Effects of Cumulative *Herpesviridae* and *Toxoplasma gondii* Infections on Cognitive Function in Healthy, Bipolar, and Schizophrenia Subjects

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ABSTRACT

Objective: Schizophrenia and bipolar disorder are associated with cognitive impairment leading to social disruption. While previous studies have focused on the effect of individual infectious exposure, namely, *Herpesviridae* viruses or *Toxoplasma gondii* (*T gondii*), on cognitive functioning, the objective of the present study was to examine the effect of multiple infections on cognitive functioning in patients with schizophrenia and bipolar disorder and in healthy controls.

Methods: Seropositivity to herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), cytomegalovirus (CMV), and *T gondii* was related to cognitive status among 423 participants (recruited between 2008 and 2014; 138 patients with bipolar disorder, 105 patients with schizophrenia [*DSM-IV* criteria], and 180 healthy controls) for episodic verbal memory (California Verbal Learning Test), working memory (Wechsler Adult Intelligence Scale, third edition), and premorbid intelligence quotient (National Adult Reading Test).

Results: Seropositivity to and antibody levels of HSV-1 were significantly associated with working memory, which persisted after correction (backward digit span: $\beta = -0.10$ [0.05], $\chi^2 = 33.89$, $P = .0001$) in the overall sample. This association was particularly strong in the control group ($\beta = -0.18$ [0.08], $P = .04$, $Z = -3.55$, $P = .0008$; corrected $P = .012$). Further, cumulative exposure to HSV-1, HSV-2, and CMV viruses and *T gondii* parasite was also associated with lower scores on working memory as measured by backward digit span in the overall sample ($Z = 2.86$, $P = .004$; $Z = 2.47$, $P = .01$; and $Z = 3.35$, $P = .01$, respectively).

Conclusions: Exposures to *Herpesviridae* and *T gondii* parasite seem to impact cognitive functioning. Because infections caused by *Herpesviridae* and/or *T gondii* parasite are quite common in the (general) population, assessing and confirming the cognitive impairment among those who have cumulative exposures is useful and of interest.

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Schizophrenia and bipolar disorder are associated with cognitive impairment leading to social disruption. Almost all cognitive domains, namely executive function, memory, and attention, are affected. Although the profile of these cognitive impairments overlaps in both schizophrenia and bipolar disorder, cognitive impairments seem much more severe in schizophrenia. They presumably stem from disordered neurodevelopment and are believed to be present even before the onset of the disease and also in the first-degree relatives.[1] Cognitive deficits in schizophrenia encompass a range of neuropsychological domains including working memory, attention/vigilance, verbal learning and memory, visual learning and memory, reasoning and problem solving, speed of processing, and social cognition.[2,3] Cognitive impairment, especially executive dysfunction that appears in the early stages of the disorder, is also found in bipolar disorder, is exacerbated during mood episodes, and persists during euthymic periods. Patients with bipolar disorder display deficits in cognitive performance in the domains of verbal learning and memory, processing speed, nonworking memory, set shifting, and rule discovery.[4,5]

Growing attention is now focused on the possible involvement of infectious agents in the development of severe psychiatric disorders. In particular, exposure to viruses, such as poliomyelitis, mumps, rubella, cytomegalovirus (CMV), and herpes simplex viruses type 1 (HSV-1) and type 2 (HSV-2); bacteria, such as *Haemophilus influenzae*; or parasites, such as *Toxoplasma gondii* (*T gondii*), has been proposed as a risk factor for developing bipolar disorder and/or schizophrenia and quite likely contributes to cognitive impairment.[6–15] For example, *T gondii* has been associated with low intelligence quotient (IQ) and a drop in IQ over time in infected children,[16,17] with a greater

Clinical Points

- Cognitive impairment is common in neuropsychiatric disorders. The way by which it occurs remains uncertain. Infectious agents such as neurotropic viruses and parasite are known to affect cognition.
- Cognitive impairment (notably in working memory) can be explained by seropositivity to herpes simplex virus type 1 and/or cumulative effect of infectious agents (herpes simplex virus type 1, herpes simplex virus type 2, cytomegalovirus, *Toxoplasma gondii*). Therefore, it would be useful to assess cognitive performances, in particular, that of working memory, among those who have cumulative exposure to infectious agents.

impairment in immediate and delayed memory in youth and elderly subjects,[17,18] and with personality/behavioral change and alteration of psychomotor performance in adults.[19] In a similar manner, CMV infection had been associated with reduced executive function performance[20] and poor episodic verbal memory in patients with schizophrenia and bipolar disorder.[21] In healthy subjects (elderly and nonelderly), seropositivity to CMV is associated with lower cognitive performance, notably on memory tasks.[22,23] In various studies, exposure to HSV-1 was associated with reduced cognitive functioning in healthy subjects but also in bipolar disorder and schizophrenia. Lower cognitive performance in healthy individuals seropositive to HSV-1 or inpatients with vascular disease has also been characterized by cognitive decline over time.[24–26] In 2 independent studies,[9,27] seropositivity to HSV-1 in patients with bipolar disorder was correlated with reduced cognitive performance with deficits in immediate memory, visuospatial/construction, verbal fluency, and attention. Another study[28] of patients with bipolar disorder showed that exposure to HSV-1 in conjunction with a genetic factor (Val158Met COMT polymorphism) affected cognitive functioning, in particular immediate and delayed memory. In the case of schizophrenia, data have consistently indicated that history of proven exposure to HSV-1 is an independent predictor of cognitive dysfunction.[9,29–32] Additional studies have revealed that HSV-1 infection has negative impacts on the domains of immediate memory[9,30]; attention[30,31]; verbal memory, vigilance, and processing speed[28,30,31,33]; and abstraction, mental flexibility, spatial memory, and spatial processing.[32] Interestingly, exposure to herpes viruses diminishes cognitive performance in patients with schizophrenia and their unaffected relatives and also in similarly exposed young, healthy residents.[34]

So far, these studies have examined the effect of individual infectious exposures on cognitive functioning. The objective of the present study is to examine the combined effect of multiple infections on cognitive functioning in patients with schizophrenia and bipolar disorder as well as in healthy subjects.

