Exposure to Herpes Simplex Virus Type 1 and Cognitive Impairments in Individuals With Schizophrenia

Konasale M. Prasad1, Annie M. M. Watson1,2, Faith B. Dickerson3, Robert H. Yolken4, and Vishwajit L. Nimgaonkar2,1

1Department of Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, Pittsburgh, PA; 2Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA; 3Stanley Research Program at Sheppard Pratt, Sheppard Pratt Health System, Baltimore, MD; 4Department of Pediatrics, Stanley Division of Developmental Neuroimaging, Johns Hopkins University School of Medicine, Baltimore, MD

*To whom correspondence should be addressed; Department of Psychiatry, University of Pittsburgh School of Medicine, TDH 441, 3811 O'Hara Street, Pittsburgh PA 15213; tel: 412-246-6353, fax: 412-246-6350, e-mail: nimga@pitt.edu

Latent infection with neurotropic herpes viruses, such as herpes simplex virus, type 1 (HSV1), has been generally considered benign in most immunocompetent individuals except for rare cases of encephalitis. However, several recent studies have shown impaired cognitive functions among individuals with schizophrenia exposed to HSV1 compared with schizophrenia patients not exposed to HSV1. Such impairments are robust and are prominently observed in working memory, verbal memory, and executive functions. Brain regions that play a key role in the regulation of these domains have shown smaller volumes, along with correlation between these morphometric changes and cognitive impairments in schizophrenia. One study noted temporal decline in executive function and gray matter loss among HSV1-exposed first-episode antipsychotic-naïve schizophrenia patients. Furthermore, a proof-of-concept double-blind placebo-controlled trial indicated improvement in cognitive performance following supplemental anti-herpes–specific medication among HSV1 seropositive schizophrenia patients. Cross-sectional studies have also identified an association between HSV1 exposure and lesser degrees of cognitive impairment among healthy control individuals and patients with bipolar disorder. These studies fulfill several Bradford-Hill criteria, suggesting etiological links between HSV1 exposure and cognitive impairment. Exposure to other human herpes viruses such as cytomegalovirus and herpes simplex virus type 2 (HSV2) may also be associated with cognitive impairment, but the data are less consistent. These studies are reviewed critically and further lines of enquiry recommended. The results are important from a public health perspective, as HSV1 exposure is highly prevalent in many populations.

Key words: cognition/schizophrenia/herpes/neuroscience/neuroimaging/HSV1

Introduction

The phenotype construct of schizophrenia is broad and heterogeneous. Extant literature clearly documents a high frequency of occurrence of a characteristic pattern of cognitive deficits in schizophrenia. Such deficits are noted before the onset of the illness, during the early course, in chronic patients, and in unaffected relatives of schizophrenia. Furthermore, these deficits remain stable throughout the illness. Therefore, cognitive impairments are considered a core deficit in schizophrenia and have been proposed as a separate domain of illness. In schizophrenia, a wealth of data links such impairments with an unfavorable long-term social outcome. Currently prescribed medications do not provide substantial benefit for cognitive impairments. Therefore, identification of etiological factors for the cognitive impairments could enable rational therapeutics.

In 1995, Becker presciently suggested that herpes simplex virus, type 1 (HSV1) has unsuspected, harmful effects on human cognition, and behavior following latent infection. This hypothesis deserves to be reexamined because several recent reports show that cognitive dysfunction is associated with exposure to HSV1. Herpes viruses are species-specific, enveloped double-stranded DNA viruses that belong to the “herpesviridae” family of DNA viruses. Eight human viruses in this family are described, namely HSV1, herpes simplex virus type 2 (HSV2), Cytomegalovirus (CMV), Epstein-Barr virus (EBV), Varicella-Zoster Virus (VZV), Human Herpes Virus 6 (HHV6), Human Herpes Virus 7 (HHV7), and Human Herpes Virus 8 (HHV8). Of these, HSV1, HSV2, EBV, VZV, and HHV6 are known to be potentially neurotropic. CMV can be neurotropic in immunosuppressed individuals. In the following sections, we critically examine studies that report associations between exposure to herpes viruses and cognitive dysfunction. The first section of this review
evaluates evidence relating HSV1 to cognitive dysfunction and morphometric changes in the brain. In the second section, explanations for the associations to HSV1 and plausible biological mechanisms are discussed. Finally, gaps in our knowledge and the implications for public health are discussed. Our primary focus is on schizophrenia, with additional relevant evidence marshaled from other groups. Though humans mount innate and acquired immune defenses against viral antigens, immunological aspects of infection are not reviewed here due to space considerations.

