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Chronic *Toxoplasma gondii* infection is associated with decreased working memory performance in women

Infecção crônica por Toxoplasma gondii *está associada à diminuição de desempenho da memória de trabalho em mulheres*

Laiany Nayara Barros Gonçalves[1], Italo Ramon Rodrigues Menezes[1], Jennifer Lee Palmer[1], Ivani Brys[1]

[1] Universidade Federal do Vale do São Francisco, Programa de Pós-Graduação em Psicologia, Grupo de Pesquisa em Neurociência e Psicologia Experimental. Petrolina, PE, Brasil. Correspondence to: I. BRYS. E-mail: <ivani.brys@univasf.edu.br>.

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Abstract

Objective
The present study sought to investigate changes in mood, inhibitory control, and working memory associated with *T. gondii* infection in a sample of Brazilian women.

Method
Twenty-eight female participants were equally distributed into two groups, according to the serology for chronic infection by *T. gondii*. The participants answered a Sociodemographic questionnaire, the CES-D, and performed Simon and N-Back tasks.

Results
Infected participants presented less accuracy and longer response time in N-Back tasks. No significant differences were found in the Simon task performance or in the depression levels.

Conclusion
Our findings suggest that chronic infection by *T. gondii* may result in impaired working memory and point out the importance of public policies aiming at preventing this infection.

Keywords: Depression; Memory, short-term; Toxoplasmosis.

Resumo

Objetivo
O presente estudo investigou alterações de humor, controle inibitório e memória de trabalho associadas à infecção por T. gondii em uma amostra de mulheres brasileiras.

Método
Vinte e oito participantes foram distribuídas igualmente em dois grupos de acordo com a sorologia

para infecção crônica por T. gondii. As participantes responderam a um questionário sociodemográfico, à CES-D e realizaram as tarefas Simon e N-Back.

Resultados

As participantes infectadas apresentaram menor acurácia e maior tempo de resposta na tarefa N-Back. Nenhuma diferença significativa foi encontrada na tarefa Simon ou na escala de depressão.

Conclusão

Nossos achados sugerem que a infecção crônica por T. gondii pode resultar em comprometimento da memória de trabalho, e apontam para a importância de políticas públicas de prevenção dessa infecção.

Palavras-chave: *Depressão; Memória de curto prazo; Toxoplasmose.*

In rodents, *T. gondii* infection has harmful effects on the organism, with infected animals losing their fear and approaching felines. Such behavioral change makes it easier for the rodent to be preyed upon, making the parasite reach its final destination – the feline intestine – more easily (Boillat et al., 2020; Omar et al., 2018). Similar results were found in chimpanzees, which lost their aversion to leopard's urine when infected with *T. gondii* (Poirotte et al., 2016). In addition, infected mice have less capacity to consolidate memories involving fear, lower serotonin levels in the amygdala, and less noradrenaline levels in the cortex and amygdala (Ihara et al., 2016).

Modern humans are no longer preyed upon by felines and, consequently, intermediate hosts of interest to *T. gondii*. However, cognitive, behavioral, and mood changes have been associated with *Toxoplasma gondii* infection in humans (de Haan et al., 2021; Martinez et al., 2018; Johnson & Johnson, 2021). Studies indicate that *T. gondii* may be associated with the occurrence of some psychiatric disorders, such as depression (Nasirpour et al., 2020; Kamal et al., 2020; Sapmaz et al., 2019), anxiety (Akaltun et al., 2018; Bay-Richter et al., 2019; Lin et al., 2020), and schizophrenia (Chaudhury & Ramana, 2019; Fond et al., 2018; Xiao et al., 2018).

Regarding cognition, *T. gondii* has been considered responsible for affecting the long-term ability of infected people to concentrate (Havlíček et al., 2001). Evidence shows that infected subjects are more likely to cause traffic accidents (Gohardehi et al., 2018), which would be associated with the change in circulating dopamine levels in the body caused by the protozoan parasite (Flegr, et al., 2009; Yereli et al., 2006). Positive serology for *T. gondii* has also been associated with aggressive reactive behaviors in women and impulsive behaviors in young men (Cook et al., 2015), suggesting that *T. gondii* affects inhibitory control.

