



Research Paper

Toxoplasma gondii seropositivity and cognitive function in adults with schizophrenia

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ABSTRACT

Introduction and methods: Based on the limited research focusing on the severity of cognitive deterioration in schizophrenia with preceding toxoplasmosis, we sampled 89 demographically matched paranoid schizophrenia patients (mean age 38.97 years) with (n = 42) and without (n = 47) seroprevalence of IgG type anti *T. gondii* antibodies as marker of past infection. They underwent examination of verbal memory (10 words Luria test), logical memory and visual memory (BVRT), processing speed (TMT-A/DSST) and executive functions (TMT-B/verbal fluency). We compared the results of both groups, taking into account the normative values for the Bulgarian population where available. We also compared the two groups in terms of clinical severity as evidenced by positive, negative and disorganization sub-scores of the PANSS.

Results: While both groups were expectedly under the population norms for verbal and logical memory, seropositive patients showed significantly bigger impairment in verbal memory (Luria Smax = 72.85 vs 78.51; p = 0.029), psychomotor speed (TMT-A 50.98 s vs 44.64 s; p = 0.017), semantic verbal fluency (27.12 vs 30.02; p = 0.011) and literal verbal fluency (17.17 vs 18.78; p = 0.014) compared to the seronegative ones. In addition to that, they gave less correct answers on the BVRT (2.98 vs 4.09; p = 0.006) while making markedly more errors (13.95 vs 10.21; p = 0.002). Despite not reaching statistical significance, past toxoplasmosis was associated with higher score on the PANSS disorganization sub-scale (16.50 points vs 14.72 points) and with lower educational attainment.

Conclusion: Our results suggest a more profound neuropathological insult(s) resulting in greater cognitive impairment in schizophrenia cases that are exposed to *T. gondii* infection.

1. Introduction

Schizophrenia is a neurodevelopmental disorder that starts prenatally and evolves in early life driven by a combination of genetic and environmental causal factors (Degenhardt, 2020). The pathological process results in structural disorganization of critical brain areas with corresponding disturbances in neurotransmission (Callicott et al., 1999), neuronal connectivity and activation (Lewis and Levitt, 2002; Marengo and Weinberger, 2000). Among the clinical implications of these changes, there is a specific pattern of neurocognitive impairment with ineffective temporo-spatial assessment of incoming information which prevents patients from proper judgments and planning of behavior (Veleva et al., 2019).

Despite the major role of heritability accounting for 60–80 % of the overall risk (Pettersson et al., 2019; Wray and Gottesman, 2012), additional environmental factors that interact with genes and trigger the illness are presumably involved. Infections and immune response disorders during the pre and postnatal period have emerged as plausible candidates for this role. Among them, the neurotrophic parasite *Toxoplasma gondii* seems particularly appropriate because it damages neurons directly, affects neurotransmitter systems, and can form cysts in the brain tissue (Ortiz-Guerrero et al., 2020; Cetinkaya et al., 2007; Fuglewicz et al., 2017). Furthermore, *Toxoplasma* IgG seropositivity is 50 % more common among schizophrenia patients compared to controls and it increases the odds of schizophrenia by 1.91-fold (Contopoulos-Ioannidis et al., 2022). Although the association between toxoplasmosis and

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schizophrenia has been established since the 1950s (Kozar, 1953), the precise neuropathological mechanism(s) that bridges both illnesses remain elusive. The infection induced low-grade inflammation process (Fuglewicz et al., 2017) and the effect of the parasite on the tryptophan-kynurenine pathway are the most popular explanations (Tutakhail et al., 2020; Grada et al., 2022). By activation of astrocytes, *T. gondii* infection increases the brain production of kynurenic acid (KYNA) from tryptophan. Elevated concentration of KYNA alters the glutamatergic, cholinergic, and dopaminergic signaling (Stone, 1993), thus playing important pathogenic role especially for cognitive symptoms (Torrey and Yolken, 2003; Schwarcz and Hunter, 2007; Brown et al., 2009; Brown, 2012; Pearce et al., 2020; Pedraz-Petrozzi et al., 2020). In addition to that, the accumulation of tryptophan degradation products leads to excessive dopaminergic activity which is considered the pathophysiological essence of schizophrenia (Miller et al., 2004).

