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Randomized controlled trial of adjunctive Valproate for cognitive remediation in early course schizophrenia

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ABSTRACT

Background: Schizophrenia (SZ) is associated with cognitive impairment that contributes to disability, but the cognitive dysfunction is relatively refractory to pharmacologic intervention. Though Valproate augmentation is reported to improve psychopathology among patients with SZ, its effects on cognitive functions have not been investigated systematically.

Methods: Using a randomized double blind placebo controlled design, the effects of Valproate or placebo as adjuncts to risperidone (RISP) treatment were evaluated among patients with early course SZ (N = 109). Domains of cognitive function, estimated using the Arabic version of the Penn Computerized Neurocognitive Battery, were the prime outcomes. Clinical severity and social function were secondary outcomes. We also explored the effects of valproate treatment on serological responses to Toxoplama Gondii (TOXO), a putative risk factor for cognitive dysfunction in SZ.

Results: There were no significant differences between Valproate and placebo (PLA) treated groups with respect to changes in cognitive functions, positive or negative symptom scores or daily function scores at the beginning and end of the study. No significant Valproate/PLA differences were noted on TOXO serostatus or TOXO-related cognitive dysfunction.

Conclusion: Valproate treatment may not be beneficial for cognitive dysfunction in SZ or for TOXO infection.

1. Introduction

Schizophrenia (SZ) has a lifetime prevalence of approximately 1%, worldwide (Saha et al., 2005). It extracts a heavy burden on patients, their families and on healthcare systems (Aliyu MH et al., 2006). Cognitive dysfunction is a core manifestation of SZ that is associated with social dysfunction and outcome (Kahn and Keefe, 2013). Though many anti-psychotic medications can alleviate psychotic features of SZ, they are relatively ineffective for the cognitive deficits associated with the disorder (Conley and Kelly, 2001) (Fusar-Poli et al., 2015; Harvey et al., 2016). As the impetus for new drug development has waned in the pharmaceutical industry (Hyman, 2012), there is growing interest in repurposed drugs, i.e., drugs that are already licensed for human use in other conditions (Lee and Kim, 2016). Sodium valproate (Depakote, DEP) was initially marketed as an anticonvulsant (Loscher, 1999), but has gained acceptance as a mood stabilizing agent in bipolar disorder (Rapoport et al., 2009). Its value in augmenting antipsychotic drugs has also been suggested among individuals with SZ (Tseng et al., 2016;

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Wang et al., 2016). Augmentation therapy with valproate was associated with more rapid response, reduced hostility and aggression (Frankenburg and Zanarini, 2002).

The beneficial effects of Valproate in SZ may be related to several effects. Adjunctive treatment with Valproate increases serum levels of haloperidol (Dose et al., 1998), risperidone (Sund et al., 2003) and clozapine (Facciola et al., 1999). The benefits of valproate could also stem from effects on catecholaminergic and GABAergic function (Guidotti et al., 2009; Guidotti and Grayson, 2014) (Ichikawa et al., 2005). Though the effects of Valproate on psychopathology have been investigated, its effects on cognitive functions have not been reported among individuals with SZ. Valproate has potent inhibitory effects on Toxoplasma Gondii (TOXO) infection *in vitro* (Therapeutic index: 12.7) (Jones-Brando et al., 2003), which led us to speculated about its possible beneficial effects for cognitive dysfunction. Several studies have reported associations between TOXO infection and SZ(Ahmad et al., 2010; Alvarado-Esquivel et al., 2011; Cetinkaya et al., 2007; Hamidinejat et al., 2010; Pedersen et al., 2011); a meta-analysis of 23 studies suggested a combined odds ratio (OR) of 2.73 (95% confidence interval, 2.10, 3.60)(Torrey et al., 2007; Yolken et al., 2017). Further, TOXO infection is also associated with cognitive impairment in some (Pearce et al., 2014), but not all studies (Ibrahim et al., 2016). Infections with TOXO are zoonotic, i.e., they normally infect rodents through cats. Following acute infection, a latent stage with cyst formation occurs in the brain. Humans are accidental hosts, and infections occur in the post-natal period (Webster, 2001). Chronic infection, with cyst formation can occur in the brain, and some studies have found worse cognitive functions in TOXO seropositive patients (Flegr et al., 2003). Further, recent *in vitro* studies indicate that many, but not all antipsychotic drugs inhibit the replication of TOXO in cell culture models (Goodwin et al., 2011; Jones-Brando et al., 2003). In a rodent model, antipsychotic drugs were found to prevent certain behavioral changes (Webster et al., 2006). Treatment with Haloperidol is associated with reduction of the level of TOXO antibodies (Leweke et al., 2004). For all these reasons, we investigated the relationship between TOXO serostatus and response to valproate. We conducted a randomized controlled trial (RCT) of adjunctive valproate among patients with SZ. The study was conducted in Egypt, where approximately half the adult population is seropositive for TOXO antibodies (Elsheikha et al., 2009; Ibrahim et al., 2009, 2016). Thus, Valproate effect on TOXO infection and TOXO-related cognitive functions could also be studied.

2. Methods

Design A randomized double-blind placebo controlled design was used to compare the effects of Valproate or PLA as adjuncts to risperidone (RISP) treatment. The study was conducted among persons with early course SZ (ECSZ) to reduce changes in cognitive functions related to chronicity. All participants were outpatients stabilized on RISP, which was selected because it is efficacious for positive symptoms of SZ, but it has marginal effects on cognitive functions and it has relatively low potency against TOXO infection (Therapeutic index: 1.7) (Jones-Brando et al., 2003). As outcomes, we evaluated cognitive variables, clinical features and overall function (including social function) and indicators of TOXO infection/Valproate activity in the serum (see Fig. 1).