Working memory is another aspect of executive functions in which the effects of *T. gondii* infection have been investigated. Wyman's et al. study (2017) found no differences in working memory between participants with negative serology and participants with positive serology for *T. gondii*. However, in the studies by Sugden et al. (2016) and Wiener et al. (2020), positive serology for *T. gondii* was associated with decreased performance in working memory.

While the changes caused by the protozoan in the behavior of rodents and non-human primates are well established (Abdulai-Saiku & Vyas, 2017; Ihara et al., 2016; Poirotte et al., 2016), studies on the effects of infection on human cognition and behavior show controversial results. It is estimated that more than one third of the world population is infected with *T. gondii* and seroprevalence data in Latin America are scarce (Beck et al., 2013; Foroutan & Ghaffarifar, 2018). In Brazil, a study carried out with pregnant women showed that antibodies to *T. gondii* were present in 67.3% of the participants (Beck et al., 2013). Cross-sectional studies performed in a small city with rural characteristics located in the Southeastern region of Brazil (Passos et al., 2018) and in

a predominantly urban small city located in the Southern region of Brazil (Mareze et al., 2019) demonstrated that, respectively, 62.3% and 73.57% of the participants were positive for *T. gondii*. However, studies on the cognitive and behavioral effects of toxoplasmosis in the Brazilian population are, to the best of our knowledge, still nonexistent. The Brazilian Ministry of Health recommends that serological screening (detection of antibodies of the IgG class for the chronic phase and the IgM class for the acute phase) be performed during prenatal care, due to the risk of infection by *T. gondii* during pregnancy, in the development of the fetus. From this, the study of the effects of *T. gondii* on the female population in this country becomes a viable and low-cost alternative, since Brazilian mothers who had prenatal care are informed about their serology results for toxoplasmosis.

In this sense, the present study sought to investigate changes in mood, inhibitory control and working memory associated with *T. gondii* chronic infection in mothers with children up to one year old. This is a pioneering study in the investigation of possible associations between infection and cognitive changes in women in the Vale do São Francisco Region in Brazil.

Method

Participants

Twenty-eight women with an average age of 27.93 (*SD* = 5.94) with children between 3 and 12 months of age participated in the study and were distributed into two groups, according to the serology for chronic infection by *T. gondii*: Infected group (*n* = 14) and Control group (*n* = 14). The inclusion criteria were: being over 18 years old and having a healthy child or children; presenting their serologic test results for chronic infection by *T. gondii* (identified by the IgG serological response), performed during the most recent prenatal care appointment; having attended childcare appointments accompanied by another adult who was responsible for the care of the child in cases when data collection occurred in health facilities.

The exclusion criteria were: being illiterate; having been diagnosed with toxoplasmosis; having been infected with Zika virus or another disease during pregnancy; using medications that act on the central nervous system; being unable to understand the research instruments and/or answer them consistently; having undergone treatment for toxoplasmosis previously; and having been infected with *T. gondii* during pregnancy (identified by the IgM serological response).

The socio-demographic characteristics of the participants were similar in both Groups, as shown in Table 1.

Instruments

Sociodemographic questionnaire – This questionnaire was created by the authors and aimed to collect information about the participants' social and economic status, pregnancy history, basic knowledge of toxoplasmosis, contact with cats, age, and functional characteristics, such as educational level and family income. Also, it aimed to record the participant's contact information.

Population Tracking Scale for Depression (CES-D) – It is used to identify depressive mood through the participants' self-report. This scale assesses the occurrence of 20 indicators (from 0 to 3 points each) of a depressive condition, with a cut-off point of 15 (Hauck Filho & Teixeira, 2011). It consists of a list of feelings and behaviors experienced in the week before the interview, which may occur as follows: rarely – for less than 1 day; for a short time – between 1 and 2 days; for a

moderate time – between 3 and 4 days; most of the time – between 5 and 7 days. Hauck Filho and Teixeira (2011) revealed in their original study, a structure of four factors for this scale: depressed mood, positive affections, somatic symptoms, and interpersonal problems. Hauck Filho and Teixeira (2011) applied the CES-D scale to Brazilian undergraduate students, finding a Cronbach's alpha of 0.89 corroborating the original model of Radloff (1977), and providing evidence of construct validity.