METHODS

Patients (both inpatients and outpatients) with bipolar disorder (type I and type II) and schizophrenia meeting *DSM-IV* criteria (American Psychiatric Association, 1994), consecutively admitted/consulted (between 2008 and 2014) at 2 university-affiliated psychiatric departments (Mondor hospital, University of Paris-Est, Créteil, France and Fernand-Widal hospital, University of Diderot, Paris, France), were included in the present study after approval by a French ethics committee (Comité de Protection des Personnes) and after written informed consent was obtained from the participants. For outpatients with bipolar disorder and schizophrenia (in steady state with Young Mania Rating Scale [YMRS][35] score < 8 and Montgomery-Asberg Depression Rating Scale [MADRS][36] score < 12 for the former and Positive and Negative Syndrome Scale [PANSS] score < 60 for the latter), cognitive evaluation was conducted in ambulatory care; while for inpatients (also reaching YMRS < 8, MADRS < 12, and PANSS < 60), cognitive evaluation was done at the end of hospitalization. Healthy subjects, hereafter designated as healthy controls, were enrolled through a clinical investigation center, also in Paris, France (Center for Biological Resources, Mondor hospital, Créteil, France). Only those without a personal or first-degree family history of psychotic or affective disorders or addictive or suicidal behavior, as measured by the Family Interview for Genetic Studies (FIGS),[37] and also without a personal or family history of autoimmune diseases (information obtained from controls/patients, first-degree relatives, or medical records) were included. Other exclusion criteria were (1) current or past immunosuppressive treatment; (2) recent infection or an ongoing inflammatory disease, namely, arthritis, ankylosing spondylitis, Crohn disease, asthma, or systemic lupus erythematous; (3) a positive serology for HIV-1/HIV-2 or hepatitis A, B, or C prior to enrollment; or (4) neurologic disorder with cognitive impairment, namely, multiple sclerosis, Parkinson disease, head injury, cerebrovascular accident, or Alzheimer disease. The age range of both patients and controls was between 18 and 65 years.

Patients were interviewed with a French version of the Diagnostic Interview for Genetic Studies (DIGS)[38] for the assessment of lifetime clinical characteristics of bipolar disorder as well as for demographic characteristics (ie, number of years of education, working status, season of birth, birth in or outside France). Current medications as well as hospitalization status were recorded. In enrollment, manic symptoms were assessed with the YMRS[35] and depressive symptoms with the MADRS[36] for bipolar disorder and the Calgary Depression Scale (CDS) for schizophrenia.[39] Participants with schizophrenia and bipolar disorder were evaluated using the PANSS[40] in enrollment. Current smoking status using the Fagerström scale[41] and recent or past alcohol or drug abuse were recorded for all the participants.

Cognitive Evaluation

All participants were evaluated for episodic verbal memory using the California Verbal Learning Test (CVLT),[42] which measures the rate of learning, learning strategy, short-term and long-term retention and retrieval, recall errors, interference effects, and ability to profit from learning cues. The working memory (backward digit span and letter number sequencing) was evaluated using the Wechsler Adult Intelligence Scale, third edition (WAIS-III), a test designed to measure intelligence using 4 indices (verbal comprehension, working memory, perceptual organization, and processing speed).[43,44] Premorbid IQ was assessed with the National Adult Reading Test (NART),[45] which estimates premorbid ability level from a word reading test that provides an estimate of vocabulary size.

The cognitive evaluation was conducted in ambulatory care for the outpatients and at the end of the hospitalization for the inpatients.

Serologic Analyses

Sera collected on enrollment were used to evaluate the evidence of exposure to HSV-1, HSV-2, and CMV by the measurement of serum immunoglobulin G (IgG) antibodies by solid immunoassay as previously described.[8] Also, we used solid phase enzyme immunoassay on these samples to measure the IgG, IgM, and IgA antibody levels against *T gondii* following previously described methods.[8] Both the qualitative (positive/negative) results and the quantitative values were reported separately for each infectious agent.

These serologic analyses were performed at the Stanley Laboratory of Developmental Neurovirology, Johns Hopkins School of Medicine, Baltimore, Maryland.

Statistical Analyses

Analyses were performed in a sample of 423 participants. The Gaussian distribution of the quantitative variables was tested using the Shapiro-Wilk statistics. Standard descriptive tests (χ^2 for categorical variables, Wilcoxon test for the association with non-normal continuous variables, and *t* test for the association with normal continuous variables) were employed to compare the patient and control groups.

Relationship between each of the infectious agents (HSV-1, HSV-2, CMV, and *T gondii*) and cognitive function (WAIS-III, CVLT, and NART scores) was analyzed using the Kruskal-Wallis test or analysis of variance. Analyses were also performed on the whole sample set as well as for each subgroup (healthy controls, bipolar disorder, and schizophrenia). The α value was set at .0018 after correction for multiple testing using the Bonferroni procedure.[46]

A multivariate regression analysis adjusted for potential confounders (age, ethnicity [Caucasian vs non-Caucasian], gender, diagnosis [schizophrenia vs bipolar disorder vs control], and education level) was performed for only HSV-1 and working memory as they exhibited significant association.