**Herpes Simplex Virus 1**

HSV1 belongs to α-herpesvirinae subfamily, with the alpha designation implying a short replicating cycle. The orofacial mucosa and occasionally the nasal or genital mucosa are preferred routes of infection. Following primary infection, the virus enters the nerve terminals and is transported through retrograde axonal transport to the sensory or autonomic ganglia. Latent HSV1 infection is maintained primarily in the trigeminal ganglia in humans. Viral particles have been found in other brain regions in postmortem samples, suggesting favored sites for replication. Within the neuron, HSV1 viral DNA enters nucleosomes of the host cells and establishes latency in the nervous system with lifelong periodic lytic cycles. The vesicular skin lesions caused by primary infections typically occur in the skin or mucous membranes of the mouth or lips, but primary infections can also be asymptomatic. Symptomatic or asymptomatic reactivation can occur with lytic cycles, especially related to stress, menstruation, and exposure to ultraviolet light. During reactivation, HSV1 particles propagate from neuronal soma in the ganglia through retrograde axonal transport to other regions of the brain and through anterograde transport to peripheral lesions where they are shed in body fluids.

**Epidemiology**

Individuals of all ages are prone to HSV1 infection, beginning in the intrauterine period. Primary infection with HSV1 generally occurs in childhood/adolescence and during young adulthood. Prevalence of HSV1 seropositivity varies with age, being approximately 40% among children, increasing to up to 70% or greater in adults over 40 years with variations among different populations related to race, gender, socioeconomic status (SES), and geographic location.

**Clinical Diagnostic Assays**

It is possible to detect HSV1 directly in body fluids using polymerase chain reaction–based assays, but they are unreliable as the virus is shed unpredictably. Antibody assays in the serum or plasma are generally used to indicate exposure to herpes viruses. The gG1 glycoprotein used for these assays allow for the distinction of HSV1 antibody from HSV2 and other herpes viruses. Detection of antibodies against gG1 surface protein on the HSV1 capsid is 100% specific and 98% sensitive for the detection of exposure to HSV1. Furthermore, because of repeated reactivation, viral titers generally remain elevated lifelong. Postmortem studies of humans and rodents suggest that the HSV1 antibody titers accurately reflect presence of HSV1 in the central nervous system. Though antibody titers are considered to be reliable indicators of exposure, they do not indicate the duration or timing of infection. “False negatives” can occur as antibody titers may decline with time particularly among persons who do not experience repeated reactivations. Because antibody titers reflect exposure as well as host-related factors such as genetic variations affecting immune response, some individuals may show lower antibody titers. Both groups of individuals would tend to “reduce” associations between HSV1 exposure and cognitive dysfunction.

**Pathology**

The trigeminal ganglion is the primary reservoir for HSV1 during latency, but HSV1 viral DNA was extracted from additional brain regions in 34% of individuals dying from nonneurological diseases. When postmortem tissue from trigeminal and olfactory ganglia were combined, viral DNA was detected in almost all the samples.

**HSV1 Encephalitis**

Encephalitis can occur during initial infection with HSV1, but after the neonatal period, it is more likely to occur following reactivation, particularly in genetically susceptible individuals. The incidence of HSV1 encephalitis is estimated at 2–4/100 000/year. The temporal and frontal lobes are typically affected, with a high case fatality rate. Survivors of acute encephalitis can manifest postencephalitic sequelae that include neurological abnormalities, seizures, behavioral abnormalities (including delusions and hallucinations), and cognitive impairments.

**Postencephalitic Changes**

Over two-thirds of survivors of HSV1 encephalitis suffer from seizures, behavioral abnormalities, and cognitive changes. The cognitive deficits involve working memory, visual object recognition, and anterograde amnesia. Impairment in working memory has also been documented in rats following HSV1 encephalitis. Although elevated rates of psychoses have been reported among survivors of HSV1 encephalitis, extensive studies have failed to detect consistent links between nonencephalitic HSV1 exposure and schizophrenia risk.

**HSV1 Exposure and Cognitive Impairment**

Individuals who were exposed to HSV1 but did not develop encephalitis were generally considered to be...
asymptomatic, but several reports have highlighted cognitive dysfunction even among adults without a clinical history of encephalitis (table 1). The first study investigated schizophrenia patients (n = 229) using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and found that individuals exposed to HSV1 had greater cognitive impairment, compared with patients not exposed to HSV1. Such associations were not detected with respect to 5 other herpes viruses. Differences between the HSV1 seropositive and seronegative groups were noted in the immediate verbal memory domain, after accounting for age and education (Cohen’s d = 0.45). The association suggests some specificity for HSV1, but this study did not examine the impact of joint exposure to the other herpes viruses.

The results of the previous study were extended in an independent sample of schizophrenia outpatients (n = 329). Patients completed the Trail Making Tests (TMT). HSV1 exposure was associated with increased response time as well as number of errors on TMT, Part B, after accounting for age and education. In this study too, the associations were observed with HSV1 but not HSV2 or a parasite, Toxoplasma gondii. CMV exposure was associated with qualitatively dissimilar impairments in TMT performance. There was no significant effect of joint exposure to HSV1 and CMV, suggesting distinctive effects of these agents.