A number of studies have addressed the association between the seroprevalence of *T. gondii* antibodies and the impairment of cognitive function in mentally healthy individuals. Most (Mendy et al., 2015; Gale et al., 2015; Gajewski et al., 2014; Pearce et al., 2014; Beste et al., 2014; Nimgaonkar et al., 2016; Rossini et al., 2019; Gale et al., 2020) but not all (Guenter et al., 2012; Sugden et al., 2016; Torniaainen-Holm et al., 2019) of them find an adverse association between toxoplasmosis and cognitive functioning. In contrast to that, only one study has examined the cognitive performance in schizophrenia patients born to *T. gondii* seropositive mothers (Brown et al., 2009).

Against this background, we examined a sample of individuals with paranoid schizophrenia (PS) divided according to the seroprevalence of IgG type anti-toxoplasma antibodies as a marker of past infection. Our goal was to analyze the results of neuropsychological tests of seropositive and seronegative subjects looking for an association between the level of cognitive performance and the serological status. Additionally, for some of the tests, we compared the performance of the two groups against the norm for the Bulgarian population.

2. Materials and methods

2.1. Sample

The study included 89 participants (55 males) treated at the Department of Psychiatry of “Dr Georgi Stranski” University Hospital in Pleven, Bulgaria between 2017 and 2018. The subjects were divided into two groups: 42 patients seropositive for anti-toxoplasma IgG antibodies constituted the *T. gondii* positive group (TG+), whereas 47 patients lacking such antibodies composed the *T. gondii* negative group (TG-). Both groups were matched by age, educational level, family history for schizophrenia, mean illness duration and mean antipsychotic dose (Table 1).

All participants were capable adults who had signed informed consent prior to performing any study related procedures. They were fluent in Bulgarian language and had at least eight years of schooling. In addition, all of them were right-handed as assessed by the Edinburgh Handedness Inventory – Short Form (Veale, 2014).

The study was approved by the Research Ethics Committee of the Medical University of Pleven. All procedures were performed in accordance with the Declaration of Helsinki (World Medical Association Declaration of Helsinki, 2001).

Participants fulfilled the following inclusion criteria: [1] Diagnosis of PS based on the ICD-10 (World Health Organization, 2016); [2] ongoing therapy with a second-generation antipsychotic that has produced a stable condition as defined by a lack of serious relapse (a change of ≥ 25 % of the total PANSS score) in the three months preceding study entry; [3] presence of clinically significant positive, negative and/or disorganization symptoms defined by a score of at least “mild” on minimum two of the corresponding PANSS items according to the five factor model of van der Gaag et al. (2006). Exclusion criteria were: [1] Lifetime history for any other psychiatric condition or history for substance use disorder

Table 1

Sociodemographic and clinical characteristic of the two groups of PS patients.

Characteristic	<i>T. gondii</i> IgG “+” (n = 42)	<i>T. gondii</i> IgG “-” (n = 47)	Total	p value
Gender				0.086
- Females	12 (28.6 %)	22 (46.8 %)	34 (38.2 %)	
- Males	30 (71.4 %)	25 (53.2 %)	55 (61.8 %)	
Age (years + SD)	39.74 ± 6.826	38.28 ± 8.665	38.97 ± 7.841	0.191
- Males	39.53 ± 6.806	38.08 ± 8.775	38.87 ± 7.722	
- Females	40.25 ± 7.149	38.50 ± 8.738	39.12 ± 8.146	
Education				0.062
- Primary or high-school graduates	34 (81.0 %)	29 (61.7 %)	63 (70.8 %)	
- College graduates or higher	8 (19.0 %)	18 (38.3 %)	26 (29.2 %)	
Family history for schizophrenia				0.901
- Family history positive	22 (52.4 %)	24 (51.1 %)	46 (51.7 %)	
- Family history negative	20 (47.6 %)	23 (48.9 %)	43 (48.3 %)	
Duration of schizophrenia (years + SD)	13.07 ± 5.989	12.15 ± 7.675	12.58 ± 6.908	0.275
Antipsychotic dose ^a (mg + SD)	302 ± 118.036	324 ± 131.339	314 ± 125.009	0.441
PANSS score	73.21 ± 7.751	70.04 ± 7.348	71.54 ± 7.665	0.072
- Positive ^b	14.19 ± 3.704	13.57 ± 3.549	13.87 ± 3.616	0.473
- Negative ^c	14.49 ± 4.026	14.22 ± 4.315	14.34 ± 4.159	0.969
- Disorganization ^d	16.50 ± 3.846	14.72 ± 4.557	15.56 ± 4.306	0.035

^a Mean antipsychotic dose has been calculated as a chlorpromazine equivalent.