The study was registered at clinical trials.gov **(NCT02011750).**

Recruitment site. The majority of patients were recruited from outpatient clinics at the Department of Psychiatry, Mansoura University Hospital (MUH), Egypt from March 2013 till August 2016. MUH is a Government funded facility that serves as the primary psychiatric care facilities for over 6 million people. The remaining patients were recruited from private psychiatry clinics in Mansoura.

Informed consent. Ethical approval was obtained from the IRBs at Mansoura University and the University of Pittsburgh (PITT). Treating physicians introduced the study to eligible participants. If they agreed to participate, written informed consent was obtained. Participants were compensated for their time and transportation costs.

Inclusion criteria. The following criteria were required for inclusion in the study: a) Written informed consent; b) Ages 18–50 years; c) Schizophrenia/schizoaffective disorder (DSM IV criteria) d) Duration of illness < 5 years following onset of psychosis; e) Receiving a stable dose of Risperidone for a month or more; f) Score 4 or more on one or more items of the Positive and Negative Syndrome Scale **(**Kay et al., 1987**).**

Exclusion criteria: Patients were excluded from the study, if they had one or more of the following features: a) Diagnosed with alcohol or substance abuse in the past month or dependence in the past 6 months (DSM IV criteria); b) History of, or current medical/neurological illnesses that could make diagnosis of SZ difficult; e.g. mental retardation (DSM-IV) or seizure disorder; c) presence of medical conditions judged to be unstable by the consulting internist and research staff (e.g., liver disease); d) pregnant or breast-feeding; e) known allergy or serious adverse event to valproate; f) Received Chlorpromazine, Trimethoprim or valproate in the 6 months prior to study entry (as these drugs can inhibit TOX replication); g) received electroconvulsive therapy (ECT) in the 6 months prior to the study.

Randomization: Placebo tablets identical in shape to the Valproate tablets were provided by the manufacturer (Alandalus Pharmaceutical Company). A dynamic treatment allocation procedure **(**Begg and Iglewicz, 1980**)** was used to randomize participants into VAL/PLA groups, while balancing allocation on gender (male/female), age ($< 25/\geq 25$years) and residence (rural/urban). Randomization was conducted at the University of Pittsburgh.

Study protocol. (Fig. 1). After written informed consent was obtained, a baseline evaluation was carried out using the diagnostic interview schedules and rating scales listed below. During the entry period, patients had a placebo run-in for two weeks after which they were evaluated for the outcome variables and then randomized to either valproate or PLA. This was followed by a two week period to adjust the dose of valproate and attain therapeutic levels (50–100 μg/mL). valproate/PLA treatment continued for 16 more weeks.

Procedures for maintaining double blind status. The patients, their treating physicians and the research staff who evaluated the patients were blind to valproate/PLA status throughout the study. The research physician who had access to the valproate levels (ST) was not involved in any of the outcome ratings. To maintain double blind status, she also altered doses of PLA for some of the patients.

Medications. The study medications were stored at MUH. The non-blind investigators directly supervised the dispensing of the study medication to subjects and/or their caregivers following permission from their treating physicians.

2.1. Evaluations of participants

Diagnostic evaluation and consensus diagnosis: Details about psychopathology and co-morbid substance abuse and medical disorders were gathered using a semi-structured interview by trained research physicians, as described (Mansour et al., 2010, 2011). This information was synthesized with available clinical data and a consensus diagnosis was established using DSM- IV criteria by two or more board certified psychiatrists. If consensus could not be attained thus, psychiatrists at PITT were consulted. If a consensus diagnosis was still not possible, the participant was not included in the study.

Socio-economic Status. Information about residence (urban/rural), the occupation of the head of the household and educational status (years of schooling/years of college education) was obtained from participants using a checklist.

Clinical Severity. Positive and Negative Syndrome Scale (PANSS) **(**Kay et al., 1987**).** The PANSS was used to rate psychopathology at visits 1,5,7 and 8.