The largest association study to date in individuals with schizophrenia examined 1308 participants from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study. Cognitive abilities were assessed using tests of visuomotor skills, verbal memory, attention, and executive functions reported to be impaired in schizophrenia. After correcting for age, race, and gender, lower composite neuropsychological summary scores were associated with HSV1 exposure (r = −2.60, P = .009). The domains that showed significant associations included verbal memory, vigilance, and processing speed.

A smaller candidate compared HSV1 seropositive schizophrenia patients (n = 25) with seronegative schizophrenia patients using TMT, the Hopkins Adult Reading Test Form B (premorbid IQ), Brief Test of Attention (auditory divided attention), the Hopkins Verbal Learning Test (verbal memory), the Brief Visuospatial Memory Test (visual memory), and modified Wisconsin Card Sorting Test (WCST) (executive functions). The psychomotor speed, executive functions, and verbal memory were significantly impaired after a conservative partial-Bonferroni correction for multiple testing that takes into account the correlation among cognitive measures. The mean effect size (Cohen’s d) was 0.45.

A cross-sectional study from India on schizophrenia patients (n = 198) and control individuals (n = 100) also reported significant impairments in 4 of 8 cognitive domains assessed using the Hindi version of the Penn Computerized Neurocognitive Battery (CNB) (Thomas et al, unpublished data). These observations concur with published studies from the West suggesting that the cognitive impairments may transcend geographic boundaries.

Another cross-sectional study on US participants with schizophrenia (n = 588) assayed HSV1 status along with C-reactive protein (CRP), a protein that plays a role in the inflammatory process and also associated with cognitive impairment. To evaluate the relative associations with HSV1 exposure and CRP levels, the sample was divided into 4 groups: HSV1-exposed/elevated CRP (≥5.0 µg/ml), HSV1-unexposed/elevated CRP, HSV1-unexposed/ lower CRP (<5.0 µg/ml), and HSV1-unexposed/ lower CRP. The last group was considered the reference. Multinomial logistic regression on the RBANS total and individual index scores revealed significantly lower RBANS total scores (<25th percentile) compared with the reference group (OR 2.89, P < .001) among the HSV1-exposed/elevated CRP group. Significant interaction between HSV1 exposure and elevated levels of CRP were not found.

Similar to schizophrenia patients, HSV1 exposure has been associated with cognitive impairments in bipolar disorder patients (n = 117; F = 20.5, P < .0001). Impairments were evaluated with the RBANS that noted significantly greater impairments in immediate verbal memory among HSV1-exposed individuals compared with HSV1 seronegative bipolar disorder patients (F = 12.07, P = .001).

Associations with cognitive impairments have also been reported among adult individuals without psychiatric disorders. In a recent study, HSV1 exposure was significantly associated with cognitive impairments among young adults without psychiatric disorder after accounting for age and SES (OR 3.2; 95% CI 1.18–8.73; n = 240, mean age 33.7 ± 11.5 y). In an independent African American sample, we examined healthy controls (n = 283), schizophrenia patients (n = 680), and their nonpsychotic relatives (n = 889; total n = 1852; mean age 42.9 ± 15.0 y; Watson et al, submitted data). Using multivariate models, cognitive performance from the Penn CNB with reliable psychometric properties was evaluated in relation to HSV1 exposure, controlling for familial and diagnostic status, sociodemographic variables, and exposure to 2 other herpes viruses. Composite variables were derived from 9 cognitive measures using principal components of heritability (PCH). Exposure was indexed by serum HSV1 antibody titers. PCH1, the most heritable component of cognitive performance (h2 = 0.6), was reduced significantly among HSV1-exposed individuals, regardless of case/relative/control group status (β = −0.22, P = .01, OR 1.25). Using the estimated ORs from these 2 studies (ie, 3.2 and 1.25) and HSV1 exposure rates of 75% for US adults in these age groups, the estimated population attributable risk (PAR) for PCH1 is 15.2% and 59.3% from these studies, assuming a causal relationship.
Table 1. Associations Between Exposure to HSV1 and Cognitive Dysfunction

