neuroimmunology*, *308*, 43–49. https://doi.org/10.1016/j.jneuroim.2017.02.020

Meyding-Lamadé, U., & Strank, C. (2012). Herpesvirus infections of the central nervous system in immunocompromised patients. *Therapeutic Advances in Neurological Disorders*, *5*(5), 279–296. https://doi.org/10.1177/1756285612456234

U.S. Department of Health and Human Services. (2018). *Meningitis and encephalitis fact sheet*. National Institute of Neurological Disorders and Stroke. Retrieved October 4, 2021, from https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Meningitis-and-Encephalitis-Fact-Sheet

Nimgaonkar, V. L., Yolken, R. H., Wang, T., Chang, C.-C. H., McClain, L., McDade, E., Snitz, B. E., & Ganguli, M. (2016). Temporal cognitive decline associated with exposure to infectious agents in a population-based, aging cohort. *Alzheimer Disease & Associated Disorders*, *30*(3), 216–222. https://doi.org/10.1097/wad.0000000000000133

Orellana, G., & Slachevsky, A. (2013). Executive functioning in schizophrenia. *Frontiers in Psychiatry*, *4*. https://doi.org/10.3389/fpsyt.2013.00035

Panza, F., Frisardi, V., Capurso, C., D'Introno, A., Colacicco, A. M., Imbimbo, B. P., Santamato, A., Vendemiale, G., Seripa, D., Pilotto, A., Capurso, A., & Solfrizzi, V. (2010). Late-life depression, mild cognitive impairment, and dementia: Possible continuum? *The American Journal of Geriatric Psychiatry*, *18*(2), 98–116. https://doi.org/10.1097/jgp.0b013e3181b0fa13

Pewter, S. M., Huw Williams, W., Haslam, C., & Kay, J. M. (2007). Neuropsychological and psychiatric profiles in acute encephalitis in adults. *Neuropsychological Rehabilitation*, *17*(4-5), 478–505. https://doi.org/10.1080/09602010701202238

Pillai, S. C., Hacohen, Y., Tantsis, E., Prelog, K., Merheb, V., Kesson, A., Barnes, E., Gill, D., Webster, R., Menezes, M., Ardern-Holmes, S., Gupta, S., Procopis, P., Troedson, C., Antony, J., Ouvrier, R. A., Polfrit, Y., Davies, N. W., Waters, P., … Dale, R. C. (2015). Infectious and autoantibody-associated encephalitis: Clinical features and long-term outcome. *Pediatrics*, *135*(4). https://doi.org/10.1542/peds.2014-2702

Prasad, K. M., Shirts, B. H., Yolken, R. H., Keshavan, M. S., & Nimgaonkar, V. L. (2006). Brain morphological changes associated with exposure to HSV1 in first-episode schizophrenia. *Molecular Psychiatry*, *12*(1), 105–113. https://doi.org/10.1038/sj.mp.4001915

Pruss, H., Holtje, M., Maier, N., Gomez, A., Buchert, R., Harms, L., Ahnert-Hilger, G., Schmitz, D., Terborg, C., Kopp, U., Klingbeil, C., Probst, C., Kohler, S., Schwab, J. M., Stoecker, W., Dalmau, J., & Wandinger, K. P. (2012). IGA NMDA receptor antibodies are markers

of synaptic immunity in slow cognitive impairment. *Neurology*, *78*(22), 1743–1753. https://doi.org/10.1212/wnl.0b013e318258300d

Quinn, J. P., Dalziel, R. G., & Nash, A. A. (2000). Herpes virus latency in sensory ganglia — a comparison with endogenous neuronal gene expression. *Progress in Neurobiology*, *60*(2), 167–179. https://doi.org/10.1016/s0301-0082(99)00024-6

Rechenchoski, D. Z., Faccin-Galhardi, L. C., Linhares, R. E., & Nozawa, C. (2017). Herpesvirus: An underestimated virus. *Folia Microbiologica*, *62*(2), 151–156. https://doi.org/10.1007/s12223-016-0482-7

