Journal of Psychiatric Research 60 (2015) 87–94

Contents lists available at ScienceDirect

Journal of Psychiatric Research

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

"Latent" infection with *Toxoplasma gondii*: Association with trait aggression and impulsivity in healthy adults

Thomas B. Cook [a], Lisa A. Brenner [b, c, d, e], C. Robert Cloninger [f], Patricia Langenberg [g], Ajirioghene Igbide [h], Ina Giegling [i], Annette M. Hartmann [i], Bettina Konte [i], Marion Friedl [i], Lena Brundin [j], Maureen W. Groer [k], Adem Can [l], Dan Rujescu [i, 1], Teodor T. Postolache [b, l, m, *, 1]

[a] Department of Public Health, Mercyhurst Institute for Public Health, Mercyhurst University, Erie, PA, USA
[b] Veterans Integrated Service Network (VISN) 19, Mental Illness Research Education and Clinical Center (MIRECC), Denver, CO, USA
[c] Department of Psychiatry, University of Colorado, Anschutz Medical Campus, Aurora, CO, USA
[d] Department of Physical Medicine and Rehabilitation, University of Colorado, Anschutz Medical Campus, Aurora, CO, USA
[e] Department of Neurology, University of Colorado, Anschutz Medical Campus, Aurora, CO, USA
[f] Department of Psychiatry, Sansone Centre for Well-Being, Washington University, St. Louis, MO, USA
[g] Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, MD, USA
[h] DC Department of Behavioral Health, Saint Elizabeths Hospital, Psychiatry Residency Program, Washington, DC, USA
[i] Department of Psychiatry, Martin-Luther-University Halle-Wittenberg, Halle, Germany
[j] Division of Psychiatry and Behavioral Medicine, College of Human Medicine, Michigan State University, Van Andel Research Institute, Grand Rapids, MI, USA
[k] University of South Florida, Tampa, FL, USA
[l] Department of Psychiatry, University of Maryland-Baltimore School of Medicine, Baltimore, MD, USA
[m] Veterans Integrated Service Network (VISN) 5, Mental Illness Research Education and Clinical Center (MIRECC), Baltimore, MD, USA

ARTICLE INFO

Article history:
Received 2 August 2014
Received in revised form
3 September 2014
Accepted 19 September 2014

Keywords:
Aggression
Impulsivity
Toxoplasma gondii
Personality

ABSTRACT

Background: Latent chronic infection with *Toxoplasma gondii (T. gondii)*, a common neurotropic pathogen, has been previously linked with suicidal self-directed violence (SSDV). We sought to determine if latent infection with *T. gondii* is associated with trait aggression and impulsivity, intermediate phenotypes for suicidal behavior, in psychiatrically healthy adults.
Methods: Traits of aggression and impulsivity were analyzed in relationship to IgG antibody seropositivity for *T. gondii* and two other latent neurotropic infections, herpes simplex virus 1 (HSV1) and cytomegalovirus (CMV). One thousand community-residing adults residing in the Munich metropolitan area with no Axis I or II conditions by SCID for DSM-IV (510 men, 490 women, mean age 53.6 ± 15.8, range 20–74). Plasma samples were tested for IgG antibodies to *T. gondii*, HSV-1 and CMV by ELISA. Self-reported ratings of trait aggression scores (Questionnaire for Measuring Factors of Aggression [FAF]) and trait impulsivity (Sensation-Seeking Scale-V [SSS-V]) were analyzed using linear multivariate methods.
Results: T. gondii IgG seropositivity was significantly associated with higher trait reactive aggression scores among women ($p < .01$), but not among men. *T. gondii*-positivity was also associated with higher impulsive sensation-seeking (SSS-V Disinhibition) among younger men ($p < .01$) aged 20–59 years old (median age = 60). All associations with HSV-1 and CMV were not significant.
Conclusions: Aggression and impulsivity, personality traits considered as endophenotypes for SSDV, are associated with latent *T. gondii* infection in a gender and age-specific manner, and could be further investigated as prognostic and treatment targets in *T. gondii*-positive individuals at risk for SSDV.
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1. Introduction