<table>
<thead>
<tr>
<th>Sample/Reference</th>
<th>N; Ages (y ± SD)</th>
<th>Cognitive Test</th>
<th>Results</th>
<th>Comments/Effect Sizes</th>
<th>Association With HSV1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SZ</strong>&lt;sup&gt;19&lt;/sup&gt;</td>
<td>N = 229; 42.1 ± 9.5 y</td>
<td>RBANS</td>
<td>HSV1-exposed patients showed decreased RBANS total scores and 4 index scores. No significant associations with other herpes viruses</td>
<td>Cohen’s $d$: total score 0.59, immediate memory 0.65, attention 0.48, visuospatial/constructional 0.41, and delayed memory 0.35</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>SZ</strong>&lt;sup&gt;20&lt;/sup&gt;</td>
<td>N = 329; 38.4 ± 9.5 y</td>
<td>TMTA, TMTB</td>
<td>TMTB time increased and accuracy decreased in HSV1 seropositive SZ. CMV exposure associated with delays on TMTB</td>
<td>Cohen’s $d = 0.5$</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>SZ</strong>&lt;sup&gt;21&lt;/sup&gt;</td>
<td>N = 1308; 40.5±11.0 years</td>
<td>Combination</td>
<td>Neurocognitive summary score significantly associated negatively with HSV1 exposure, nonsignificant association with CMV exposure</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>SZ, Relatives of SZ, HC</strong>&lt;sup&gt;*&lt;/sup&gt;</td>
<td>N = 680 SZ, 38.9 ± 11.2 y; N = 889 non-SZ relatives, 45.8 ± 16.4 y; N = 283 HC, 40.8 ± 14.9 y</td>
<td>Penn CNB&lt;sup&gt;22,23&lt;/sup&gt;</td>
<td>Principal Component of Heritability (PCH1) derived from cognitive domains. PCH1 negatively associated with HSV1 and CMV exposure</td>
<td>Combined exposure to HSV1/CMV/HSV2 more significant. No significant association to only HSV2 infection. Combined exposure association: medium effect size (OR = 1.25)</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>SZ</strong>&lt;sup&gt;24&lt;/sup&gt;</td>
<td>N = 25 HSV1-exposed SZ; N = 15 HSV1 unexposed SZ; 39.1 ± 10.9 y</td>
<td>TMT, HVLT</td>
<td>Psychomotor speed and verbal memory significantly impaired in HSV1-exposed cases</td>
<td>Cohen’s $d = 0.45$</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>SZ</strong>&lt;sup&gt;25&lt;/sup&gt;</td>
<td>N = 588; 40.0 ± 11.6 y</td>
<td>RBANS</td>
<td>Decreased cognitive functioning associated independently and additively with HSV1 exposure and C-reactive protein (CRP) levels</td>
<td>Participants grouped by HSV1 status and CRP levels OR = 2.89</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>SZ, HC</strong>&lt;sup&gt;**&lt;/sup&gt;</td>
<td>N = 198 SZ; 30.79 ± 9.1 y; N = 100 HC; 32.4 ± 9.6 y</td>
<td>Hindi Penn CNB</td>
<td>Attention, spatial memory, spatial ability, sensorimotor dexterity impaired in individuals with HSV1 exposure</td>
<td>Study conducted in India. Interaction between SZ/HC status and HSV1 exposure not a significant predictor of cognitive variables. Attention (beta = -.375), Spatial (memory beta = -.213), spatial ability (beta = -.178), Sensorimotor dexterity (beta = -.204) impaired in individuals with HSV exposure</td>
<td>Yes</td>
</tr>
<tr>
<td>Bipolar disorder (BP), HC&lt;sup&gt;26&lt;/sup&gt;</td>
<td>N = 117 BP, 41.4 ± 11.2 y; N = 100 HC, 36.0 ± 13.3 y</td>
<td>RBANS</td>
<td>Total scores and 3 index scores decreased in HSV1 positive BP patients (immediate memory, visuospatial/constructional, and attention. No significant associations with other herpes viruses</td>
<td>Effect size $d = 0.8$ for total scores</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Table 1. Continued

<table>
<thead>
<tr>
<th>Sample/Reference</th>
<th>( N; ) Ages (y ± SD)</th>
<th>Cognitive Test</th>
<th>Results</th>
<th>Comments/Effect Sizes</th>
<th>Association With HSV1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly HC with Vascular disease(^{27})</td>
<td>( N = 383; ) 80.0 ± 5.0 y</td>
<td>MMSE</td>
<td>MMSE decreased with increasing viral burden for HSV1, CMV, and HSV2 (( P = .03 )). Cognitive decline over 1 y correlated with viral burden</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>HC(^{28})</td>
<td>240 HC; 33.7 ± 11.5 y</td>
<td>RBANS; WCST</td>
<td>RBANS total scores and delayed memory index scores decreased in HSV1 positive participants; increased perseverative errors on WCST</td>
<td>Effect size, Cohen’s ( d = 0.3 ), calculated from a larger sample (Dickerson, Personal communication)</td>
<td></td>
</tr>
<tr>
<td>Community cohort(^{29})</td>
<td>( N = 1204; ) 70.3 ± 6.8 y</td>
<td>MMSE</td>
<td>Nonsignificant association with HSV1 exposure</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

Note: RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SZ, Schizophrenia; HC, Healthy Control; BP, Bipolar; TMTA, TMTB, Trail making tests A and B; Penn CNB, University of Pennsylvania Computerized Neurocognitive Battery; HVLT, Hopkins Verbal Learning Test; MMSE, Mini-Mental State Examination; WCST, The Wisconsin Card Sorting Test; CMV, Cytomegalovirus (*Watson et al, submitted data; **Thomas et al, unpublished data).
to HSV1. Such data could also help to develop neuroimaging biomarkers to link with cognitive phenotypes.