Cognition: (1) Arabic version of the Penn Computerized

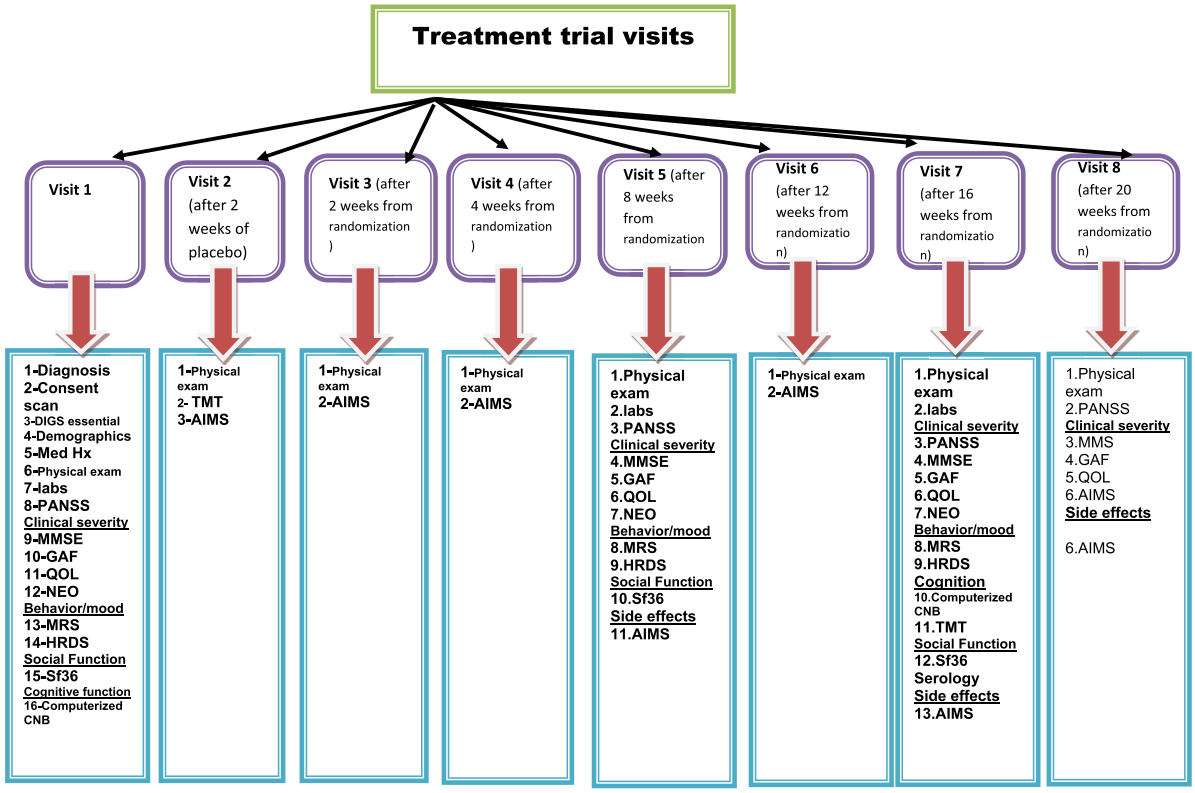

Fig. 1. Schedule for assessment of study participants
MMSE: mini mental state examination**; PANSS:** Positive and negative syndrome scale**; GAF:** global assessment of functioning**; NEO:** NEO Personality Inventory-Revised**; SF-36:** The Short Form (36)**; TMT:** trail making test**; AIMS:** Abnormal Involuntary Movement Scale**; QOL:** the World Health Organization Quality of Life (WHOQOL-BREF)**; CNB:** Arabic version of the Penn Computerized Neuropsychological Battery (CNB)**; MRS:** The Mania Rating Scale**; HRDS:** Hamilton Rating Scale for Depression. **Labs:** laboratory investigations.

Neuropsychological Battery (CNB) (Ibrahim et al., 2015)**. The Arabic** Penn CNB consists of 14 tests: Motor Praxis Test (MPRAXIS) for assessment of sensorimotor integration speed; the Penn Continuous Performance Test–Number (PCPT-n) for assessment of attention; face memory (immediate and delayed) with the Penn Face Memory Test (CPF) and Penn Face Memory Test–Delayed Memory (CPFd); the Penn Conditional Exclusion Task (PCET) for assessment of abstraction and mental flexibility; Short Computerized Finger-Tapping Task (sCTAP) for assessment of manual dexterity; Short Visual Object Learning Test (sVOLT) and Short Visual Object Learning Test Delayed Memory (sVOLTd) for visual object learning and memory; the Penn Matrix Reasoning Test (PMAT) for assessment of nonverbal reasoning; the Short Penn Line Orientation Test (sPLOT) for spatial orientation; the Age Differentiation Test (ADT) for social cognition; Penn Emotion Recognition Task (ER40); the Measured Emotion Differentiation Test (MEDF); and, finally, the Short Fractal N-Back (SFNB2) for assessment of working memory.

(2)Trail Making Test (TMT)(partA&B) (Horton, 1979) This paper and pencil test estimates attention, visual motor speed and working memory.

(3)Mini mental state examination (Folstein et al., 1975)

Scales for behavioral and mood assessment: (1) The Young Mania Rating Scale (YMRS) (Young et al., 1978); (2) Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960).

Personality assessment. Arabic version of the NEO Personality Inventory-Revised (NEO PI-R) (Costa and McCrae, 1995) to assess changes in impulsiveness and 'novelty seeking'.

Overall Social function (1) Global Assessment of Function (GAF) a global measure of function and symptom severity (Endicott et al., 1976). (2) The Short Form (36) (Al Abdumohsin et al., 1997), a multi-item scale of daily function that consists of 8 scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0–100 scale on the assumption that each question carries equal weight. (3) the World Health Organization Quality of Life (WHO QOL-BREF) (Arabic version): measures interpersonal, social and occupational functioning (Ohaeri and Awadalla, 2009).

Side effects: (1) Abnormal Involuntary Movement Scale (Guy, 1976) This scale rates the severity of dyskinetic movements. Orofacial, neck-trunk and distal (limb) movements are rated separately. The study was monitored by Data and Safety Monitoring Board (DSMB).

Physiological variables: (i) Body weight; (ii) Blood pressure in the supine/standing position (Pickering, 1994; Wallymahmed, 2008); (iii) Body mass index (BMI).

Laboratory investigations. At study entry, all participants were assessed for complete blood counts, liver function tests, random blood glucose level and pregnancy tests. valproate levels were also monitored (Fig. 1). Venous samples were collected in tubes with and without anticoagulant for plasma/serum extraction. The samples were centrifuged within 2 h of collection.

