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Cytomegalovirus infection and IQ in patients with severe mental illness and healthy individuals

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ABSTRACT

Cytomegalovirus (CMV) infection in immunocompetent adults is usually asymptomatic, but results in lifelong latency. Infection occurring congenitally or in immunodeficiency can lead to cognitive impairment. We aimed to investigate the associations between CMV exposure and intelligence quotient (IQ) in patients with schizophrenia spectrum disorders (SZS), bipolar spectrum disorders (BDS) and healthy controls (HC). CMV immunoglobulin G antibody concentrations were measured by immunoassay and expressed as dichotomous measures (seropositive/CMV+ vs. seronegative/CMV-). Based on a significant CMV-by-diagnosis-by-sex interaction on IQ, we investigated main and interaction effects of CMV and sex on IQ in each diagnostic category. Significant CMV-by-sex interactions were found in patient groups. In SZS, CMV+ female patients (n = 50) had significantly lower IQ than CMV- female patients (n = 33), whereas CMV+ (n = 48) and CMV- (n = 45) male patients did not differ in IQ. In BDS, CMV+ (n = 49) and CMV- (n = 37) female patients did not differ in IQ, whereas CMV+ male patients (n = 33) had significantly higher IQ than CMV- male patients (n = 32). Among HC, CMV+ (n = 138) and CMV- (n = 118) male participants as well as CMV+ (n = 125) and CMV- (n = 93) female participants did not differ in IQ. Our findings suggest that CMV exposure may affect IQ in patients with severe mental illness but not HC.

1. Introduction

The herpes virus cytomegalovirus (CMV) has a seroprevalence of 40-100% in different populations, mainly depending on sex, age, ethnicity and socioeconomic status (Cannon et al., 2010; Dupont and Reeves, 2016). In contrast to the substantial morbidity and mortality in the context of congenital CMV infections and infections of immunocompromised individuals, postnatal infection of immunocompetent individuals is usually asymptomatic (Dupont and Reeves, 2016). Even when asymptomatic, CMV is never cleared and the initial infection

results in lifelong latency in human cells, first shown for the hematopoietic system (Dupont and Reeves, 2016; Wills et al., 2015). The latent CMV infection is considerably more active than previously thought (Dupont and Reeves, 2016), and a notable fraction of host immune system focuses its adaptive resources on CMV immunosurveillance (Derhovanessian et al., 2009). More recent research suggests similar latencies in the central nervous system where neural progenitor stem cells are the main CMV targets (Cheeran et al., 2009; Kawasaki et al., 2017; Teissier et al., 2014).

There is a well-established association between congenital CMV

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infection and mental retardation (Cheeran et al., 2009; Fowler et al., 1992; Kawasaki et al., 2017). It is also well-established that postnatal CMV infection is associated with central nervous system pathology when human immune system is deficient (Vancikova and Dvorak, 2001). For instance, CMV has been found to play a role in AIDS dementia (Fiala et al., 1993; Goplen et al., 2001). A series of recent studies has suggested immune system abnormalities in schizophrenia and bipolar disorder (Muller and Schwarz, 2010; Rosenblat and McIntyre, 2017; van Kesteren et al., 2017). Further, CMV brain invasion is enhanced when blood-brain barrier (BBB) is deficient, while an inflammatory environment facilitates CMV reactivation rates (Dupont and Reeves, 2016; Kawasaki et al., 2017). Importantly, both conditions have been suggested to occur in severe mental illness (SMI) (Goldsmith et al., 2016; Hope et al., 2009; Najjar et al., 2017; Patel and Frey, 2015). In this context, interleukin 6 (Il-6), a pro-inflammatory cytokine which profoundly facilitates CMV reactivations (Reeves and Compton, 2011), is increased in patients with schizophrenia (Potvin et al., 2008) as well as in children with an increased future risk for psychosis (Khandaker et al., 2014). These findings might suggest that patients with SMI may be particularly susceptible to CMV infection.

Cognitive deficits are core features in schizophrenia (Green et al., 2019), are suggested to reflect underlying neurodevelopmental disturbances (Melle, 2019), and are often present prior to the onset of psychotic symptoms (Ohi et al., 2017). Comparing estimated premorbid and current intelligence quotient (IQ) in schizophrenia patients, a substantial IQ decline is observed in some (deteriorated IQ) but not all patients (preserved IQ) (Ohi et al., 2017). In bipolar patients, there is a less severe cognitive dysfunction compared to schizophrenia patients (Green, 2006; Tsitsipa and Fountoulakis, 2015), and further, both higher and lower premorbid cognitive function have been associated with higher risk of developing bipolar disorder (Gale et al., 2013; MacCabe et al., 2010; Tiihonen et al., 2005). This observed heterogeneity (Vaskinn et al., 2020) in terms of IQ in both schizophrenia and bipolar disorder raises the possibility of genetic and/or environmental factor influence, including pathogens such as CMV, on IQ in SMI.