Finally, to test if there was any cumulative effect of seropositivity on cognitive functioning, we introduced an infectious agent score (0, 1, 2, 3, or 4 infectious agents) and used the Kruskal-Wallis test or analysis of variance to compare the cognitive function among this score. The pairwise comparisons between groups were performed using the kwallis2 software package. We also performed stratified subgroup (healthy controls, bipolar disorder, and schizophrenia) analysis.

The α value was set at .02 after correction for multiple testing using the false discovery rate procedure that controls the expected proportion of incorrect null hypotheses.[47] These analyses were conducted using STATA 13 (Stata Statistical Software: Release 13).[48]

The aim of the current study is to explore the role of cumulative exposure of viruses (HSV) and parasite (*T gondii*) on cognition among patients with bipolar disorder and schizophrenia and among healthy subjects.

RESULTS

Demographic and Clinical Variables

The sample consisted of 423 participants: 138 with bipolar disorder, 105 with schizophrenia, and 180 healthy controls. Among them, 44% were men (47.1% for bipolar disorder, 30.5% for schizophrenia, and 54.4% for healthy controls) with a mean (SD) age at interview of 44.35 (13.3) years for bipolar disorder, 36.73 (11.6) for schizophrenia, and 40.10 (13.8) for healthy controls as shown in Table 1. Patients with bipolar disorder were significantly older than patients with schizophrenia and healthy controls ($z = 4.48$, $P < .0001$ and $z = 2.71$, $P = .007$, respectively). For patients with bipolar disorder, the mean scores of depression (measured with the MADRS) and of mania (measured with YMRS) were 7.1 (8.9) and 3.7 (5.1), respectively. In the sample of patients with schizophrenia, mean scores of depression (measured with the CDS) and of psychiatric symptoms (measured with the PANSS) were 2.41 (3.9) and 70.4 (22.2), respectively. A majority of those were chronic patients with a mean duration of illness of 17.96 (13.1) years for patients with bipolar disorder and 13.47 (11.5) years for patients with schizophrenia, and all of them were taking medications. Patients with bipolar disorder received either lithium (34%) or anticonvulsants (34%) or atypical antipsychotics (3%) alone or a combination of 2 mood stabilizers (6%) or a combination of a mood stabilizer with an atypical antipsychotic (23%). Patients with schizophrenia received either an atypical antipsychotic (66%) or a typical antipsychotic (11%) or a combination of a mood stabilizer with an atypical antipsychotic (17%) or 2 antipsychotics (6%) (Table 1).

Viral and Parasitic Exposure: Prevalence

A total of 87 patients with bipolar disorder (63.0%), 64 patients with schizophrenia (61.0%), and 130 healthy controls (72.0%) were IgG seropositive to HSV-1, while 33 patients with bipolar disorder (23.9%), 16 patients with schizophrenia (15.2%), and 51 healthy controls (28.3%) were IgG seropositive for HSV-2. A total of 79 patients with bipolar disorder (57.2%), 62 patients with schizophrenia (59.0%), and 119 healthy controls (66.1%) were IgG seropositive to CMV, whereas 103 patients with bipolar disorder (74.6%), 67 patients with schizophrenia (63.8%), and 105 healthy

Table 1. Sociodemographic, Clinical, Serologic, and Cognitive Variables Between Patients With Bipolar Disorder, Patients With Schizophrenia, and Healthy Controls