Simon Task (Simon & Wolf, 1963) – It aims to assess skills, such as inhibitory control and selective attention (Trevisan, 2010). In our study, the words "right and left" were used, and the participant should press the "L" key whenever the word "right" appeared on the screen and the "A" key whenever the word "left" appeared, regardless of which side they appeared on. The stimuli were presented on the screen in a congruent manner (key on the keyboard and word stimulus on the screen in the same position) and incongruent (key on the keyboard and word stimulus on the screen in opposite positions). Responses are faster when stimuli are congruent. Based on this, the Simon Effect is given by the difference between Manual Reaction Times (MRTs), in the condition in which the stimulus is incongruent (longer MRTs), compared to the condition in which they are congruent (minor MRT; Hommel, 2011).

Table 1
Socioeconomic and demographic characteristics of the participants. The table shows the distribution of participants by group (Control and Infected), at each level of socioeconomic and demographic variables

Socioeconomic and Demographic Variables	Control (*n* = 14)		Infected (*n* = 14)	
	n	%	*n*	%
Educational level				
Elementary school (incomplete)			1	7.1
Elementary school (complete)				
High school (incomplete)			3	21.4
High school (complete)	5	35.7	7	50.0
College degree (incomplete)	2	14.3	1	7.1
College degree (complete)	7	50.0	2	14.3
Monthly Household Income				
Less than one minimum salary/month	1	7.1	2	14.3
Between one and three minimum salaries/month	3	21.4	8	57.1
Between four and six minimum salaries/month	10	71.4	4	28.6
Beneficiary of Social Program (*Bolsa Família*[2])				
Receives Financial Aid	2	14.3	3	21.4
Does not Receive Financial Aid	12	85.7	11	78.6
Basic sanitation				
Has	10	71.4	13	92.9
Does not have	4	28.6	1	7.1
Cat				
Has	6	42.9	6	42.9
Does not have	8	57.1	8	57.1
Comorbidity				
Has	2	14.3		
Does not have	12	85.7	14	100.0
Pregnancy Problems				
Had	3	21.4	2	14.3
Did not have	11	78.6	12	85.7
Toxoplasmosis Information				
Knows something about it	5	35.7	7	50
Has heard of it	9	64.3	6	42.9
Does not know anything about it			1	7.1

Note: The absence of values means that there were no participants with this characteristic in the sample. Bolsa Família (Family Allowance) was a Brazilian Federal Government Program that offered low-income families the monthly sum of US$ 12,11 for children and adolescents under 15 years of age

N-Back task (Dobbs & Rule, 1989) – The N-Back task was used to assess working memory. This was done by presenting a stimulus to the participant, who should memorize it while evoking the stimulus that was presented to them in previous positions (Dobbs, & Rule, 1989). In the version used in this study, the participant was exposed to a sequence of stimuli, after being instructed to identify the stimulus presented three (3-back) positions before each new stimulus, by pressing the M key. For the other conditions, they should press the N key. The participant had to check, therefore, if the stimulus presented at that moment was equal to the antepenultimate one presented. Correct and incorrect responses, omissions and response times were counted for each type of response.

The procedures adopted in this research followed the Ethics Criteria in Research with Human Beings, according to Resolutions nº. 466/2012 and 510/2016 of the National Health Council. The Ethics Committee of the Federal University of Vale do São Francisco approved the project (CAAE nº. 86671318.4.0000.5196).

Procedures

Participants were recruited during visits to Basic Health Units and through social networks. Eight women were recruited through visits to the Basic Health Units in the city of Petrolina (PE, Brazil), and 20 through dissemination on social networks.

After accepting and signing the Informed Consent Form, the participant's medical records or the results of the prenatal exams were consulted to verify the occurrence of *T. gondii* infection and to define which group she would belong to: Infected or Control.

Then, the participants answered the sociodemographic questionnaire and, subsequently, the scales (in printed format). Cognitive tasks were applied individually using notebook computers, in a room free of interruptions.

Data Analysis

Fisher's exact test and Chi-square analysis were performed to check for significant socioeconomic and demographic differences between groups. The Shapiro-Wilk test was used to assess the normality of data provided by CES-D and computerized tasks. This test pointed out that the N-Back accuracy score and the response time for correct answers in other N-Back conditions have a non-parametric distribution ($p < 0.05$), all other variables in this study have a normal distribution ($p > 0.05$).

