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# Assessment of cognitive impairment in HSV-1 positive schizophrenia and bipolar patients: Systematic review and meta-analysis

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ABSTRACT

A common characteristic among schizophrenia and bipolar disorder patients is cognitive dysfunction, especially for memory and attention. Recent evidence has suggested that cognitive impairment in schizophrenia and bipolar disorder patients could be associated with herpes simplex virus 1 (HSV-1) infection, due to the ability of HSV-1 to infect neurons in the temporal lobe, which plays a key role in the formation of memory and processing of sensory input. The objective of this review is to analyze the aggregate neuropsychological testing data from previous studies regarding the impact of HSV-1 infection on cognitive function in schizophrenia and bipolar disorder. A systematic literature search generated a total of 379 articles; 12 full-text case control and cross-sectional studies met the eligibility criteria to be included in the review. Pooled effects assessed the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total scores and the three index scores for immediate memory, delayed memory, and attention in a random effects model. The overall effect for RBANS total score was in favor of the HSV-1 positive group ($z = 3.10$, $p = 0.002$). A statistically significant overall effect of cognitive impairment for memory and attention indices was in favor of HSV positive schizophrenia patients ($z = 5.95$ $p < 0.00001$). The findings from the meta-analysis suggest that serological evidence of HSV-1 infection has a significant impact on cognitive function with small to moderate effect sizes ($-0.23$ to $-0.49$), particularly affecting memory and attention, in schizophrenia and bipolar patients.



## 1. Introduction

Schizophrenia (SZ) and bipolar disorder (BP) are psychiatric disorders that interfere with a person's ability to think clearly, manage emotions, make decisions and relate to others. SZ, a complex, long-term illness affecting 1% of Americans, can present with sleep problems and irritability, progressing to hallucinations, delusions, and cognitive impairment. BP, affecting approximately 2.6% of the U.S. population, dramatically shifts a person's mood, energy and ability to think clearly (NAMI: National Alliance on Mental Illness, 2019). Although a single etiology has not been identified, genetics, brain chemistry, and environment are thought to play a role in the development of these disorders. Previous studies have also suggested that infectious pathogens, such as herpesviruses, *Toxoplasma gondii*, or influenza, could potentially be associated with pathogenesis of SZ and BP disorder (Gerber et al., 2012). Each of these pathogens gains access to the brain during infection, which could contribute to psychotic symptoms, behavioral abnormalities and cognitive impairment characterizing the disorders (Hannachi et al., 2014).

Due to high prevalence and predilection for the central nervous system (CNS), infection with herpesviruses has been hypothesized as a potential etiological factor for cognitive deficits commonly associated with mental illnesses. (Prasad et al., 2012). The herpesviridae family consists of nine herpesviruses, three of which are neurotropic. The alphaherpesviruses, herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), and varicella zoster virus (VZV), infect peripheral sensory and autonomic neurons during primary infection, where they establish latency for the life of the host. The alphaherpesviruses can also reach the CNS during primary infection, or following reactivation in peripheral neurons (Baringer and Pisani, 1994; Gilden et al., 2001; Lee et al., 2015; Mitchell et al., 2003; Nagel et al., 2014; Ohashi et al., 2011; Prasad et al., 2012; Richter et al., 2009). HSV-1 infection can lead to encephalitis and other neurological impacts (Prasad et al., 2012).

Recent evidence shows HSV-1 is associated with neuroanatomical changes in key areas of the brain that may contribute to cognitive impairment. A recent longitudinal study showed that HSV-1 seropositive

*Abbreviations:* HSV-1, Herpes Simplex Virus 1; HSV-2, Herpes Simplex Virus 2; VZV, Varicella- Zoster Virus; CMV, Cytomegalovirus; EBV, Epstein-barr Virus; HHV6A and B, Herpes Virus 6A and B; HHV7, Herpes Virus 7; HHV8, Kaposi's Sarcoma; SZ, Schizophrenia; BP, Bipolar Disorder; HC, healthy controls; MRI, Magnetic resonance imaging; BOLD, Blood Oxygen Level Dependent; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; JAMA, Journal of American Medical Association; CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; MD, mean difference; NIH, National Institute of Health; TMT, Trial Making Test Part A and B; HVLT, Hopkins Verbal Learning Test; WCS, Wisconsin Card Sorting Test.

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schizophrenia patients had significant neuroanatomic morphological changes and grey matter loss over a one-year period (Prasad et al., 2011). Magnetic resonance imaging (MRI) showed HSV-1 positive SZ patients, compared to HSV-1 negative SZ patients, had less grey matter volume in Brodmann's area 8, 9, and 32, which regulates motor, language, executive functions, memory and attention processes (Prasad et al., 2011; Trans Cranial Technologies, 2012). Findings also revealed a significant correlation between decline in executive function and grey matter loss in the posterior cingulate, involved in executive control and working memory, in HSV-1 positive SZ and BP patients (Prasad et al., 2011; Trans Cranial Technologies, 2012). A similar study found decreased grey matter volume in the bilateral anterior cingulate gyrus and cerebellum in HSV-1 positive SZ patients (Schretlen et al., 2010). These neuroanatomical changes associated with HSV-1 infection may contribute to dysfunction in cognitive processes, such as memory and attention in SZ and BP patients.

BP patients seropositive for another herpesvirus, cytomegalovirus (CMV), had a statistically significant decrease in right hippocampal volume, compared to seronegative CMV BP patients (Houenou et al., 2014). The hippocampus is a part of the limbic system that regulates emotions and formation of long-term memory (Mandal, 2018; Phelps, 2018). Reduction in hippocampal volume could contribute to mood instability, memory dysfunction, and other symptoms in BP disorder. Recent studies have shown a positive association between CMV and BP disorder, but research on HSV-1 and BP is limited, and findings have been mixed. In a recent systematic review by Barichello et al., two of five studies that evaluated perinatal exposure to bornavirus, herpesviruses, influenza, and toxoplasmosis found an association between HSV-1 and BP disorder (Barichello et al., 2016).

Neuroanatomical changes may elucidate impairment of memory and attention, since HSV-1 is apt to target regions of the brain responsible for memory and attention processes, such as the posterior gyrus and hippocampus (Prasad et al., 2011). However, HSV-1 may also impact neurophysiological mechanisms of cognitive processes. HSV-1 seropositive SZ patients, unlike HSV-1 seronegative SZ patients and controls, initiated regions of the brain outside of the prefrontal cortex and posterior parietal cortex that activates the classical working memory network, while undergoing letter n-back cognitive testing during functional MRI and blood oxygen level dependent (BOLD) responses (D'Aiuto et al., 2015). Since SZ patients have shown significant differences in brain activation patterns (D'Aiuto et al., 2015) and both SZ and BP patients present neuroanatomical changes (Houenou et al., 2014; Prasad et al., 2011; Schretlen et al., 2010), these results support the hypothesis that alphaherpesviruses are potentially an independent predictor of cognitive impairment. Several studies have evaluated the correlational relationship between HSV-1 and cognitive impairment by conducting a variety of neuropsychological tests with SZ and BP patients to deduce the degree of cognitive impairment and areas of cognition that are affected. Thus, existing evidence suggests a positive relationship between the two variables.