^b Positive sub-score of the PANSS includes items P1, P3, P5, P6, G1, G9.

^c Negative sub-score of the PANSS includes items N1, N2, N3, N4, N6, G7, G16.

^d Disorganization sub-score of the PANSS includes items P2, N5, N7, G5, G10, G11, G12, G13, G15.

(s) in the past 12 months; [2] any neurological condition and/or physical illness/impairment that interferes with the proper execution of study procedures.

The ELISA method was used to test for specific anti-toxoplasma antibodies. We employed NovaTec® *Toxoplasma* IgG and NovaTec® *Toxoplasma* IgM diagnostic kits (Immunodiagnostica, Germany). All participants positive for IgG anti-toxoplasma antibodies were also tested for IgM antibodies to rule out acute toxoplasmosis. The quantity of anti-toxoplasma antibodies was measured using an automatic ELISA plate reader with a wavelength range 420–650 nm. The results as measured in international units per milliliter were interpreted as follows: *T. gondii* IgG antibodies <30 IU/ml = negative result; 30–35 IU/ml = borderline result; >35 IU/ml = positive result. IgM antibodies were measured in NovaTec® units (NTU) with positive result defined as 11 NTU or higher.

All the patients underwent complete physical and psychiatric examination supplemented by medical and family psychiatric history. Neuropsychological examination was performed after an antipsychotic free period of at least 12 h. The following tools were used in the specified order:

- **10 Words Luria Test:** a verbal memory (VM) test measuring fixation (immediate recall), retention and reproduction (delayed recall) of a list of words. The first five repetitions follow one after the other and test fixation, while delayed repetition (after 1 h) tests for

reproduction/delayed recall. Retention is tested by the number of repeated words after a final sixth reading, performed shortly after the reproduction test. Intrusions, i.e. reproducing words that are not part of the set are also noted. Results are calculated by means of formula to produce % value of the mean fixation success rate (S_{mf}), maximal fixation (S_{max}), retention success rate (S_{ret}) and reproduction success rate (S_{rep}). For Bulgarians the values of S_{mf} , S_{max} , S_{ret} and S_{rep} are interpreted as follows: $\geq 84\%$ = no deficit; 68% – 84% = mild deficit; 51% – 68% = moderate deficit; 51% – 34% = substantial deficit; $< 34\%$ = severe deficit

- **Trail Making Test parts A & B (TMT A&B)** is a standardized test for assessment of processing speed, attention switching, cognitive flexibility, distributed and selective attention, as well as the ability to form concepts. In addition to that, part B of the test (TMT-B) assesses executive functions.
- The **Logical Memory Test** measures episodic memory and thinking disorders and consists of memorizing and reproducing two short stories (LM1 and LM2) that are read to the participant. Each of the stories contains 24 elements (N1-N24). Results are presented in % by means of the formula $N \times 100 / 24$. Their interpretation is the same as in the Luria test.
- **Digit Symbol Substitution Test (DSST)** is a sub-part of the Wechsler Adult Intelligence Scale (WAIS) designed to measure visuo-perceptual functions, attention, executive functions (including working memory) and motor speed (Jaeger, 2018).
- **Verbal fluency test (VF)** grades executive functions and semantic memory. Lower VF scores indicate deficit in processing of semantic information. VF is subdivided into semantic VF (VF_s) measured by Isaac's Set Test (IST) (Bulgarian norm > 30 words/min) and literal VF (VF_l) assessed by the number of words beginning with a certain letter that can be produced in 60 s (Bulgarian norm > 20 words)
- **Benton Visual Retention Test (BVRT)** is a tool developed to assess visual perception, visual memory, and basic visual abilities, visuo-motor coordination and perceptual-motor integration. For the Bulgarian population the mean value of correct scores is 8.20 and the normal mean number of errors is 5.5.