Raschilas, F., Wolff, M., Delatour, F., Chaffaut, C., De Broucker, T., Chevret, S., Lebon, P., Canton, P., & Rozenberg, F. (2002). Outcome of and prognostic factors for herpes simplex encephalitis in adult patients: Results of a multicenter study. *Clinical Infectious Diseases*, *35*(3), 254–260. https://doi.org/10.1086/341405

Sahar, N., Nurre, A. M., & Simon, R. Q. (2019). Infectious trigger for autoimmune encephalitis: A case report and literature review. *Case Reports in Infectious Diseases*, *2019*, 1–4. https://doi.org/10.1155/2019/5731969

Saleh, D., Yarrarapu, S. N. S., & Sharma, S. [Updated 2021 Aug 31]. *Herpes Simplex Type 1*. In: StatPearls [Internet]. StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482197/.

Schaefer, J., Giangrande, E., Weinberger, D. R., & Dickinson, D. (2013). The global cognitive impairment in schizophrenia: Consistent over decades and around the world. *Schizophrenia Research*, *150*(1), 42–50. https://doi.org/10.1016/j.schres.2013.07.009

Skelley, S. L., Goldberg, T. E., Egan, M. F., Weinberger, D. R., & Gold, J. M. (2008). Verbal and visual memory: Characterizing the clinical and intermediate phenotype in Schizophrenia. *Schizophrenia Research*, *105*(1-3), 78–85. https://doi.org/10.1016/j.schres.2008.05.027

Sutter, R., Kaplan, P. W., Cervenka, M. C., Thakur, K. T., Asemota, A. O., Venkatesan, A., & Geocadin, R. G. (2015). Electroencephalography for diagnosis and prognosis of acute encephalitis. *Clinical Neurophysiology*, *126*(8), 1524–1531. https://doi.org/10.1016/j.clinph.2014.11.006

Suvisaari, J., Torniainen-Holm, M., Lindgren, M., Härkänen, T., & Yolken, R. H. (2017). Toxoplasma gondii infection and common mental disorders in the Finnish general population. *Journal of Affective Disorders*, *223*, 20–25. https://doi.org/10.1016/j.jad.2017.07.020

Steiner, I., Kennedy, P. G. E., & Pachner, A. R. (2007). The neurotropic herpes viruses: Herpes simplex and varicella-zoster. *The Lancet Neurology*, *6*(11), 1015–1028. https://doi.org/10.1016/s1474-4422(07)70267-3

Strandberg, T. E., Pitkala, K. H., Linnavuori, K. H., & Tilvis, R. S. (2003). Impact of viral and bacterial burden on cognitive impairment in elderly persons with cardiovascular diseases. *Stroke*, *34*(9), 2126–2131. https://doi.org/10.1161/01.str.0000086754.32238.da

Tarter, K. D., Simanek, A. M., Dowd, J. B., & Aiello, A. E. (2014). Persistent viral pathogens and cognitive impairment across the life course in the Third National Health and Nutrition Examination Survey. *The Journal of Infectious Diseases*, *209*(6), 837–844. https://doi.org/10.1093/infdis/jit616

Tucker, J. D., & Bertke, A. S. (2019). Assessment of cognitive impairment in HSV-1 positive schizophrenia and bipolar patients: Systematic Review and meta-analysis. *Schizophrenia Research*, *209*, 40–47. https://doi.org/10.1016/j.schres.2019.01.001

Tzeng, N. S., Chung, C. H., Lin, F. H., Chiang, C. P., Yeh, C. B., Huang, S. Y., Lu, R. B., Chang, H. A., Kao, Y. C., Yeh, H. W., Chiang, W. S., Chou, Y. C., Tsao, C. H., Wu, Y. F., & Chien, W. C. (2018). Anti-herpetic medications and reduced risk of dementia in patients with herpes simplex virus infections—a nationwide, population-based cohort study in Taiwan. *Neurotherapeutics*, *15*(2), 417–429. https://doi.org/10.1007/s13311-018-0611-x