Differences in the CES-D scale were assessed using the t-test for independent samples. To analyze the N-Back, the number of errors, correct answers, omissions, the response time, and accuracy were used, which is the percentage of attempts correctly answered. To analyze the Simon task performance, the number of errors, correct answers, omissions, response time, accuracy and Simon Effect were used, which is the subtraction of the average time of correct answers in attempts in congruent and incongruent conditions, corresponding to the period that it takes to inhibit an automated procedure. Also, these variables were compared between groups using the t-test and the Mann-Whitney test. The Cronbach's alpha of the Simon task was calculated using the average time to correctly answer in congruent and incongruent conditions.

The criterion for statistical significance adopted was $p < 0.05$, and all tests were performed using the IBM®SPSS® (version 21).

Results

Participants are at Risk for Depression, which was not Associated with *T. gondii* Infection

The occurrence of depressive symptoms was tracked through the application of CES-D. 46.4% of the participants had a score equal to or higher than 16 on the CES-D scale, indicating that they can be considered at risk for depression or in need of treatment. In the Infected group, the percentage of participants with a score equal to or greater than 16 was 57.1%, while in the Control group it was 35.7%. However, the t-test pointed out that there were no significant differences between the scores of the groups in the CES-D [t (26) = -0.552, p = 0.57], see Table 2.

Table 2
Table 2 contains the descriptive data used to perform group comparisons

Measure	Group	
	Control	Infected
CES-D Score	*M* = 15 (*SD* = 3.234)	*M* = 15.79 (*SD* = 4.228)
Accuracy (Simon Task)	*M* = 94.42 (*SD* = 4.036)	*M* = 92.83 (*SD* = 3.872)
Simon effect	*M* = 37.22 (*SD* = 77.350)	*M* = 86. 955 (*SD* = 86.855)
Average response time for correct answers in congruent conditions (Simon Task)	*M* = 847.13 ms (*SD* = 101.646)	*M* = 884.91 ms (*SD* = 146.172
Average response time for correct answers in incongruent conditions (Simon Task)	*M* = 884.35 ms (*SD* = 97.645)	*M* = 901. 361 ms (*SD* = 159.206)
Accuracy (N-Back)	*Mdn* = 75.85 *	*Mdn* = 68.35
Time used in correct answers in other conditions (N-back)	*Mdn* = 606.02 ms *	*Mdn* = 740. 5635 ms
Average response time used in correct answers in the 3-back condition	*M* = 839.86 ms (*SD* = 163.75)	*M* = 871.32 ms (*SD* = 206.9)

Note: ***** Represents a significant difference between groups (p < 0.05). M: Mean; SD: Standard Deviation ff Mean; ms: Millisecond; Mdn: Median.

T. gondii Infection is not Associated with Decreased Inhibitory Control

The inhibitory control was assessed using a software version of the Simon task (Cronbach's alpha of 0.88, with an amplitude of 26.83 and a variance of 360.06). No significant differences in task performance were found between the Infected and Control groups with respect to accuracy [t (26) = -1.06, p = 0.28, Figure 1A], Simon effect [t (26) = -0.698 , p = 0.48, Figure 1B], average response time for correct answers in congruent conditions [t (26) = -0.794, p = 0.42], or average response time for correct answers in incongruent conditions [t (26) = -0.341, p = 0.72], see Table 2.

T. gondii Infection is Associated with Decreased Working Memory Performance

Working memory was assessed using the computerized N-Back task. In this task, the variables analyzed were accuracy, the average response time for correct answers in the condition in which the participant should press M (3-back), and the average response time for correct responses when the participant should press N (Other conditions). Significant differences were found between the groups regarding accuracy [U = 40, p < 0.05, Figure 2A] and response time for correct answers in other conditions [U = 32, p < 0.005, Figure 2B], with infected participants presenting being less accurate and taking longer response times for correct answers in conditions other than 3-back. The average response time for correct answers in the 3-back condition was similar (p > 0.05) between the Control: *M* = 839.86 milliseconds (ms), *SD* = 163.75 ms and Infected groups: *M* = 871.32 ms, *SD* = 206.9 ms.