2.2. Statistics

Analysis was performed via descriptive and correlation statistical techniques. Demographic and clinical characteristics of $TG+$ and $TG-$ patients were compared using One-tailed t -test for independent samples (for normal distribution), Mann-Whitney U test (for asymmetrical distribution) and chi-squared tests for categorical data. We used the Cohen's D method and Cramer's V to compute the intensity of the relationship between groups or sets of variable effect size. Calculations were made by SPSS v.28.0 for Windows based PCs. All results were processed within a 95 % confidence interval.

3. Results

3.1. Associations between the serological status and the clinical and socio-demographic characteristics

To test for association between the serological status and the age of onset of schizophrenia, we calculated correlation coefficient Eta. The difference between the two groups was not statistically significant ($U = 975.500$, $N = 89$, $z = 0.095$, $d = 0.02$, $p > 0.05$), i.e. seropositivity was not associated with earlier or later age of onset of the mental disease ($\eta = 0.042$, $N = 89$).

With respect to the overall clinical severity, both groups did not differ significantly in the total, positive and negative PANSS score (Table 1). However, disorganization symptoms sub-score did show significantly higher value in the $TG+$ group under one-tailed test ($t = 767.500$, $N = 87$, $d = 0.42$, $p = 0.035$).

We did not find association between the serological status and the

level of education ($\chi^2(2) = 4.491$, $p > 0.05$, Cramer's $V = 0.225$). However, $< 20\%$ of $TG+$ patients had college degree or higher educational attainment vs nearly 40 % in the $TG-$ group – a finding that suggests higher educational achievement of the latter.

3.2. Associations between the serological status and the performance on neurocognitive tests

Verbal memory: according to the Bulgarian norm, patients from both groups had a moderate decrease in S_{mf} , mild deficit in S_{max} and in S_{rep} , and moderate deficit in S_{ret} . Seropositive patients had lower S_{mf} and S_{ret} and significantly lower S_{max} results compared to seronegative ones, while the difference in reproduction and number of intrusions between the two groups was negligible.

Logical memory: Both groups had severe impairment against the population norm with $TG+$ patients performing insignificantly worse than $TG-$ ones.

Visual memory (BVRT): in this task, $TG-$ patients gave significantly more correct answers ($U = 657.500$, $N = 89$, $z = -2.740$, $d = 0.60$, $p = 0.006$) and made significantly less errors ($U = 609.500$, $N = 89$, $z = 3.111$, $d = 0.70$, $p = 0.002$) compared to $TG+$ ones. However, there was not significant difference in the type of errors ($p > 0.05$). Besides, both groups gave less correct answers and made more errors compared to the population norm.

Processing speed (TMT-A/DSST): Seronegative patients performed significantly better than seropositive ones in terms of processing speed as measured by the TMT-A ($U = 696.500$, $N = 89$, $z = 2.390$, $d = 0.52$, $p = 0.017$). DSST performance was also in favor of $TG-$ patients, albeit the difference was not so substantial (35.70 vs 32.62 points).

Executive functions (TMT-B): seropositive patients needed more time to complete this test compared to seronegative ones (115.0 s vs 101.34 s) although this difference was not statistically significant.

Verbal fluency: with educational level taken into account, both $TG+$ and $TG-$ groups' mean VF_s and VF_l results were below the population norms. Compared to the seropositive patients, seronegative ones had significantly better result for both VF_s ($t = 2.326$, $df = 87$, $d = 0.50$, $p = 0.011$) and VF_l ($t = 2.227$, $df = 87$, $d = 0.48$, $p = 0.014$).

4. Discussion

The present study compared the cognitive performance of two groups of paranoid schizophrenia patients - one with and the other without past *T. gondii* infection - as evidenced by the presence or absence of IgG toxoplasma antibodies. The results will be briefly reviewed below.