Human (Coccaro, 2006; Coccaro et al., 2014; Graham et al., 2006; Ranjit et al., 2007; Suarez, 2003, 2004) and non-human animal studies (Bhatt et al., 2008; Patel et al., 2010; Pesce et al., 2011; Zalcman and Siegel, 2006) suggest that behavioral traits that

* Corresponding author. University of Maryland School of Medicine-Baltimore, Mood & Anxiety Program, 685 W. Baltimore Street, MSTF Building Room 930, Baltimore, MD 21201, USA. Tel.: +1 410 706 2323; fax: +1 410 706 0751.
E-mail addresses: tpostolache@psych.umaryland.edu, teopostolache@gmail.com (T.T. Postolache).
[1] Teodor T. Postolache and Dan Rujescu equally contributed and share senior authorship.

http://dx.doi.org/10.1016/j.jpsychires.2014.09.019
0022-3956/Published by Elsevier Ltd.

have been proposed as endophenotypes of suicidal behavior (Mann et al., 2009) (hostility, anger, aggressive tendencies and behavior) are associated with elevations in inflammatory markers. While these elevations could represent epiphenomena, or be consequences of stress or arousal, experimental studies suggest that low-grade immune activation directly *causes* aggressive behavior. (Bhatt et al., 2008) The underlying causes of the low-grade immune activation observed in suicidal patients are not known, but could include chronic "latent" infections in immune-competent hosts. Neurotropic pathogens, including the protozoan parasite *Toxoplasma gondii (T. gondii)* and herpes viruses (cytomegalovirus, HSV1), have been linked to multiple psychiatric disorders including schizophrenia and bipolar disorder. (Pearce et al., 2012; Prasad et al., 2012; Tedla et al., 2011; Torrey et al., 2012).

Latent toxoplasmosis, the asymptomatic persistence of cysts in host tissues, including the brain, is prevalent in 25–30% of the global population (Pappas et al., 2009) with a relatively lower prevalence (10–15%) reported in the US (Dubey and Jones, 2008). Though previously considered harmless in immune-competent adults, latent toxoplasmosis has recently been associated with suicidal self-directed violence (SSDV), although the mechanisms underlying this association are not fully understood (Arling et al., 2009; Ling et al., 2011; Okusaga et al., 2011; Pedersen et al., 2012; Postolache and Cook, 2013; Yagmur et al., 2010; Zhang et al., 2012b). Sub-clinical personality traits, (Fekadu et al., 2010; Flegr and Havlicek, 1999; Flegr and Hrdy, 1994; Flegr et al., 2000; Flegr et al., 1996; Lindova et al., 2010, 2006) subtle neurological deficits, (Havlicek et al., 2001) and risk of motor vehicle accidents (Flegr et al., 2002; Kocazeybek et al., 2009; Yereli et al., 2006) have been previously reported in association with latent *T. gondii* infection.

T. gondii has also been linked to major psychiatric illness such as schizophrenia, (Torrey et al., 2012) bipolar disorder, (Pearce et al., 2012) and personality disorders, (Hinze-Selch et al., 2010) which individually carry an elevated risk of suicidal self-directed violence (SSDV). Each of these psychiatric disorders linked to *T. gondii* are also associated with heightened aggression (Ballester et al., 2012; Bo et al., 2013; Goodman and New, 2000; Latalova et al., 2013; Soyka, 2011; Volavka and Citrome, 2011) and impulsivity. (Chamorro et al., 2012; Moeller et al., 2001; Swann et al., 2009) Trait impulsivity and behavioral disinhibition are common among psychiatric and personality disorders and suicidal behavior. (Oquendo et al., 2004) Thus, *T. gondii*-infection, either directly or via immune activation, might induce or worsen trait aggression or impulsivity, important endophenotypes of suicidal behavior. (Baud, 2005; Kovacsics et al., 2009; Turecki, 2005) To our knowledge, trait aggression and impulsivity have never been investigated in relation to latent toxoplasmosis using a study design to minimize confounding effects of mental illness. We hypothesized that *T. gondii*-seropositivity would predict heightened trait aggression and impulsivity. We also explored sex and age effects based on previous evidence of both sex and age-related associations of personality traits with *T. gondii* infection. (Flegr and Hrdy, 1994; Flegr et al., 2000; Lindova et al., 2006).

