Brain, Behavior, and Immunity xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

# Infectious disease burden and cognitive function in young to middle-aged adults

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ARTICLE INFO

*Article history:*
Received 2 July 2015
Received in revised form 23 October 2015
Accepted 23 October 2015
Available online xxxx

*Keywords:*
Neurocognitive function
NHANES
Infectious disease
Toxocariasis
Toxoplasmosis
Hepatitis
Herpes
Cytomegalovirus

ABSTRACT

Prior research has suggested an association between exposure to infectious disease and neurocognitive function in humans. While most of these studies have explored individual viral, bacterial, and even parasitic sources of infection, few have considered the potential neurocognitive burden associated with multiple infections. In this study, we utilized publically available data from a large dataset produced by the Centers for Disease Control and Prevention that included measures of neurocognitive function, sociodemographic variables, and serum antibody data for several infectious diseases. Specifically, immunoglobulin G antibodies for toxocariasis, toxoplasmosis, hepatitis A, hepatitis B, and hepatitis C, cytomegalovirus, and herpes 1 and 2 were available in 5662 subjects. We calculated an overall index of infectious-disease burden to determine if an aggregate measure of exposure to infectious disease would be associated with neurocognitive function in adults aged 20–59 years. The index predicted processing speed and learning and memory but not reaction time after controlling for age, sex, race-ethnicity, immigration status, education, and the poverty-to-income ratio. Interactions between the infectious-disease index and some sociodemographic variables were also associated with neurocognitive function. In summary, an index aggregating exposure to several infectious diseases was associated with neurocognitive function in young- to middle-aged adults.



## 1. Introduction

Exposure to infectious disease has been associated with cognitive function in humans. In one study of older adults, cognitive decline was associated with cytomegalovirus (CMV) but not herpes simplex virus type 1 (HSV-1) (Aiello et al., 2006), and in another study, Tarter et al. (2014) found that both HSV-1 and CMV were associated with cognition in children, younger adults, and older adults (Tarter et al., 2014). Adults over age 60 with previous hepatitis A virus (HAV) infection but intact liver function and no other hepatitis viruses had slower psychomotor speed than controls (Hsieh et al., 2009). Similarly, some patients with chronic hepatitis C virus (HCV) have cognitive deficits even in the absence of severe hepatic fibrosis (Perry et al., 2008). In addition to associations between viral infection and cognitive function, parasitic infections have also been related to cognitive impairment. *Toxoplasma gondii* (*T. gondii*) has been associated with cognitive impairment in adults (Flegr et al., 2003; Gajewski et al., 2014; Gale et al., 2015a; Mendy et al., 2015; Pearce et al., 2014), and *Toxocara* species have been associated with cognitive impairment in children (Walsh and Haseeb, 2012) and in adults (Erickson et al., 2015).

Many of the infectious diseases associated with cognition in humans have widespread distributions. The seroprevalence of CMV in the United States is approximately 59%, although the seroprevalence varies significantly with age and sociodemographic variables (Cannon et al., 2010; Staras et al., 2006). For example, the seroprevalence of CMV in children ages 6–11 years is approximately 36.3% increasing to 41.7% for ages 12–19 years (Staras et al., 2006). The overall seroprevalence of HSV-1 and HSV-2 have been reported as approximately 53.9% and 15.7%, respectively (Bradley et al., 2014). The prevalences of HSV-1 and HSV-2 are typically lower in children compared to adults with the prevalence of HSV-1 in adolescents 12–19 years of age being approximately 44% (Schillinger et al., 2004). The worldwide immunoglobulin G antibody (IgG) seroprevalence of *T. gondii* is approximately 30%, and its overall seroprevalence in the United States is estimated at 22% (Jones et al., 2001), with a prevalence of approximately 9% in adolescents and 8% in children (Jones et al., 2003). Similarly, the

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http://dx.doi.org/10.1016/j.bbi.2015.10.014
0889-1591/

overall seroprevalence of *Toxocara* species in the United States is approximately 14% (Lee et al., 2014a), and the prevalence in children is slightly lower at approximately 12% (Nelson et al., 1996; Walsh and Haseeb, 2012). The seroprevalence of HAV in the United States prior to availability of the vaccine has been reported to have been approximately 30% overall and 8% in children (Klevens et al., 2011). The prevalence of HCV is approximately 1% in the United States (Denniston et al., 2014) and approximately 0.3% in children (Alter et al., 1999). Finally, the prevalence of hepatitis B (HCB) is approximately 5% overall and 1.2% in children (Wasley et al., 2010). As can be seen, these infectious diseases vary by age with a higher prevalence associated with increasing age. With these individual widespread distributions, some people may possess antibodies for multiple infectious diseases, any one of which could influence cognition, but not necessarily to the same degree. Further, prior studies have shown that many of these infectious diseases may not only affect cognition but multiple infections may interact to affect cognitive function (Gale et al., 2015b).

To more fully investigate the cumulative effect of more than one infectious disease, Katan et al. (2013) evaluated the association between several viral and bacterial infections and cognition in a sample of older adults (mean age = 69). They calculated the effect of these infections on cognition by weighting the ability of each infection to predict cognitive function and then summing these weights into an overall index of infectious disease burden. They included CMV, HSV-1, HSV-2, *Helicobacter pylori* (*H. pylori*), and *Chlamydia pneumoniae* (*C. pneumoniae*) and found that a greater infectious-disease index was associated with poorer cognitive function.