Both seropositive and seronegative patients showed deficit in verbal memory (Luria test), especially in the fixation/registration of new words (immediate recall). This deficit was markedly more pronounced in $TG+$ patients. While the worse performance relative to the general population may be explained by the impairment of consolidation of new information typical for schizophrenia (Keefe and Harvey, 2012), the intergroup difference deserves more attention as it replicates previously reported data. Specifically, Gajewski et al. (2014) have found poorer performance in verbal memory affecting both immediate and delayed recall in *T. gondii* seropositive seniors in Germany. As these authors have explored mentally fit individuals, it could be speculated that *T. gondii* infection, even when asymptomatic, may be associated with a specific type of memory deterioration. With respect to the retention and reproduction part of the Luria test (measuring delayed recall and hence indicative of long-term semantic memory), both groups performed worse against the norm whereas they did not differ significantly compared to each other (Table 2). While this last finding is in discord with the abovementioned German study which showed substantial advantage of $TG-$ patients in the recall from long-term semantic memory, it should be emphasized that Gajewski et al. have measured

Table 2
Results of the neurocognitive test battery in TG+ and TG- patients.

Parameter/ test	Seronegative (TG-)	Seropositive (TG+)	Mann- Whitney U/t- test	Asymp. sig. (2-tailed)
<i>10 Words Luria Test</i>				
S_{mf}	66.21 ± 13.143	61.76 ± 14.994	778.000	0.085
S_{max}	78.51 ± 12.850	72.85 ± 14.863	728.000	0.029
S_{rep}	74.92 ± 12.549	74.46 ± 14.494	962.000	0.839
S_{ret}	58.94 ± 13.868	55.24 ± 14.523	834.000	0.200
Intrusions	0.62 ± 0.922	0.83 ± 1.167	922.000	0.544
<i>Logical memory test</i>				
LM-1	32.17 ± 12.487	30.58 ± 14.604	867.000	0.324
LM-2	25.70 ± 13.460	22.11 ± 12.012	775.000	0.078
<i>Benton Visual Retention Test</i>				
BVRT- correct	4.09 ± 1.730	2.98 ± 1.944	657.500	0.006
BVRT-error	10.21 ± 4.383	13.950 ± 6.052	609.500	0.002
<i>Digit Symbol Substitution Test</i>				
DSST	35.70 ± 10.885	32.62 ± 9.197	826.000	0.187
<i>Trail Making Test parts A & B</i>				
TMT-A sec	44.64 ± 18.652	50.98 ± 17.506	696.500	0.017
TMT-B sec	101.34 ± 35.073	115.00 ± 41.282	824.500	0.183
<i>Verbal fluency test</i>				
VF-s	30.02 ± 6.124	27.12 ± 5.584	2.326	0.011
VF-l	18.79 ± 3.759	17.17 ± 3.012	2.227	0.014

S_{mf} - mean fixation success; S_{max} - maximum success; S_{rep} - reproduction success; S_{ret} - retention success; LM_1 - logical memory first text; LM_2 - logical memory second test; VF_s - semantic verbal fluency; VF_l - literal verbal fluency; TMT-A = trail making test part - A; TMT-B = trail making test part - B; DSST - digit symbol substitution test; $BVRT_{correct}$ - number of correct answers; $BVRT_{error}$ - number of errors.

Values in bold-italics are statistically significant.

this component based on the Word-Fluency-Test. When the results from the same test in our study are taken into account, the difference between the two groups becomes visible, i.e. *T. gondii* negative patients perform significantly better (mean 30.56 vs 26.55, $U = 910$, $Z = -3.369$, $p = 0.001$). A separate comment requires the significant impairment in retention seen in both samples. This finding contradicts the prevailing view for larger deficits in learning than in retention in schizophrenia (Keefe and Harvey, 2012). While the small size of our sample could account for it, this result nevertheless needs to be emphasized as it complies with a large meta-analysis (Fioravanti et al., 2012) reporting substantial heterogeneity in the results of studies exploring memory functioning in schizophrenia.

Logical memory was severely deficient in both groups compared to normative results but again, seronegative patients performed better by reproducing more items of the test material. In addition to that, their performance was affected by interferences to a lesser extent. The likely explanation for the huge difference from normal values as well as between the groups is the disorganization symptoms which were more expressed in TG+ patients. As shown by at least one previous study (O'Leary et al., 2000), disorganization symptoms correlate with lower

verbal IQ results thus implying poorer verbal comprehension. Backing this possibility, a meta-analysis of schizophrenia neurocognition studies (Ventura et al., 2010) has shown that disorganization symptoms are related to a more severe impairment across all cognitive domains including verbal memory.