The first study to examine structural magnetic resonance imaging (MRI) in relation to HSV1 exposure among schizophrenia patients (11 HSV1 seropositive and 21 HSV1 seronegative) investigated 5 morphometric indices using a 1 Tesla magnet and 8 mm slices. HSV1 seropositive schizophrenia patients showed evidence of cortical atrophy, smaller left frontal area, and larger second quadrant of the corpus callosum. These observations suggest that exposure to HSV1 could affect broad measures of brain morphometry, specifically in the frontal region and white matter. Healthy controls were not included in this study; therefore, comparative evaluation of similar effects among the controls cannot be made. Furthermore, the parcellation of brain regions used in the study was not adequately refined to correlate with regions implicated in the regulation of cognitive domains. In addition, examination of thicker slices and lower magnet strength could also impact the results.

Two other brain morphometric studies specifically addressed these concerns. One study examined first-episode, antipsychotic-naïve schizophrenia patients \( (n = 30) \) and matched healthy control individuals from the same geographic region \( (n = 44) \). Examining patients in their first-episode who were antipsychotic-naïve offers an unprecedented advantage by minimizing the dual confounds of prolonged illness and antipsychotic exposure. Brain morphometric data were acquired on 1.5 Tesla scanner with 1 mm slices that provides high-resolution images for more accurate quantification of morphometric measures. These data were analyzed using an automated computational whole-brain voxel-wise approach that would eliminate confounds inherent in manual tracing of regions-of-interest methods such as rater drift, restricting to a few hypothesized regions, and individual variations in anatomical boundaries. This approach also has the advantage of examining the entire brain in an unbiased manner while controlling for multiple testing. The investigators noted a significant main effect of HSV1 serological status on prefrontal gray matter volumes among schizophrenia patients. Schizophrenia patients exposed to HSV1 had decreased gray matter volume in the Brodmann areas 9 (dorsolateral prefrontal cortex) and 32 (anterior cingulate cortex) compared with schizophrenia patients not exposed to HSV1. Such differences were not detected among controls. This study did not find changes in the temporal regions—a hallmark of HSV1 encephalitis, suggesting that HSV1 exposure without encephalitis may affect brain regions different from those affected during encephalitis. This study, however, did not concurrently examine cognitive impairments associated with HSV1 exposure and correlate with brain morphometric changes.

Such associations between morphometric changes and cognitive impairments were examined in another study, which acquired brain morphometric data on a 3 Tesla scanner and used whole-brain voxel-wise analysis similar to Prasad et al. In addition, they also conducted regression analysis to correlate neurocognitive variations with brain morphometric changes. These investigators also noted significant gray matter volume reduction in the anterior cingulate gyrus (but not in the dorsolateral prefrontal cortex) and cerebellum. Psychomotor speed and verbal memory were significantly impaired among HSV1-exposed schizophrenia patients compared with unexposed schizophrenia patients.

Longitudinal imaging studies could identify brain regions that are vulnerable to chronic HSV1 exposure. One study followed up first-episode schizophrenia patients who were antipsychotic-naïve at baseline and healthy controls for 1 year. The longitudinal trajectory of gray matter volumes was estimated using deformation fields analysis, which is sensitive to dynamic changes in gray matter volumes while addressing concerns arising from cross-registration errors and inherent bias in estimating the regional volumes manually. In addition, this approach examines changes in the entire brain in an automated manner blind to the hypothesis. The observed differences were corrected for multiple comparisons for the whole-brain using the false discovery rate (FDR). This study showed significant gray matter loss in the left posterior cingulate cortex (PCC) among HSV1 seropositive schizophrenia patients \( (T = 13.77, \ FDR \ P = .034) \) and a trend for the right PCC \( (T = 9.93, \ FDR \ P = .07) \) over 1 year. The reduction was estimated to be 1.6 cc on the left PCC and 0.66 cc on the right relative to baseline. Control individuals (regardless of serological status) and HSV1 seronegative schizophrenia patients did not show significant gray matter loss over 1 year in any brain region. PCC has been implicated in executive control. The PFC, although was reduced in volume, did not show progression over 1 year.

The imaging studies reveal decreased volumes in some brain regions that have been implicated in the regulation of the affected cognitive functions. The mechanisms underlying the decreased volumes are speculative. Animal studies strongly implicate neuronal death related to repeated reactivations. Therefore, it is possible that the neuronal loss secondary to HSV1 reactivation underlies the observed volumetric reductions. However, postmortem evidence suggests reductions in neuropil (synapses, dendrites, and interneuronal axons) rather than neuronal loss. Hence, the volumetric reduction could also be due to other neuropathological changes unrelated to cell loss, such as increased packing density, decreased neuronal size, or decreased neuropil without alterations in the cell numbers.