CMV infection has a profound impact on host immune system (Picarda and Benedict, 2018), and further, there is indication from both animal and human studies that the CMV impact may differ between males and females (Di Benedetto et al., 2015; Ghosh and Klein, 2017; Traub et al., 2012; van der Heiden et al., 2016; Villacres et al., 2004). In particular, studies on murine CMV, which is genetically similar to human CMV, have shown a sexual dimorphism favoring males (Ghosh and Klein, 2017). Of note, upon CMV infection, female mice had substantially increased mortality and diminished activation of innate immunity compared with male mice (Traub et al., 2012). Among middle-aged adults, a more profound CMV impact on T cell subsets was found in men (van der Heiden et al., 2016), and a more enhanced CMV effect on cytokine secretion in women (Villacres et al., 2004). Further, in a CMV study on elderly adults and young adults, although there were no significant sex-dependent CMV effects in young adults, the proportion of CD4+ naïve T cells was significantly lower in seronegative (CMV-) elderly women compared to CMV- young women, but not in seropositive (CMV+) elderly women compared to CMV+ young women, and in CMV+ elderly men compared to CMV+ young men, but not in CMV- elderly men compared to CMV- young men, indicating that the CMV effect after infection may differ between men and women (Di Benedetto et al., 2015). Finally, females appear to be more susceptible in the context of congenital CMV infection (Picone et al., 2005; Watt et al., 2016). These findings might suggest that a putative association between latent CMV infection and IQ may differ between men and women.

We studied the role of CMV exposure on general intelligence in patients with schizophrenia spectrum disorders (SZS), bipolar spectrum disorders (BDS) and healthy controls (HC). We hypothesized that putative associations between CMV exposure and IQ may be stronger in patients and may differ between men and women.

2. Methods

2.1. Participants

The study included 176 patients with SZS, 151 patients with BDS and 474 HC within the age range 18-64 years. In the category SZS, patients with schizophrenia (N = 90), schizophreniform disorder (N = 15), schizoaffective disorder (N = 22) and other psychosis (N = 49) were included. In the category BDS, patients with bipolar I disorder (N = 89), bipolar II disorder (N = 55) and bipolar disorder not otherwise specified (N = 7) were included. The patients were recruited from outpatient and inpatient psychiatric units in Oslo, Norway, as part of the Thematically Organized Psychosis (TOP) Research study, whereas the HC were randomly recruited from the national Norwegian population register.

Only Caucasians were included for study (both parents were Caucasians according to self-report). Exclusion criteria for all participants: WASI IQ < 70, age outside the range of 18–65 years; previous moderate or severe head injury or a neurological disorder; medical conditions thought to interfere with brain function. For the premorbid IQ analysis, as National Adult Reading Test (NART) is a reading test of Norwegian words, only patients with Norwegian as mother tongue or those who had completed all formal education in Norway were included, and participants with dyslexia were excluded (Vaskinn et al., 2020). Patients were clinically examined by medical doctors and clinical psychologists, and diagnoses were assessed with the Structured Clinical Interview for DSM-IV axis 1 disorder (SCID-I) module A-E (Spitzer et al., 1988). Healthy individuals were assessed with the Primary Care Evaluation of Mental Disorders (Prime-MD) in order to exclude individuals with previous or current psychiatric disorders including substance or alcohol misuse (Spitzer et al., 1994).

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the local ethics committee and the Norwegian Data Inspectorate.

2.2. Measures

Current general intellectual level was assessed using a licensed translated version of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 2007). The Norwegian WASI version was developed in 2001 and made available in 2007. To estimate premorbid IQ, we used the Norwegian version of the NART (Sundet and Vaskinn, 2008) and applied a formula adjusting for NART errors and age (Vaskinn et al., 2020). We also computed the estimated IQ decline after the disease onset (estimated premorbid IQ – current WASI full IQ). Patients were further evaluated with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), the Inventory of Depressive Symptoms, clinician rated (IDS-C) (Rush et al., 1996) and the Young Mania Rating Scale (YMRS) (Young et al., 1978).

2.3. CMV IgG seropositivity

Blood samples were drawn from all participants. Serology assessments were performed at the Stanley Neurovirology Laboratory (Johns Hopkins University School of Medicine, Baltimore, MD, USA). CMV immunoglobulin G (IgG) antibody concentrations were measured by solid-phase immunoassay and expressed as dichotomous measures, i.e. seropositivity/seronegativity, derived via comparisons of the reactivity generated by the sera in the immunoassay with the optical density generated by standard samples (Dickerson et al., 2003).

2.4. Statistics

In the first level of the analysis, among all participants, we applied a full factorial three-way analysis of covariance (ANCOVA) investigating

main and interaction effects of CMV IgG status (seronegativity/seropositivity), diagnostic group (SZS/BDS/HC) and sex on current IQ, whilst controlling for age. The alpha level for the three-way interaction (CMV IgG status-by-diagnostic group-by-sex) was set at 0.05 as we conducted one ANCOVA. In the second level of the analysis, we followed up the significant three-way interaction by applying a two-way ANCOVA in each diagnostic group (SZS, BDS and HC). Specifically, we explored main and interaction effects of CMV IgG status and sex on current IQ, whilst controlling for age. The alpha level for the two-way interactions was set at 0.05 as the three ANCOVAs were applied in three independent samples/groups and were the follow-up analyses of a significant three-way interaction. In the third level of the analysis, we followed up statistically significant two-way interactions with simple main effect analyses. Specifically, we interpreted the simple main effect of CMV IgG status on current IQ in males and the simple main effect of CMV IgG status on current IQ in females, and we thereby accepted statistical significance for the simple main effects at a Bonferroni-adjusted alpha level of 0.025 (0.05/2).

