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Cytomegalovirus seropositivity and serointensity are associated with hippocampal volume and verbal memory in schizophrenia and bipolar disorder

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ABSTRACT

Introduction: Cytomegalovirus (CMV) is a member of the herpesviridae family that has a limbic and temporal gray matter tropism. It is usually latent in humans but has been associated with schizophrenia, bipolar disorder and cognitive deficits in some populations. Hippocampal decreased volume and dysfunction play a critical role in these cognitive deficits. We hypothesized that CMV seropositivity and serointensity would be associated with hippocampal volume and cognitive functioning in patients with schizophrenia or bipolar disorder.
Methods: 102 healthy controls, 118 patients with bipolar disorder and 69 patients with schizophrenia performed the California Verbal Learning Test (CVLT) and had blood samples drawn to assess CMV IgG levels. A subgroup of 52 healthy controls, 31 patients with bipolar disorder and 27 patients with schizophrenia underwent T1 MRI for hippocampal volumetry. We analyzed the association between CMV serointensity and seropositivity with hippocampal volume. We also explored the correlation between CMV serointensity and seropositivity and CVLT scores.
Results: In both patient groups but not in controls, higher CMV serointensity was significantly associated with smaller right hippocampal volume. Further, in the group of patients with schizophrenia but not bipolar disorder, CMV serointensity was negatively correlated with CVLT scores.
Conclusion: CMV IgG titers are associated with decreased hippocampal volume and poorer episodic verbal memory in patients with schizophrenia or bipolar disorder. The mechanism of this association warrants further exploration.

1. Introduction

Human cytomegalovirus (CMV) is a member of the herpesviridae family. Herpesviruses are large enveloped DNA viruses. CMV is being transmitted by intimate contact with infected excretions such as saliva, urine, cervical and vaginal excretions, semen, breast milk, or blood. Risk factors for CMV exposure are breast-feeding, crowding, increased contact with infants and toddlers, poor hygiene, multiple sex partners and promiscuity (Gaytant et al., 2002). The prevalence of CMV infection in adults is at least 60% in developed countries and 80% in developing countries (Gaytant et al., 2002; Staras et al., 2006). CMV is neurotropic and asymptomatic in humans, except in certain conditions (congenital infection, immunodepression) (Bristow et al., 2011). In immunocompetent subjects, CMV infection is considered to be latent, asymptomatic and non-pathogenic. Some authors have nevertheless suggested a neuronal, or at least gray-matter, tropism of CMV during this latent phase (Perron et al., 2009; Shinmura et al., 1997; Tsutsui, 2009; Tsutsui et al., 2005). CMV has an affinity for the limbic structures

Abbreviations: CMV, cytomegalovirus; BD, bipolar disorder; HC, healthy controls; CVLT, California Verbal Learning Test; CVLT-RC-A, CVLT Recall score for list A; PANSS, Positive and Negative Syndrome Scale; YMRS, Young Mania Rating Scale; MADRS, Montgomery–Asberg Depression Scale.

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(Yolken and Torrey, 2008) and for the temporal lobe (Hoffmann et al., 2010) as described for other herpesviruses. Animal models suggest that CMV may persistently infect neuronal cells, with a specific tropism for the hippocampus (Arai et al., 2003; Shinmura et al., 1997).

Several but not all studies have reported an association between CMV antibody status and schizophrenia and bipolar disorder (BD). Elevated levels of CMV antibodies in cerebrospinal fluid of patients with schizophrenia and BD have been observed (Albrecht et al., 1980; Rimon et al., 1986; Torrey et al., 1982). More specifically, CMV may be associated with cognitive deficits in schizophrenia, while such an association is not present in healthy young adults. Shirts et al. reported an association between CMV and Trail Making Test performance in patients with schizophrenia (Shirts et al., 2008). Dickerson et al. reported an association between CMV seropositivity and deficit schizophrenia (F. Dickerson et al., 2006). Deficit schizophrenia is a putative schizophrenia subtype characterized by primary and enduring negative symptoms. Patients suffering from deficit schizophrenia have poor cognitive performance (Cascella et al., 2008) and hippocampal dysfunction (Mucci et al., 2007). Interestingly, in healthy elderly subjects, CMV titers were associated with cognitive decline (episodic memory) in a prospective study (Aiello et al., 2006).

Most studies have focused solely on CMV seropositivity as a measure of previous exposure (F. Dickerson et al., 2006; Shirts et al., 2008; Watson et al., 2012). But one research group has demonstrated a dose–response relationship between CMV serointensity (titer) and cognition (Aiello et al., 2006). It has been suggested that this association between CMV latent infection and decreased cognitive performance may be mediated by chronic inflammatory response and subsequent decreased hippocampal volume (Almanzar et al., 2005).

Decreased hippocampal volume is consistently described in schizophrenia (Adriano et al., 2012). In BD, hippocampal volume is usually reported normal, but decreased only in the most severe forms of BD (Strasser et al., 2005). Postmortem, spectroscopy and neuropsychological studies also add evidence for alterations in hippocampal structure and function in BD (Frey et al., 2007). Declarative memory impairment is also common in euthymic BD (Bora et al., 2009).