Diagnosis of Toxo was done by detection of IgG antibody assay using principle combines a two-step enzyme immunoassay sandwich

method with a final fluorescent detection (ELFA). The assay is completed using automated quantitative test of anti-toxoplasma IgG on VIDAS "biomerieux SA" instrument. The results are automatically calculated by using calibration curves stored on the VIDAS instrument as " < 4 IU/ml" interpreted as Negative, "4 ≤ titre < 8 IU/ml" interpreted as Equivocal, and "≥ 8 IU/ml" interpreted as Positive.

Safety Measures: A physical exam was conducted at study entry and at each visit during the study. Liver function tests (LFTs) and fasting blood glucose levels were completed at the same time points and were repeated if there were clinical indications. Side effects were recorded at each clinic visit (7 times during the trial).

Compliance: Compliance was monitored through pill counts and Valproate levels. If a participant missed more than 25% of the prescribed medication on two consecutive visits, s/he was withdrawn from the study (visits from 1 to 4 are 2 weeks apart then visits from 4 to 8 are 4 weeks apart). To improve compliance, we also used telephone reminders and we provided the prescribed antipsychotic free of charge throughout the study.

Data analysis: To assess the treatment effect over time, a mixed effect linear model was employed to account for within subject correlation over longitudinal measurements and to characterize the within and between subject variability. The tests of the CNB were the primary outcome. Fixed effects included time (visit 1, visit 7), TOXO serostatus and treatment (Valproate/PLA), as well as their interactions, controlling for gender, age and residence. The overall treatment effect (the improvement at visit 7, controlling for baseline value at visit 1) was tested using a T-test, and the treatment effect was also tested within TOXO seropositive and TOXO seronegative groups. To assess the TOXO effect at baseline, for each dependent variable, a linear model was employed with TOXO exposure status as the main independent variable, and age, gender and residence as covariates. All analyses were conducted using SAS 9.3 proc glm (for analyses of baseline values) or proc mixed (for longitudinal analyses). The prior power calculation showed that with n = 100 subjects, we have 80% power to detect the treatment effect with an effect size d = 0.57, or we have 85% power to detect the treatment effect with an effect size d = 0.6 (alpha = 0.05, two sided test).

3. Results

The flow of participants is shown in Fig. 2. Among the participants who consented to the study (N = 109), 94 were randomized. Among those who were not randomized (N = 15), the reasons for exclusion are as follows: moved to another study (N = 2), elevated liver enzyme levels (N = 1), travelled to another city (N = 5), opted to leave the study (N = 5), and side effects on switching to risperidone before starting Valproate/PLA (N = 2). Among the patients who were randomized

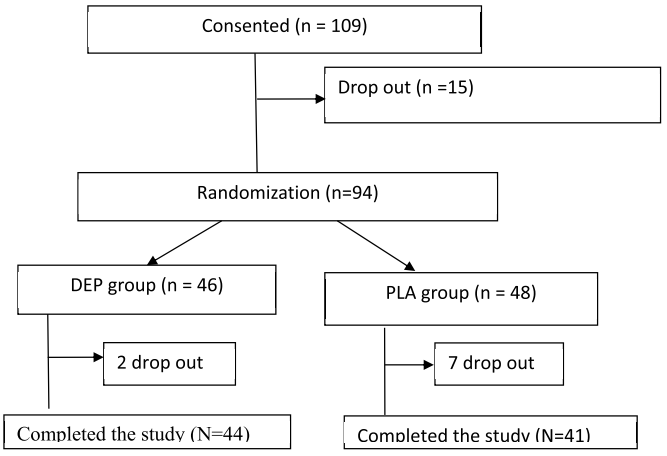

Fig. 2. Flow of participants in the study.

(N = 94), 46 patients received Valproate and 48 received PLA. During the study, 9 patients dropped out due to non-compliance on treatment and they missed their visits (PLA, N = 7; Valproate, N = 2). No statistically significant difference was found related to drop out rates (X^2 = 1.7, 1 d.f., p = 0.18). Thus, 85 patients completed the entire study; of whom 44 received Valproate and 41 received PLA (dose of Valproate ranging from 500 to 1500 mg).

Demographic and clinical features: (Table 1). At the start of the trial, there were no significant differences between the Valproate and PLA groups with regard to current age, gender, educational/marital status or residence (urban/rural). The prevalence of TOXO seropositive status was 41.49% in the entire sample (Table 1). At study entry, there were no significant differences between the TOXO seropositive and the TOXO seronegative patients with regard to age, gender, educational status or residence (urban/rural). There were also no significant differences between the TOXO seropositive and seronegative patients with regard to positive or negative symptom scores, NEO personality scores, cognitive functions or quality of life scores, after adjusting for age, gender and residence. Twenty patients of the 46 randomized to Valproate and 19 of the 48 patients in the placebo group were seropositive with regard to TOXO antibody titers (X = 0.14, p = 0.83, 1 d.f.).

Effects of Valproate/PLA treatment, regardless of Toxo status: There were no significant effects between the valproate and PLA groups with respect to CNB tests' scores (Table 2), PANSS scores or Quality of life scores after corrections for multiple comparisons were applied. Similarly, no valproate/PLA differences were observed when TOXO serostatus was accounted for. However, some marginally significant differences were observed in view of the raw p-values, as follows:

- For estimates of speed, there was a nominally significant difference in five tests out of 13, with PLA treatment being superior: Line orientation test (p = 0.04), Face memory, Delayed (p = 0.04), Measured emotion differentiation test (p = 0.01), Visual object learning test (p = 0.05) and Short fractal N back test (p = 0.01, all uncorrected for multiple comparisons).
- On estimates of accuracy, changes in scores for Face memory improvement were nominally better in the placebo group (p = 0.03, uncorrected for multiple comparisons).