2. Methods

2.1. Sample

Participants ($N = 1000$) were recruited as healthy controls as part of a case-control study of schizophrenia at the University of Munich, Germany. (Okusaga et al., 2013) To qualify as controls participants had to screen negatively for Axis I and Axis II disorders by Structured Clinical Interview for DSM-IV, and never have attempted suicide. Blood samples were drawn for all participants and plasma IgG antibodies to *T. gondii* and two other neurotropic pathogens (HSV1, CMV) were measured using ELISA. Of those tested for IgG antibodies, 51 (5%) did not have complete data on the personality scales and were excluded from analysis. All the participants provided written informed consent after the study procedures were explained in detail. The study was approved by the local ethics committee of Ludwig Maximilians University, Munich, Germany.

2.2. Measures

Participants were assessed by the Questionnaire for Measuring Factors of Aggression (FAF-Fragebogen zur Erfassung von Aggressivitätsfaktoren), a German version of the Buss-Durkee Hostility Questionnaire. (Buss and Durkee, 1957; Hampel and Selg, 1975) The self-administered FAF is composed of 76 items, of which 66 explore five components of aggressive behavior including FAF-Self-Aggression (11 items), FAF-Total Aggression (35 items) and its three component subscales: FAF-Spontaneous Aggression (19 items); FAF-Reactive Aggression (13 items); FAF-Irritability (13 items). Cronbach's alpha values range from 0.61 to 0.79, indicating good internal consistency with evidence of good test-retest reliability. (Buss and Durkee, 1957).

Impulsive sensation-seeking was measured using the Disinhibition [SSS-V (DIS)] subscale of the Sensation Seeking Scale-V. (Zuckerman, 1979) The SSS-V is a reliable and valid forced-choice inventory comprised of 40 items, developed to evaluate differences in individuals' needs for stimulation and arousal. (Roberti et al., 2003; Zuckerman, 1994) SSS-V (DIS) has previously been shown to have the strongest association with risky driving (Constantinou et al., 2011) and reckless behavior (Jonah et al., 2001; Roberti, 2004; Trimpop et al., 1998) of the four SSS-V subscales. Based on prior evidence of association between *T. gondii* and risk of motor vehicle accidents, (Flegr et al., 2002; Kocazeybek et al., 2009; Yereli et al., 2006) SSS-V (DIS), a measure of impulsive sensation-seeking, was selected as the primary measure of impulsivity. The SSS-V (DIS) sub-scale has previously been associated with repeated suicide attempts (Laget et al., 2006) and higher aggression. (Wilson and Scarpa, 2013).

2.3. Statistical analysis

Global tests of association between the FAF aggression scales (MANOVA) and SSS-V Disinhibition scale (ANOVA) scores by *T. gondii* seroposivity status were used to test the hypothesized association between latent toxoplasmosis and trait aggression and impulsivity. After overall tests, multivariate regression models were assessed for interactions among age, sex and *T. gondii*-positivity with adjustment for HSV-1, CMV serum status and education level. Univariate models for each FAF sub-scale and SSS-V DIS were then used to test for evidence of interactions among *T. gondii*-positivity, sex and age. Multiple linear regression models were used to obtain final estimates of scale score differences by *T. gondii*-positivity, adjusting for age, sex, education level and HSV1 and CMV antibody status. Parallel analyses were performed for both HSV1 and CMV to determine if the observed effects for *T. gondii* were agent-specific or, perhaps, reflecting more general behavioral effects of low grade immune activation related to chronic infection. (Dickerson et al., 2013; Novotna et al., 2005) Model assumptions were evaluated and final results were checked for robustness to transformations and non-linear specifications of the dependent and independent variables.

3. Results

Approximately half of the sample ($N = 475$, 50.1%) tested positively for *T. gondii* by ELISA based on IgG titer ≥ 0.8 with higher