Considering the association of CMV with cognitive deficits in schizophrenia and BD, its gray matter, limbic and temporal affinity, and the known hippocampal dysfunctions in BD and schizophrenia, we hypothesized that CMV seropositivity and/or antibody levels would be associated with altered hippocampal volume and function, as measured by a verbal memory test in patients. The CVLT (California Verbal Learning Test) is a widely used test of episodic verbal memory in psychiatric populations and is strongly but not exclusively, related to hippocampal functioning (Alexander et al., 2003; Chepenik et al., 2012; van Erp et al., 2008). We included two groups of patients, schizophrenia and BD, as elevated rates of CMV antibodies do not seem specific to schizophrenia but are also present in patients with BD (Tedla et al., 2011; Torrey et al., 1982).

2. Methods

2.1. Participants

We included 102 healthy controls (HC), 69 patients with schizophrenia and 118 patients with BD who underwent the clinical, cognitive and serological assessment ("CVLT sample") (California Verbal Learning Test) (Table 1). Among them, 52 HC, 27 patients with schizophrenia and 31 patients with BD additionally underwent an MRI scanning ("MRI sample") (Table 2). Patients were recruited from two psychiatry departments of university-affiliated hospitals (Créteil and Paris, France). HC were recruited through advertisements. They differed from the "MRI sample" in the sex ratio and from the "CVLT sample" in age, sex ratio and level of education (Tables 1 and 2).

Inclusion criteria for study participation were ages between 18 and 65, no history of alcohol or drug abuse/dependence, no history of mental retardation, no previous head trauma with loss of consciousness, and no current or past cardiac or neurological disease. We excluded subjects with any significant cerebral anatomic anomaly.

In addition, HC were free of any personal past or present personal psychiatric disorder and first-degree family history of schizophrenia, schizoaffective disorder or BD. Participants were not included for MRI if MRI was contraindicated or if pregnant. The study was approved by the local IRB (Henri Mondor Hospital, Créteil, France). After complete description of the study to the subjects, written informed consent was obtained.

Table 1
Sociodemographic and clinical characteristics of the "CVLT sample".

Mean (SD)	Healthy controls	Patients with BD	Patients with schizophrenia	p-Value
N	102	118	69	
Age	37.8 (13.9)	45.3 (12.6)	39.4 (13.1)	$p < 0.05$
N males	65	59	50	$p < 0.05$
Years of education	12.4 (2.6)	13.0 (2.6)	10.9 (2.5)	$p < 0.05$
CMV IgG (optical density ratio)	2.98 (2.0)	2.63 (2.0)	2.24 (1.7)	$p < 0.05$
Age at onset		26.3 (10.2)	23.9 (6.8)	NS
PANSS			68.0 (27.3)	
MADRS		7.0 (9.3)		
YMRS		3.8 (5.4)		
CVLT Recall for List A	54.0 (8.3)	47.4 (11.4)	38.1 (11.5)	$p < 0.05$
CVLT Recognition Score	14.8 (1.8)	13.9 (2.4)	13.4 (2.4)	$p < 0.05$

2.2. Clinical and cognitive assessment

DSM-IV personal and familial diagnoses were assessed using the diagnostic interview for genetic study (DIGS) and the family interview for genetic study (FIGS) (Elizabeth, 1992; Nurnberger et al., 1994). All patients had a state evaluation of their symptoms with PANSS, YMRS and MADRS (Kay et al., 1987; Montgomery and Asberg, 1979; Young et al., 1978). The verbal memory evaluation consisted of a California Verbal Learning Test (Delis et al., 1988). We calculated the CVLT Recall for list A (number of total correct answers in list A; CVLT-RC-A) and CVLT-Recognition scores (recognition hits). We chose 1/a total learning score as both short and long delayed recall tests but also total learning scores have been proven associated with hippocampus (Tischler et al., 2006; van Norden et al., 2012; Ystad et al., 2010) 2/CVLT-Recognition score as neuroimaging evidence indicates that hippocampus is crucial for achieving recognition memory tasks (Heun et al., 2006; Reed and Squire, 1997; Wais et al., 2006).

2.3. MRI procedure

All images were acquired on the same Siemens 3T Tim Trio MRI system, equipped with a standard 12-channel head coil at NeuroSpin (Saclay, France). T1 data were obtained using a 3DT1-weighted

Table 2
Sociodemographic and clinical characteristics of the "MRI sample".

Mean (SD)	Healthy controls	Patients with BD	Patients with schizophrenia	p-Value
N	52	31	27	
Age	36.6 (11.8)	38.2 (12.5)	31.4 (9.9)	NS
N males	21	21	7	$p < 0.05$
N left handed	2	2	2	NS
Years of education	12.3 (2.9)	13.1 (2.4)	11.8 (2.9)	NS
CMV IgG (optical density ratio)	2.7 (2.0)	2.5 (1.9)	2.7 (1.7)	NS
Right hippocampal volume (mm3)	3880 (475)	4026 (370)	3786 (506)	NS
Left hippocampal volume (mm3)	3913 (397)	3907 (403)	3746 (509)	NS
Age at onset		23.0 (8.4)	22.7 (4.6)	NS
PANSS			71.6 (20.6)	
MADRS		6.2 (7.0)		
YMRS		3.9 (5.9)		