The impact of *Toxoplasma gondii* infection on cognitive deficits, other symptoms and digital neuroscience-informed cognitive training in patients with schizophrenia

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INTRODUCTION

Schizophrenia is a complex debilitating neuropsychiatric disorder and its prevalence is estimated in approximately 1% of the world population **(SAHA *et al.*, 2005)**. Subjects with schizophrenia present a large range of symptoms, which significantly impact their quality of life and about 85% of them have some degree of cognitive impairment **(RITSNER, 2007)**. The etiology of schizophrenia remains unknown, although several risk factors have been identified. For instance, infectious agents, such as *Toxoplasma gondii (T. gondii)*, are environmental factors that significantly increase the risk of schizophrenia **(YOLKEN *et al.*, 2008)**. However, it is not clear how *T. gondii* infection affects schizophrenia, especially in terms of cognitive impairment and specific clinical symptoms associated with the disorder. Considering the uncertain impact *T. gondii* infection may have on schizophrenia, we posed two questions: 1) Is previous contact with the parasite associated with poorer cognitive performance and increased symptoms? 2) Could this previous contact with *T. gondii* result in different responses to neuroscience-informed digital cognitive training?

MATERIALS AND METHODS

To answer these questions, we measured IgG titers for *T. gondii* from individuals with schizophrenia who participated in a randomized, double-blind clinical trial on auditory versus visual cognitive training **(SCORIELS *et al.*, 2020)**. Blood samples and cognitive and symptoms assessments were collected before and after cognitive training. Statistical analyses were performed using IBM SPSS (28.0 version) and STATA (Version 8.0) Softwares.

RESULTS AND DISCUSSION

Table 1. Participants' baseline characteristics

	All subjects (n=60)	TOXO- (n=35)	TOXO+ (n=25)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	Uncorrected t or χ^2 / N^o (p)*	Age-corrected β or F (p)*
Age (years)	39 (11)	37 (12)	42 (10)	**4.09 (0.04)**	
Female/male	18/44	10/27	8/17	0.17 (0.67)	
Education (years)	11.3 (2.7)	11.9 (2.4)	10.6 (3)	*1.70 (0.09)*	
IQ	101 (13)	104 (12)	98 (14)	*1.81 (0.07)*	
Years of Illness	16 (10)	15 (9)	20 (11)	-1.34 (0.19)	
CPZ equivalent (mg)	483 (403)	463 (346)	516 (488)	0.01 (0.91)	
Baseline cognition (z-scores)					
Speed of processing	-1.34 (2.26)	-1.07 (2.17)	-1.73 (2.37)	1.42 (0.23)	-0.19 (0.80)
Attention	-1.32 (1.40)	-0.97 (1.17)	-1.81 (1.56)	**2.41 (0.01)**	-0.55 (0.32)
Working memory	-0.26 (1.13)	-0.07 (1.23)	-0.54 (0.87)	1.63 (0.10)	1.91 (0.17)
Verbal learning	-0.11 (1.14)	0.15 (1.19)	-0.49 (0.97)	*1.26 (0.67)*	**4.48 (0.03)**
Visual learning	-1.52 (1.40)	-1.32 (1.35)	-1.81 (1.44)	1.22 (0.22)	0.17 (0.67)
Reasoning and problem solving	-0.08 (0.68)	-0.05 (0.66)	-0.11 (0.80)	0.03 (0.87)	-0.00 (0.99)
Social cognition	-0.57 (0.72)	-0.18 (0.74)	-0.67 (0.59)	**2.52 (0.01)**	**5.71 (0.02)**
Global cognition	-0.75 (0.83)	-0.50 (0.78)	-1.05 (0.82)	**2.59 (0.01)**	**3.78 (0.05)**
Baseline clinical measures (range)					
HAM-D (0-54)	6.36 (5.70)	6.83 (6.02)	6.17 (5.31)	0.07 (0.78)	0.00 (1.00)
HAM-A (0-56)	7.00 (6.73)	6.94 (6.77)	7.08 (6.81)	0.13 (0.71)	1.00 (0.57)
PANSS Positive score (7-49)	13 (5)	14 (5)	13 (5)	0.00 (0.60)	0.19 (0.66)
PANSS Negative score (7-49)	15 (6)	16 (6)	15 (8)	0.98 (0.65)	0.32 (0.57)
PANSS General score (16-112)	28 (7)	29 (7)	28 (7)	0.02 (0.49)	0.39 (0.53)
PANSS Total Score (30-210)	58 (14)	59 (15)	56 (13)	0.82 (0.49)	0.45 (0.50)
T. gondii IgG level			79.08 (23.68)		

Table 2. . Changes in cognition and symptoms after digital training among TOXO+ and TOXO- groups

	TOXO- (n=35)	TOXO+ (n=25)	Statistics
	Mean (SD)	Mean (SD)	Uncorrected t or χ^2 (p)*	Age-corrected β (p)*
Changes in cognition (z-scores)				
Speed of processing	-0.37 (1.98)	-0.09 (1.91)	0.09 (0.92)	-0.05 (0.82)
Attention	0.17 (0.63)	0.69 (1.12)	**5.47 (0.01)**	**0.64 (0.02)**
Working memory	-0.00 (0.71)	0.09 (0.83)	-0.49 (0.62)	0.16 (0.68)
Verbal learning	-0.09 (0.82)	0.11 (0.71)	0.70 (0.40)	0.32 (0.13)
Visual learning	0.32 (1.12)	0.35 (1.37)	0.06 (0.79)	0.29 (0.24)
Reasoning and problem solving	0.27 (0.49)	0.39 (0.74)	0.05 (0.82)	0.11 (0.52)
Social cognition	0.04 (0.31)	0.24 (0.61)	2.41 (0.12)	**0.49 (0.03)**
Global cognition	0.06 (0.40)	0.32 (0.51)	**22.37 (0.02)**	0.18 (0.25)
Changes in symptoms (raw data)				
HAM-D	-1.08 (4.15)	-0.17 (4.06)	-0.82 (0.41)	0.00 (1.00)
HAM-A	-0.65 (5.30)	-1.04 (5.38)	1.17 (0.27)	-1.00 (0.42)
PANSS Positive	-1.06 (2.75)	-2.87 (3.55)	**2.18 (0.03)**	2.48 (0.12)
PANSS Negative	-0.37 (5.23)	-0.78 (4.69)	0.00 (0.95)	0.00 (1.00)
PANSS General	-2.20 (5.92)	-1.39 (5.68)	0.00 (0.94)	-0.42 (0.83)
PANSS Total	-3.63 (9.99)	-4.17 (8.33)	0.43 (0.50)	-4.00 (0.15)

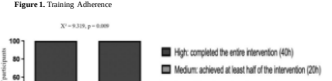

Figure 1. Training Adherence

CONCLUSION

In conclusion, we found that previous *T. gondii* infection was associated with worse cognition and higher symptoms of schizophrenia. Notwithstanding, the TOXO+ group showed larger gains in attention and social cognition after neuroscience-informed cognitive training, with higher adherence. Thus, although presenting worse cognition and clinical status, schizophrenia subjects with previous *T. gondii* infection are able to engage and benefit from a digital cognitive intervention.

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