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Failure to replicate associations between *Toxoplasma gondii* or hepatitis C virus infection and personality traits

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Abstract

Background: Infections with *Toxoplasma gondii* (Toxo), a protozoan that can infect the brain, have been reported to alter behavior in rodents and humans; several investigators have related Toxo infection to personality traits such as novelty seeking in humans. We investigated human personality traits in relation to Toxo in Egypt, where such infection is common.

Results: In a community-based sample of Egyptian adults ($N = 255$), Toxo infection were indexed by levels of IgG antibodies. Viruses like hepatitis C virus (HCV) have also been associated with cognitive dysfunction and mood disorders; therefore, HCV antibody titers were also assayed for comparison. The antibody levels were analyzed in relation to the Arabic version of the NEO personality inventory (NEO-FFI-3), accounting for demographic variables. No significant correlations were noted with Toxo or HCV antibody levels, after co-varying for demographic and socio-economic factors and following corrections for multiple comparisons.

Conclusions: Infection with Toxo or HCV infection was not associated with variations in personality traits in a sample of Egyptian adults. The possible reasons for the discordance with prior reported associations are discussed.

Keywords: *Toxoplasma gondii*, Personality, HCV, NEO, Egypt

Background

Toxoplasma gondii (Toxo), a protozoan organism, can infect all warm blooded animals. Felines serve as the definitive host. In some rodent models, Toxo-infected rats or mice show increased exploratory behavior and reduced fear of cats, potentially facilitating their capture by cats [1]. This exemplifies a mechanism through which infectious agents can ensure their survival by affecting the behavior of more complex hosts [2, 3].

Humans are accidental hosts for Toxo. Yet, Toxo can cause extensive pathology, including abortions, encephalitis, seizures, and deaths in immunosuppressed persons [4]. Infection can also occur in neonates [5]. Analogous to the rodent models, it has been reported that sub-clinical Tox infection, indexed by levels of antibodies to Toxo, is also associated with subtle changes in human behavior, such as proneness to road traffic accidents and suicide [6, 7] and even enduring changes in personality traits. Many of the behavioral changes are associated with infection are non-specific but pioneering observational and experimental studies by Dr. Flegr and his colleagues indicate more subtle variation [8], reviewed by [9] (Table 1). For example, changes in "novelty seeking," self-control, and "superego strength" have been reported [10, 11]. Other investigators have reported increase in suspiciousness, particularly among women [12]. In summary, exposure to Toxo can be associated with accentuation of certain

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Table 1 Studies reporting on toxoplasmosis and human personality trait variation

Reference	Sample	Scale	Results and conclusions
Flegr and Hrdy 1994	University staff and biology students (195 men and 143 women)	Cattell's 16-factor questionnaire	Significant correlation between chronic toxoplasmosis and two personality factors: G—low superego strength ($P=0.003$)—and L—protension (suspecting, jealous, and dogmatic) ($P=0.002$)
Flegr et al. 1996	First sample: 224 men and 170 women (university staff and students) Second sample: 190 men diagnosed with Toxo in various Prague hospitals	Cattell's 16-factor questionnaire	For men, factor G (superego strength), L (protension), O (guilt proneness), and Q2 (self-sufficiency) were positively associated with infection. For women, the associated factors were A (Affectothymia), L (protension), O (guilt proneness), and Q2 (self-sufficiency) in the first sample. Second sample: positive correlation between the duration of latent toxoplasmosis and intensity of superego strength decrease ($P<0.02$)
Flegr et al. 1998	University students and faculty members (243 men and 343 women)	Cattell's 16-factor questionnaire	Contact with cats and history of consumption of raw meat associated with specific personality traits (high "ergic" tension: tense, frustrated, high energy, and time driven). Other traits associated with anti-Toxo cellular immunity
Flegr and Havlicek 1999	Pregnant women ($N=191$; 18–39 years old)	Cattell's 16-personality factor (16PF)	Subjects with latent infection (asymptomatic) showed higher intelligence, lower guilt proneness, and higher "ergic" tension (tense, high energy, impatient, driven, frustrated, over wrought, time driven)
Flegr et al. 2000	Women diagnosed with acute toxoplasmosis ($N=230$)	Cattell's 16 PF questionnaire mailed to participants	Significant correlation between duration of toxoplasmosis and scores on factors G (high superego strength) and Q3 (high strength of self-sentiment)
Flegr et al. 2003	Male military conscripts ($N=857$)	Cloninger's Temperament and Character Inventory (TCI)	Toxoplasma-seropositive participants had lower novelty seeking scores
Lindova et al. 2006	University students ($N=263$)	Double-blind behavioral experiments	Significant interaction between gender and *Toxoplasma gondii* seropositivity for composite behavioral variables (self-control and clothes tidiness, analogous to the 16PF factors G—conscientiousness—and Q3—self-control)
Novotna et al. 2005	Military personnel ($N=533$) tested for cytomegalovirus and toxoplasma gondii exposure	Cloninger's Temperament and Character Inventory (TCI) personality test	Toxoplasma and cytomegalovirus exposure were associated with a reduction in novelty seeking
Hashim et al. 2011	Pregnant women ($N=86$, toxoplasma antibody seropositive, $N=68$, toxoplasma seronegative)	A semi- structured interview for assessment of personality and behavior changes	Rates of pseudo-psychopathic and limbic personality epilepsy syndrome were significantly higher among toxoplasma seropositive pregnant women