### 1.1. Objective

The objective of this review was to analyze the aggregate neuropsychological testing data from previous studies regarding the impact of HSV-1 infection on cognitive function in SZ and BP disorder. We also assessed impairment in memory and attention in HSV-1 positive SZ and BP patients, compared to HSV-1 negative patients and healthy controls (HC).

## 2. Methods

### 2.1. Eligibility criteria

Case control (comparison of groups) and/or cross-sectional study (representative subset of a population) designs published from 2000 to 2017 were included; these study designs were not mutually exclusive. Studies considered for eligibility included diagnosis-by-HSV-1 status as the predictor variable, cognitive function/impairment as outcome variable, and comparison of neuropsychological test scores were between HSV-1 positive SZ or BP patients and HSV-1 negative SZ or BP patients and/or HC.

### 2.2. Types of outcome measures

Outcomes were based on studies that implemented neuropsychological tests that measured cognitive impairment of executive functioning/reasoning, immediate, delayed, verbal and working memory, attention, processing speed, psychomotor ability (accuracy and speed), cognitive flexibility, learning, vigilance, delayed recall, visuospatial/constructional abilities, language, and positive and negative symptoms. The primary outcome is the pooled effect of diagnosis-by-HSV-1 status effect of Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total score. The RBANS is a brief, individually administered test measuring attention, language, visuospatial/constructional abilities, immediate memory, and delayed memory (Randolph et al., 1998), consisting of 12 subsets, which yield five index scores and total scale score (Duff et al., 2008). The secondary outcome is the pooled effects of diagnosis-by-HSV-1 status effect of the RBANS three index scores for immediate memory, delayed memory, and attention. A few studies adjusted for gender, age, race, socioeconomic status or other demographic variables to control for confounding, but due to missing data, the results for adjusted data were not analyzed.

### 2.3. Search methods for identification of studies

A literature search was conducted from June 2017 to October 2017. The following search terms were used to search articles in Pubmed, Elsevier, Science Direct, Journal of American Medical Association (JAMA) Network, and Proquest: "*herpesviruses AND schizophrenia*," "*herpesviruses AND bipolar*," "*herpesviruses AND psychiatric disorders*," *herpesviruses AND psychiatric disorders AND cognitive impairment*," "*herpesviruses AND neurotic disorders*," "*herpesviruses AND cognitive impairment*," *and* "*herpes simplex virus 1 AND schizophrenia*." Customized publication dates (2000 to 2017) were used to search for articles and then sorted by the "relevance" or "best match" option in the databases.

### 2.4. Searching other resources

Two included studies (Bolu et al., 2016; Dickerson et al., 2003) were identified from references in other articles selected to be included in the review.

### 2.5. Selection of studies

The search strategies generated a total of 379 articles, which were initially screened and selected based on the title's relevance to "schizophrenia," "bipolar," and "herpesviruses" or "HSV-1." After the first phase of screening, 87 articles were pulled from the database searches and two articles were pulled from other references, 21 duplicates were removed, and 66 articles remained for the second phase of screening. After screening abstracts for eligibility, 47 articles were excluded and 19 articles were selected for the third phase of screening. In the final full-text screening, 12 articles met the eligibility criteria to be included in the review and seven were excluded. In Fig. 1, the PRISMA flow diagram illustrates the screening process and selection of studies.

### 2.6. Data collection and analysis

Data were collected from the 12 studies using an extraction form, similar to Cochrane extraction form, including check boxes for: study is included or excluded, reason for exclusion, author, journal, date,

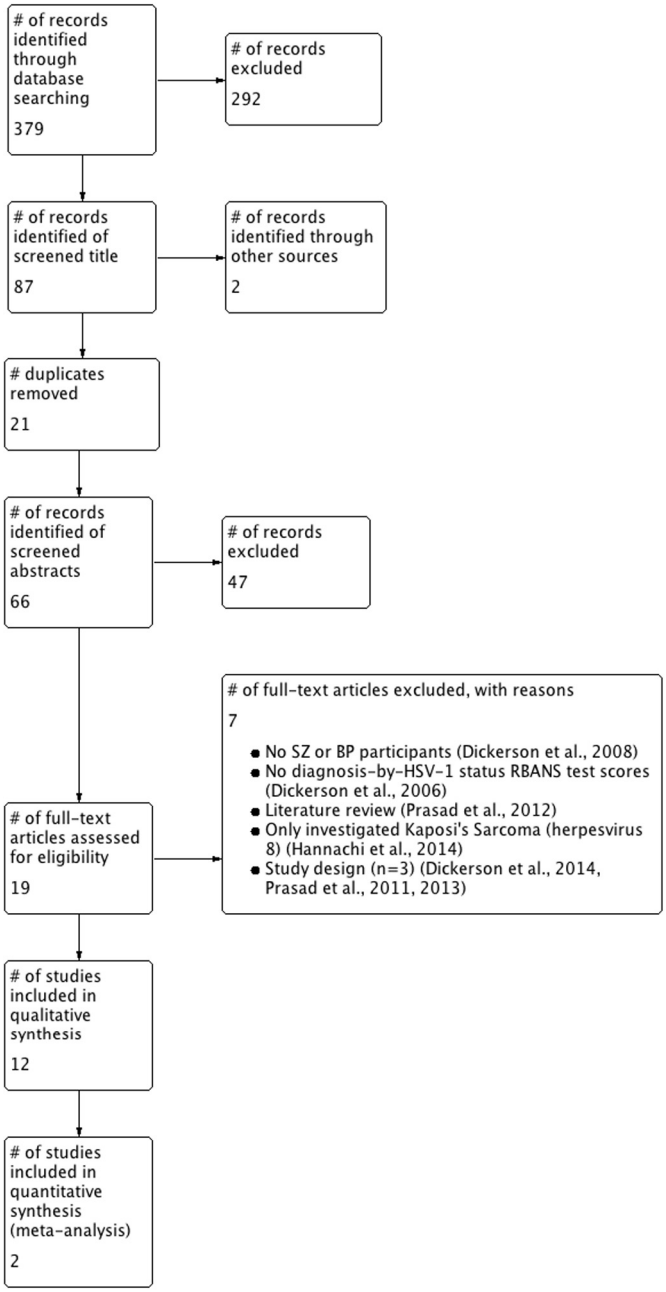


**Fig. 1.** Flow diagram of selected studies.

year, study design, setting, population, sample size, assessment used, number of cases, number of controls, data from results, and statistical significance. Studies used for the meta-analysis were selected based on use of the same measurement scale; the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) test, which was used in nine of the 12 studies. However, only two studies reported means and standard deviation, which were required for the meta-analysis.