**Correlations Between HSV1 Associated Cognitive Impairments and Brain Morphometric Changes**

Correlating cognitive variations with brain morphometric changes within the same cohort is essential for delineating...
putative pathogenic pathways. In addition, the precise significance of the direction of volumetric changes is difficult to interpret without directly correlating the behavioral/cognitive performance with the volumetric changes or other imaging measures within the same cohort. Schretlen et al.\textsuperscript{24} were the first to report significant correlation between anterior cingulate gyrus gray matter volume reductions and performance on TMT part B such that the lower the volume of anterior cingulate gyrus, the poorer the performance on TMT part B. Previous studies have replicated the involvement of anterior cingulate gyrus in the regulation of executive function, error monitoring, error correction, and working memory.\textsuperscript{40} Thus, decreased volumes correlating with poor performance on TMT B suggest that the cognitive functions assessed by the TMT B may be related to anterior cingulate volume reduction.

Another recent study examined this issue using a longitudinal design.\textsuperscript{33} In this study, executive functions were measured using the WCST and the change in regional brain volume over 1 year was estimated using deformation fields analysis. The change in PCC volume over 1 year correlated with the change in the number of perseverative errors (an index of the degree of cognitive flexibility and set shifting) such that the increased number of perseverative errors correlated with longitudinal reduction in the PCC volume over 1 year.

Although these studies examined small numbers of participants, they suggest that HSV1 exposure may lead to cognitive impairments by affecting specific brain regions implicated in the regulation of cognitive processing by human brain imaging and animal studies. Such observations are important because both these correlative studies used a whole-brain computational approach in which significantly affected regions are identified without any operator-introduced bias (table 2).

**Do the Associations Between HSV1 Exposure and Cognitive Dysfunction Inform Etiological Links?**

Koch’s classical etiological postulates were formulated primarily for infectious diseases, but they may not be applicable to complex disorders where an infectious agent may be one of several risk factors. In the case of HSV1 and schizophrenia, the study of possible causal associations is also limited by the fact that HSV1 cannot usually be detected in blood samples, or other body fluids from asymptomatic individuals and the cognitive dysfunction may reflect remote exposure. Moreover, the cognitive dysfunction cannot be considered a “disease” based on the current evidence. Thus, the Bradford-Hill criteria are more applicable to evaluate the observed associations because they were designed to understand the complex causation of chronic diseases.\textsuperscript{41} These criteria have been suggested in order to evaluate a putative causal relationship between exposure to a risk factor and a specified health outcome. Each of these criteria is discussed below in the context of exposure to HSV1 and cognitive impairments.

**Strength of the Association**

The strength of the association does not prove causality per se, although larger effect sizes are more persuasive. The association between HSV1 exposure and cognitive impairment has medium to large effect sizes among schizophrenia patients, with smaller effects among community-based controls (table 1).

**Consistency of the Associations**

Impairments across a range of cognitive domains have been observed repeatedly among HSV1-exposed individuals with a range of diagnostic categories as well as apparently healthy individuals. Within the affected cognitive domains, working memory, executive functions, and verbal memory appear to be more prominently affected suggesting a consistent pattern across the studies. The associations have been observed in different settings, using different measurement instruments demonstrating consistency of associations, thus providing perhaps the best evidence for causation.

**Specificity**

Several alternative explanations for the observed associations should be considered. Because HSV1 seropositivity is more common among individuals with lower SES,\textsuperscript{9} the observed associations could arguably reflect a primary effect of lower SES (or other nonviral variables correlated with SES). Most of the studies reviewed in table 1 investigated individuals from a range of SES groups and controlled for SES, using different proxy variables. Thus, SES is unlikely to be the primary cause for the association. Another concern is the impact of psychotropic medications, but 4 studies reviewed here did not include psychiatrically ill individuals. One of these studies also did not find associations with bacterial infections,\textsuperscript{27} suggesting a degree of specificity.