In our final models, we controlled for putative confounders, when indicated in the bivariate analysis (Table 1). Education level, as a continuous and as a categorical variable, has been extensively used as an indicator of socioeconomic status capturing the important transition from parental to own socioeconomic status (Galobardes et al., 2006). Years of education were here used as proxy indicator for socioeconomic status. As education level in our patient groups is likely impacted by their illness, in patient analyses, the categorical maternal education 1-3 level variable (1. primary school; 2. upper secondary school; 3. college/university) was used in addition. In the patient groups, we calculated

the duration of illness, defined as the duration since the first psychotic episode in SZS and the first affective episode in BDS as well as the use of antipsychotic, antiepileptic, lithium, antidepressive and other psychotropic (sedatives or stimulants) medication, and the chlorpromazine equivalents (Eq-CPZ) in mg/day (Andreasen et al., 2010) for patients on antipsychotics.

All analyses were conducted with IBM SPSS Statistics 25.

3. Results

3.1. Sample characteristics

Demographic and clinical characteristics of SZS and BDS patients are displayed in Table 1, and of the HC in Table 2. There were no significant differences between CMV- and CMV+ patients in the analyzed groups in terms of age, education years, duration of illness, PANSS, YMRS and IDS-C scores, tobacco use or handedness. Differences in medication variables between CMV- and CMV+ patients are shown in Table 1. For 71 patients, we had data on maternal education level. Maternal education level was not associated with CMV IgG status ($p = 0.491$). CMV+ male HC were older than CMV- male HC, while there was a higher frequency of right-handedness in CMV+ female HC than CMV- female HC.

The frequency of CMV IgG seropositivity did not differ ($p = 0.962$) between SZS patients (56%), BDS patients (54%) and HC (55%), and there were not such differences either when men and women were analyzed separately ($p = 0.867$ and 0.885, respectively).

In SZS, 89.8% of patients were on any psychotropic medication. Specifically, 84.7%, 17%, 2.8%, 32.4% and 10.8% of patients were on

Table 1

Number of patients, mean current IQ (standard deviation (SD)), mean age (SD), mean education years (SD), mean duration of illness (SD), mean Positive and Negative Syndrome Scale (PANSS), Inventory of Depressive Symptoms, clinician rated (IDS-C) and Young Mania Rating Scale (YMRS) scores (SD), daily use of tobacco, handedness (right-handedness vs. left-handedness/ambidexterity), and the percentage of patients on psychotropic medications among cytomegalovirus (CMV) immunoglobulin G (IgG) seronegative (CMV-) and seropositive (CMV+) men and women with schizophrenia spectrum disorders (SZS) and bipolar spectrum disorders (BDS). For 322, 319 and 270 patients, we had data on PANSS total score, YMRS score and IDS-C score, respectively. 231 patients were on antipsychotics; we had data on current chlorpromazine equivalents (Eq-CPZ) for 228 patients. P values of t-tests for continuous variables and chi-square tests for categorical variables are demonstrated with values < 0.05 shown in bold.

	SZS Men			Women			BDS Men			Women		
	CMV-	CMV+	P value	CMV-	CMV+	P value	CMV-	CMV+	P value	CMV-	CMV+	P value
N	45	48		33	50		32	33		37	49	
Current IQ	106.33	108.23	0.471	107.77	100.38	**0.021**	106.66	115.73	**0.004**	109.27	109.16	0.964
(SD)	(12.95)	(12.33)		(12.19)	(14.24)		(12.66)	(11.51)		(10.41)	(11.42)	
Age	30.24	31.25	0.585	32.73	31.54	0.628	35.72	36.61	0.784	30.73	33.10	0.280
(SD)	(8.27)	(9.36)		(11.98)	(10.10)		(12.32)	(13.59)		(8.14)	(12.06)	
Education years	12.36	13.17	0.090	13.27	12.82	0.432	13.53	13.67	0.776	13.72[4]	13.94	0.686
(SD)	(2.34)	(2.23)		(2.70)	(2.46)		(1.59)	(2.18)		(2.31)	(2.52)	
Duration of illness	5.61[4]	7.02	0.309	8.52	7.04[3]	0.430	12.38	12.58	0.938	10.87	12.90	0.339
(SD)	(6.84)	(6.34)		(8.39)	(8.08)		(11.49)	(9.32)		(8.83)	(10.33)	
PANSS total score	60.43	59.34	0.769	52.31	57	0.485	47.91	45.61	0.416	45.38	42.81	0.160
(SD)	(19.05)	(16.21)		(14.86)	(17.02)		(13.93)	(7.73)		(8.09)	(8.39)	
YMRS score	4.11	4.02	0.894[2]	3.32	3.98	0.502[2]	3.03	2.79	0.596[2]	2.69	4.15	0.410[2]
(SD)	(4.74)	(4.37)		(4.08)	(5.08)		(5.94)	(3.95)		(3)	(5.37)	
IDS-C score	14.97	14.59	0.884	13.37	10.29	0.203	15.57	15.90	0.915	16.79	16.44	0.878
(SD)	(10.3)	(10.81)		(2.79)	(1.63)		(10.77)	(12.78)		(9.66)	(10.74)	
Tobacco use (%)	60	44.68[4]	0.141	40.63[4]	54	0.237	65.63	45.45	0.102	51.35	46.94	0.685
Handedness (right-handedness %)	84.44	93.75	0.189[1]	87.88	90	1.000[1]	78.13	72.73	0.614	97.3	89.8	0.230[1]
Antipsychotics (%)	91.11	81.25	0.171	93.94	76	**0.033**	65.63	57.58	0.505	48.65	48.98	0.976
Eq-CPZ	407.36	330.95	0.185	388.88	377.22	0.891	234.98	217.39	0.711	215.42	168.39	0.353
(SD)	(288.26)	(212.98)		(431.1)	(270.75)		(146.14)	(147.26)		(157.59)	(157.25)	
Antiepileptics (%)	11.11	10.42	1.000[1]	27.27	22	0.583	34.38	36.36	0.867	51.35	34.69	0.130
Lithium (%)	0	0	-	6.1	6	1.000[1]	18.75	18.18	0.953	21.62	14.29	0.375
Antidepressants (%)	15.56	37.5	**0.017**	33.33	42	0.427	18.75	30.3	0.280	48.65	36.74	0.268
Other psychotropic medication (%)	13.33	6.25	0.307	15.15	10	0.509	3.13	9.1	0.613	10.81	10.2	1.000