Variable	No. Of Participants	BD	BD vs HC[a] Statistical Test	BD vs HC[a] P	Schizophrenia	Schizophrenia vs HC[a] Statistical Test	Schizophrenia vs HC[a] P	HC	BD vs Schizophrenia[a] Statistical Test	BD vs Schizophrenia[a] P
No. of participants (BD/SZ/HC): 423	138/105/180									
Sociodemographic and clinical variables										
Age, mean (SD), y	138/105/179	44.35 (13.3)	**z = 2.71**	**.007**	36.73 (11.6)	z = 1.84	.064	40.10 (13.8)	**z = 4.49**	**<.0001**
Gender, male, n (%)	138/105/180	65 (47.1)	χ^2 = 1.70	.194	32 (30.5)	χ^2 = 15.30	**<.001**	98 (54.4)	χ^2 = **6.87**	**.009**
Caucasian, yes (%)	116/82/163	104 (89.7)	χ^2 = **20.33**	**<.001**	62 (75.6)	χ^2 = 2.24	.134	108 (66.3)	χ^2 = **6.99**	**.008**
Educational level, high school, n (%)	134/88/180	80 (59.7)	χ^2 = **9.38**	**.002**	23 (26.1)	χ^2 = 6.56	.01	76 (42.2)	χ^2 = **24.10**	**<.001**
Married, yes, n (%)	134/88/180	62 (46.3)	χ^2 = 2.93	.087	9 (10.2)	χ^2 = **20.50**	**<.001**	66 (36.7)	χ^2 = **31.71**	**<.001**
Birth place, urban, n (%)	133/88/179	120 (90.2)	χ^2 = 0.06	.809	83 (94.3)	χ^2 = 1.75	.185	160 (89.4)	χ^2 = 1.19	.276
Childhood upbringing, urban, yes, n (%)	133/88/179	120 (90.2)	χ^2 = 0.01	.935	80 (90.9)	χ^2 = 0.06	.803	161 (89.9)	χ^2 = 0.03	.865
Smoker, yes, n (%)	134/88/179	58 (43.3)	χ^2 = **46.01**	**<.0001**	48 (54.5)	χ^2 = **62.75**	**<.0001**	18 (10.1)	χ^2 = 2.70	.100
Alcohol abuse, yes, n (%)	123/75/161	16 (13.0)	χ^2 = **22.19**	**<.001**	9 (12.0)	χ^2 = **20.08**	**<.001**	0 (0)	χ^2 = 0.04	.836
Age at onset, mean (SD), y	136/104	26.79 (10.6)			23.48 (7.8)				z = 1.80	.072
Duration of the disease, mean (SD), y	138/105	17.96 (13.1)			13.47 (11.5)				**z = 2.83**	**.005**
MADRS, mean (SD)	138	7.1 (8.9)								
YMRS, mean (SD)	138	3.7 (5.1)								
CDS, mean (SD)	105				2.41 (3.9)					
PANSS positive, mean (SD)	127/87	8.3 (3.2)			15.6 (6.7)				**z = 9.90**	**<.0001**
PANSS negative, mean (SD)	127/87	9.2 (4.4)			20.2 (8.6)				**z = 9.90**	**<.0001**
PANSS general, mean (SD)	127/87	21.3 (9.0)			34.6 (11.9)				**z = 9.10**	**<.0001**
PANSS total score, mean (SD)	127/87	38.7 (14.2)			70.4 (22.2)				**z = 10.20**	**<.0001**
Serologic variables										
HSV-1, positive, n (%)	138/105/180	87 (63.0)	χ^2 = 3.03	.081	64 (61.0)	χ^2 = 3.87	.049	130 (72.2)	χ^2 = 0.11	.739
HSV-2, positive, n (%)	138/105/180	33 (23.9)	χ^2 = 0.79	.376	16 (15.2)	χ^2 = 6.32	.012	51 (28.3)	χ^2 = 2.78	.095
CMV, positive, n (%)	138/105/180	79 (57.2)	χ^2 = 2.61	.106	62 (59.0)	χ^2 = 1.43	.232	119 (66.1)	χ^2 = 0.08	.778
T gondii, IgG positive, n (%)	138/105/180	103 (74.6)	χ^2 = **9.17**	**.002**	67 (63.8)	χ^2 = 0.83	.362	105 (58.3)	χ^2 = 3.32	.068
Cognitive variables										
Verbal memory (CVLT), mean (SD)										
Short-term memory[b] (raw scores)	124/74/160	47.12 (11.2)	**z = 4.46**	**<.0001**	37.89 (11.3)	**z = 8.73**	**<.0001**	53.29 (8.6)	**z = 5.02**	**<.0001**
Long-term recognition (total correct)	124/74/160	13.91 (2.4)	**z = 3.66**	**.0002**	13.43 (2.4)	**z = 4.68**	**<.0001**	14.75 (1.6)	z = 1.61	.107
Short cued recall[c] (raw scores)	134/92/178	13.24 (10.8)	**z = 2.60**	.120	13.64 (11.1)	**z = 3.53**	**.0027**	15.29 (12.0)	z = 1.44	.149
Long cued recall[d] (raw scores)	134/91/178	10.44 (3.2)	**z = 3.35**	**.0004**	8.03 (3.6)	**z = 7.49**	**<.0001**	11.62 (2.6)	**z = 4.79**	**<.0001**
Premorbid IQ estimate (NART), mean (SD)	125/89/172	108.3 (8.3)	**z = 3.75**	**.001**	102.7 (8.6)	**z = 2.30**	**.02**	105.3 (7.3)	**z = 4.67**	**<.0001**
Working memory (WAIS-III), mean (SD)										
Backward digit span (standard scores)	123/75/159	8.43 (2.6)	z = 0.62	.272	7.18 (2.7)	**z = 4.64**	**.0001**	8.73 (2.0)	**z = 3.41**	**.0016**
Letter number sequencing (standard scores)	134/94/179	5.26 (1.8)	z = 2.09	.038	4.79 (1.5)	**z = 4.13**	**<.0001**	5.66 (1.6)	z = 2.00	.045

[a]Boldface indicates significant difference.
[b]Total correct for trials 1 to 5.
[c]Total correct from list A at short term.
[d]Total correct from list A at long term with cue.
Abbreviations: BD = bipolar disorder, CDS = Calgary Depression Scale, CMV = cytomegalovirus, CVLT = California Verbal Learning Test, HC = healthy controls, HSV-1 = herpes simplex virus type 1, HSV-2 = herpes simplex virus type 2, IgG = immunoglobulin G, MADRS = Montgomery-Asberg Depression Rating Scale, NART = National Adult Reading Test, PANSS = Positive and Negative Syndrome Scale, *T gondii* = *Toxoplasma gondii*, WAIS-III = Wechsler Adult Intelligence Scale, third edition, YMRS = Young Mania Rating Scale.

controls (58.3%) were IgG seropositive to *T gondii*. None of the participants was positive for IgM or IgA antibodies to *T gondii*. The majority of patients and controls were seropositive to more than 1 of the tested infectious agents (74% for bipolar disorder, 67% for schizophrenia, and 77% for healthy controls).

Comparison Between Groups on the Neuropsychological Measures

Pairwise comparisons indicated significant differences in neuropsychological functions between groups for most of the test scores. The results remained significant after adjusting for age, gender, level of education, ethnicity, and premorbid IQ.