Some investigators have reported associations between exposure to CMV or HSV2 and cognitive impairments, but this question has not been addressed as extensively as the studies of HSV1 exposure. Like HSV1, CMV also causes lifelong infection, with intermittent latent and reactivation phases. Similar to HSV1, CMV-induced encephalitis is rare, being reported in immunocompromized individuals.\textsuperscript{42} Although CMV infection in utero causes a variety of neurological deficits and intellectual disability, longitudinal studies of children with asymptomatic congenital CMV have been inconsistent with regard to progressive cognitive impairment.\textsuperscript{43} Cross-sectional studies relating cognitive deficits to CMV exposure among adults have also been inconsistent. A prospective cohort–based study of Mexican Americans showed an association...
between elevated CMV antibody titers and rates of cognitive decline over 4 years assessed with the MMSE ($n = 1204$).\textsuperscript{29} Our cross-sectional study on individuals with schizophrenia/schizoaffective disorder ($n = 329$) exposed to CMV showed impaired performance on the TMT, part B,\textsuperscript{20} but others did not detect similar associations.\textsuperscript{19,21,26} HSV2, a sexually transmitted disease can also cause intellectual disability, low-normal IQ, language deficits, and motor disability following prenatal or perinatal infection.\textsuperscript{44} A retrospective cohort study among schizophrenia cases ($n = 23$) suggested association between maternal HSV2 exposure and impaired verbal memory and neuromotor functioning in the offspring.\textsuperscript{45} No significant associations between cognitive impairment and other herpes viruses (EBV, HHV6, and VZV) were found in a cross-sectional schizophrenia study.\textsuperscript{26} Two cross-sectional studies have suggested cumulative effects of exposure to CMV, HSV1, and HSV2\textsuperscript{25} (Watson et al, unpublished). In contrast, a study restricted to schizophrenia patients did not find significant evidence for interaction between joint exposure to HSV1 and CMV\textsuperscript{20} (table 1). Thus, the question of specificity needs further investigations.

**Temporality**

In the cross-sectional studies reviewed above, it is not possible to judge whether the HSV1 exposure predated the cognitive dysfunction; such evidence is vital to infer causation. The evidence from 3 longitudinal studies is mixed, with 2 studies reporting greater decline among HSV1-exposed persons and one negative study.\textsuperscript{27,29,33} although the studies were conducted on different diagnostic categories. Therefore, longitudinal studies on schizophrenia subjects or cohort-based studies are needed to replicate the existing findings.

**Biological Gradient**

It is difficult to establish a dose-response relationship between the exposure dose and cognitive impairment because antibody titers are not linearly correlated with the dose of infection. Furthermore, current technology does not allow for direct quantification of viral particles in the brain of living individuals. However, an earlier study noted a negative correlation between antibody levels and cognitive performance on RBANS among schizophrenia subjects.\textsuperscript{19}

**Plausibility**

Plausible mechanisms are summarized in figure 1. The cognitive impairment is unlikely to represent postencephalitic sequelae (which is rare), but it may stem from neurodevelopmental aberrations secondary to prenatal exposure (though transplacental transmission of HSV1 is rare\textsuperscript{46}). Alternatively, maternal immune modulation associated with HSV1 exposure could also affect neurodevelopment.\textsuperscript{47} Repeated cycles of latency and reactivation that occur during chronic (persistent) infection could also cause incremental damage leading to cognitive impairment. The latent infection that is generally considered benign may itself cause neuronal dysfunction. In addition, neuronal dysfunction may be secondary to immunological response to the infection.\textsuperscript{7} Cognitive impairments could occur as a result of cytokines released peripherally during reactivation or following local immune response in the brain during reactivation and latency.\textsuperscript{48} Inflammatory cytokines such as interleukin-6 (IL-6), IL-1\alpha are known to be elevated following HSV1 infection.\textsuperscript{49} These proinflammatory cytokines may affect working memory and learning.\textsuperscript{50} Regardless of the mechanisms, the cognitive impairments appear to be accompanied by structural brain changes that may progress with time (see “Herpes Simplex Virus 1” section).

**Coherence**

Congruence between epidemiological and laboratory findings supports a causal relationship, but Hill also noted, “...lack of such evidence cannot nullify the epidemiological effect on associations.” Latent infection has not been modeled adequately in human neuronal cells, though some rodent models suggest host cellular changes following latent infection.\textsuperscript{51}

**Experiment**

We recently concluded a randomized double-blind placebo-controlled trial of Valacyclovir (VAV), an agent that specifically targets herpes viruses.\textsuperscript{33} VAV or placebo was administered as adjuncts to standard antipsychotic (AP) therapy in HSV1-exposed early course schizophrenia patients ($n = 24$). Schizophrenia patients in the VAV + AP group showed significantly greater improvement in the processing speed of verbal memory and the accuracy of working memory and visual memory without
significant improvements in psychotic symptom severity. The results suggest that HSV1 associated cognitive dysfunction may be remediable among individuals with early course schizophrenia.

**Analogy**

One animal study supports the human cross-sectional studies. Rats were chronically infected with HSV1 and tested in a radial maze. Compared with mock-infected animals, the infected rats showed impairment in spatial recognition memory.15

**Summary of Evidence in Relation to the Bradford-Hill Criteria**

The association between HSV1 exposure and cognitive impairment is consistent, plausible and has a modest effect size. It is not attributable to obvious confounding factors. A temporal relationship between exposure and dysfunction has been suggested in 2 studies. It is difficult to test a “biological gradient” between exposure dose and dysfunction severity. This is because assaying for HSV1 antibody titers is the only practical way to detect exposure, however, the antibody titers do not conclusively reflect the severity or duration of exposure. Thus, the bulk of the available evidence is consistent with a causal relationship between HSV1 exposure and cognitive dysfunction, but additional evidence is needed.