[1] Fisher's exact test
[2] Mann-Whitney U Test
[3] Missing values for 2 participants
[4] Missing value for 1 participant

Table 2
Number of healthy controls (HC), mean IQ (standard deviation (SD)), mean age (SD), mean education years (SD), tobacco use and handedness (right-handedness vs. left-handedness/ambidexterity) among cytomegalovirus (CMV) immunoglobulin G (IgG) seronegative (CMV-) and seropositive (CMV+) men and women. P values of t-tests for continuous variables and chi-square tests for categorical variables are demonstrated with values < 0.05 shown in bold.

	HC Men CMV-	CMV+	P value	Women CMV-	CMV+	P value
N	118	138		93	125	
IQ	115.84	114.41	0.233	112.46	112.66	0.883
(SD)	(8.81)	(10.36)		(9.82)	(10.09)	
Age	31.45	33.79	**0.018**	32.03	33.26	0.346
(SD)	(7.69)	(7.95)		(10.01)	(9.05)	
Education years	14.53	14.49	0.888	14.10	14.44	0.248
(SD)	(2.34)	(2.18)		(2.31)	(2.05)	
Tobacco use (%)[2]	17.39	18	0.938	6.52	14.04	0.338[1]
Handedness (right-handedness %)	88.98	88.41	0.885	82.8	93.6	**0.012**

[1] Fisher's exact test.
[2] For 199 HC, we had data on tobacco use at the time of the IQ measurement.

antipsychotics, antiepileptics, lithium, antidepressants and other psychotropic medications (sedatives and/or stimulants), respectively. In BDS, the corresponding frequencies were 82.1% 54.3%, 39.1%, 17.9%, 34.4% and 8.6%, while the corresponding statistics for all diagnoses are presented in Supplementary Table 1.

3.2. All participants analysis

Applying a full factorial three-way ANCOVA investigating main and interaction effects of CMV IgG status, diagnosis (SZS/BDS/HC) and sex on current IQ, whilst controlling for age, we found a significant three-way CMV IgG status-by-diagnosis-by-sex interaction on current IQ, F $(2,788) = 5.685$, $p = 0.004$.

3.3. Analysis by diagnostic category

3.3.1. Patients with schizophrenia spectrum disorders

In our full factorial two-way ANCOVA, there was a statistically significant interaction between CMV IgG status and sex on current IQ, whilst controlling for age, $F(1, 171) = 5.397$, $p = 0.021$, partial $\eta^2 = 0.031$. Among men, the effect of CMV IgG status on IQ was not statistically significant, $F(1, 171) = 0.550$, $p = 0.459$, partial $\eta^2 = 0.003$, whereas among women, the effect of CMV IgG status on IQ was statistically significant, $F(1, 171) = 6.156$, $p = 0.014$, partial $\eta^2 = 0.035$. Specifically, adjusted mean IQ in CMV- women was higher than in CMV+ women, a statistically significant difference of 7.27 IQ units (95% CI, 1.48 to 13.05), $p = 0.014$ (Fig. 1 and Supplementary Table 2). No violations of the model assumptions were detected, while sensitivity analysis with non-parametric testing confirmed the results (Supplementary material).

