

# C-reactive protein is associated with severity of thought and language dysfunction in patients with schizophrenia

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**Background:** Numerous studies have demonstrated an association between C-reactive protein (CRP) levels and schizophrenia. However, the findings on psychotic severity and cognition remain inconsistent. The relationship between CRP and formal thought disorder in subdomains remains unclear.

**Methods:** We enrolled stable patients (defined as those who had no treatment changes during the 4-week period before evaluation) with a diagnosis of schizophrenia or schizoaffective disorder, according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition. We used the 30-item Thought and Language Disorder (TALD) scale to evaluate thought and language dysfunction over four subscales. We assessed psychotic symptoms using the Positive and Negative Syndrome Scale (PANSS). We collected fasting venous blood and measured plasma CRP levels.

**Results:** We enrolled 60 patients with schizophrenia. All patients received TALD and PANSS evaluation, and 33 of them had their CRP levels checked. The multivariate regression analysis indicated that CRP levels were significantly associated with the total score on the TALD ( $t=2.757$ ,  $P=0.010$ ) and the TALD Objective Positive subscale ( $t=2.749$ ,  $P=0.011$ ), after sex, age, duration of illness (in years), and use of atypical antipsychotics were adjusted for. Additionally, CRP was significantly associated with the PANSS positive subscale ( $t=2.102$ ,  $P=0.045$ ). A significantly positive correlation was observed between the total scores on the TALD scale and PANSS ( $\rho =0.751$ ,  $P<0.001$ ).

**Conclusion:** Our results suggest that abnormal CRP levels are significantly associated with formal thought and language dysfunction in the Objective Positive subdomain and positive psychotic symptoms.

**Keywords:** C-reactive protein, formal thought disorder, schizophrenia

## Introduction

C-reactive protein (CRP) is the primary inflammation biomarker in clinical practice.<sup>1</sup> Numerous studies have identified an association between chronic inflammation and schizophrenia.<sup>2,3</sup> A meta-analysis included 26 longitudinal or cross-sectional trials and reported moderately increased CRP levels in patients with schizophrenia irrespective of antipsychotic use.<sup>2</sup> The CRP levels were also reported to increase with the severity of positive symptoms but not with negative symptoms.<sup>2</sup> By contrast, other studies have demonstrated that abnormally elevated CRP levels are not associated with the severity of psychotic symptoms.<sup>4-8</sup> Although inconsistent, these findings suggest that CRP is associated with positive but not

negative symptoms; these effects may be confounded by factors such as different psychotic phases (eg, acute or chronic phase).<sup>9</sup> For instance, three trials with community-dwelling stabilized outpatients observed no association between elevated CRP and psychotic severity.<sup>6,10,11</sup>

Many studies have suggested that high CRP levels are also associated with varying levels of cognitive performance impairment in patients with schizophrenia.<sup>4,9,12–14</sup> Moreover, abnormally elevated CRP levels are associated with different cognitive function impairments, including impairments in short-term memory,<sup>15</sup> abstract reasoning, working memory, learning ability, semantic memory, mental flexibility, visual attention, and processing speed.<sup>14</sup> However, other studies have observed no significant correlations between abnormal CRP levels and cognitive functions.<sup>16–18</sup> Boozalis et al observed that CRP was correlated with negative symptoms but not cognitive function.<sup>18</sup>

Formal thought disorder (FTD), a core schizophrenia symptom, is characterized by disorganized speech and a deficit in the ability to organize thought; FTD results from the inappropriate use of aspects of language (particularly, semantics). Previous studies have demonstrated that FTD is a marker of psychotic severity<sup>19,20</sup> and impaired cognition in schizophrenia.<sup>21</sup> A recent meta-analysis reported that neurocognitive and linguistic capabilities are correlated with positive and negative FTD.<sup>22</sup> However, the relationship between CRP and FTD remains unclear. Moreover, a study recommended objective and subjective FTD assessment in addition to the assessment of positive and negative subdomains.<sup>23</sup> On the basis of these studies, we hypothesize that CRP is associated with FTD in different subdomains. Therefore, in this study, we investigated the relationship between CRP levels and the 30-item Thought and Language Disorder (TALD) scale scores. We studied the objective and subjective subdomains as well as the positive and negative subdomains in patients with schizophrenia.