As shown in Table 1, healthy controls had significantly higher scores than the patient groups (schizophrenia and bipolar disorder) on verbal memory as measured by the CVLT and working memory as measured by the WAIS-III compared to the schizophrenia group only. Significant differences between patients with schizophrenia and bipolar disorder were observed in short-term memory, long cued recall and working memory (backward digit span), and premorbid IQ. Patients with bipolar disorder had significantly higher scores on premorbid IQ (measured by the NART) than patients with schizophrenia and healthy controls (Table 1). The results remained significant after adjusting for age, gender, level of education, ethnicity, and premorbid IQ.

Association Between Seropositivity to Infectious Agents and Neuropsychological Measures

Individual infectious agents exposure. Bivariate analysis between infectious agents (HSV-1, HSV-2, CMV, and *T gondii*) and neuropsychological measures revealed a significant association between seropositivity to HSV-1 and working memory (backward digit span) in the overall sample (backward digit span, $\chi^2 = 33.89$, $P = .0001$, nonparametric analysis). This association was particularly strong in healthy controls ($Z = -3.55$, $P = .0008$). A significant association between the HSV-1 antibody levels and working memory (backward digit span) was found for only the overall sample and the control group ($\beta = -0.10$ [0.05], $P = .05$ and $\beta = -0.18$ [0.08], $P = .04$, respectively).

We did not observe any association between the seropositivity to HSV-1 and short-term memory, short and long cued recall, or letter number sequencing. Seropositivity to HSV-2, CMV, and *T gondii* (IgG, IgA, and IgM, analyzed separately) was not found to be associated with short-term memory, long-term recognition, short and long cued recall, backward digit span, or letter number sequencing either for the whole sample or for any of the subgroups (Table 2).

Multivariate Analysis

A multivariate regression analysis adjusted for the potential confounders of age, ethnicity (Caucasian vs non-Caucasian), gender, diagnosis (schizophrenia vs bipolar disorder vs controls), and education level was performed to evaluate the association between exposure to individual infectious agents and working memory (the only cognitive score significantly associated with infectious agents exposure in crude analysis). A significant association between seropositivity to HSV-1 working memory persisted after false discovery rate correction (backward digit span, $\chi^2 = 33.89$, $P = .0001$, nonparametric analysis) in the overall sample. This association was particularly strong in healthy controls (corrected $P = .012$) (data not shown). For the whole sample, we also found an association between the seropositivity to HSV-1 and premorbid IQ ($\beta = -2.5$, $P = .004$) as measured by the NART with only a trend for bipolar disorder ($\beta = -3.72$, $P = .03$).

Multiple Infectious Agents Exposure

To evaluate the impact of multiple exposure on cognitive performance, we fit a model that includes a combined viruses and/or parasitic exposure, with a score of 0 corresponding to no exposure, 1 to one infectious agent, 2 to two infectious agents, 3 to three infectious agents, and 4 to four infectious agents. We found that seropositivity either to 2 or 3 or 4 infectious exposure all versus to none were individually and significantly associated with lower scores on working memory as measured by backward digit span ($z = 2.86$, $P = .004$; $Z = 2.47$, $P = .01$; and $Z = 3.35$, $P = .01$, respectively) in the whole sample. However, the cumulative effect of infectious agents on working memory within the bipolar disorder and schizophrenia groups was not significant for any of the pairwise comparisons and was only significant in the control group (Table 3).

When the potential confounders (age, gender, ethnicity, educational level) are taken into account in the analysis, the positive association between working memory and multiple exposures failed to persist.

When excluding the patients seropositive to HSV-1 virus, the association between multiple exposure and working memory did not persist. However, a past exposure to at least 1 virus (HSV-1, HSV-2, CMV) or parasite (*T gondii*) is associated with worse score on working memory ($P = .0004$).

Finally, the combined seropositivity to infectious agents was not associated with premorbid IQ (NART), short-term memory, short and long cued recall, or letter number sequencing either in the whole sample or within any of the diagnostic subgroups.

DISCUSSION

In the present study, we found that infectious exposure to neurotropic HSV-1 virus is associated with relative deficits in working memory (as measured by backward digit span) in a sample of patients with schizophrenia or bipolar disorder. Interestingly, such association was particularly strong in otherwise healthy individuals. In addition, we found that the cumulative exposure to HSV-1 and HSV-2, CMV viruses, and *T gondii* parasite was significantly associated with low scores on working memory in the overall sample.

Table 2. Bivariate Analysis Between Seropositivity to Each Infectious Agent (HSV-1, HSV-2, CMV, and *T gondii*) and Neuropsychological Measures in the Whole Sample and in Each Subgroup (Bipolar Disorder, Schizophrenia, and Healthy Controls)[a]