*2.6.1. Data extraction and management*

Data were extracted and recorded in an excel file, including numbers of HSV-1 negative (n = HSV-1-), HSV-1 positive (n = HSV-1+), and total cases (n). The RBANS total mean scores and index scores for immediate memory, delayed memory and attention, all with standard deviations, were extracted for the meta-analysis. The statistical analysis used (e.g. wald $x^2$, F-test, *t-test*, wilk's λ) for total score and/or index scores from all included studies were extracted and recorded on the data collection form. If given, odds ratios, relative risks, confidence intervals, effect sizes, and *p* values were also extracted and recorded on the data collection form to evaluate measure of association, significance of results, and effect size.

*2.6.2. Assessment of risk of bias in included studies*

Risk of bias was assessed using the National Institute of Health (NIH) quality assessment tools for cross-sectional and case-control studies ("Study Quality Assessment Tools | National Heart, Lung, and Blood Institute (NHLBI)", n.d.). The quality assessment includes ten domains for cross-sectional and case-control studies; risk of bias was based on whether the studies addressed each domain; studies were defined as "low risk," (yes), "unclear risk" (undefined), or "high risk" (no).

The ten domains for case-control studies included research question defined, study population defined, sample size justification, controls recruited from same population, inclusion/exclusion criteria specified, cases defined, exposure assessed prior to the outcome, exposure measures/assessment defined, assessor blinded, and control for confounding variables. The cross-sectional studies included the same domains as case-control studies with a few exceptions; sample size justification was replaced with sample size/power analysis/effects specified, and exposure measures/assessment defined was replaced with exposure/independent variable defined and outcome/dependent variable defined domains.

*2.6.3. Assessment of heterogeneity*

Heterogeneity was assessed using Review Manager 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. Heterogeneity was determined using the $I^2$ and $Tau^2$. Meta-analyses with an $I^2 > 80\%$ were considered to be very heterogeneic and were not used. For the heterogeneity $I^2$ tests, values 25%, 50%, and 75% were considered low, medium, and high respectively.

*2.6.4. Data synthesis*

Outcomes for RBANS total score and three index scores for immediate memory, delayed memory, and attention were analyzed separately using Review Manager 5.3. To assess the pooled effects of the RBANS total scores and the three index scores, the mean scores and standard deviations were entered as continuous variables into a random effects model with the following parameters: the generic inverse variance method, the mean difference for effects measure, and a 95% confidence interval. Subtotal and total overall effects were generated from the three index scores analysis. Using the mean difference, the standard deviations and sample sizes were entered into Review Manager 5.3 to calculate and assign weights to the included studies. To assess statistical significance of the pooled overall effect, the z test was used at the 5% level ($p < 0.05$).

## 3. Results

*3.1. Results of the search*

The search methods generated 379 articles; 12 studies met the eligibility criteria (Fig. 1). Seven studies were case-control and five were cross-sectional studies. Three studies included bipolar patients (Dickerson et al., 2004; Dickerson et al., 2006b; Gerber et al., 2012), eight included SZ patients (Bolu et al., 2016; D'Aiuto et al., 2015; Dickerson et al., 2012; Dickerson et al., 2003; Schretlen et al., 2010; Shirts et al., 2008; Thomas et al., 2013; Yolken et al., 2011), and one examined both BP and SZ patients (Tanaka et al., 2017) as the study population. Five studies (Dickerson et al., 2012; Dickerson et al., 2004; Dickerson et al., 2006b; Dickerson et al., 2003; Gerber et al., 2012) implemented the RBANS test, but only two cross-sectional studies reported the mean scores with standard deviations that could be included in the meta-analysis (Dickerson et al., 2012; Dickerson et al., 2003). Characteristics of the

studies are provided in Table 1 for reference, year, study design, setting, patients, sample size (n=), test, main findings, and conclusions.

### 3.2. Excluded studies

Of the original records identified through the search methods, 292 records were excluded based on title (Fig. 1). Twenty-one duplicates were also removed. Based on abstract screening, another 47 records were excluded. Seven additional articles were excluded upon full-text review for the following reasons: study sample evaluated non-psychiatric patients (Dickerson et al., 2008), article was a literature review (Prasad et al., 2012), study only evaluated the association between cognitive impairment in SZ patients with Kaposi's Sarcoma (Hannachi et al., 2014), study did not investigate RBANS test scores for diagnosis-by-HSV-1 status (Dickerson et al., 2006a), and three additional studies were excluded because they were not case-control or cross-sectional study designs (Dickerson et al., 2014; Prasad et al., 2011; Prasad et al., 2013).

### 3.3. Included studies

The 12 studies selected for inclusion and analysis included a total of 3603 participants with a mean sample size of 300 participants across all studies. A total of 286 participants were BP patients, 2831 were SZ patients, and 486 were HSV positive and negative healthy controls (HC). The sample size ranged from 42 to 298 participants for the case-control studies and 40 to 1308 for cross-sectional studies. Two studies that included RBANS mean scores with standard deviation were included in the meta-analysis (Dickerson et al., 2012; Dickerson et al., 2003).

### 3.4. Risk of bias in included studies

The risk of bias was assessed using the National Institute of Health (NIH) quality assessment tools for cross-sectional and case-control studies. All 12 studies contained a low risk of bias for the research question defined, study population specified, and exposure measures

