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David Goldsmith 10/12/2020

Inflammatory markers are associated with decreased psychomotor speed in patients with schizophrenia

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Inflammatory markers are associated with decreased psychomotor speed in patients with schizophrenia

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M.D., Emory University, 2012
B.S., University of Maryland College Park, 2002

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Abstract

Inflammatory markers are associated with decreased psychomotor speed in patients with schizophrenia
By David R. Goldsmith

Previous data have demonstrated that administration of inflammatory cytokines or their inducers leads to altered basal ganglia function associated with reduced psychomotor speed. Decreased psychomotor speed, referred to clinically as psychomotor retardation, is a core cognitive domain in patients with schizophrenia, and has been associated with poor functional outcomes. We therefore examined the cross-sectional association between plasma inflammatory markers and psychomotor speed in forty-three patients with schizophrenia. Psychomotor speed was assessed by a range of neuropsychological tests from purely motor (e.g., finger tapping tasks) to those that involve motor activity with increasing cognitive demand and cortical participation (e.g., trail making task and symbol coding task). Linear regression analyses were performed to determine the relationship of inflammatory markers and psychomotor task performance. Models were adjusted for age, race, sex, smoking status, and body mass index. Schizophrenia patients demonstrated decreased psychomotor speed on all tasks relative to published normative data from healthy controls. Interleukin-10 (IL-10) was associated with decreased performance on the finger tapping task with the non-dominant hand (β = -0.41, p = 0.012, 95% CI = -98.3, -12.79) and the trail making task (β = 0.433, p = 0.007, 95% CI = 0.123, 0.704). Soluble IL-6 receptor (sIL-6r) was associated with increased performance on the finger tapping task with the dominant hand (β = 0.395, p = 0.016, 95% CI = 0.118, 1.070). Taken together, the data indicate that a peripheral inflammatory profile including increased IL-10 and decreased sIL-6r is consistently associated with psychomotor speed in patients with schizophrenia. These data are consistent with data demonstrating that inflammation can impact basal ganglia function and indicate that tasks of psychomotor speed may be viable outcome variables in trials of anti-inflammatory therapies in schizophrenia and other neuropsychiatric disorders with increased inflammation.

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INTRODUCTION

Schizophrenia is a chronic and debilitating psychiatric disorder affecting 1% of the population worldwide, and accounting for over $60 billion in costs to the national healthcare system (1). The disorder is a major public health concern, and many individuals with schizophrenia suffer chronic debilitating symptoms including treatment resistance, have high rates of unemployment and homelessness, and have a significantly reduced life expectancy (2-8). Patients suffer from a constellation of symptoms including delusions, hallucinations, trouble expressing their thoughts, and a lack of motivation.

In addition to these symptoms, most patients with schizophrenia also exhibit cognitive deficits, on the order of 1-2 standard deviations below their premorbid cognitive performance (9, 10). Some evidence suggests that these deficits may be present prior to the onset of psychosis (11, 12). Moreover, these cognitive symptoms appear unresponsive to antipsychotic medications, and there are no treatments currently approved to target these cognitive deficits (13, 14). Importantly, these cognitive deficits are those symptoms that are significantly associated with poor functional outcomes in patients with schizophrenia (15, 16).

Psychomotor slowing has been described clinically in patients with schizophrenia and has also been reliably demonstrated in research settings (17). Psychomotor slowing was considered a core feature of the illness in early descriptions of schizophrenia (18, 19). More recent work has implicated psychomotor processing speed as an independent cognitive domain impaired in patients (20). Indeed, the most well

established cognitive battery, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB), includes a task of psychomotor speed (trail making task, part A) and a task of psychomotor processing speed (symbol coding task) (21).

It is not fully understood what might be driving psychomotor deficits in patients with schizophrenia, though a few studies have implicated dysfunction in basal ganglia circuitry (22-25). This is consistent with similar findings in the basal ganglia, specifically the dorsal striatum, in patients with major depressive disorder who also exhibit psychomotor retardation (26, 27). This study seeks to address the role of inflammation as a potential mechanism of psychomotor slowing in patients with schizophrenia. The immune system has been thought to be involved in the pathophysiology of schizophrenia and inflammatory markers have been shown to be altered in some patients with the disorder (28, 29). Previous work has implicated inflammation as targeting the basal ganglia with specific effects on the dorsal striatum that has been associated with psychomotor slowing in healthy controls and individuals with depression (30, 31). Based on these findings, we sought to examine the relationship between an array of inflammatory markers and a large battery of neurocognitive tests of psychomotor speed in patients with schizophrenia.