## Methods

### Study population

The Institutional Review Board of China Medical University Hospital approved this study (CMUH107-REC3-055). We followed the Declaration of Helsinki recommendations. In this study, all participants provided written informed consent.

We recruited patients, from a chronic ward and an outpatient clinic, with a diagnosis of either schizophrenia

or schizoaffective disorder. We obtained demographic data on age, sex, age of onset, duration of illness, years of education, and body mass index (BMI).

### Inclusion criteria

We enrolled stable patients (defined as patients with no treatment changes during a 4-week period before evaluation) with the diagnosis of schizophrenia or schizoaffective disorder, according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition. Diagnosis was confirmed by trained psychiatrists.

### Exclusion criteria

We excluded patients with a history of neurological disorders, including stroke, epilepsy, and the effects of head injury. Patients with any current major infectious or inflammatory diseases, particularly autoimmune diseases such as lupus and rheumatoid arthritis, were excluded. We also excluded patients who used corticosteroids or non-steroidal anti-inflammatory drugs.

### Sample collection and CRP measurement

We collected fasting venous blood and measured plasma CRP levels. In this study, we used a particle-enhanced immunoturbidimetric assay (IMMULITE1; Diagnostic Products Corp., Los Angeles, California, USA) to measure high-sensitivity CRP. The coefficient of variation was 5% at 0.02 mg/dL CRP.

### Thought language function and psychotic symptoms

We used the 30-item TALD scale<sup>23</sup> to evaluate thought and language dysfunction. The TALD scale comprises four subscales: Objective Positive, Objective Negative, Subjective Positive, and Subjective Negative. We used the Positive and Negative Syndrome Scale (PANSS) to assess psychotic symptoms.<sup>24</sup> The PANSS comprises three subscales: positive, negative, and general.

### Statistical analysis

We provided descriptive statistics of the mean, median and standard deviation. A multivariate regression analysis was used to evaluate the associations between the CRP and TALD scale scores and between the CRP and the PANSS scores. We measured the correlation between the TALD scale and PANSS and calculated Spearman's rank correlation. We performed the analyses using IBM SPSS, version

20 (IBM Corp., Armonk, NY, USA), and statistical significance was defined as a two-tailed  $P < 0.05$ .

## Results

Our sample comprised 60 patients with schizophrenia. The demographic and clinical characteristics of the sample are detailed in Table 1. There were 51.7% men in the sample population. The mean age of the patients was  $44.78 \pm 9.88$  years, and the mean age during schizophrenia

onset was  $25.40 \pm 8.17$  years. The mean duration of illness was  $19.38 \pm 8.019$  years, and the mean PANSS total score was  $69.98 \pm 7.02$ . Among the 60 subjects, 57 patients were diagnosed as having schizophrenia and 3 as having schizoaffective disorder. All patients were interviewed with the TALD scale and received a PANSS evaluation, and 33 of them had their CRP levels checked. All patients were receiving antipsychotic treatment when they were enrolled. The major antipsychotics used were second-generation antipsychotics (in 52/60 or 86.67% of patients), and the three leading second-generation antipsychotics were olanzapine, aripiprazole, and risperidone. Among the 60 patients, one was enrolled from an outpatient clinic, and the other 59, from a chronic ward.