3.3.2. Patients with bipolar spectrum disorders

In our full factorial two-way ANCOVA, there was a statistically significant interaction between CMV IgG status and sex on current IQ, whilst controlling for age, $F(1, 146) = 5.687$, $p = 0.018$, partial $\eta^2 = 0.037$. Among men, there was a statistically significant effect of CMV
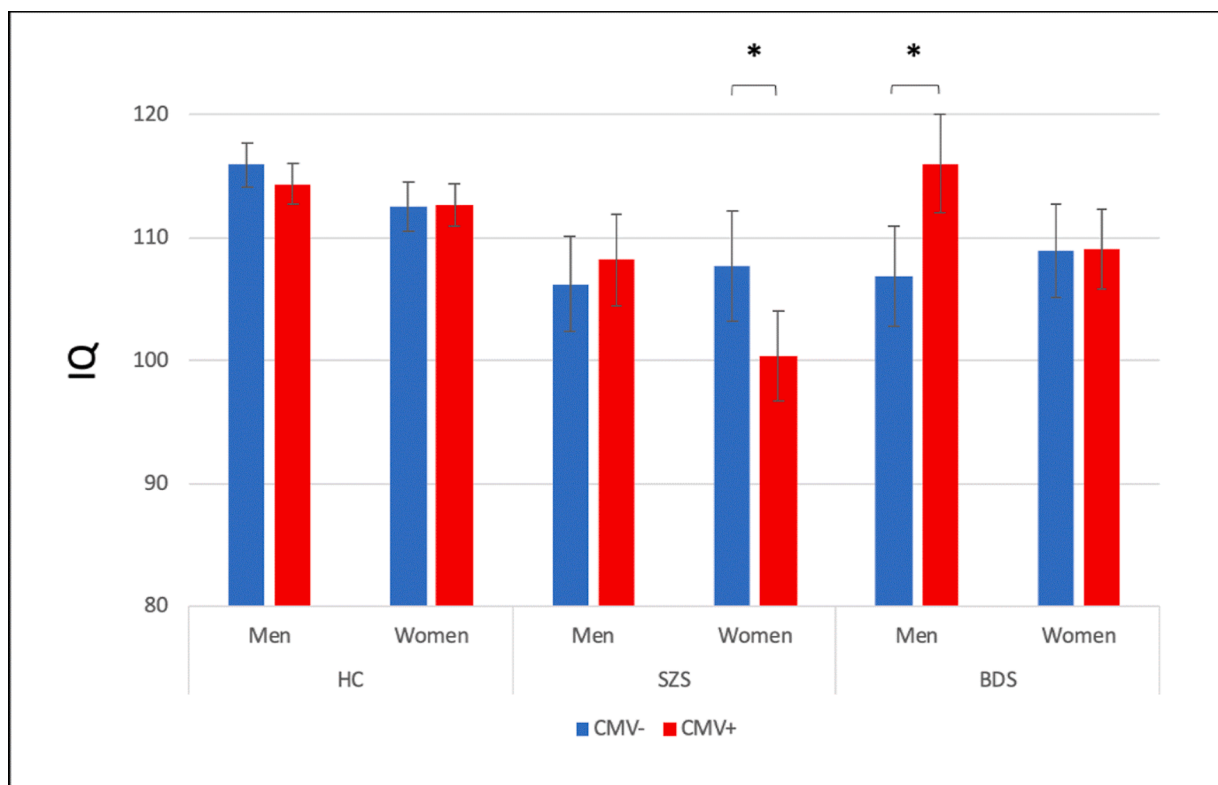
Fig. 1. Adjusted intelligence quotient (IQ) means with 95% confidence intervals in cytomegalovirus (CMV) immunoglobulin G (IgG) seronegative (CMV-) and seropositive (CMV+) healthy controls (HC) and patients with schizophrenia spectrum disorders (SZS) and bipolar spectrum disorders (BDS). The IQ differences between CMV- and CMV+ SZS women ($p = 0.014$) and CMV- and CMV+ BDS men ($p = 0.002$) were statistically significant. 118 CMV- male HC, 138 CMV+ male HC, 93 CMV- female HC, 125 CMV+ female HC, 45 CMV- male SZS, 48 CMV+ male SZS, 33 CMV- female SZS, 50 CMV+ female SZS, 32 CMV- male BDS, 33 CMV+ male BDS, 37 CMV- female BDS and 49 CMV+ female BDS were analyzed
*statistically significant difference at a Bonferroni-adjusted alpha level.

IgG status on IQ, F(1, 146) = 10.393, p = 0.002, partial η^2 = 0.066, whereas among women, there was no effect of CMV IgG status on IQ, F (1, 146) = 0.003, p = 0.955, partial η^2 < 0.001. Specifically, adjusted mean IQ in CMV- men was lower than in CMV+ men, a statistically significant difference of 9.16 IQ units (95% CI, 3.55 to 14.78), p = 0.002 (Fig. 1 and Supplementary Table 2). Although not statistically significant, 20% more CMV- bipolar men reported daily use of tobacco compared to CMV+ bipolar men (*p* = 0.102) (Table 1). The tobacco variable was thereby inserted into the ANCOVA; the association between CMV seropositivity and IQ in bipolar men did not change (*p* = 0.006). No violations of the model assumptions were detected, while sensitivity analysis with non-parametric testing confirmed the results (Supplementary material).

3.3.3. Healthy controls

In our full factorial two-way ANCOVA, there was no statistically significant interaction between CMV IgG status and sex on IQ, whilst controlling for age, F(1, 469) = 0.878, p = 0.349, partial η^2 = 0.002. Men had 2.56 units higher IQ than women (*p* = 0.005), whereas there was no main effect of CMV IgG status (*p* = 0.425). Stratifying by sex, there were still no CMV effects on IQ, whilst controlling for age (*p* = 0.295 and *p* = 0.999 in men and women, respectively). There was a significant difference in handedness between CMV+ and CMV- women (*p* = 0.012) (Table 2). The handedness variable was inserted in the ANCOVA, but this did not change any results. No violations of the model assumptions were detected (Supplementary material).