**Table 1**
Characteristics of included studies.

| Reference, year | Study design | Setting | Patients | Sample Size (n=) | Test | Main findings | Conclusions |
|---|---|---|---|---|---|---|---|
| Bolu et al., 2016 | Case control | Ankara, Turkey | SZ vs. HC | 180 | SAPS and SANS | Significant difference between two groups (HSV-1 IgG (−) vs. HSV-1 IgG(+)) SANS mean scores ($p = 0.046$) | The results suggest a role of HSV-1 infection in negative symptoms. |
| D'Auito et al., 2015 | Case control | | SZ vs. HC | 42 | LNB | 2 back response: diagnosis-by-HSV-1 status interaction, trend towards significance ($p = 0.058$) | The fMRI results affirm association between nonecephalitic HSV-1 infection and functional brain changes linked with working memory impairment. |
| Dickerson et al., 2004 | Case control | USA | BP vs. HC | 217 | RBANS | HSV-1 was associated with decreased cognitive function on RBANS total score compared to controls ($p = 0.00002$) | Serological evidence of HSV-1 infection is associated with cognitive impairment in BP patients |
| Dickerson et al., 2003 | Cross section | USA | SZ | 229 | RBANS | HSV-1 significantly associated with lower RBANS total score, immediate memory, visuospatial construct, and attention ($p < 0.001$). Immediate memory has the strongest association. | Serological evidence of HSV-1 infection is associated with cognitive impairment in SZ patients. |
| Dickerson et al., 2006a, b | Case control | USA | BP vs. HC | 202 | RBANS | Significant association between COMT Val158/Met/HSV-1 (+) and RBANS total score ($p = 0.000002$), immediate memory ($p = 0.006$), and delayed memory ($p = 0.00002$) | Both the COMT Vall58Met polymorphism and serological evidence of HSV-1 infection affect cognitive functioning in individuals with bipolar disorder. |
| Dickerson et al., 2012 | Cross section | USA | SZ | 588 | RBANS | Significant difference among the HSV-1 (−)/ normal CRP group and HSV-1 (+)/normal CPR group in RBANS total score, immediate memory, attention, and visual constructional scores ($p < 0.001$) | That cognitive functioning in SZ patients is associated both with serological evidence of infection with HSV-1 and an activated immune system evidenced by elevated levels of CPR. |
| Gerber et al., 2012 | Case control | EU | BP vs. HC | 50 | RBANS, TMT A and B, LNB | HSV-1 (+) is a significant independent predictor of cognitive impairment for RBANS index verbal and attention scores ($p = 0.009$) and ($p = 0.046$) respectively. | HSV-1 is a possible cofactor for cognitive dysfunction in patients with Bipolar disorder, that was not found in the unaffected controls |
| Shirts et al., 2008 | Cross section | USA | SZ | 329 | TMT A and B | HSV-1 (+) significantly associated with slower times and errors on TMT Part B ($p = 0.040$) | Suggests HSV-1 associated with impaired cognitive function, particularly with working memory. |
| Shretlen et al., 2010 | Cross section | USA | SZ | 40 | TMT A and B, BTA, HVLT, BVMT 1–4, WCS | HSV-1 (+) performed significantly worse than HSV-1 (−) for psychomotor speed ($p = 0.037$), executive functioning ($p = 0.004$), verbal memory ($p = 0.041$ and $p = 0.020$) | HSV-1 seropositive SZ patients performed worse than seronegative patients on several neuropsychological tests. |
| Tanaka et al., 2017 | Case control | USA | SZ and BP vs. HC | 120 | BACS | There was no significant association between HSV-1 (+) SZ patients ($p = 0.582$) nor the HSV-1 (+) BP patients ($p = 0.636$) and BACS scores | Increased exposure to HSV-1 and increased levels of inflammatory markers suggest that these indices may influence cognitive abilities in mental illnesses. |
| Thomas et al., 2013 | Case control | India | SZ | 298 | Penn CB | Diagnosis and HSV-1 exposure status interaction did not significantly predict any of the domains or indices: accuracy, speed, or efficiency. | No significant interaction between Diagnosis and HSV-1 exposure status predicting accuracy, speed, and efficiency was observed, though such an effect may be detectable in a larger sample. |
| Yolken et al., 2011 | Cross section | USA | SZ | 1308 | GPT, WAIS-RDS, COWAT, HVLT, WCS, WISC_RM, LNB | Significant association between lower summary scores ($t = -2.60$, $p = 0.009$) for verbal memory ($t = -3.01$, $p = 0.003$), processing speed ($-2.76$, $p = 0.006$), and vigilance ($t = -2.88$, $p = 0.004$) and HSV-1 exposure | Affirms the association between HSV-1 infection and neurocognitive performance. |

a SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms; LNB, Letter n-Back Test; TMT A and B, Trial Making Test Part A and B; BTA, Brief Test of Attention; HVLT, Hopkins Verbal Learning Test; BVMT 1-4, Brief Visuospatial Memory Test (trials 1-4); WCS Wisconsin Card Sorting Test; BACS, Brief Assessment of Cognition in Schizophrenia, Penn CB, University of Pennsylvania Neuroncognitive Computerized Battery; GPT, Grooved Pegboard Test; WAIS-RDS, WAIS-R Digit Symbol test, COWAT, Controlled Oral Word Association Test; WISC-RM,WISC-R Mazes; EU, Europe; SZ, Schizophrenia; BP, Bipolar; HC, healthy controls.

defined (Fig. 2). For all 12 of the studies, there was an unclear risk if exposure occurred prior to the outcome. In 11 of the studies, neither the patients nor the assessors were blinded given the inherent nature of the disorders. Furthermore, the neuropsychological tests were intended to be given to a population in which diagnosis was already known. One study (Yolken et al., 2011) was at a low risk for blinding; the study used public data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), a prior double-blinded randomized control trial.

In all seven of the case-control studies, the sample size was not justified, placing them at high risk for sample size justification domain (Fig. 2A). Two studies (Bolu et al., 2016; D'Aiuto et al., 2015) (28%) out of the seven were at high risk for control of confounding variables. One study (D'Aiuto et al., 2015) (14%) had an unclear risk if controls were recruited from the same population as the cases.

In the cross-sectional studies (Fig. 2B), two studies (Shirts et al., 2008; Yolken et al., 2011) were at high risk for sample size, power analysis, or effects specified domain. One study (Shirts et al., 2008) (20%) was also at high risk for control of confounding variables domain.

### 3.5. HSV-1 impact on cognition in schizophrenia patients

Six of the nine studies included in the review found a significant association between HSV-1 positive status and cognitive impairment in SZ patients. One case-control study (Bolu et al., 2016) implemented the Scale for the Assessment of Positive Symptoms (SAPS) and Scale for the Assessment of Negative Symptoms (SANS) to evaluate impairment in SZ patients and HC, finding a significant difference in SANS scores between HSV-1 IgG-positive SZ patients compared to HSV-1 IgG-negative SZ patients and both HSV-1 IgG+ and IgG- controls. This finding suggested that HSV-1 has a role in negative symptoms, including affective flattening, alogia, avolition, anhedonia, and attention (Andreasen, 1982). Shretlen et al. showed that HSV-1 positive SZ patients' psychomotor speed, executive functioning, and verbal memory were significantly worse than HSV-1 negative SZ patients, by assessing performance on the Trial Making Test Part A and B (TMT), Brief Test of Attention, Hopkins Verbal Learning Test (HVLT), Brief Visuospatial Memory Test (trials 1–4), and Wisconsin Card Sorting Test (WCS) (Schretlen et al., 2010). Similarly, Shirts et al. showed that the HSV-1 positive SZ patients had significantly slower times and more errors on the TMT part B, which measures executive functioning, compared to HSV-1 negative SZ patients (Shirts et al., 2008). Using the Grooved Pegboard Test, WAIS-R Digi Symbol test, Controlled Oral Word Association Test, HVLT, WCS, WISC-R Mazes, and Letter-n-back Test, Yolken et al. found a significant association between lower summary score for verbal memory, processing speed, and vigilance and HSV-1 infection (Yolken et al., 2011). Dickerson et al. found HSV-1 positive SZ patients had a significant decrease in the RBANS total score, immediate memory, visuospatial construct, and attention (Dickerson et al., 2003). Through an additional study in 2012, Dickerson et al. determined that HSV-1-positive SZ patients with abnormal high serum levels of C-reactive protein (CRP), an inflammatory marker, performed significantly worse on the RBANS indices and total score compared to other groups of SZ patients (Dickerson et al., 2012).