**Table 1** Clinical and demographic characteristics of individuals with schizophrenia (N=60)

	Mean or N (%)	S.D.
Age	44.78 (9.877)	
Gender, male	31 (51.7%)	
Education	11.18	2.891
Age of onset	25.4	8.166
Illness duration (years)	19.38	8.019
PANSS Positive	16.55	2.594
PANSS Negative	17.48	1.855
PANSS General	35.95	4.276
PANSS Total	69.98	7.019
TALD Objective Positive	13.85	9.231
TALD Objective Negative	3.00	2.731
TALD Subjective Positive	1.98	1.996
TALD Subjective Negative	9.70	5.036
TALD Total	28.53	12.506
First generation antipsychotics	16 (26.67%)	
Second generation antipsychotics	52 (86.67%)	
Olanzapine	9 (15.0%)	
Aripiprazole	9 (15.0%)	
Risperidone	9 (15.0%)	
Quetiapine	8 (13.3%)	
Paliperidone	7 (11.7%)	
Clozapine	7 (11.7%)	
Amisulpride	5 (8.3%)	
Zotepine	2 (3.3%)	
DM	6 (10.0%)	
Hypertension	12 (20.0%)	
BMI	25.97	4.809
CRP	0.405	0.879
CRP, mg/dL	0.14 [0.065, 0.365]	Median [Q1, Q3]
CRP level after log-transformation	$-1.86 \pm 1.32$	Mean $\pm$ SD

**Abbreviations:** PANSS, Positive and Negative Syndrome Scale; TALD, Thought and Language Disorder Scale; DM, diabetes mellitus; BMI, body mass index; CRP, C-reactive protein.

## CRP and thought and language dysfunction

The multivariate regression analysis indicated that CRP levels were significantly associated with scores on the TALD scale ( $t=2.757$ ,  $P=0.010$ ), after sex, age, duration of illness (in years), and use of atypical antipsychotics were adjusted for. Additionally, in the analysis of the four TALD subscales, CRP was significantly associated with the Objective Positive subscale of the TALD ( $t=2.749$ ,  $P=0.011$ ), but associations with the other three TALD subscales were nonsignificant (Table 2).

## CRP and psychotic symptoms

In this study, CRP levels were associated with PANSS scores, but the association was nonsignificant ( $t=1.744$ ,  $P=0.092$ ), after sex, age, duration of illness (in years), and use of atypical antipsychotics were adjusted for. Additionally, in the analysis of the four PANSS subscales, CRP was significantly associated with the positive subscale of the PANSS ( $t=2.102$ ,  $P=0.045$ ), but the association with the other two PANSS subscales was nonsignificant (Table 2).

## Thought, language dysfunction and psychotic symptoms

A significantly positive correlation was observed between the total score on the TALD and PANSS total score ( $\rho=0.751$ ,  $P < 0.001$ ; Figure 1). In the subscale analysis, the TALD Objective Positive subscale was significantly correlated with three subscales of the PANSS ( $\rho=0.481$ ,  $0.540$ , and  $0.585$ , respectively,  $P < 0.001$ ). The TALD Subjective Positive subscale was significantly correlated

Table 2 Multivariate regression analysis

Independent variables	Dependent variables								
	TALD total score	TALD Objective Positive	TALD Objective Negative	TALD Subjective Positive	TALD Subjective Negative	PANSS total score	PANSS positive subscale	PANSS negative subscale	PANSS general subscale
(N=33)									
Intercept	45.862 (10.707)*	18.599 (7.996)*	3.493 (2.581)	6.021 (1.435)*	17.749 (4.467)*	79.640 (6.332)*	21.282 (2.006)*	18.813 (1.562)*	39.545 (4.028)*
CRP	6.872 (2.493)*	5.117 (1.862)*	0.390 (0.601)	0.432 (0.334)	0.932 (1.040)	2.572 (1.474)	0.982 (0.467)*	0.025 (0.364)	1.565 (0.938)
Sex	-3.047 (4.386)	-2.452 (3.276)	1.605 (1.057)	-1.036 (0.588)	-1.164 (1.830)	-0.984 (2.594)	-0.547 (0.822)	-0.072 (0.640)	-0.365 (1.650)
Age	-0.311 (0.256)	-0.116 (0.191)	0.001 (0.062)	-0.098 (0.034)*	-0.098 (0.107)	-0.211 (0.151)	-0.080 (0.048)	-0.025 (0.037)	-0.107 (0.096)
Illness duration	-0.148 (0.352)	0.067 (0.263)	-0.058 (0.085)	0.021 (0.047)	-0.177 (0.147)	0.048 (0.208)	-0.030 (0.066)	-0.010 (0.051)	0.088 (0.133)
Atypical antipsychotics	-2.029 (7.659)	-1.305 (5.720)	-1.119 (1.846)	1.534 (1.027)	-1.140 (3.196)	2.992 (4.530)	0.444 (1.435)	0.880 (1.118)	1.668 (2.882)

Notes: Numbers in each cell are multivariate regression coefficients and numbers in parentheses are the standard error values. \*Significant at the 95% confidence level. Abbreviations: PANSS, Positive and Negative Syndrome Scale; TALD, Thought and Language Disorder Scale.