Figure 1

T. gondii *infection is not associated with decreased inhibitory control. No significant differences between groups were found in the Simon task*

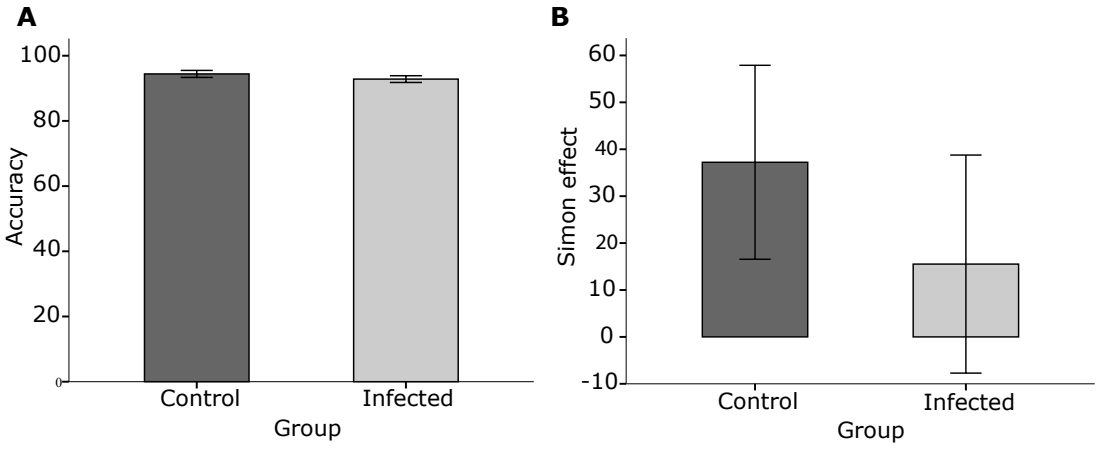
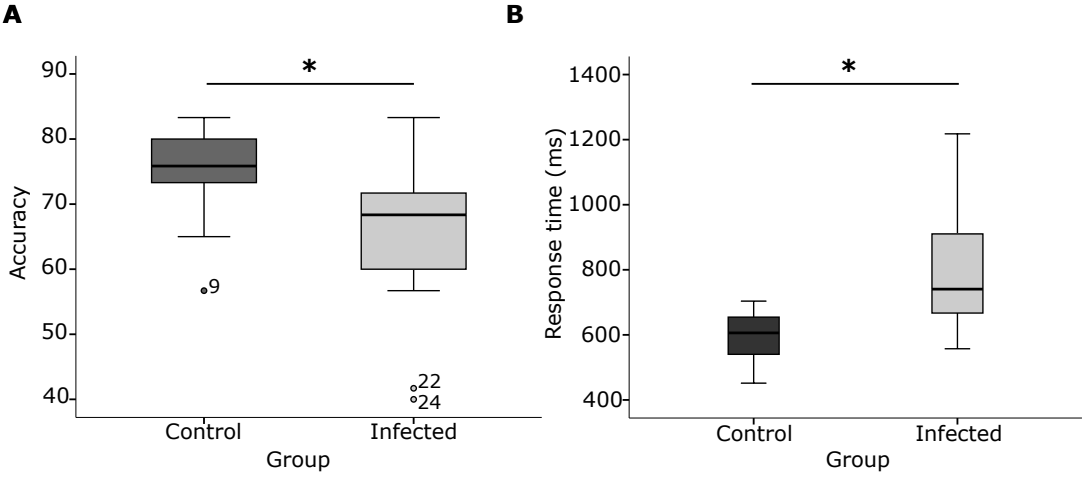


Figure 2

T. gondii infection is associated with decreased performance in the N-Back task



Note: * Represents a significant difference between groups ($p < 0.05$).

Discussion

In this study we investigated the association between *Toxoplasma gondii* infection and mood, and cognitive changes in a sample of women from the Vale do São Francisco region. Our results showed that infected and uninfected participants do not present differences in depression indices, assessed using a CES-D scale. These data are in line with a meta-analysis study (Chegeni, 2019) and other studies (Alvarado-Esquivel et al., 2017; Shiadeh et al., 2016), which demonstrated that there is no association between the presence of *T. gondii* antibodies and depressive symptoms, suggesting that *T. gondii* infection cannot be considered a risk factor for the development of depression even in the postnatal period (Gao et al., 2019).

However, although we did not find a significant association between *T. gondii* infection and depressive symptoms, our data demonstrate that more than half of the infected participants are at

risk of depression, suggesting that the occurrence of depressive symptoms may happen according to the levels of infection by the parasite as demonstrated by Shiadeh et al. (2016). To better address the association between *T. gondii* infection and mood alterations, it would be important to investigate if the inflammatory process caused by the invasion of the parasite is associated with the appearance and maintenance of depressive symptoms in studies performed with larger sample sizes.