Despite the use of a variety of different tests for cognitive impairment, each of these studies identified impaired functioning in HSV-1 seropositive SZ patients, compared to HSV-1 seronegative SZ patients and healthy controls (HCs). In contrast, other studies (D'Aiuto et al., 2015; Tanaka et al., 2017; Thomas et al., 2013), did not find a significant association between HSV-1 infection and cognitive impairment in SZ patients. However, D'Auito et al. reported a trend towards significance on the 2-back section of the letter-n-back test for working memory (D'Aiuto et al., 2015).

### 3.6. HSV-1 impact on cognition in bipolar patients

Of the four studies that tested neurological and HSV-1 status in BP patients, three found that HSV-1 seropositivity had a significant association with cognitive impairment (Dickerson et al., 2004; Dickerson et al., 2006b; Gerber et al., 2012). Dickerson et al. found HSV-1 positive BP patients had a significant decrease in the RBANS total score compared to HSV-1 positive and negative HCs (Dickerson et al., 2004). In a follow-up study, Dickerson et al. determined that the presence of valine/methionine polymorphism of the catechol *O*-methyltransferase gene at amino acid 158 (COMT VAL158MET), in addition to HSV-1 serum antibodies, was a risk factor for impairment in BP patients, who had significantly lower immediate memory and delayed memory RBANS index and total scores compared to the other groups (Dickerson et al., 2006b). Thus, an interaction may occur between specific genetic polymorphisms and the virus that may negatively impact memory. Analogous to Dickerson's study, Gerber et al. found that seropositivity of HSV-1 was a significant independent predictor of cognitive impairment for verbal memory and attention RBANS index scores in BP patients that was not observed in HC (Gerber et al., 2012). Conversely,

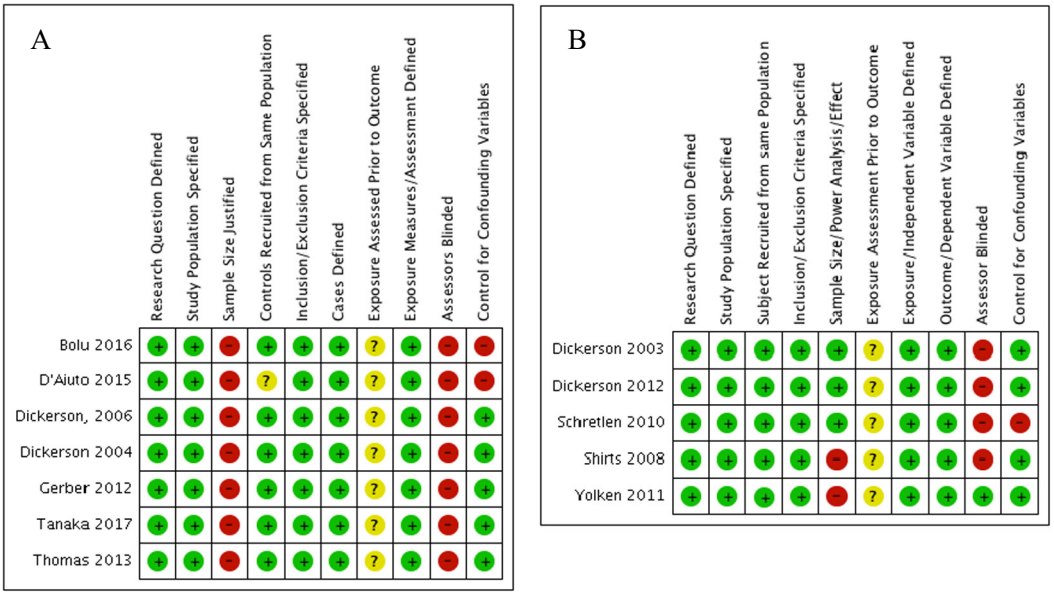


**Fig. 2.** Risk of bias summary within studies. A) Case control studies. B) Cross-sectional studies.

Tanaka et al. found no significant association between HSV-1 infection and cognitive impairment in BP patients (Tanaka et al., 2017).

### 3.7. Association of HSV-1 with cognitive impairment from RBANS total score

The RBANS total score is a composite score of five indices, including immediate memory, delayed memory, language, attention, and visuospatial/constructional. The RBANS total score (Fig. 3) was assessed in two studies, including a total of 609 SZ patients:101 seropositive and 128 seronegative patients (Dickerson et al., 2003) and 163 seropositive and 217 seronegative patients with ≤5μg/ml CRP, which is considered normal CRP range (Dickerson et al., 2012). Combining the two studies showed that the mean difference (MD) for the overall effect of the RBANS total score is −6.33 (95% CI = −10.32 to −2.33). The overall effect was in favor of the HSV-1 positive group, indicating that the HSV-1 positive SZ patients performed significantly worse on the RBANS test than HSV-1 negative SZ patients ($z = 3.10$, $p = 0.002$). Heterogeneity was not significant for the RBANS total score ($p > 0.05$). The pooled effect size ($d$) for the RBANS total score is −0.45. Thus, HSV-1 positive SZ patients have significantly greater cognitive impairment based on lower mean composite RBANS scores than HSV-1 negative SZ patients.

### 3.8. Association of HSV-1 with cognitive impairment from memory and attention indices

Individual RBANS indices of memory and attention (Fig. 4) were also assessed in the two studies (Dickerson et al., 2012; Dickerson et al., 2003). The MD for the total overall effect for three RBANS index scores, including immediate memory, delayed memory, and attention, is −6.44 (95% CI = −8.57 to −4.32). The MD subtotal overall effect of immediate memory and delayed memory indices was −8.57 (95% CI = −12.75 to −4.40) and − 4.36 (95% CI = −7.83 to −0.90) respectively. The MD overall effect of attention was −6.12 (95% CI = −9.09 to −3.15). The overall effect for cognitive impairment for memory and attention indices was in favor of HSV-1 positive schizophrenia patients ($z = 5.95$ ($p < 0.00001$). Heterogeneity was not significant for immediate memory, delayed memory, or attention ($p > 0.05$). The pooled effect sizes ($d$) for the RBANS immediate memory, delayed memory, and attention are −0.49, −0.23, and −0.37, respectively. Thus, HSV-1 positive SZ patients have significantly greater cognitive impairment of memory and attention based on lower mean RBANS index scores than HSV-1 negative SZ patients.

## 4. Discussion

The aggregate findings from the review reveal that HSV-1 infection does have a strong influence on cognition. It is evident that HSV-1 seropositive SZ and BP patients performed worse than controls. However, it is noteworthy to point out that HSV-1 seropositive SZ and BP patients performed worse, with a higher degree of cognitive impairment, than HSV-1 seronegative SZ and BP patients. Thus, HSV-1 negative SZ and BP patients are impaired, but HSV-1 infection exacerbates cognitive impairment in patients with the same disorders. Although multiple areas of cognition were affected and results varied, memory impairment was a common denominator in both SZ and BP across all studies that found an association. The findings from the meta-analysis suggest that serological evidence of HSV-1 infection significantly impacts performance and cognition in SZ patients, particularly affecting impairment in memory and attention (−0.23 to −0.49). The largest effect size of impairment was seen with immediate memory (−0.49).