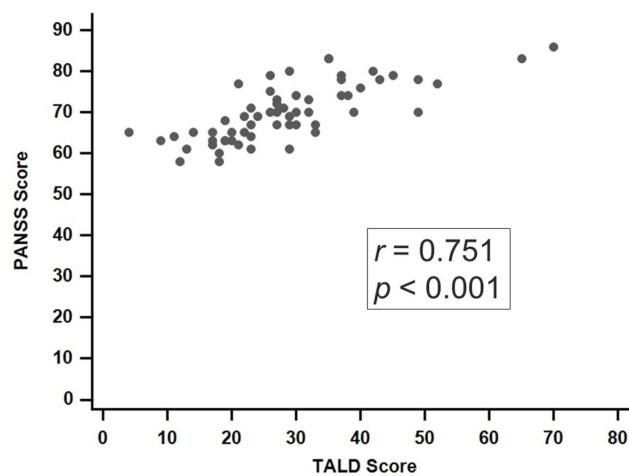
with the PANSS positive subscale ( $\rho=0.264$ ,  $P=0.042$ ), and the TALD Subjective Negative subscale was significantly correlated with both the PANSS positive and negative subscales ( $\rho=0.528$ ,  $P<0.001$ ;  $\rho=0.335$ ,  $P=0.009$ ; Table 3).

### Discussion

To our knowledge, this is the first study to investigate the association between CRP and FTD. The findings of this study are as follows: (a) CRP levels are significantly associated with the total scores on the TALD and the TALD Objective Positive subscale, (b) CRP levels are significantly associated with the PANSS positive subscale, and (c) the total score on the TALD and some TALD subscale scores are significantly correlated with all scores on the PANSS.

In this study, the multivariate regression analysis indicated that CRP levels are significantly associated with the total score on the TALD ( $t=2.757$ ,  $P=0.010$ ) after sex, age, duration of illness (in years), and atypical antipsychotic use were adjusted for. Furthermore, in the analysis of the four TALD subscales, CRP was significantly associated with the TALD Objective Positive subscale ( $t=2.749$ ,  $P=0.011$ ). This is the first study to investigate the association between CRP and FTD in the four subscales. Kircher and his colleagues invented a comprehensive assessment tool, the TALD scale,<sup>23</sup> to evaluate four FTD subdomains: Objective Positive, Objective Negative, Subjective Positive, and Subjective Negative. Earlier FTD rating scales were in the descriptive psychopathological tradition.<sup>25,26</sup> Furthermore, we observed a significantly positive correlation between the total score on the TALD and PANSS total score ( $\rho=0.751$ ,  $P<0.001$ ; Figure 1). In subscale analysis, the TALD Objective Positive subscale score was significantly correlated with three PANSS subscales ( $\rho=0.481$ ,  $0.540$ , and  $0.585$ , all  $P<0.001$ ; Table 3). Our findings agree with the results of Kircher and his colleagues, who observed a correlation between the TALD Objective Positive subscale and the Scale for the Assessment of Positive Symptoms (SAPS;  $\rho=0.925$ ,  $P<0.01$ ).<sup>23</sup> A study that examined 51 patients with schizophrenia also reported a significant correlation between the TALD Objective Positive subscale score and executive dysfunctions.<sup>27</sup> Further investigation may be needed on the relationships between CRP, FTD, and cognition.