Visual memory was more impaired in TG+ patients as they had significantly more errors and less correct answers in the BVRT in which neither of the two groups reached population norms. Insofar as the performance on visual memory tests closely correlates with executive function (Obayashi et al., 2003; Kim et al., 2008), these results are indicative of more severe deterioration in this cognitive domain in TG+ patients as opposed to TG- ones. Further support for such an inference was the results of TMT-A and B tests. As shown on Table 2, they outlined a clear underperformance of TG+ patients in terms of psychomotor processing speed (TMT-A/DSST) and executive functions (TMT-B).

The greater impairment of executive functions that we observed in TG+ patients may be explained in several ways. First, it could be a direct consequence of the slower psychomotor processing speed. Supporting such a hypothesis, seropositive patients performed worse on both TMT-A and DSST tests which reflect the overall rate of psychomotor processing (Jaeger, 2018; Laere et al., 2018). It is also possible that the finding reflects a deeper cognitive problem in reasoning and problem-solving - either a deficit in planning the necessary action sequence or a deficit in set-shifting, i.e., the ability to switch mental sets in order to perform a certain task. Finally, it may reflect a more global neurocognitive deficit affecting visual perception, problem-solving, working memory, and processing speed (Harvey et al., 2019). Regardless of its causality, this finding is consistent with studies on schizophrenia patients (Brown et al., 2009), mentally healthy subjects with toxoplasmosis (Mendy et al., 2015; Gale et al., 2015; Gajewski et al., 2014; Pearce et al., 2014; Beste et al., 2014; Nimgaonkar et al., 2016; Rossini et al., 2019; Gale et al., 2020) and animal models (Kannan and Pletnikov, 2012) and supports the assumption that executive functioning may be particularly vulnerable to the effects of pre- and postnatal damages on the developing brain (Brown et al., 2009; Kannan and Pletnikov, 2012).

Finally, regarding verbal fluency assessment, again seronegative patients had statistically significant advantage in both the semantic (VF_s) and literal (VF_l) components of these tests. In this respect, our results are in disparity with what has been reported by Brown et al. (2009). These authors have noticed significant difference between schizophrenia patients that have and have not been exposed to *T. gondii* infection prenatally for VF_s only and not for VF_l . A likely reason for this incongruence could be methodological differences (Brown et al. have explored the seroprevalence of *T. gondii* IgG antibodies in mothers and not in patients themselves) as well as sample differences in terms of age, education, social background, illness duration and severity.

Several limitations of the present work need mentioning. First, as a result of the cross-sectional design we employed, the principal question remains of whether the observed cognitive deficit in seropositive patients has occurred after the infection or has predated it. Furthermore, even if we assume that the infection precedes and (possibly) accounts for the greater cognitive deficit, there is the uncertainty of whether toxoplasmosis has been congenital or if it was acquired later in life (before or after the onset of schizophrenia). Finally, it should be noted that both cognitive functioning and cognitive tests performance are phenomena with a multifactorial determination, i.e., they are influenced by a range of factors such as genetics (Burdick et al., 2013; Zai et al., 2017), intelligence (Bleecker et al., 1988), individual experience (Diamond, 2013) occupation and education (Singh-Manoux et al., 2011), motivation (Beck et al., 2018), as well as the broader sociocultural environment (Diamond, 2013).

5. Conclusion

Our study showed that PS patients seropositive for IgG anti-

toxoplasma antibodies have more severe impairment across a range of cognitive domains – verbal/visual memory, psychomotor speed and executive functions – compared to seronegative PS patients. In addition to that, the seroprevalence of IgG antibodies was associated with higher score on the PANSS disorganization sub-scale and with lower educational attainment. Considering the comparable overall illness severity between the two groups, these results are suggestive of a more profound neuropathological insult(s) in schizophrenia cases in which there is a superimposed *T. gondii* infection. Thus, it may be assumed that the latter alone or in combination with other causal factors acting in the intra-uterine period or later in life, could disrupt the process of brain development.

A deeper insight in the neuropathological mechanisms that underlie the greater cognitive impairment in schizophrenia cases that have been exposed to toxoplasmosis would potentially enhance our understanding of the etiopathogenesis of both disorders and open up new therapeutic approaches. Hence, future studies similar to the current one but with larger samples and longitudinal design combined with contemporary neurobiological assessments are warranted.

CRedit authorship contribution statement

All authors of this publication have read and accepted the revised version of the paper.

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