Immediate and delayed memory, as well as working memory and attention, may be more susceptible to impairment, due to the ability of HSV-1 to infect the trigeminal and olfactory nerves and disseminate to the temporal lobes and limbic system, which are responsible for executive function and memory (Barnett et al., 1994; Beers et al., 1995; Stretton and Thompson, 2012). In addition, the immune response and chronic inflammation due to HSV-1 infection and persistence in the central nervous system (CNS) results in damage to neurons (Dickerson et al., 2012; Tanaka et al., 2017). Virus-induced hyperplastic astrocytes are present in the hippocampus, amygdala, piriform, entorhinal cortex, and cingulate cortex of rats intranasally inoculated with HSV-1, coincident with behavioral impairment, and latent HSV-1 nucleic acids were found in the hippocampus and entorhinal areas in all rats tested (Beers et al., 1995). Thus, latent HSV-1 in the CNS produces pathology in the limbic system consistent with effects on spatial memory deficits and behavior. A previous study had similar findings in humans, identifying HSV-1 in tissue samples of the hippocampus in four out of six schizophrenia cases (Gordon et al., 1996). Additionally, reactivation of HSV-1 has been associated with neuronal dysfunction due to presence of neuroinflammatory markers (toll-like receptor-4, interferon α/β, and p-IRF3) and neurodegenerative markers (phospho-tau and TauC3) in the cerebral cortex and trigeminal nerve of mice (Martin et al., 2014). Therefore, there is speculation that cognitive impairment in HSV-1 positive SZ patients could be enhanced by pathophysiology that is not present in healthy controls or in HSV-1 negative SZ patients.

Evidence also suggests that other herpesviruses are associated with cognitive dysfunction and symptoms of other psychiatric disorders. Six of the twelve studies included in the review also investigated an association between CMV and cognitive impairment; 50% of the studies (Bolu et al., 2016; Tanaka et al., 2017; Yolken et al., 2011) found significant impairment of cognition in SZ and BP patients with CMV infection. A significant association between human herpesvirus 6 (HHV6A and B) and impairment in delayed memory has also been reported (Gerber et al., 2012). Human herpesvirus 8 (HHV8) seroprevalence was also found to be higher in SZ patients than controls, significantly associated with positive symptoms (hallucinations, delusions) using the Scale for the Assessment of Positive Symptoms (SAPS) (Hannachi et al., 2014). HSV-1 has also been associated with obsessive-compulsive disorder (Khanna et al., 1997). Alice in Wonderland Syndrome, an uncommon disorder characterized by distorted perception and visual disturbances, is of unknown etiology. However, EBV infection is commonly reported in Alice in Wonderland Syndrome patients, suggesting a possible association that may warrant further investigation (Cinbis and Aysun, 1992; Liaw and Shen, 1991; Perez Mendez et al., 2001; Piessens et al., 2011).

Several limitations exist in this review and meta-analysis. Due to differences of neuropsychological tests and scoring used to measure cognitive function, the meta-analysis only investigated cognitive impairment in SZ patients from two studies. Therefore, findings from the test scores of SZ patients cannot be generalized for BP patients, nor could conclusions be drawn for BP patients. Furthermore, the second study may have included a subset of the patients included in the second, potentially skewing the results, although both studies found an association

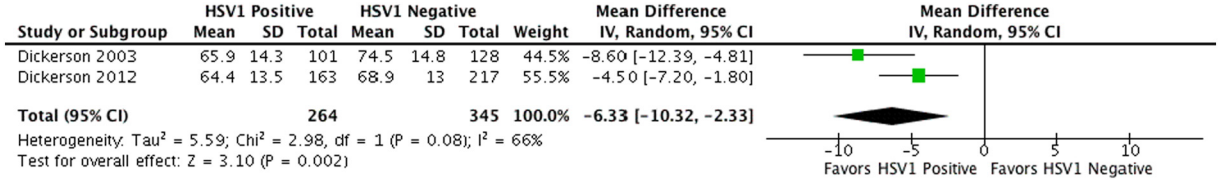


**Fig. 3.** Meta-analysis for Repeatable Battery for Neuropsychological Status (RBANS) test total score.

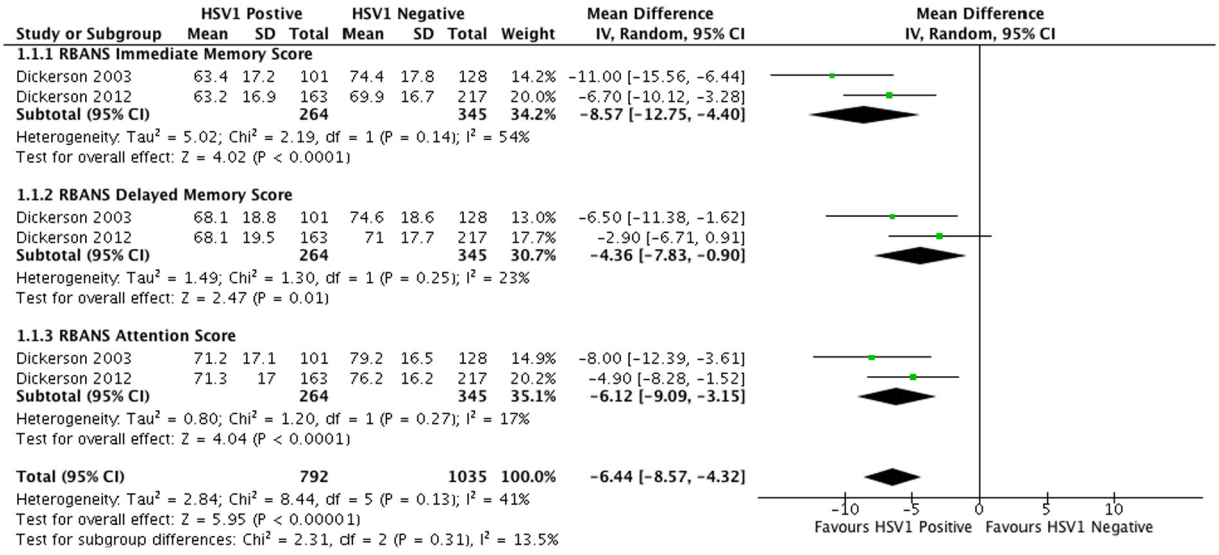


**Fig. 4.** Meta-analysis for Repeatable Battery for Neuropsychological Status (RBANS) test three index scores, immediate memory, delayed memory, and attention.

between HSV-1 seropositivity and cognitive impairment. Even though both studies included in the meta-analysis (Dickerson et al., 2003, 2012) reported data that controlled for confounding variables, the means and standard deviations for the adjusted data were not reported. Therefore, the data pooled from the two studies did not control for confounding factors (gender, age, socioeconomic status, education) that could affect cognitive function, nor were these variables examined in this review. Another limitation is the potential for common source bias, since the RBANS test was implemented mostly by the same group of authors and the two studies in the meta-analysis were conducted by the same author. Even though the literature review and selection process followed a rigorous methodical approach, selection bias is a limitation since only one reviewer selected the studies. Contrary to the limitations, a strength of this systematic review and meta-analysis is it supports the hypothesis that HSV-1 is associated with cognitive impairment, which could be an etiological link to elucidate the symptoms of some psychiatric disorders.