Table 1 (continued)

Reference	Sample	Scale	Results and conclusions
Khademvata et al. 2013	University students ($N=237$; 111 men and 126 women)	Cattell's 16 personality factor questionnaire	Women with latent toxoplasmosis had a significantly different personality profile from women without toxoplasmosis, namely higher O (apprehension), N (privateness) and Q4 (tension) scores, and lower Q1 (openness to change) scores. Infected men had significantly higher L (vigilance, mistrust) scores compared to non-infected men. Factors E (dominance) and Q1 (openness to change) tended to be higher in infected men than non-infected men, but the difference was not quite statistically significant
Cook et al. 2015	Participants ($N=1000$) were recruited as healthy controls as part of a case-control study of schizophrenia at the University of Munich, Germany	Participants were assessed by the Questionnaire for Measuring Factors of Aggression, a German version of the Buss-Durkee Hostility Questionnaire. Impulsive sensation-seeking was measured using the disinhibition subscale of the Sensation Seeking Scale-V	In a large community sample of psychiatrically healthy volunteers, latent infection with *T. gondii* was significantly associated with multiple measures of trait aggression and impulsivity. These differences were largely specific to combinations of age and sex. In particular, latent toxoplasmosis was associated with higher reactive aggression scores among women, with an opposite pattern among men. Impulsive sensation-seeking was also associated with *T. gondii* status among males under age 60

personality traits depending on the disease, duration of therapy, and psycho-social impact of the diagnosis [13].

The reported associations between Toxo infection and behavioral changes could be modulated by the effects of the parasite on neurotransmitters in the brain such as dopamine via parasite-encoded tyrosine hydroxylase) [14, 15]. The effects could also be related to direct toxic effects of the parasite on neural or non-neural tissues and the effects could be neutral or advantageous to the parasite in terms of survival, e.g., increasing the likelihood that infected hosts yield to feline predation thus Toxoplasma gains a reproductive advantage [16].

The potential effects of infectious agents on human host cognition and behavior not only have public health impacts, but they also raise important ethical and philosophical questions, such as the existence of free will [17] and whether geographical variation in infections could contribute to "modal" personality groups in different nations [18].

The studies with Toxoplasma also raise the possibility that similar or analogous behavioral changes could be induced by other agents that cause chronic infections in humans. Viruses can infect humans and herpes viruses are associated with cognitive dysfunction [19, 20]. Accumulating evidence also links infection with hepatitis C virus (HCV) with human behavioral dysfunction. Though HCV is well known as a cause of hepatic diseases, virions have also been detected in the brain [21, 22]. HCV patients have abnormalities in cerebral metabolites and P300 evoked potentials, suggesting direct effects of HCV on the human brain [23, 24]. In addition, several studies have reported downregulated mitochondrial oxidative phosphorylation genes and reduced expression of specific ribosomal protein genes in postmortem brain tissue from HCV-seropositive patients [25]. We have recently reported on cognitive dysfunction in association with hepatitis C virus infection (HCV) [26]. Many investigators have reported increased prevalence of depression among HCV-infected individuals [27–29]. Others have reported increased prevalence of personality disorders among HCV-infected individuals, including prisoners as well as community dwelling samples [30–33]. The personality clusters associated with HCV infection include cluster-B personality disorders [34], as well as impulsiveness [35].