	HSV-1			HSV-2			CMV			*T gondii*		
Cognitive Variable, Mean (SD)	No	Yes	*P*	No	Yes	*P*	No	Yes	*P*	No	Yes	*P*
Whole sample												
Short-term memory	48.9 (11.7)	47.5 (11.6)	.1609	47.3 (11.8)	50.1 (11.1)	.0617	48.8 (10.8)	47.5 (12.2)	.4186	49.4 (12.1)	47.2 (11.4)	.0702
Long-term recognition	14.1 (2.7)	14.3 (1.8)	.0585	14.2 (2.0)	14.2 (2.5)	.4513	14.3 (2.1)	14.1 (2.2)	.2075	14.5 (1.8)	14.0 (2.3)	.0759
Short cued recall	14.6 (11.1)	14.1 (11.7)	.2816	10.3 (3.4)	10.8 (3.2)	.2285	10.7 (3.4)	10.2 (3.3)	.1319	10.5 (3.6)	10.3 (3.2)	.3818
Long cued recall	10.6 (3.5)	10.3 (3.3)	.1050	14.1 (11.5)	14.8 (11.4)	.2133	14.6 (11.8)	14.0 (11.3)	.0800	15.8 (13.3)	13.4 (10.2)	.0500
Premorbid IQ estimate (NART)	107.1 (7.9)	104.9 (8.2)	.0122	105.3 (7.8)	107.0 (9.3)	.0218	107.0 (7.1)	104.8 (8.7)	.0199	103.9 (7.7)	106.6 (8.3)	.0018
Backward digit span	**5.7 (1.7)**	**5.1 (1.7)**	**.0002**	5.3 (1.7)	5.5 (1.8)	.1681	5.6 (1.7)	5.2 (1.7)	.0382	5.6 (1.8)	5.2 (1.6)	.0497
Letter number sequencing	8.4 (2.4)	8.3 (2.5)	.5083	8.2 (2.4)	8.7 (2.6)	.0410	8.5 (2.3)	8.2 (2.5)	.2042	8.1 (2.6)	8.4 (2.4)	.1309
Bipolar disorder patients												
Short-term memory	48.5 (11.8)	46.3 (10.8)	.2549	46.9 (11.0)	47.9 (11.9)	.5697	47.7 (10.7)	46.7 (11.6)	.6591	48.0 (10.1)	46.8 (11.6)	.7393
Long-term recognition	13.9 (2.6)	13.9 (2.3)	.8539	13.9 (2.3)	13.8 (2.9)	.8973	13.8 (2.7)	14.0 (2.2)	.8132	14.4 (1.6)	13.8 (2.6)	.3028
Short cued recall	13.1 (9.5)	13.3 (11.6)	.4981	13.1 (10.7)	13.5 (11.5)	.8446	13.1 (10.3)	13.4 (10.8)	.5887	15.2 (14.1)	12.6 (9.6)	.3551
Long cued recall	10.9 (3.1)	10.2 (3.3)	.2703	10.5 (3.1)	10.2 (3.6)	.8260	10.5 (3.3)	10.4 (3.1)	.8461	11.2 (3.3)	10.2 (3.2)	.1347
Premorbid IQ estimate (NART)	110.4 (6.5)	107.0 (9.0)	.0485	107.6 (7.8)	110.3 (9.4)	.0252	108.0 (6.6)	108.5 (9.4)	.2495	106.9 (5.5)	108.7 (8.9)	.0619
Backward digit span	5.7 (1.7)	5.0 (1.9)	.0208	5.2 (1.7)	5.6 (2.2)	.4496	5.3 (1.8)	5.3 (1.9)	.9745	5.7 (2.1)	5.1 (1.7)	.1900
Letter number sequencing	8.6 (2.6)	8.3 (2.7)	.7585	8.3 (2.6)	8.8 (2.9)	.2784	8.3 (2.3)	8.5 (2.9)	.7531	8.2 (3.0)	8.5 (2.6)	.4518
Schizophrenia patients												
Short-term memory	40.3 (11.4)	36.4 (11.1)	.1031	37.9 (11.3)	37.8 (11.5)	.9016	41.7 (10.8)	35.2 (10.9)	.0179	36.6 (11.6)	38.6 (11.2)	.4141
Long-term recognition	13.2 (3.1)	13.6 (1.9)	.9109	13.4 (2.5)	13.8 (1.6)	.9334	14.1 (1.8)	13.0 (2.7)	.0607	13.4 (2.6)	13.5 (2.3)	.8908
Short cued recall	14.9 (12.0)	12.8 (10.5)	.1693	13.5 (11.2)	14.8 (11.3)	.6009	14.5 (11.3)	13.0 (11.1)	.1573	14.7 (12.5)	13.0 (10.2)	.8375
Long cued recall	8.2 (3.9)	7.9 (3.3)	.7602	8.0 (7.2)	8.3 (5.8)	.9320	8.8 (3.7)	7.5 (3.3)	.0653	7.3 (3.6)	8.5 (3.5)	.1239
Premorbid IQ estimate (NART)	104.2 (8.5)	101.7 (8.6)	.1795	102.6 (8.4)	103.8 (10.6)	.8002	105.3 (8.0)	100.9 (8.7)	.0142	100.0 (9.1)	104.4 (7.9)	.0242
Backward digit span	5.0 (1.7)	4.6 (5.0)	.1807	4.8 (1.5)	5.0 (1.7)	.6947	5.2 (4.6)	4.5 (4.1)	.0312	4.8 (1.8)	4.8 (1.4)	.5874
Letter number sequencing	7.5 (2.6)	7.0 (2.7)	.2558	7.1 (2.6)	7.7 (2.8)	.6331	7.7 (2.4)	6.8 (2.8)	.0644	8.2 (3.0)	8.5 (2.6)	.2581
Healthy controls												
Short-term memory	54.9 (7.7)	52.7 (8.9)	.0819	53.0 (8.8)	54.1 (7.9)	.6050	53.9 (8.0)	53.0 (8.9)	.6447	55.2 (8.6)	52.0 (8.4)	.0131
Long-term recognition	14.8 (2.4)	14.7 (1.2)	.1225	14.8 (1.2)	14.6 (2.4)	.8418	15.0 (1.1)	14.6 (1.8)	.1785	15.0 (1.2)	14.6 (1.8)	.1657
Short cued recall	15.8 (11.9)	15.1 (12.1)	.1470	15.1 (12.3)	15.7 (11.5)	.6021	16.0 (13.1)	14.9 (11.5)	.0820	16.7 (13.4)	14.3 (10.9)	.0804
Long cued recall	12.1 (2.4)	11.5 (2.6)	.1511	11.6 (2.7)	11.7 (2.3)	.9119	12.0 (2.6)	11.4 (2.6)	.0806	11.8 (2.8)	11.5 (2.4)	.3196
Premorbid IQ estimate (NART)	106.1 (7.6)	105.0 (7.1)	.3687	105.2 (6.8)	105.5 (8.5)	.4047	107.2 (6.9)	104.3 (7.3)	.0202	104.7 (7.1)	105.7 (7.4)	.3315
Backward digit span	**6.3 (1.6)**	**5.4 (1.6)**	**.0008**	5.7 (1.7)	5.7 (1.5)	.8047	6.1 (1.8)	5.5 (1.6)	.0210	5.9 (1.7)	5.5 (1.6)	.0718
Letter number sequencing	8.8 (2.0)	8.7 (2.0)	.5152	8.6 (1.9)	9.0 (1.9)	.2482	9.1 (2.2)	8.5 (1.9)	.1218	8.5 (2.2)	8.9 (1.9)	.3110