**Gaps in Our Knowledge, Implications for Public Health**

**Gaps in Our Knowledge**

Becker’s hypothesis, which suggested a causal relationship between HSV1 exposure and cognitive impairment, is gaining support. Importantly, it is uncertain whether viral exposure is also associated with impairments in daily functioning. It is also unclear whether the cognitive impairment reflects a greater impact in subgroups of individuals, such as those with genetic susceptibility to viral infections or its pathogenic effects or in individuals with certain diagnosis. The bulk of the evidence comes from studies on schizophrenia. Several schizophrenia susceptibility genes may also enhance vulnerability to HSV1 infection.52 Although available data indicate that the rate of HSV1 exposure in individuals with schizophrenia does not differ from the rate in controls, genetic variants that increase schizophrenia risk may arguably enhance the impact of HSV1 exposure. Because of the difficulties in isolating the putative causal agents (eg, herpes viruses from human brains) during latent infection and the multifactorial nature of cognitive impairment, a single study may not satisfactorily resolve the question of causation. Rather, several studies that evaluate predictions from the causal hypothesis may be needed. This situation is reminiscent of bygone debates about the impact of lead exposure on childhood neurodevelopment. Though incident cohort studies could test the hypothesis more convincingly,
they are difficult to motivate due to their cost. Moreover, interpretation may be difficult because multiple infections with herpes viruses can occur. Therefore, more longitudinal studies of virus-exposed and unexposed individuals or treatment trials of exposed persons are worthwhile. Animal models can investigate latent or persistent HSV1 exposure, but interpretation is difficult because HSV1 viruses are species specific. The mechanisms related to latency/activation could be tested using cellular models. Cellular models have extensively investigated acute and latent infection, but those studies utilized older gene expression arrays. Updated studies using human cells are desirable. Such studies may also suggest biomarkers of infection that may be detectable in the serum or plasma.

Related, but equally important questions arise in relation to schizophrenia. Why does the association between HSV1 exposure and cognitive dysfunction have a bigger effect size among schizophrenia cases than among controls? Are the schizophrenia patients more vulnerable to virus-related cognitive dysfunction as well as HSV1-related skin lesions? Does it reflect host genetic variation that also increases susceptibility to schizophrenia? If patients are more vulnerable, does the vulnerability reflect an increased impact against the background of the disorder-related cognitive impairment, or is it related specifically to viral infection? Should the issue of herpes viral exposure and risk for developing schizophrenia be revisited?

**Implications for Clinical Practice**

The observed links between herpes virus exposure and cognitive impairment have potential diagnostic and therapeutic implications. If the initial longitudinal studies of schizophrenia are confirmed, it would be informative to know if exposure predicts cognitive impairment in schizophrenia and, in turn, its long-term outcome. If these predictions are correct, efficacious antiviral agents with relatively few side effects could be evaluated, thus holding a promise for therapeutic benefits. Although HSV1 exposure is not considered a risk factor for schizophrenia, investigation of HSV1 exposure could still highlight some of the pathophysiological pathways leading to cognitive disability. If our PAR estimates among community samples reflect true risks (see “Herpes Simplex Virus 1” section), such benefits may even extend to the general population, particularly for individuals with nonpsychotic cognitive disorders. As viral exposure rates are typically higher in developing countries and among socioeconomically deprived groups, these studies have greater implications for many disadvantaged populations. Developing preventive approaches including effective vaccines may be worthwhile.

**Conclusions**

Herpes viruses cause a spectrum of pathology in the human brain, ranging from apparently asymptomatic latent infection to catastrophic encephalitis. A growing body of evidence suggests that individuals exposed chronically to herpes viruses, particularly HSV1, have impaired cognitive performance compared with unexposed individuals. The differences are detectable among otherwise healthy individuals; they are more substantial among persons with schizophrenia. Similar associations have also been observed among patients with bipolar disorder, suggesting that the HSV1 associations may not be restricted to a particular psychiatric diagnostic group. Although causal relationships should not be inferred from cross-sectional studies, suggestive longitudinal studies and a treatment trial in schizophrenia motivate further studies to evaluate etiological links. Such lines of enquiry may enable rational therapies and thus avert cognitive deficits among vulnerable groups of individuals.

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**References**

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19. Dickerson FB, Boronow JJ, Stallings C, Origoni AE, Ruslanova I, Yolken RH. Association of serum antibodies to herpes simplex virus 1 with cognitive deficits in individuals with schizophrenia. *Arch Gen Psychiatry*. 2003;60:466–472.