The majority of these studies have been conducted in developed nations, particularly among individuals reporting Caucasian ancestry. It is necessary to conduct similar studies in other ethnic groups in order to evaluate their generalizability. Therefore, we investigated the relationship between Toxo and HCV infection and personality traits using a cross-sectional design in Egypt where there is a relatively high prevalence of Toxo (40–60%) and HCV infections (14.7% %) [36, 37]. We selected a community-based sample in which rates of self-reported abuse of alcohol or illicit substances are low.

Methods

Participants

This is a cross-sectional study where we will recruit Egyptian people with age ranging from 21 to 62 years old. Participants signed an informed consent after the study procedures are explained to them. We assumed within group standard deviation of 1 and alpha = 0.05 using the GPower software. We estimated power at seropositivity (exposure) rates of around 50% for Toxoplasma, based on the expected age/ethnicity distribution of our sample. At these exposure levels, our sample of 250 individuals has over 80% power.

Inclusion criteria

1. Egyptian nationality
2. Age from 18 to 65
3. Both genders
4. Written informed consent

Exclusion criteria

1. Presence of psychotic disorders
2. Current alcohol or illicit substance abuse or substance abuse in the past 6 months (DSM IV criteria)
3. Individuals who were unable to read or write
4. Severe medical condition that would affect cognitive performance such as epilepsy, history of encephalitis or severe head trauma, or any other reported neurological disorder of the central nervous system

The study was approved by the Ethics Committee at Mansoura University and the Institutional Review Board at the University of Pittsburgh.

Clinical assessment

Standard for Clinicians' Interview in Psychiatry (SCIP) [38]

A semi-structured questionnaire was administered to all participants to evaluate for the presence of psychopathology or presence of alcohol/substance abuse.

Sociodemographic data and medical history checklists

Sociodemographic data and medical history checklists were used to obtain demographic details, including occupation, handedness, level of education, and marital status, as well as history of medical disorders.

Arabic version of NEO Personality Inventory-Revised (NEO FFI-3) [39]

The NEO-FFI-3 is a 60 item version of the NEO-PI-3 that provides a brief, comprehensive measure of the five domains of personality, namely neuroticism (N), extraversion (E), openness to experience (O), agreeableness (A), and conscientiousness (C). It consists of five 12-item scales that evaluate each domain. The respondent is asked to respond along a five-point scale, varying from strongly disagree to strongly agree. The personality factors are defined by groups of correlated traits. By describing the individual's standing on each of the 5 factors, the NEO inventories provide a comprehensive evaluation of an individual`s emotional, interpersonal, experiential, attitudinal, and motivational style. NEO-PI-3 domain scales and factors measure personality at this level; facet scales offer a more fine-grained analysis by measuring specific traits within each of 5 domains. The first step in interpreting a NEO-PI-3 profile is to examine the five domain scales to understand personality at the broadest.

Serological assays

Venous blood samples were obtained from all participants (10 ml), spun down and serum extracted and stored. IgG assays for antibodies to *Toxoplasma gondii* and hepatitis C were conducted and antibody levels were estimated [40, 41]. Venous blood samples were obtained from all participants and stored at – 80 °C. IgG antibodies to HCV were assayed in the serum or plasma using a commercial enzyme-linked fluorescent assay at the certified Pathology laboratories of the Mansoura School of Medicine ("http://www.biomerieux-diagnostics.com/vidas-hepatitis-panel"). Seropositivity was defined as HCV antibodies titer > 1 as specified by the manufacturer. IgG antibodies to TOX were assayed together using solid-enzyme IgG immunoassays to estimate at the Stanley Laboratory of Developmental Neurovirology, Baltimore, Maryland [41]. Based on the distribution of TOX antibody levels, seropositivity was defined as IgG titer > 2 units.

Statistical analysis

Initially, correlations between toxoplasma antibody levels, HCV antibody levels, demographic variables, and personality domains were estimated. Separate linear regressions were conducted using the standardized score for each personality domains as the dependent variable, with HCV antibody levels, TOX antibody levels, age, gender, and years of education as independent variables. The SPSS 22 software package was used to analyze the data.

Results

Demographic and clinical characteristics

Among the participants ($N=255$), the majority were men (86.3%). They were likely to be married (92.5%) and to be in full time paid employment (92.2%). Their ages ranged from 21 to 62 years, with a mean of 40.61 and SD 11.237. The duration of education ranged from 4 years to 20 years, with a mean of 12.76 and SD of 2.846. More than a third of the participants (36.5%) were machine operators and semiskilled workers, 39.6% were unskilled workers, and the remainder had administrative, executive, or other occupations. Based on the distribution of TOX antibody levels, seropositivity was defined as IgG level > 2 units, and seropositivity was defined as HCV antibodies level > 1 as specified by the manufacturer (Fig. 1). The prevalence of toxoplasma infection and HCV infection, based on seropositivity was 52.9% and 17.6%, respectively.