In this study, CRP was significantly associated with the PANSS positive subscale ( $t=2.102$ ,  $P=0.045$ ), although CRP's associations with the PANSS total score and the



**Figure 1** Scatter plots and correlation analysis between the TALD scale and PANSS.

**Abbreviations:** PANSS, Positive and Negative Syndrome Scale; TALD, Thought and Language Disorder Scale.

two PANSS subscales of negative and general were non-significant. Our findings agree with a previous meta-analysis<sup>2</sup> in which meta-regression analyses suggested that the PANSS positive subscale was positively related to CRP levels (slope=0.12, 95% CI=0.03–0.23,  $P=0.013$ ), but the association between the PANSS total score and PANSS negative subscale was nonsignificant. A study on 26 patients with either schizophrenia or schizoaffective disorder reported that patients with greater CRP levels had a significantly greater PANSS total score, negative subscale score, and general subscale score relative to patients with normal CRP levels ( $P=0.017$ , 0.016, and 0.014, respectively).<sup>28</sup> Another study whose sample comprised 48 patients with first-episode psychosis and 74 patients with schizophrenia in an acute exacerbation phase observed a positive correlation between high-sensitivity CRP levels and the severity of positive symptoms ( $\rho=0.494$ ,  $P=0.004$ ).<sup>29</sup> Two studies have observed that CRP is correlated with negative symptoms.<sup>18,30</sup> However, some studies have observed no significant correlation between abnormal CRP levels and psychotic severity.<sup>4,6,8</sup>

These discrepancies warrant further meta-analyses, trials with larger sample sizes, and comprehensive analyses of confounding factors to investigate the subgroup that is patients with severe psychosis.

We propose two reasons that CRP is associated with psychotic positive symptoms and impaired cognition: First, increased CRP may indirectly cause hypofunction of the N-methyl-D-aspartate (NMDA) receptor pathway that plays a crucial role in schizophrenia and cognition.<sup>31,32</sup> Studies have observed that peripheral CRP can increase the permeability of the blood–brain barrier by influencing the tight junction<sup>33</sup> that plays a role in psychiatric disorders.<sup>34,35</sup> After entering the brain, CRP can induce an inflammatory state in the microglia,<sup>36</sup> which then releases interleukin (IL)-6 and transforming growth factor  $\beta$ .<sup>36,37</sup> This induces the astrocytes to metabolize tryptophan into kynurenic acid, which may result in hypoglutamatergic function because it acts as an antagonist to NMDA receptors as well as dopaminergic hyperfunction in the limbic system. These functions are involved in the development of positive psychotic symptoms in schizophrenia.<sup>38–41</sup> Second, CRP may act as a proxy for IL-6, correlated with positive psychotic symptoms.<sup>37,42</sup>

## Limitations

This study has several limitations. First, we did not assess the cognitive functions using standard tools. Standard cognitive measurements should be used to evaluate the relationships between CRP, cognitive functions, and thought dysfunction in future studies. Second, we only evaluated CRP; other inflammatory biomarkers such as IL-6 were not evaluated. The results pertaining to CRP levels were based on only 33 patients. Further investigation should be conducted with a larger sample of patients in different psychotic phases. Third, additional factors, such as alcohol and substance abuse, were not included in our analysis. Furthermore, to confirm the diagnoses of the patients, we recommend further trials that use standardized clinical

**Table 3** Correlations between the four subdomains of the TALD scale and three subdomains of the PANSS

PANSS three subdomains	TALD four subdomains			
	Objective Positive	Objective Negative	Subjective Positive	Subjective Negative
Positive	0.481**	0.206	0.264*	0.528**
Negative	0.540**	0.080	0.062	0.335**
General	0.585**	0.250	0.193	0.189

**Notes:** \*\*Correlation is significant at the 0.01 level (2-tailed). \*Correlation is significant at the 0.05 level (2-tailed).

**Abbreviations:** PANSS, Positive and Negative Syndrome Scale; TALD, Thought and Language Disorder Scale.

examination methods such as the Structured Clinical Interview for Mental Disorders.

## Conclusion

CRP was significantly associated with formal thought and language dysfunction in the subgroup of patients that score highly on the TALD Objective Positive subscale and have positive psychotic symptoms.

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## Disclosure

The authors report no conflicts of interest in this work.

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