3.3.4. Medication variables

Antipsychotic dosage has been associated with cognitive impairment (Ballesteros et al., 2018; Elie et al., 2010), while switching from antipsychotic polypharmacy to monotherapy has been associated with cognitive improvement (Hori et al., 2013). We investigated the putative correlation between Eq-CPZ and IQ. Totally, 231 patients (149 SZS and 82 BDS patients) were on antipsychotics, and for 228 of them we could calculate current Eq-CPZ . Mean Eq-CPZ (SD) was 316.41 (271) mg/day. Across the analyzed groups, there was no correlation between Eq-CPZ and WASI IQ assessed with Spearman's correlation, $r_s(226)$ = -0.073, p = 0.270. When we stratified the analysis by diagnostic group and sex, we found that there was no significant correlation in any group, $r_s(77)$ = -0.197, p = 0.082, $r_s(67)$ = 0.171, p = 0.160, $r_s(37)$ = -0.126, p = 0.443, and $r_s(39)$ = -0.004, p = 0.983 for SZS men, SZS women, BDS men and BDS women, respectively. Among patients on antipsychotics, inserting the Eq-CPZ variable in our ANCOVAs did not change any results (p = 0.985, 0.005, 0.005 and 0.606 for the association between CMV IgG status and IQ in SZS men, SZS women, BDS men and BDS women, respectively).

We further investigated putative correlations between the binary medication variables and current IQ across the patient groups. The use of antipsychotics, but not the use of other medication categories, was inversely correlated with IQ assessed with point-biserial correlation, $r_{pb}(325)$ = -0.169, p = 0.002. Inserting the antipsychotic use variable in our ANCOVAs did not change any results (*p* = 0.513, 0.011, 0.002 and 0.951 for the association between CMV IgG status and IQ in SZS men, SZS women, BDS men and BDS women, respectively). Among SZS men,

there was a significant difference in antidepressant use (*p* = 0.017) between CMV+ and CMV- participants (Table 1); adding the antidepressant use variable in the analysis of SZS patients did not change any results.

3.3.5. Estimated premorbid IQ and IQ decline

We investigated if the IQ difference between CMV+ and CMV- SZS women and between CMV+ and CMV- BDS men found in our main analysis were present prior to the disease onset. As shown in Table 3, CMV+ BDS men had significantly higher estimated premorbid IQ than CMV- BDS men (4 units IQ difference, *p* = 0.034), and further, no IQ decline, whereas CMV- BDS men showed 4 units IQ decline after the disease onset (*p* = 0.036 for IQ decline difference). Although non-statistically significant, CMV+ SZS women had lower premorbid IQ (3 units IQ difference, *p* = 0.094) and larger IQ decline (3 units IQ decline difference, *p* = 0.163) compared to CMV- SZS women. Finally, no differences in premorbid IQ or IQ decline estimates were found between CMV+ and CMV- SZS men or BDS women (Table 3).

4. Discussion

In the present study, the main findings were the diagnosis- and sex-dependent associations between CMV IgG seropositivity and IQ in SMI, and the absence of CMV-IQ association in HC. CMV seropositivity, reflecting previous CMV exposure, was associated with *lower* current intelligence among women with SZS (7 units IQ decrease), and unexpectedly with *higher* current intelligence among men with BDS (9 units IQ increase).

The expression of susceptibility in SZS and BDS in opposite directions could be due to non-shared genetic or immune system alterations in the two diagnostic groups modulating host immune response and thereby CMV central nervous system implications. Schizophrenia and bipolar disorder show a partial genetic overlap with shared but also independent genetic influences (Cardno and Owen, 2014). Importantly, in a recent study, most schizophrenia risk alleles were associated with lower intelligence, whereas most bipolar disorder risk alleles were associated with higher intelligence (Smeland et al., 2019). Further, a recent meta-analysis has pointed to common cytokine network alterations in chronically ill patients with schizophrenia and euthymic bipolar disorder, but not in bipolar depression, compared to controls (Goldsmith et al., 2016). Our results support the traditional concept of the Kraepelinian dichotomy viewing schizophrenia and bipolar disorder as different entities.

4.1. Patients with schizophrenia spectrum disorders

An association between CMV exposure and cognition in schizophrenia has been explored in some studies, with inconsistent results. One study among patients with schizophrenia and schizoaffective disorder reported association between CMV IgG seropositivity and cognitive impairment as measured with the Trail Making Test (Shirts et al., 2008). Watson et al. investigated a large sample consisting of patients with schizophrenia, their unaffected relatives and controls, and found that CMV IgG seropositivity was similarly associated with diminished

Table 3

Estimated premorbid IQ and IQ decline among cytomegalovirus (CMV) immunoglobulin G (IgG) seronegative (CMV-) and seropositive (CMV+) men and women with schizophrenia spectrum disorders (SZS) and bipolar spectrum disorders (BDS). P values of t-tests are demonstrated with values < 0.05 shown in bold.

| | SZS | | | | | | BDS | | | | | |
| | Men | | | Women | | | Men | | | Women | | |
	CMV-	CMV+	P value	CMV-	CMV+	P value	CMV-	CMV+	P value	CMV-	CMV+	P value
N	38	42		29	39		28	32		34	44	
Premorbid IQ (SD)	112.03 (6.78)	112.66 (5.49)	0.644	113.03 (6.53)	110.14 (7.2)	0.094	111.37 (6.31)	114.92 (6.32)	**0.034**	113.12 (6.03)	112.54 (4.55)	0.638
IQ decline (SD)	4.69 (10.29)	2.93 (10.42)	0.451	4.58 (9.43)	8.02 (10.27)	0.163	4.44 (11.46)	-0.99 (8.03)	**0.036**	3.39 (8.77)	3.31 (11.39)	0.973

mean cognitive performance regardless of case/relative/control group status (Watson et al., 2013). Prasad et al. showed that CMV+ participants (first-episode antipsychotic-naïve schizophrenia patients and healthy controls) had impaired executive functioning as evidenced by a lower number of Wisconsin Card Sorting Test categories completed compared to CMV- participants (Prasad et al., 2011). By contrast, Dickerson et al. failed to show an association between CMV IgG seropositivity and cognitive functioning indexed by Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total score among patients with schizophrenia (39% women) (Dickerson et al., 2003). Yolken et al. reported no association between CMV IgG seropositivity and a neurocognitive summary score among 1308 participants (25% women) in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial (Yolken et al., 2011). To our knowledge, these earlier studies have not investigated interaction sex-by-CMV effects and further, different cognitive measures and different populations under study may also explain the apparent discrepancies in effects of CMV infection on cognition.