For the NEO PI-R, there was a nominally significant difference only on the agreeableness scale (p = 0.01, uncorrected; Supplementary Table 2).

For those findings with nominal significance, the effect sizes are as follows:

Line orientation test: d = 0.51
Face memory Delayed: d = 0.46
Measured emotion differentiation test: d = 0.67
Visual object learning test: d = 0.50
Short fractal N back test: d = 0.69
CNB accuracy (FACE Memory: d = 0.45)
NEO PI-R (agreeableness scale: d = 0.50)

4. Discussion

To our knowledge, this is the first study to investigate valproate -related effects on cognitive function in SZ in Egypt. Valproate was well tolerated by the participants, but we did not detect any significant differences between the Valproate and PLA treated groups with respect to cognitive functions, psychopathology or quality of life scores. Indeed, valproate -treated patients performed marginally worse than PLA for some cognitive functions. The non-significant effects on psychopathology are consistent with a prior randomized double blind multicenter study of Valproate combined with RISP or olanzapine versus placebo (N = 402 participants) but that study was conducted among

Table 1
Demographic and clinical features of the sample.

	Randomization		P value	TOXO serostatus		P value
	Valproate (N = 46)	Placebo (N = 48)		Negative (N = 55)	Positive (N = 39)	
Sex (Female/Male)	(18/28)	(19/29)	0.96	(20/35)	(17/22)	0.48
Marital status: Never married/ever married	36/10	33/15	0.30	44/11	25/14	0.09
Residence (rural/urban)	(33/13)	(36/12)	0.72	(39/16)	(30/9)	0.52
Age (years)	25.24 ± 4.8	26.02 ± 5.8	0.48	25.18 ± 4.8	26.28 ± 6.02	0.33
Years of Education	13.37 ± 2.6	12.60 ± 3.4	0.22	13.38 ± 2.9	12.41 ± 3.2	0.13
PANSS_total	51.783 ± 24.904	49.771 ± 24.082		50.855 ± 24.541	50.615 ± 24.462	

All ages and PANSS total score shown as mean ± standard deviation.

hospitalized patients with an acute exacerbation of psychosis, unlike patients with early onset psychosis reported on here (Casey et al., 2009). A recent Cochrane meta-analysis of 14 studies indicated significant clinical improvement with combination therapy of valproate and antipsychotics, with the caveat that the results were biased towards open trials (Wang et al., 2016). Another meta-analysis found that the treatment effect was significantly better for patients with schizophrenia or schizoaffective disorder with treatment duration less than 4 weeks who received Valproate augmentation therapy than those receiving antipsychotic monotherapy (Tseng et al., 2016). Off label use of sodium valproate in schizophrenia is common in the USA; one study estimates that about one third of schizophrenic patients receive valproate (Pickar et al., 2008).

The relatively high Toxo exposure rates in our sample enabled optimal power for the analyses in relation to Toxo status, but we did not find any differential effect of Valproate among TOXO seropositive patients. Our results are inconsistent with prior rodent model studies indicating that TOXO infection is associated with impaired motor performance (Hay et al., 1983, 1984b), deficits in learning capacity and memory (Kannan et al., 2010; Witting, 1979), lower ability to discriminate between familiar and novel surroundings (Hay et al., 1984a), and longer reaction times (Hrda et al., 2000). Infected rats also have lower neophobia (fear of novelty) in addition to a loss of the rat's natural aversion to the smell of cats (Kannan et al., 2010; Webster, 2001). There are several plausible reasons for the negative results. It is plausible that TOXO is not associated with cognitive dysfunction in Egypt. Though we monitored Valproate levels among participants, the optimal serum levels of Valproate that inhibit TOXO are not currently known. It is also plausible that the relatively small sample size may be our main possible reason for the negative results.

Some limitations of our study should be kept in mind. The relatively small sample restricted the power to detect relatively small effects. Further, all patients were stabilized on antipsychotic medications when they consented to the RCT, further limiting detectable beneficial effects of valproate. The prior treatment could also have ameliorated detrimental effects of TOXO infection on psychopathology or cognitive

Table 2
Effect of treatment (adjunctive VAL vs. PLA) on cognitive functions measured by the CNB battery.

Test	Label	Accuracy		Speed	
		T	P*	T	P*
Motor Praxis	treatment effect	−0.14	0.89	1.03	0.31
	treatment effect (tox + vs tox-)	0.65	0.51	−0.72	0.47
Face memory	treatment effect	−2.15	0.03	0.48	0.64
	treatment effect (tox + vs tox-)	−0.36	0.72	0.98	0.33
Continuous Performance test – number	treatment effect	−1.50	0.14	1.58	0.12
	treatment effect (tox + vs tox-)	−0.20	0.84	1.68	0.10
Penn Matrix	treatment effect	−0.80	0.42	0.56	0.57
	treatment effect (tox + vs tox-)	−1.33	0.19	−0.13	0.89
Line orientation test	treatment effect	0.34	0.73	2.07	0.04
	treatment effect (tox + vs tox-)	0.51	0.61	−0.09	0.93
Face memory Delayed	treatment effect	−1.04	0.30	2.05	0.04
	treatment effect (tox + vs tox-)	−0.68	0.50	1.17	0.24
Measured emotion differentiation test	treatment effect	0.73	0.47	2.84	0.01
	treatment effect (tox + vs tox-)	0.94	0.35	0.26	0.80
Penn conditional exclusion test	treatment effect	−1.88	0.06	1.48	0.14
	treatment effect (tox + vs tox-)	−1.41	0.16	0.07	0.94
Finger tapping	treatment effect	−1.11	0.27	NA	NA
	treatment effect (tox + vs tox-)	−1.66	0.10	NA	NA
Visual object learning test	treatment effect	0.37	0.71	2.02	0.05
	treatment effect (tox + vs tox-)	−0.93	0.36	−0.64	0.52
Emotion recognition	treatment effect	0.62	0.54	1.53	0.13
	treatment effect (tox + vs tox-)	−0.81	0.42	−0.39	0.69
Short fractal N back test	treatment effect	−0.83	0.41	2.89	0.01
	treatment effect (tox + vs tox-)	0.44	0.66	−0.61	0.54
Age differentiation test	treatment effect	1.41	0.16	0.83	0.41
	treatment effect (tox + vs tox-)	0.43	0.67	−0.23	0.82
Visual object test delayed	treatment effect	0.43	0.67	1.35	0.18
	treatment effect (tox + vs tox-)	−0.67	0.51	−1.08	0.28