Based on the associations between viral, bacterial, and parasitic diseases and cognitive function in humans and the relationship between an index of total infectious-disease burden and human cognitive function, we hypothesized that the association between an infectious-disease burden taking into account total exposure to the viruses herpes types 1 and 2, hepatitis A, B, and C, and CMV, the protozoan *T. gondii*, and the nematodes *Toxocara cati* and *Toxocara canis* would be associated with neurocognitive function in a sample of young- and middle-aged adults. We chose these particular pathogens because they either had been previously associated with human cognitive impairment or were related to infectious diseases previously associated with cognitive impairment. We chose covariates *a priori* to reflect factors that we have found in prior work to affect the association between cognition and certain pathogens (Erickson et al., 2015; Gale et al., 2015a,b). Specifically, we controlled for socioeconomic status, educational attainment, and ethnicity and investigated interactions between these covariates and the pathogens.

## 2. Materials and methods

### 2.1. Study sample

We used data from the publically available, anonymized, cross-sectional, multi-stage Third National Health and Nutrition Examination Survey (NHANES III) carried out from 1988 to 1994 by the United States' National Center for Health Statistics at the Centers for Disease Control and Prevention (CDC) for adults aged 20–59 years. NHANES III was the most recent wave of the various NHANES data sets that contained the necessary variables for us to test our hypothesis of an association between an infectious-disease index and neurocognitive function in adults. Although NHANES III contains data on over 30,000 participants, only 11,306 were aged 20–59. According to the study design, half of these participants were randomly selected to complete the cognitive functioning tests (Centers for Disease Control and Prevention (CDC), 1996), resulting in a final sample size of 5662.

### 2.2. Cognitive function

To evaluate cognitive function in adults aged 20–59 years, the NHANES III used computer-based simple reaction time (SRT), symbol-digit substitution (SDT), and serial-digit learning (SDL) tasks. We did not transform the cognitive scores, and on all tests, higher scores indicate worse performance. For example, the score for the SRT is reaction time, the SDL test score represents the number of trials needed to complete two trials without error, and the SDS score is obtained by dividing time in seconds by number of correct responses. For detailed descriptions of these measures including information regarding reliability and validity, we recommend the paper by Krieg et al. (2001).

### 2.3. Infectious diseases

NHANES III serum samples for *Toxocara* were analyzed via an indirect enzyme immunoassay developed by the CDC based on optical density (Centers for Disease Control, 2007, Documentation, codebook and frequencies; surplus sera laboratory component: antibody to Toxocara larva migrans. NHANES III, series 11 Data Files 26A), an assay sensitive to both *T. canis* and *T. cati* (Won et al., 2008). In the NHANES III dataset, optical density readings with an antibody level >7 IU/mL were considered positive for *T. gondii* (Pearce et al., 2014). CMV immunoglobulin G antibody (IgG) was measured using an enzyme linked immunosorbent assay (ELISA) available through Question International (Staras et al., 2006). Seropositivity to HSV-1 and HSV-2 antibodies was assessed using the glycoprotein gG-1 and gG-2 antigen by immunodot assay (Schillinger et al., 2004). Hepatitis A (HAV) and Hepatitis C (HCV) were measured by solid-phase competitive enzyme immunoassay while Hepatitis B (HBV) was measured by sandwich enzyme-immunoassay (Centers for Disease Control, 1996, Laboratory Procedures Used for the Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994, VII-V-1 to VII-Z-1). Although seropositivity for HAV can be due to a history of either vaccination or infection, the Hepatitis A vaccine was not available in the United States until 1995 (Klevens et al., 2011), which occurred after the period of data collection for the NHANES III. Thus, all participants in the current study with antibodies to HAV had the antibodies due to a past infection and not vaccination. Finally, approximately 50% of the analytic sample did not have valid IgG antibody data for *H. pylori*. Although definitive recommendations for an upper limit of missing data are not available, we did not include *H. pylori* in our analyses because it had an inordinate amount of missing data approximately twice the amount of the variable with the next most missing data.

### 2.4. Infectious disease burden index

To estimate an infectious disease burden index based on the method described by Elkind et al. (2010), we calculated regression estimates (unstandardized coefficients) for the association between each individual infectious disease and each of the three cognitive tests, resulting in eight coefficients for each of the three cognitive tests. We treated each parameter estimate as a weighted individual representation of the strength of association between the infectious disease and the cognitive measure and summed the coefficients for each subject's total infectious burden (i.e., a subject seropositive for both *Toxocara* and *T. gondii* but no other infectious disease would have a total infectious burden equal to the summed coefficients of *Toxocara* and *T. gondii* alone).[1] In that

[1] The coefficient for the relationship between Hepatitis C and SRT was slightly negative, although not statistically significant (see Fig. 1). We treated this as a null relationship and used 0 as the weight for Hepatitis C in the infectious burden measure for SRT.

Please cite this article in press as: Gale, S.D., et al. Infectious disease burden and cognitive function in young to middle-aged adults. Brain Behav. Immun. (2015), http://dx.doi.org/10.1016/j.bbi.2015.10.014