Initial analyses indicated significant positive correlations between HCV level and age ($r=0.439$, $P=0.0001$) and NEO agreeableness domain ($r=0.195$, $p=0.002$). There were significant negative correlations between HCV levels and education ($r=-0.185$, $p=0.003$) and NEO openness domain ($r=$-0.186, $p=0.003$). No significant correlations were noted with Toxo levels (Table 2).

Regression analysis

Regression analyses were next conducted with NEO domains as the dependent variables, and the predictors are years of education, gender, toxoplasma level, HCV level, and age. No significant associations were noted between Toxo and HCV levels and any of the NEO domains (following corrections for multiple comparisons), though a nominally significant negative association between HCV levels and the "openness" domain was noted, consistent with the initial correlation analyses. A nominally significant association between age and neuroticism, as well as a highly significant association between gender and extraversion were also noted (Table 3). Similar patterns of associations were noted when seropositivity (based on cutoff values) was used instead of antibody levels.

Discussion

Toxo antibody levels were not significantly associated with scores on the NEO questionnaire after accounting for demographic variables, though univariate analyses indicated that HCV levels were positively correlated with "agreeableness" and negatively correlated with openness. These traits are more likely to be noted among "traditionalists," i.e., individuals who rely on the values and beliefs of their family and heritage in seeking the best way for people to live and who believe that that following the

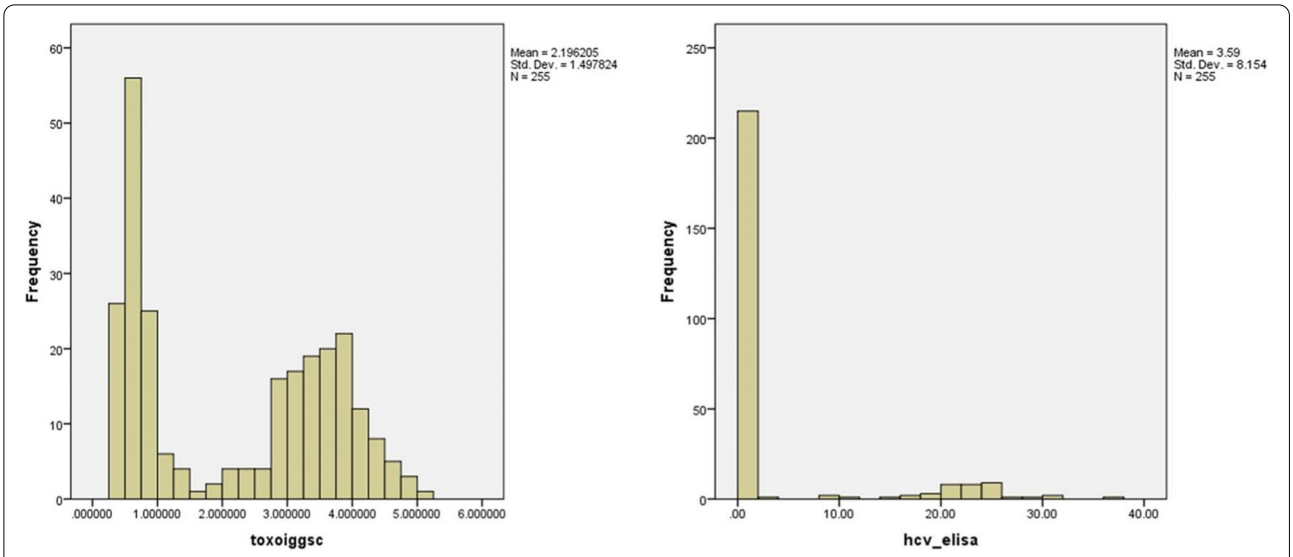

Fig. 1 Antibody titers for toxoplasma and HCV in our sample

Table 2 Correlations between antibody levels and demographic variables/personality variation