Torniainen-Holm, M., Suvisaari, J., Lindgren, M., Härkänen, T., Dickerson, F., & Yolken, R. H. (2019). The lack of association between Herpes Simplex Virus 1 or Toxoplasma gondii infection and cognitive decline in the general population: An 11-year follow-up study. *Brain, Behavior, and Immunity*, *76*, 159–164. https://doi.org/10.1016/j.bbi.2018.11.016

Venkatesan, A., & Murphy, O. C. (2018). Viral encephalitis. *Neurologic Clinics*, *36*(4), 705–724. https://doi.org/10.1016/j.ncl.2018.07.001

Venkatesan, A., Tunkel, A. R., Bloch, K. C., Lauring, A. S., Sejvar, J., Bitnun, A., Stahl, J. P., Mailles, A., Drebot, M., Rupprecht, C. E., Yoder, J., Cope, J. R., Wilson, M. R., Whitley, R. J., Sullivan, J., Granerod, J., Jones, C., Eastwood, K., Ward, K. N., … Cherry, J. (2013). Case definitions, diagnostic algorithms, and priorities in encephalitis: Consensus statement of the International Encephalitis Consortium. *Clinical Infectious Diseases*, *57*(8), 1114–1128. https://doi.org/10.1093/cid/cit458

Vora, N. M., Holman, R. C., Mehal, J. M., Steiner, C. A., Blanton, J., & Sejvar, J. (2014). Burden of encephalitis-associated hospitalizations in the United States, 1998-2010. *Neurology*, *82*(5), 443–451. https://doi.org/10.1212/wnl.0000000000000086

Wang, H., & Xiao, Z. (2020). Current progress on assessing the prognosis for anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis. *BioMed Research International*, *2020*, 1–8. https://doi.org/10.1155/2020/7506590

Weickert, T. W., Goldberg, T. E., Gold, J. M., Bigelow, L. B., Egan, M. F., & Weinberger, D. R. (2000). Cognitive impairments in patients with schizophrenia displaying preserved and compromised intellect. *Archives of General Psychiatry*, *57*(9), 907. https://doi.org/10.1001/archpsyc.57.9.907

Winkelmann, A., Loebermann, M., Reisinger, E. C., Hartung, H.-P., & Zettl, U. K. (2016). Disease-modifying therapies and infectious risks in multiple sclerosis. *Nature Reviews Neurology*, *12*(4), 217–233. https://doi.org/10.1038/nrneurol.2016.21

World Health Organization. (2020). Globally, An estimated two-thirds of the population under 50 are infected with Herpes Simplex Virus Type 1. World Health Organization. Retrieved October 3, 2021, from https://www.who.int/news/item/28-10-2015-globally-an-estimated-two-thirds-of-the-population-under-50-are-infected-with-herpes-simplex-virus-type-1.

Wozniak, M. A., Frost, A. L., & Itzhaki, R. F. (2009). Alzheimer's disease-specific tau phosphorylation is induced by Herpes Simplex Virus Type 1. *Journal of Alzheimer's Disease*, *16*(2), 341–350. https://doi.org/10.3233/jad-2009-0963

Yaffe, K., Gore, R., Blackwell, T., Sands, L., Reus, V., & Browner, W. (1999). Depressive symptoms are associated with cognitive decline in nondemented elderly women: Evidence from a prospective study. *The American Journal of Geriatric Psychiatry*, *7*, 27–28. https://doi.org/10.1097/00019442-199911001-00094

Zambrano, Á., Solis, L., Salvadores, N., Cortés, M., Lerchundi, R., & Otth, C. (2008). Neuronal cytoskeletal dynamic modification and neurodegeneration induced by infection with Herpes Simplex Virus Type 1. *Journal of Alzheimer's Disease*, *14*(3), 259–269. https://doi.org/10.3233/jad-2008-14301