Our results are indicative of a deleterious CMV effect on cognitive functioning among women with SZS. Congenital CMV infection has an incidence of 0.2-2% (Kawasaki et al., 2017), with a recent Norwegian study pointing to the lower limit of the range (0.22%) (Barlinn et al., 2018). The congenital CMV infection is lethal in approximately 1/10 of cases (Kawasaki et al., 2017). Among survivors, approximately 9/10 have been reported to be asymptomatic at birth (Townsend et al., 2013), and these asymptomatic CMV+ individuals do not differ in IQ assessed in childhood and adolescence relative to CMV- individuals (Lopez et al., 2017). In the present study, more than half of the participants were CMV+ suggesting that there are very few if any CMV+ participating individuals having been infected antenatally. We therefore consider that it is not likely that the observed IQ difference between CMV+ and CMV- individuals is associated with a non-lethal 'mild' congenital CMV infection. Our results are therefore rather suggestive of a postnatal CMV infection being associated with the impaired cognition; however, we cannot know when the primary infection occurred, or whether the lower IQ in CMV+ women with SZS is related to the primary CMV infection, a subsequent lifelong latent CMV infection or to CMV reactivations. Finally, based on premorbid IQ estimations, we have an indication that the IQ difference between CMV+ and CMV- SZS women may have been present prior to the psychosis onset, but further increased during the symptomatic phase of psychosis. This may be explained by an interplay between the schizophrenia-related inflammatory environment and the CMV infection as described below.

The peripheral levels of Il-6 have been reported increased in patients with schizophrenia (Potvin et al., 2008) but also in children with increased future risk for psychosis (Khandaker et al., 2014). Of note, Il-6 robustly enhances CMV reactivation (Reeves and Compton, 2011). Thus, among patients with psychosis or individuals at high risk for psychosis, CMV exposure may facilitate for a latent CMV infection with more severe or frequent reactivations. The CMV-infected cells secrete numerous cytokines with Il-6 being one of the most abundant (Compton et al., 2003; Dumortier et al., 2008) which further enhance the inflammatory environment. The notion that CMV is an important non-heritable factor that shapes the immune system and alters Il-6 levels and signaling properties (Brodin et al., 2015) is also supported by a report showing substantially reduced correlations of serum cytokine concentrations, including Il-6, and cell signaling responses among discordant (CMV+/CMV-) monozygotic twins relative to concordant (CMV-) monozygotic tweens (Brodin et al., 2015). Taken together, an interplay between inflammatory environment in psychosis and CMV infection may result in increased inflammation shown mainly as Il-6 increase. Importantly, higher Il-6 levels have been associated with cognitive impairment in patients with schizophrenia (Frydecka et al., 2015) which may explain the observed IQ difference between CMV+ and CMV- women with SZS.

The results may be also explained in the context of

neurodevelopment. Schizophrenia is a neurodevelopmental disorder with developmental insults in early life (Fatemi and Folsom, 2009), with several lines of evidence suggesting disturbances of brain maturation. For instance, in the prefrontal cortex of individuals with schizophrenia, the normal age-related decline in gene expression associated with developmental processes, including neuronal differentiation, is slowed (Torkamani et al., 2010) and further, a transcriptional immaturity is present in different cell types (Hagihara et al., 2014). Given that CMV effects on progenitor/immature nerve cells can be detrimental (Cheeran et al., 2009; Kawasaki et al., 2017), whereas differentiated/mature cells have been shown to be more resilient to CMV infection (Cheeran et al., 2009), we are tempted to speculate that a schizophrenia-related maturation disturbance could make this patient group particularly susceptible to CMV effects. Our finding that women are especially susceptible to latent CMV infection is partially in line with what has been observed in the context of congenital CMV infection. Congenital human CMV infection results in more symptomatic cases in females than males (Watt et al., 2016) and has been associated with significantly higher risk of abnormal brain development in females (Picone et al., 2005). Animal studies have also shown an increased susceptibility to congenital CMV infection among females (Geurs et al., 2012; Traub et al., 2012).