* p values uncorrected for multiple comparisons.“ treatment effect (tox + vs tox -)” is the interaction effects (treatment by tox status), which is calculated as the treatment effect in tox + group minus the treatment effect in tox- group.
A positive T value of the treatment effect means the response value (T7-T1) is larger in VAL group. Depending on the meaning of the response value, it could mean favoring VAL (for example accuracy) or it could mean favoring Placebo (for example speed).

functions. Once infection with TOXO occurs, levels of IgG antibodies against TOXO typically remain elevated lifelong, particularly in areas with endemic TOXO infection such as Egypt. Therefore, we did not evaluate changes in TOXO antibody titers. We reasoned that evaluating cognitive functions before and after Valproate treatment would provide a direct, clinically relevant endpoint for the trial we conducted.

In conclusion, we did not detect significant beneficial effects of Valproate on psychopathology, cognitive functions, or social functions in patients with early course SZ. In addition, our analyses did not show significant detrimental effects of Toxoplasma infection on these measures.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.08.011.

References

Ahmad, D., Mehdi, S., Sayed, H.H., Sayed, A.K., Shirzad, G., 2010. Serological survey of toxoplasma gondii in schizophrenia patients referred to psychiatric hospital, Sari city, Iran. Trop. Biomed. 27 (3), 476–482.
Al Abdumohsin, S., Coons, S., Draugalis, J., Hays, R., 1997. Translation of the RAND 36-item Health Survey 1.0 (Aka SF-36) into Arabic. published by RAND, Washington DC.
Aliyu, M.H., Calkins, M.E., Swanson Jr., C.L., Lyons, P.D., Savage, R.M., May R, W.H., McLeod-Bryant, S., Nimgaonkar, V.L., Ragland, J.D., Gur, R.E., Gur, R.C., Bradford, L.D., Edwards, N., Kwentus, J., McEvoy, J.P., Santos, A.B., McCleod-Bryant, S., Tennison, C., Go, R.C., TB, A., Group, P.S., 2006. Project among African-Americans to explore risks for schizophrenia (PAARTNERS): recruitment and assessment methods. Schizophr. Res. 87 (1–3), 32–44.
Alvarado-Esquivel, C., Urbina-Alvarez, J.D., Estrada-Martinez, S., Torres-Castorena, A., Molotla-de-Leon, G., Liesenfeld, O., Dubey, J.P., 2011. Toxoplasma gondii infection and schizophrenia: a case control study in a low Toxoplasma seroprevalence Mexican population. Parasitol. Int. 60 (2), 151–155.
Begg, C.B., Iglewicz, B., 1980. A treatment allocation procedure for sequential. Clin. Trials Biom. 36 (1), 81–90.
Casey, D.E., Daniel, D.G., Tamminga, C., Kane, J.M., Tran-Johnson, T., Wozniak, P., Abi-Saab, W., Baker, J., Redden, L., Greco, N., Saltarelli, M., 2009. Divalproex ER combined with olanzapine or risperidone for treatment of acute exacerbations of schizophrenia. Neuropsychopharmacology 34 (5), 1330–1338.
Cetinkaya, Z., Yazar, S., Gecici, O., Namli, M.N., 2007. Anti-Toxoplasma gondii antibodies in patients with schizophrenia–preliminary findings in a Turkish sample. Schizophr. Bull. 33 (3), 789–791.
Conley, R.R., Kelly, D.L., 2001. Management of treatment resistance in schizophrenia. Biol. Psychiatry 50 (11), 898–911.
Costa Jr., P.T., McCrae, R.R., 1995. Domains and facets: hierarchical personality assessment using the revised NEO personality inventory. J. Personal. Assess. 64 (1), 21–50.
Dose, M., Hellweg, R., Yassouridis, A., Theison, M., Emrich, H.M., 1998. Combined treatment of schizophrenic psychoses with haloperidol and valproate. Pharmacopsychiatry 31 (4), 122–125.
Elsheikha, H.M., Azab, M.S., Abousamra, N.K., Rahbar, M.H., Elghannam, D.M., Raafat, D., 2009. Seroprevalence of and risk factors for Toxoplasma gondii antibodies among asymptomatic blood donors in Egypt. Parasitol. Res. 104 (6), 1471–1476.
Endicott, J., Spitzer, R., Fleiss, J., Cohen, J., 1976. The global assessment scale. Arch. Gen. Psychiatr. 33, 766–771.
Facciola, G., Avenoso, A., Scordo, M.G., Madia, A.G., Ventimiglia, A., Perucca, E., Spina, E., 1999. Small effects of valproic acid on the plasma concentrations of clozapine and its major metabolites in patients with schizophrenic or affective disorders. Ther. Drug Monit. 21 (3), 341–345.
Flegr, J., Preiss, M., Klose, J., Havlíček, J., Vitáková, M., Kodym, P., 2003. Decreased level of psychobiological factor novelty seeking and lower intelligence in men latently infected with the protozoan parasite Toxoplasma gondii Dopamine, a missing link between schizophrenia and toxoplasmosis? Biol. Psychol. 63 (3), 253–268.
Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 12, 189–198.
Frankenburg, F.R., Zanarini, M.C., 2002. Divalproex sodium treatment of women with borderline personality disorder and bipolar II disorder: a double-blind placebo-controlled pilot study. J. Clin. Psychiatry 63 (5), 442–446.
Fusar-Poli, P., Papanastasiou, E., Stahl, D., Rocchetti, M., Carpenter, W., Shergill, S., McGuire, P., 2015. Treatments of negative symptoms in schizophrenia: meta-analysis of 168 randomized placebo-controlled trials. Schizophr. Bull. 41 (4), 892–899.
Goodwin, D.G., Strobl, J.S., Lindsay, D.S., 2011. Evaluation of five antischizophrenic agents against Toxoplasma gondii in human cell cultures. J. Parasitol. 97 (1), 148–151.
Guidotti, A., Dong, E., Kundakovic, M., Satta, R., Grayson, D.R., Costa, E., 2009. Characterization of the action of antipsychotic subtypes on valproate-induced chromatin remodeling. Trends Pharmacol. Sci. 30 (2), 55–60.
Guidotti, A., Grayson, D.R., 2014. DNA methylation and demethylation as targets for antipsychotic therapy. Dialogues Clin. Neurosci. 16, 419–429.