Research is beginning to understand how genetics, environmental factors, stress and trauma are risk factors influencing HSV-1 pathogenesis, as well as the relationship between the pathogenesis of HSV-1 and immune response and inflammation. Research is also beginning to shed light on how the CNS is affected by HSV-1. However, limited research exists on how alphaherpesviruses affect neuroanatomical and neurophysiological changes in SZ and BP patients, as well as other psychiatric disorders. Additional prospective studies, comparing individual SZ patients with non-psychiatric controls, are needed to understand the relationship and impact of these viruses on behavior and cognition. Furthermore, more research is needed to understand if treatment with antivirals, such as acyclovir, could improve cognition and symptoms of psychiatric disorders and prevent neuroanatomical changes and further cognitive decline.

In conclusion, the systematic review and meta-analysis indicates that serological evidence of HSV-1 infection impacts cognitive function across several different cognitive testing platforms, particularly affecting memory and attention.

#### Conflict of interest

The Authors have declared that there are no conflicts of interest in relation to the subject of this study.

## Contributions of authors

Joanna Tucker performed the literature search and meta-analysis, Joanna Tucker and Andrea Bertke wrote the systematic review.

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#### CRediT authorship contribution statement

**Joanna D. Tucker:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing - original draft. **Andrea S. Bertke:** Supervision, Writing - review & editing.

## CRediT authorship contribution statement

**Joanna D. Tucker:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing - original draft. **Andrea S. Bertke:** Supervision, Writing - review & editing.

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## References

Andreasen, N.C., 1982. Negative symptoms in schizophrenia. Definition and reliability. Arch. Gen. Psychiatry 39 (7), 784–788.

Barichello, T., Badawy, M., Pitcher, M.R., Saigal, P., Generoso, J.S., Goularte, J.A., Simoes, L.R., Quevedo, J., Carvalho, A.F., 2016. Exposure to perinatal infections and bipolar disorder: a systematic review. Curr. Mol. Med. 16 (2), 106–118.

Baringer, J.R., Pisani, P., 1994. Herpes simplex virus genomes in human nervous system tissue analyzed by polymerase chain reaction. Ann. Neurol. 36 (6), 823–829.

Barnett, E.M., Jacobsen, G., Evans, G., Cassell, M., Perlman, S., 1994. Herpes simplex encephalitis in the temporal cortex and limbic system after trigeminal nerve inoculation. J. Infect. Dis. 169 (4), 782–786.

Beers, D.R., Henkel, J.S., Kesner, R.P., Stroop, W.G., 1995. Spatial recognition memory deficits without notable CNS pathology in rats following herpes simplex encephalitis. J. Neurol. Sci. 131 (2), 119–127.

Bolu, A., Oznur, T., Tok, D., Balikci, A., Sener, K., Celik, C., Gulsun, M., 2016. Seropositivity of neurotropic infectious agents in first-episode schizophrenia patients and the relationship with positive and negative symptoms. Psychiatr. Danub. 28 (2), 132–138.

Cinbis, M., Aysun, S., 1992. Alice in wonderland syndrome as an initial manifestation of Epstein-Barr virus infection. Br. J. Ophthalmol. 76 (5), 316.

D'Aiuto, L., Prasad, K.M., Upton, C.H., Viggiano, L., Milosevic, J., Raimondi, G., McClain, L., Chowdari, K., Tischfield, J., Sheldon, M., Moore, J.C., Yolken, R.H., Kinchington, P.R., Nimgaonkar, V.L., 2015. Persistent infection by HSV-1 is associated with changes in functional architecture of iPSC-derived neurons and brain activation patterns underlying working memory performance. Schizophr. Bull. 41 (1), 123–132.

Dickerson, F.B., Boronow, J.J., Stallings, C., Origoni, A.E., Ruslanova, I., Yolken, R.H., 2003. Association of serum antibodies to herpes simplex virus 1 with cognitive deficits in individuals with schizophrenia. Arch. Gen. Psychiatry 60 (5), 466–472.