4.2. Patients with bipolar spectrum disorders

The association between CMV exposure and cognition in bipolar disorder has not been thoroughly explored. In a recent study, CMV IgG seropositivity was not associated with cognitive performance in patients with bipolar disorder, schizophrenia or HC (Hamdani et al., 2017). Further, there was no association between CMV seropositivity and cognition indexed by RBANS total score among patients with bipolar disorder (35/117 were men) (Dickerson et al., 2004). Unexpectedly, our results showed that CMV+ bipolar men had significantly *higher* current IQ compared to CMV- bipolar men, suggesting that CMV exposure and subsequent latency may have a beneficial effect in terms of IQ among bipolar men. To the best of our knowledge, the documented advantageous effects of CMV have largely unknown etiology and have not been previously reported among patients with psychiatric disorders. However, there are numerous reports of CMV beneficial effects from transplantation research. Whereas CMV infection and CMV reactivation are generally detrimental in immunosuppressed individuals, a CMV-related anti-leukemic effect after allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia, but not for other malignancies, has been confirmed in a series of studies (Litjens et al., 2018). A beneficial effect of CMV infection on liver graft acceptance has also been suggested (Litjens et al., 2018). CMV exposure has been associated with improved immune responses and protection against heterologous infections in specific settings, indicating that CMV may not only have detrimental effects on the immune system and overall health, especially in youth (Sansoni et al., 2014).

As a result of latent CMV infection, a significant fraction of the adaptive immune resources commits to CMV immunosurveillance (Derhovanessian et al., 2009) with a decrease of naïve and an expansion of late-differentiated T cell subtypes (van der Heiden et al., 2016). Di Benedetto et al. found a lower frequency of CD4+ naïve T cells in CMV+ elderly men compared with CMV+ young men, but not between CMV- elderly and CMV- young men, and the opposite among women, suggesting a sex-dependent CMV-associated immunosenescence (Di Benedetto et al., 2015). The CMV-driven T cell differentiation has been associated with age-related mortality and is generally considered to be deleterius, but may also have survival benefits (Derhovanessian et al., 2009). This may explain the positive association between CMV and IQ found among men but not women with BDS.

4.3. Healthy individuals

The literature results regarding CMV and cognitive measures among

individuals with no mental disorder are inconclusive. In line with the present results among HC, Dickerson et al. failed to find association between CMV IgG seropositivity and cognitive function among 100 adults with mean age 36 years (Dickerson et al., 2004). The cognitive functioning was assessed with RBANS total score, a measure reported to be highly correlated with IQ in schizophrenia (Gold et al., 1999). Further, in a recent large longitudinal study with 4324 participants in the 11-years follow-up, CMV IgG seropositivity or antibody titers were not significantly associated with cognitive decline or cross-sectional cognitive performance among middle-aged or elderly adults (Torniai-nen-Holm et al., 2018). By contrast, among almost 5000 middle-aged adults (mean age 37), but not children or elderly adults, Tarter et al. reported an association between CMV IgG seropositivity and impaired cognitive functioning (impaired coding speed, learning and recall) (Tarter et al., 2014). Further, among 521 adults (mean age 33 years), Dickerson et al. reported that higher CMV antibody titers were inversely associated with RBANS total score (Dickerson et al., 2014). And a prospective study in elderly with more than 1000 participants showed that those with the highest CMV IgG levels at baseline developed a more rapid cognitive decline, assessed with Mini-Mental State Examination, over a 4-year period compared to individuals with the lowest CMV IgG titers (Aiello et al., 2006). The observed discrepancy in the literature may be due to different cognitive measures investigated as well as the use of CMV IgG titers instead of seropositivity in some studies. In the present study, we failed to find any difference in general intelligence between CMV- and CMV+ HC (age range 18-64 years old), suggesting a lack of CMV effect on IQ in healthy non-elderly adults.

Unexpectedly, there was a significantly higher proportion of right-handed women among CMV+ healthy women compared to CMV- healthy women. The ontogenesis of handedness is a complex phenomenon with both genetic and environmental factors being implicated (Ocklenburg et al., 2014). It has been shown that the contribution of environmental factors on human handedness is about 75% (Medland et al., 2009). Lateralization research has shown that right-handedness is associated with increased asymmetry between left and right hemispheres (Li et al., 2014). Our results may thereby indicate that CMV infection is an environmental factor associated with right-handedness and possibly increased brain lateralization among women.

The present study has certain limitations. First, the number of individuals in the groups where we found the significant IQ differences were relatively small; however, these were follow-up analyses of the significant three-way interaction from the whole group analysis, where we included 801 individuals. Further, despite the fact that we have accounted for putative confounders in the patient groups, including age, duration of illness, medication use and education status as a proxy for socioeconomic status, we cannot exclude that other unknown factors may influence the association between CMV and IQ. Further, the positive association between CMV seropositivity and IQ in BDS men was unexpected and requires replication in independent samples. Another limitation is that we do not know when during the lifespan the CMV exposure occurred. This is a cross-sectional study and long-term course is not known. Based on premorbid IQ and IQ decline estimations (Table 3), we have found indication that the IQ differences between CMV+ and CMV- BDS men and possibly between CMV+ and CMV- SZS women were present prior to the psychiatric disease onset, but further increased during the symptomatic phases of the disorders.

In conclusion, our findings indicate that CMV exposure, reflected by IgG seropositivity, may affect IQ in some patients with SMI, but not in HC. CMV seropositivity was negatively associated with IQ among women but not men with SZS, and positively associated with IQ among men but not women with BDS, whereas there was no evidence of similar associations among the HC.

Contributors

DA drafted the manuscript, performed the statistical analysis and interpreted the data. DA and IA conceptualized and designed the work. IA initiated and supervised the study. RHY was responsible for the serology assessments. All co-authors had substantial contributions to the interpretation of data, critically revised the manuscript for important intellectual content and approved the final version to be published.

Data statement

The data associated with the manuscript is available on reasonable request.

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Declaration of Computing Interest

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Supplementary materials

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