It is important to note that, in the present study, we did not aim to investigate the association between other factors and the occurrence of depressive symptoms. However, considering the high incidence of depressive symptoms in the participants, we emphasize the importance of conducting further studies with this population of mothers to better understand these findings. Depression has been identified as a multifactorial mood disorder, and social factors, such as the quality of support received by the mother during this period, can contribute to the onset of depressive symptoms in the postnatal period (Piccinini et al., 2014). Also, whether the pregnancy was planned or not and the mother's socioeconomic status are risk factors for postpartum depression (Carlesso et al., 2019). Future studies should investigate how the interaction between these social and biological factors contribute to the mother's disease in this period and seek to develop prevention and care strategies for women after the baby is born.

Contrary to what has been demonstrated in some studies, our results indicate that the infected participants did not show significant differences in performance regarding the inhibitory control, assessed through the Simon task. This contradiction can be explained, at least partially, by methodological differences between the studies, since we did not find another study that used the Simon task or that assessed inhibitory control similarly. The studies we found (Cook et al., 2015; Sugden et al., 2016) assessed complex behaviors, such as non-suicidal self-injury, which are influenced by inhibitory control, but also involving other constructs.

Our results are an addition to those of Cook et al. (2015) and those of Sugden et al. (2016), which demonstrated little or no effect of infection by the protozoan parasite on inhibitory control. The first used a questionnaire to assess five factors related to aggression and found a difference between women in the Control group and the Infected group only in reactive aggressiveness (Cook et al., 2015). The second study assessed the relationship between positive serology for *T. gondii* and impaired impulse control. For this, four factors were examined: non-suicidal self-harm, attempted suicide, criminal convictions, infractions, and traffic accidents. The only association found by the authors was between infection by *T. gondii* and suicide attempts (Sugden et al., 2016). Such results need to be further investigated in future studies that can assess the relationship between inhibitory control, infection by *T. gondii*, and complex behaviors such as suicide attempts or aggressive acts.

In our study, working memory was the only variable that significantly differed between groups. The Infected group showed less accuracy and longer reaction time for responses other than the 3-back in the N-Back task when compared to the Control group. These results are in line with studies that have shown an association between *T. gondii* infection and memory impairment in humans (Sugden et al., 2016) and animals (Ihara et al., 2019). In rodents, Ihara et al. (2016) demonstrated that infected animals have reduced capacity to consolidate the fear memory.

Using methodology similar to the present study, Gajewski et al. (2014) demonstrated that elderly people infected with *T. gondii* present impaired performance in working memory, evidenced by greater number of omissions in the N-Back task, with a 2-back condition. Our results, therefore, add to the literature evidence that infection by *T. gondii* may be associated with cognitive impairments, specifically associated with working memory.

It is important to note that the present study was performed with a small sample of Brazilian women and non-parametric tests were used, which compromises the generalizability of the findings. Furthermore, the present study has as a limitation the fact that the serological examination for *T. gondii* was previously performed by participants in the public health care system or by private health insurance companies. This made it possible to carry out the study because it would be financially unfeasible for the researchers to perform the serology, but it limited the population from which the sample was taken. Another important limitation concerns the time between the moment the participants did the serological test and our data collection. The participants were mothers with children up to one year old, in an attempt to minimize this time and the chances of the woman being infected until participating in the study. However, we emphasize that studies carried out with financial support must perform serological testing at the time of data collection to ensure whether the participant has been previously exposed to the parasite or not.

Conclusion

Our results show that chronic *T. gondii* infection is associated with decreased memory performance in a sample of Brazilian women. To the best of our knowledge, this is the first study showing that chronic *T. gondii* infection may be associated with cognitive changes in the Brazilian population. We conclude, therefore, that the development of public policies aiming at preventing *T. gondii* infection should be considered by the Brazilian health and sanitary authorities.

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Contributors

L. N. B. GONÇALVES was responsible for the conception and design of the research, data collection, interpretation of data and writing the manuscript. I. R. M. RODRIGUES helped with data collection, was responsible for data analysis and reviewed the final version of the manuscript. J. L. PALMER was responsible for creating the online version of the cognitive tasks. I. BRYS was responsible for the conception and design of the research, supervised the study, reviewed and approved the final version of the manuscript.