Dickerson, F.B., Boronow, J.J., Stallings, C., Origoni, A.E., Cole, S., Krivogorsky, B., Yolken, R.H., 2004. Infection with herpes simplex virus type 1 is associated with cognitive deficits in bipolar disorder. Biol. Psychiatry 55 (6), 588–593.
Dickerson, F., Kirkpatrick, B., Boronow, J., Stallings, C., Origoni, A., Yolken, R., 2006a. Deficit schizophrenia: association with serum antibodies to cytomegalovirus. Schizophr. Bull. 32 (2), 396–400.
Dickerson, F.B., Boronow, J.J., Stallings, C., Origoni, A.E., Cole, S., Leister, F., Krivogorsky, B., Yolken, R.H., 2006b. The catechol O-methyltransferase Val158Met polymorphism and herpes simplex virus type 1 infection are risk factors for cognitive impairment in bipolar disorder: additive gene-environmental effects in a complex human psychiatric disorder. Bipolar Disord. 8 (2), 124–132.
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 Behav. Immun. 22 (7), 1103–1107.
Dickerson, F., Stallings, C., Origoni, A., Vaughan, C., Khushalani, S., Yolken, R., 2012. Additive effects of elevated C-reactive protein and exposure to herpes simplex virus type 1 on cognitive impairment in individuals with schizophrenia. Schizophr. Res. 134 (1), 83–88.
Dickerson, F., Schroeder, J., Stallings, C., Origoni, A., Katsafanas, E., Schwienfurth, L.A., Savage, C.L., Khushalani, S., Yolken, R., 2014. A longitudinal study of cognitive functioning in schizophrenia: clinical and biological predictors. Schizophr. Res. 156 (2–3), 248–253.
Duff, K., Humphreys Clark, J.D., O'Bryant, S.E., Mold, J.W., Schiffer, R.B., Sutker, P.B., 2008. Utility of the RBANS in detecting cognitive impairment associated with Alzheimer's disease: sensitivity, specificity, and positive and negative predictive powers. Arch. Clin. Neuropsychol. 23 (5), 603–612.
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. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 36 (1), 110–116.
Gilden, D.H., Gesser, R., Smith, J., Wellish, M., Laguardia, J.J., Cohrs, R.J., Mahalingam, R., 2001. Presence of VZV and HSV-1 DNA in human nodose and celiac ganglia. Virus Genes 23 (2), 145–147.
Gordon, L., McQuaid, S., Cosby, S.L., 1996. Detection of herpes simplex virus (types 1 and 2) and human herpesvirus 6 DNA in human brain tissue by polymerase chain reaction. Clin. Diagn. Virol. 6 (1), 33–40.
Hannachi, N., El Kissi, Y., Samoud, S., Nakhli, J., Letaief, L., Gaabout, S., Ali, B.B., Boukadida, J., 2014. High prevalence of human herpesvirus 8 in schizophrenic patients. Psychiatry Res. 216 (2), 192–197.
Houenou, J., d'Albis, M.A., Daban, C., Hamdani, N., Delavest, M., Lepine, J.P., Vederine, F.E., Carde, S., Lajnef, M., Cabon, C., Dickerson, F., Yolken, R.H., Tamouza, R., Poupon, C., Leboyer, M., 2014. Cytomegalovirus seropositivity and serointensity are associated with hippocampal volume and verbal memory in schizophrenia and bipolar disorder. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 48, 142–148.
Khanna, S., Ravi, V., Shenoy, P.K., Chandramuki, A., Channabasavanna, S.M., 1997. Cerebrospinal fluid viral antibodies in obsessive-compulsive disorder in an Indian population. Biol. Psychiatry 41 (8), 883–890.
Lee, S., Ives, A.M., Bertke, A.S., 2015. Herpes simplex virus 1 reactivates from autonomic ciliary ganglia independently from sensory trigeminal ganglia to cause recurrent ocular disease. J. Virol. 89 (16), 8383–8391.
Liaw, S.B., Shen, E.Y., 1991. Alice in wonderland syndrome as a presenting symptom of EBV infection. Pediatr. Neurol. 7 (6), 464–466.
Mandal, A., 2018. Hippocampus Functions. In: Robertson, S. (Ed.), News Medical Life Sciences.
Martin, C., Aguila, B., Araya, P., Vio, K., Valdivia, S., Zambrano, A., Concha, M.I., Otth, C., 2014. Inflammatory and neurodegeneration markers during asymptomatic HSV-1 reactivation. J. Alzheimers Dis. 39 (4), 849–859.
Mitchell, B.M., Bloom, D.C., Cohrs, R.J., Gilden, D.H., Kennedy, P.G., 2003. Herpes simplex virus-1 and varicella-zoster virus latency in ganglia. J. Neuro-Oncol. 9 (2), 194–204.
Nagel, M.A., Rempel, A., Huntington, J., Kim, F., Choe, A., Gilden, D., 2014. Frequency and abundance of alphaherpesvirus DNA in human thoracic sympathetic ganglia. J. Virol. 88 (14), 8189–8192.
NAMI: National Allicance on Mental Illness, 2019. What is Schizophrenia? Namiorg
Ohashi, M., Bertke, A.S., Patel, A., Krause, P.R., 2011. Spread of herpes simplex virus to the spinal cord is independent of spread to dorsal root ganglia. J. Virol. 85 (6), 3030–3032.
Perez Mendez, C., Martin Mardomingo, M., Otero Martinez, B., Lagunilla Herrero, L., Fernandez Zurita, C., 2001. Alice in wonderland syndrome due to Epstein-Barr virus infection. An. Esp. Pediatr. 54 (6), 601–602.
Phelps, J.R., 2018. Memory, Learning, and Emotion: The Hippocampus. PsychEducation.org.
Piessens, P., Indesteege, F., Lemkens, P., 2011. Alice in wonderland syndrome and upper airway obstruction in infectious mononucleosis. B-ENT 7 (1), 51–54.
Prasad, K.M., Eack, S.M., Goradia, D., Pancholi, K.M., Keshavan, M.S., Yolken, R.H., Nimgaonkar, V.L., 2011. Progressive gray matter loss and changes in cognitive functioning associated with exposure to herpes simplex virus 1 in schizophrenia: a longitudinal study. Am. J. Psychiatry 168 (8), 822–830.
Prasad, K.M., Watson, A.M., Dickerson, F.B., Yolken, R.H., Nimgaonkar, V.L., 2012. Exposure to herpes simplex virus type 1 and cognitive impairments in individuals with schizophrenia. Schizophr. Bull. 38 (6), 1137–1148.
Prasad, K.M., Eack, S.M., Keshavan, M.S., Yolken, R.H., Iyengar, S., Nimgaonkar, V.L., 2013. Antiherpes virus-specific treatment and cognition in schizophrenia: a test-of-concept randomized double-blind placebo-controlled trial. Schizophr. Bull. 39 (4), 857–866.
Randolph, C., Tierney, M.C., Mohr, E., Chase, T.N., 1998. The repeatable battery for the assessment of neuropsychological status (RBANS): preliminary clinical validity. J. Clin. Exp. Neuropsychol. 20 (3), 310–319.
Richter, E.R., Dias, J.K., Gilbert 2nd, J.E., Atherton, S.S., 2009. Distribution of herpes simplex virus type 1 and varicella zoster virus in ganglia of the human head and neck. J. Infect. Dis. 200 (12), 1901–1906.
Schretlen, D.J., Vannorsdall, T.D., Winicki, J.M., Mushtaq, Y., Hikida, T., Sawa, A., Yolken, R.H., Dickerson, F.B., Cascella, N.G., 2010. Neuroanatomic and cognitive abnormalities related to herpes simplex virus type 1 in schizophrenia. Schizophr. Res. 118 (1–3), 224–231.
Shirts, B.H., Prasad, K.M., Pogue-Geile, M.F., Dickerson, F., Yolken, R.H., Nimgaonkar, V.L., 2008. Antibodies to cytomegalovirus and herpes simplex virus 1 associated with cognitive function in schizophrenia. Schizophr. Res. 106 (2–3), 268–274.
Stretton, J., Thompson, P.J., 2012. Frontal lobe function in temporal lobe epilepsy. Epilepsy Res. 98 (1), 1–13.
Tanaka, T., Matsuda, T., Hayes, L.N., Yang, S., Rodriguez, K., Severance, E.G., Yolken, R.H., Sawa, A., Eaton, W.W., 2017. Infection and inflammation in schizophrenia and bipolar disorder. Neurosci. Res. 115, 59–63.
Thomas, P., Bhatia, T., Gauba, D., Wood, J., Long, C., Prasad, K., Dickerson, F.B., Gur, R.E., Gur, R.C., Yolken, R.H., Nimgaonkar, V.L., Deshpande, S.N., 2013. Exposure to herpes simplex virus, type 1 and reduced cognitive function. J. Psychiatr. Res. 47 (11), 1680–1685.
Trans Cranial Technologies, 2012. Cortical Functions Reference. Trans Cranial Technologies Ldt., Wanchai, Hong Kong.
Yolken, R.H., Torrey, E.F., Lieberman, J.A., Yang, S., Dickerson, F.B., 2011. Serological evidence of exposure to herpes simplex virus type 1 is associated with cognitive deficits in the CATIE schizophrenia sample. Schizophr. Res. 128 (1–3), 61–65.