Guy, W., 1976. Assessment Manual for Psychopharmacology. ECDEU. Department of health, education and welfare, Washington DC.
Hamidinejat, H., Ghorbanpoor, M., Hosseini, H., Alavi, S.M., Nabavi, L., Jalali, M.H., Borojeni, M.P., Jafari, H., Mohammadaligol, S., 2010. Toxoplasma gondii infection in first-episode and inpatient individuals with schizophrenia. Int. J. Infect. Dis. 14 (11), e978–981.
Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.
Harvey, R.C., James, A.C., Shields, G.E., 2016. A systematic review and network meta-analysis to assess the relative efficacy of antipsychotics for the treatment of positive and negative symptoms in early-onset schizophrenia. CNS Drugs 30 (1), 27–39.
Hay, J., Aitken, P.P., Graham, D.I., 1984a. Toxoplasma infection and response to novelty in mice. Z. Parasitenkd. 70 (5), 575–588.
Hay, J., Aitken, P.P., Hair, D.M., Hutchison, W.M., Graham, D.I., 1984b. The effect of congenital Toxoplasma infection on mouse activity and relative preference for exposed areas over a series of trials. Ann. Trop. Med. Parasitol. 78 (6), 611–618.
Hay, J., Hutchison, W.M., Aitken, P.P., Graham, D.I., 1983. The effect of congenital and adult-acquired Toxoplasma infections on activity and responsiveness to novel stimulation in mice. Ann. Trop. Med. Parasitol. 77 (5), 483–495.
Horton, A.M.J., 1979. Some suggestions regarding the clinical interpretation of the trail making test. Clin. Neuropsychol. 1 (1), 20–23.
Hrda, S., Votypka, J., Kodym, P., Flegr, J., 2000. Transient nature of Toxoplasma gondii-induced behavioral changes in mice. J. Parasitol. 86 (4), 657–663.
Hyman, S.E., 2012. Revolution stalled. Sci. Transl. Med. 4 (155) 155cm111.
Ibrahim, H.M., Huang, P., Salem, T.A., Talaat, R.M., Nasr, M.I., Xuan, X., Nishikawa, Y., 2009. Short report: prevalence of Neospora caninum and Toxoplasma gondii antibodies in northern Egypt. Am. J. Trop. Med. Hyg. 80 (2), 263–267.
Ibrahim, I., Salah, H., El Sayed, H., Mansour, H., Eissa, A., Wood, J., Fathi, W., Tobar, S., Gur, R.C., Gur, R.E., Dickerson, F., Yolken, R.H., El Bahaey, W., Nimgaonkar, V., 2016. Hepatitis C virus antibody titers associated with cognitive dysfunction in an asymptomatic community-based sample. J. Clin. Exp. Neuropsychol. 38 (8), 861–868.
Ibrahim, I., Tobar, S., Elassy, M., Mansour, H., Chen, K., Wood, J., Gur, R.C., Gur, R.E., El Bahaei, W., Nimgaonkar, V., 2015. Practice effects distort translational validity estimates for a Neurocognitive battery. J. Clin. Exp. Neuropsychol. 37 (5), 530–537.
Ichikawa, J., Chung, Y.C., Dai, J., Meltzer, H.Y., 2005. Valproic acid potentiates both typical and atypical antipsychotic-induced prefrontal cortical dopamine release. Brain Res. 1052 (1), 56–62.
Jones-Brando, L., Torrey, E.F., Yolken, R., 2003. Drugs used in the treatment of schizophrenia and bipolar disorder inhibit the replication of Toxoplasma gondii. Schizophr. Res. 62 (3), 237–244.
Kahn, R.S., Keefe, R.S., 2013. Schizophrenia is a cognitive illness: time for a change in focus. JAMA Psychiatr. 70 (10), 1107–1112.
Kannan, G., Moldovan, K., Xiao, J.C., Yolken, R.H., Jones-Brando, L., Pletnikov, M.V., 2010. Toxoplasma gondii strain-dependent effects on mouse behaviour. Folia Parasitol. 57 (2), 151–155.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.
Lee, H.M., Kim, Y., 2016. Drug repurposing is a new opportunity for developing drugs against neuropsychiatric disorders. Schizophr. Res. Treat. 2016 6378137.
Leweke, F.M., Gerth, C.W., Koethe, D., Klosterkotter, J., Ruslanova, I., Krivogorsky, B., Torrey, E.F., Yolken, R.H., 2004. Antibodies to infectious agents in individuals with recent onset schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci. 254 (1), 4–8.
Loscher, W., 1999. Valproate: a reappraisal of its pharmacodynamic properties and mechanisms of action. Prog. Neurobiol. 58 (1), 31–59.
Mansour, H., Chowdari, K., Fathi, W., Elassy, M., Ibrahim, I., Wood, J., Bamne, M., Tobar, S., Yassin, A., Salah, H., Elsayed, H., Eissa, A., El-Boraie, H., Ibrahim, N.E., Elsayed, M., El-Bahaei, W., Gomaa, Z., El-Chennawi, F., Nimgaonkar, V.L., 2011. Does telomere length mediate associations between inbreeding and increased risk for bipolar I disorder and schizophrenia? Psychiatry Res. 188 (1), 129–132.
Mansour, H., Fathi, W., Klei, L., Wood, J., Chowdari, K., Watson, A., Eissa, A., Elassy, M., Ali, I., Salah, H., Yassin, A., Tobar, S., El-Boraie, H., Gaafar, H., Ibrahim, N.E., Kandil, K., El-Bahaei, W., El-Boraie, O., Alatrouny, M., El-Chennawi, F., Devlin, B., Nimgaonkar, V.L., 2010. Consanguinity and increased risk for schizophrenia in Egypt. Schizophr. Res. 120 (1–3), 108–112.
Ohaeri, J., Awadalla, A., 2009. The reliability and validity of the short version of the WHO quality of life instrument in an Arab general population. Ann. Saudi Med. 29 (2) 98.
Pearce, B.D., Kruszon-Moran, D., Jones, J.L., 2014. The association of Toxoplasma gondii infection with neurocognitive deficits in a population-based analysis. Soc. Psychiatry Psychiatr. Epidemiol. 49 (6), 1001–1010.
Pedersen, M.G., Stevens, H., Pedersen, C.B., Nørgaard-Pedersen, B., Mortensen, P.B., 2011. Toxoplasma infection and later development of schizophrenia in mothers. Am. J. Psychiatry 168 (8), 814–821.
Pickar, D., Vinik, J., Bartko, J.J., 2008. Pharmacotherapy of schizophrenic patients: preponderance of off-label drug use. PLoS One 3 (9), e3150.
Pickering, T.G., 1994. Blood pressure measurement and detection of hypertension. Lancet