[a]Boldface indicates significant difference.
Abbreviations: CMV = cytomegalovirus, HSV-1 = herpes simplex virus type 1, HSV-2 = herpes simplex virus type 2, IQ = intelligence quotient, NART = National Adult Reading Test, *T gondii* = *Toxoplasma gondii*.

Table 3. Multivariate Analysis of Working Memory Considering Individual and Multiple Exposure to Infectious Agents (HSV-1, HSV-2, CMV, and *T gondii*)[a]

	Individual Infectious Agents Exposure		Healthy Controls Individual Infectious Agents Exposure		Bipolar Disorder Individual Infectious Agents Exposure		Schizophrenia Individual Infectious Agents Exposure	
	β Coefficient	*P*	β Coefficient	*P*	β Coefficient	*P*	β Coefficient	*P*
Overall mean (SE)	5.68 (0.37)		7.0 (0.50)		5.2 (0.90)		4.9 (1.00)	
Covariates								
Infectious agents exposure								
HSV-1	−0.43 (0.19)	**.02**	−0.74 (0.27)	**.006**	−0.38 (0.36)	.29	−0.19 (0.40)	.65
HSV-2	0.40 (0.21)	.06	0.26 (0.26)	.32	0.44 (0.38)	.25	**0.03 (0.69)**	.97
CMV	−0.09 (0.18)	.64	−0.28 (0.25)	.27	0.31 (0.34)	.37	−0.26 (0.46)	.97
T gondii	−0.36 (0.21)	.1	−0.04 (0.28)	.89	−0.82 (0.43)	.06	−0.26 (0.46)	.58
Diagnostic group								
Healthy controls (vs schizophrenia and bipolar disorder)	0.63 (0.18)	**.0005**						
Age	−0.02 (0.008)	**.01**	−0.03 (0.01)	**.005**	−0.20 (0.01)	.16	**−0.01 (0.02)**	.65
Gender (male)	0.09 (0.18)	.6	0.31 (0.24)	.2	0.003 (0.34)	.99	0.41 (0.50)	.41
Ethnicity (white)	0.63 (0.22)	**.005**	0.57 (0.27)	**.04**	1.02 (0.57)	.08	0.35 (0.53)	.51
Educational level (high school)	0.53 (0.18)	**.003**	0.12 (0.24)	.62	1.08 (0.34)	**.002**	**−0.06 (0.45)**	.9

[a]Values are mean (SE). Boldface indicates significant difference.
Abbreviations: CMV = cytomegalovirus, HSV-1 = herpes simplex virus type 1, HSV-2 = herpes simplex virus type 2, *T gondii* = *Toxoplasma gondii*, SE = standard error.

The association between HSV-1 seropositivity and memory deficits has been consistently found in previous studies.[8,20,29–31] The first study linking exposure to HSV-1 and cognitive functioning found that the domain most affected by exposure to this virus was immediate memory in schizophrenia[8] and delayed memory in controls.[29] A second study found a link between exposure to HSV-1 and working memory as measured by the Trail Making Test.[20] Including more than 1,300 patients with schizophrenia from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial, a third study found an association between HSV-1 exposure and the Verbal Memory composite score of neurocognition.[30] In another study,[31] an additive effect of inflammation (assessed by circulating CRP level) and history of HSV-1 infection on immediate memory was found. The evidence of an association between HSV-1 exposure and cognitive deficits in bipolar disorder, notably for immediate verbal memory, has also been described.[9,27]

Herpes viruses that include the herein studied HSV-1 and HSV-2 belong to the *Herpesviridae* family with characteristic features of viral DNA integration in the host cell genome and establishment of latency in the sensory nerve ganglia, the cortical regions, and the limbic system with periodic lytic cycles.[49] Such repeated latency/reactivated cycles over time can lead to a decrease in cortical gray matter with consequent cognitive impairment and may participate in the pathological processes of severe psychiatric disorders such as schizophrenia and bipolar disorder.[33,50]