	Toxoplasma level, *p* (r)	HCV level, *p* (r)
Age	0.219 (0.077)	**< 0.0001 (0.439)**
Gender	0.83 (− 0.013)	0.622 (− 0.031)
Years of education	0.06 (− 0.118)	0.003 (− 0.185)
Occupation	0.064 (− 0.117)	0.092 (0.107)
Residence	0.655 (0.028)	0.978 (− 0.002)
Neuroticism	0.297 (− 0.066)	0.208 (− 0.079)
Extraversion	0.286 (− 0.067)	0.176 (− 0.085)
Openness	0.739 (− 0.021)	**0.003 (− 0.186)**
Agreeableness	0.19 (0.082)	**0.002 (0.195)**
Conscientiousness	0.587 (− 0.034)	0.843 (− 0.012)

established rules without questions is the best way to ensure peace and prosperity [42].

Our report differs from several studies, in which correlations with a variety of traits were reported (Table 1). Consistent and significant differences in Cattell's personality factors were found between Toxoplasma infected and uninfected subjects in 9 of 11 studies, some of which reported that men infected with Toxo were more likely to disregard rules and were more expedient, suspicious, jealous, and dogmatic. Infected women, in contrast, showed higher warmth and higher superego strength (factors A and G on Cattell's 16PF). There are several possible reasons for the differences between the published associations and the present negative report. The majority of the prior studies were conducted in European or US samples and were influenced by the type of residence (rural versus urban). Similar associations might not be detectable in other countries such as Egypt because of strain variation, because the patterns of Toxo effects are different, or because of cultural differences that impact the variations in personality traits [43]. Other differences between our study and the prior reports include having a small sample size. The associations are generally stronger among older individuals, suggesting that the effect size of the association is related to the duration of infection [44].

Table 3 Regression analysis with NEO domains

	Toxoplasma IgG level, *p* (b)	HCV IgG level, *p* (b)	Age, *p* (b)	Gender, *p* (b)	Years of education, *p* (b)
Neuroticism	0.407 (− 0.262)	0.976 (− 0.002)	0.030 (− 0.104)	0.549 (0.830)	0.570 (0.097)
Extraversion	0.375 (− 0.289)	0.121 (− 0.104)	0.503 (0.033)	< 0.001 (5.182)	0.565 (0.102)
Openness	0.852 (− 0.058)	0.048 (− 0.124)	0.018 (− 0.111)	0.098 (− 2.236)	0.039 (− 0.343)
Agreeableness	0.317 (0.451)	0.086 (0.159)	0.056 (0.131)	0.030 (4.286)	0.342 (− 0.232)
Conscientiousness	0.67 (− 0.178)	0.685 (− 0.035)	0.761 (0.019)	0.157 (2.589)	0.889 (− 0.032)

The NEO domains were the dependent variables and the predictors were years of education, gender, antibody levels, and age

In a similar vein, we did not detect significant associations between HCV levels and personality traits using the NEO inventory, though several studies have reported on associations between HCV infection and personality traits [30–32] [33] as well as depressed mood [28, 45, 46].

Some limitations of the present study need to be considered. Men were over-represented in the sample, with predominantly employed and married individuals. Thus, the sample represents only one segment of the Egyptian population. In addition, it included relatively healthy individuals; thus, possible effects related to symptomatic infection with Toxo or HCV could not be investigated. As infection was identified on the basis of antibody levels in the serum, the precise timing or the duration of infection could not be estimated.

Conclusions

Toxo or HCV infections were not associated with variation in personality traits in a community-based sample of Egyptian adults. Further studies, including investigations of more severely infected individuals, as well as older individuals are indicated.

Abbreviations

DSM IV: The Diagnostic and Statistical Manual of Mental Disorders; : Fourth Edition; HCV: Hepatitis C virus; IgG: Immunoglobulin G; NEO-FFI-3: NEO personality inventory; Toxo: Toxoplasma gondii.

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Authors' contributions

Il helped in the design, interviewing the subjects, and writing the manuscript.
ST helped in the design of the study and writing of the manuscript.
HS helped in interviewing the subjects.
HE helped in interviewing the subjects.
HM helped in the design of the study and in writing the manuscript.
AE helped in interviewing the subjects.
JW helped in the data analysis.
WF helped in interviewing the subjects.
FD helped in the design of the study and in writing the manuscript.
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WE helped in the design of the study and in writing the manuscript.
VN helped in the design of the study and in writing manuscript.
The authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee at Mansoura University and the Institutional Review Board at the University of Pittsburgh.

Consent for publication

Not applicable

Competing interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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