344 (8914), 31–35.
Rapoport, S.I., Basselin, M., Kim, H.W., Rao, J.S., 2009. Bipolar disorder and mechanisms of action of mood stabilizers. Brain Res. Rev. 61 (2), 185–209.
Saha, S., Chant, D., Welham, J., McGrath, J., 2005. A systematic review of the prevalence of schizophrenia. PLoS Med. 2 (5) e141.
Sund, J.K., Aamo, T., Spigset, O., 2003. Valproic acid and risperidone: a drug interaction? J. Am. Acad. Child Adolesc. Psychiatry 42 (1), 1–2.
Torrey, E.F., Bartko, J.J., Lun, Z.R., Yolken, R.H., 2007. Antibodies to Toxoplasma gondii in patients with schizophrenia: a meta-analysis. Schizophr. Bull. 33 (3), 729–736.
Tseng, P.T., Chen, Y.W., Chung, W., Tu, K.Y., Wang, H.Y., Wu, C.K., Lin, P.Y., 2016. Significant effect of valproate augmentation therapy in patients with schizophrenia: a meta-analysis study. Medicine (Baltim.) 95 (4), e2475.
Wallymahmed, M., 2008. Blood pressure measurement. Nurs. Stand. 22 (19), 45–48.
Wang, Y., Xia, J., Helfer, B., Li, C., Leucht, S., 2016. Valproate for schizophrenia (review). Cochrane Database Syst. Rev. 11.
Webster, J.P., 2001. Rats, cats, people and parasites: the impact of latent toxoplasmosis on behaviour. Microb. Infect. 3 (12), 1037–1045.
Webster, J.P., Lamberton, P.H., Donnelly, C.A., Torrey, E.F., 2006. Parasites as causative agents of human affective disorders? The impact of anti-psychotic, mood-stabilizer and anti-parasite medication on Toxoplasma gondii's ability to alter host behaviour. Proc. Biol. Sci. 273 (1589), 1023–1030.
Witting, P.A., 1979. Learning capacity and memory of normal and Toxoplasma-infected laboratory rats and mice. Z. Parasitenkd. 61 (1), 29–51.
Yolken, R., Torrey, E.F., Dickerson, F., 2017. Evidence of increased exposure to Toxoplasma gondii in individuals with recent onset psychosis but not with established schizophrenia. PLoS Neglected Trop. Dis. 11 (11), e0006040.
Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. Br. J. Psychiatry : J. Ment. Sci. 133, 429–435.