In the present study, the HSV-1/working memory association is particularly strong among the control group, which is in line with previous studies.[28,32,51] At present, it is unclear why such association is more pronounced among controls than in patients with schizophrenia or bipolar disorder. One explanation could reside with the use of atypical antipsychotics in the patients' group as a previous study reported that atypical antipsychotics can potentially inhibit microglial activation and HSV-1–induced behavioral changes in vitro by binding to a variety of microglial surface receptors and/or by inhibiting proinflammatory cytokines involved in the activation of microglia.[52] Indeed in our sample, two-thirds of patients with schizophrenia and a quarter of patients with bipolar disorder were under atypical antipsychotic medications (alone or in association with a mood stabilizer). However, it is not certain that the in vitro action of atypical antipsychotics on HSV-1 replication is relevant in vivo. It is well known that genital herpes and recurrent labial herpes seem to remit in patients taking lithium.[53,54] Furthermore, it has been demonstrated that lithium is associated with a significant reduction of cytokines as observed in healthy volunteers[55] and bipolar or unipolar patients during lithium treatment.[56] About one-third of patients with bipolar disorder in our study were treated with lithium. Therefore, the immunomodulatory and/or antiviral properties of both lithium and antipsychotics can explain our negative association among seropositive patients to HSV-1, considering the deficit on working memory. It would have been interesting to exclude, in a second analysis, the patients treated by lithium and atypical antipsychotics and measure the impact of HSV viruses on cognition. However, the weak remaining sample after excluding these patients could not allow us to make robust statistical analyses.

We also found a trend toward association between seropositivity to HSV-1 and premorbid IQ in the bipolar disorder subgroup but not in patients with schizophrenia or healthy controls. To our knowledge, this is the first study linking premorbid IQ to HSV-1 in psychiatric disorders except for a previous report on dementia.[57] Latent HSV-1 infection can generate viral particles in reactivation phase and colonize the cortical brain regions, the favored sites of replication. This may explain the low premorbid IQ score observed among subjects exposed to this infectious agent.[58] However, premorbid IQ can vary across different definitions of the disease as demonstrated in schizophrenia.[59]

Finally, we tested the cumulative effects of seropositivity to infectious agents on cognitive functioning and found that seropositivity to 2, 3, or 4 (vs 0) infectious exposures was associated with deficits in working memory in the whole sample (which did not persist when considering potential confounders), and the effect was evident only in the healthy control group, in line with 2 previous studies.[24,34] Indeed, in a study of elderly patients with cardiovascular diseases, exposure to herpes viruses (HSV-1 and HSV-2 and CMV) was reported to be associated with cognitive impairment with a graded effect.[24] Studying psychiatric patients (schizophrenia and schizoaffective subjects), their relatives, and controls, the effect of multiple viral exposures (HSV-1 and HSV-2 and CMV) was found to diminish cognitive performance with no effect of diagnosis.[34]

In the present study, we found that in addition to those *Herpesviridae* viruses, *T gondii* parasite does also play a major role in cognition. According to the literature, *T gondii* has been associated with a greater impairment in immediate and delayed memory in youth and elderly subjects.[17,18] Therefore, it seems to be useful to take into account *T gondii* seroinfection when measuring cognitive performances. However, the direct role of *T gondii* on cognitive decline was not found in our study. *T gondii* seems, here, to impact working memory in addition with HSV and CMV viruses.

It is possible that both *Herpesviridae* and *T gondii* infections can lead to inflammation-mediated structural and functional alterations in the brain and secondarily to cognitive dysfunction. Several lines of observations may support this assumption: (1) malaria-induced neuroinflammation in animal models influences neurotrophin expression, impairs adult hippocampal neurogenesis, and increases hippocampal cell death in association with memory impairment[60]; (2) anti-inflammatory drugs improve cognitive performance in Alzheimer disease[61] and in memory loss of aging[62] as well as in schizophrenia[63]; and (3) antiviral agents, namely, valacyclovir, seem to improve cognitive impairment in infected subjects in terms of improved verbal memory, working memory, and visual object learning in schizophrenia.[64]

However, when excluding HSV-1 positive patients, the association between multiple exposures and working memory disappears. This may mean that the bulk of multiple exposure cases have HSV-1 positivity and the reasons could be either that HSV-1 infection facilitates subsequent other infections (thus may become a bonafide marker for others) or that HSV-1 is the most common in that geographical area and hence frequently will co-occur with other infrequent infections.

The limitations of the present study include small sample size limited to schizophrenia and bipolar disorder, cross-sectional design, and lack of elaborate assessment of executive functions. In addition, owing to the absence of information on the timing of primary infection and subsequent duration in patients (important parameters in neurodevelopmental disorders), we were unable to determine their sequential impact on cognition.

However, we did not assess precisely the possible impact of such infectious agents using a polymerase chain reaction amplification approach for detection of HSV and *T gondii* DNA.

The strength of our study is the simultaneous exploration of schizophrenia, bipolar disorder, and stringently explored healthy controls and also the use of an extensive neurocognitive battery.

Exposures to *Herpesviridae* viruses and *T gondii* parasite seem to play a role in cognition. Seroinfection to *Herpesviridae* viruses and/or *T gondii* parasite are common in the French population (67% for HSV-1, 17.2% for HSV-2, 43.7% in women for CMV, and 48% for *T gondii*[65–67]). Thus, it is tempting to question if a significant proportion of such cognitive impairment is attributable to neurotropic viral exposure. Additional studies are needed to answer this question and, in particular, the relationship between cumulative exposures and working memory.

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