BACKGROUND

Psychomotor slowing has been shown to be present in individuals experiencing their first episode of psychosis and remains present throughout the course of illness, often-times worsening over the lifespan (32). There is some evidence of psychomotor slowing in individuals at clinical high risk for psychosis whose symptoms have not yet met criteria for the diagnosis of a primary psychotic disorder (33). Moreover, psychomotor deficits have been demonstrated in unaffected first-degree relatives of patients with schizophrenia, which suggests that these deficits may be related to underlying genetic risk for the disorder and could represent an intermediate phenotype (34). Importantly, deficits in psychomotor speed do not appear to respond to treatment with antipsychotic medications, and there are currently no treatments that appear to improve these symptoms (13, 14). Psychomotor slowing has also been shown to be associated with worse functional outcomes in patients with schizophrenia (15, 35, 36). As such, novel mechanisms and treatment targets are necessary to discover effective treatments for these debilitating symptoms.

One pathway that may contribute to psychomotor slowing in patients with schizophrenia is inflammation. Multiple lines of evidence have implicated inflammation and other immune system abnormalities in the neurodevelopment and psychopathology of schizophrenia. Early epidemiological studies demonstrated that exposure to infections in utero and in childhood increase risk for the disorder (37-39). These findings are further supported by maternal immune activation models whereby pregnant laboratory animals are exposed to inflammatory stimuli (i.e., lipopolysaccharide,

poly(I:C), cytokines) and their pups show behavioral, neuroanatomical, neurochemical, and electrophysiologic abnormalities akin to what has been shown in patients with schizophrenia (40). Autoimmune disorders are more prevalent in both individuals with schizophrenia and their first-degree unaffected relatives (41, 42). Genetic studies have implicated single nucleotide polymorphisms in cytokine genes, and genome-wide association studies have consistently shown as association between schizophrenia and the major histocompatibility complex region on chromosome 6 (43-46). These findings are consistent with recent data that the complement pathway (innate immune system) may play a fundamental role in the development and progression of the disorder via effects on synaptic pruning (38). Finally, numerous studies have reported alterations in inflammatory cytokine concentrations (both in peripheral blood as well as in cerebrospinal fluid) in patients with schizophrenia, including in individuals at clinical high risk, at first-episode, in acute psychosis, and in psychiatrically stable individuals with chronic schizophrenia (28, 47-52).

Regarding the potential mechanism of the impact of inflammation on psychomotor speed, laboratory animals exposed to inflammatory cytokines or other inflammatory stimuli have been shown to have decreased locomotor activity (53, 54). In humans, neuroimaging studies have consistently demonstrated that exposure to various inflammatory stimuli (i.e., interferon-alpha, typhoid vaccination, and endotoxin) alters both neural activity and dopamine metabolism in the basal ganglia, including the dorsal striatum in association with psychomotor slowing (30, 55-57).

Similar to patients with schizophrenia, individuals with major depressive disorder also have psychomotor retardation as a core symptom of the disorder. Slowing on

psychomotor tasks has been shown to be associated with increased inflammatory marker concentrations in both pure motor tasks as well as psychomotor tasks (31). Moreover, patients with depression have been shown to have decreased connectivity in motor circuits between the dorsal striatum and the ventromedial prefrontal cortex. This decreased connectivity has been shown to be sensitive to the effects of inflammation as measured by C-reactive protein (CRP), an acute phase reactant synthesized by the liver in response to systemic peripheral inflammation. Individuals with high CRP (>3mg/L) were shown to have less connectivity in this motor circuit, which in turn was associated with psychomotor slowing as assessed by a finger tapping task as well as a trail making task (58).

Inflammatory markers have been shown to be associated with negative symptoms (deficits in expressivity and motivated behaviors) and deficit schizophrenia (marked by persistent and enduring negative symptoms), which have previously been shown to be associated with psychomotor deficits (59, 60). Much of my work thus far has focused on the role of inflammatory markers and negative symptoms, and as such, I sought to examine the relationship between inflammatory markers and psychomotor task performance in patients with schizophrenia. The tasks included in this analysis reflect both pure motor activity (e.g., finger tapping) as well as those that involve more cognitive demand and cortical activity (e.g., trail making task and symbol coding task). This approach will allow for further understanding of potential distinctions between tasks of psychomotor speed and tasks of psychomotor processing speed (e.g., symbol coding), as there is some discrepancy in the literature as to whether they reflect different processes. Moreover, we sought to measure a large panel of inflammatory

markers to investigate whether specific markers might be associated with psychomotor slowing.

METHODS

Specific Aim and Hypothesis

The specific aim of this research is to determine the cross-sectional association between inflammation and measures of psychomotor speed in patients with schizophrenia. Briefly, forty-three patients with schizophrenia were recruited and their performance on the following psychomotor tasks were measured: Finger Tapping Test (FTT; both dominant and nondominant hands), Trail Making Task (TMT), and Symbol Coding Task (SC). Peripheral inflammatory markers were assessed, including interleukin (IL)-6, tumor necrosis factor (TNF), IL-10, IL-1beta, monocyte chemoattractant protein 1 (MCP1), IL-1 receptor antagonist (IL-1ra), TNF receptor 2 (TNFR2), and soluble IL-6 receptor (sIL-6r), which have all been shown to be altered in individuals with schizophrenia (28). The hypothesis of this aim is that increased inflammation is associated with impairments in tasks of psychomotor speed, in a cross-sectional study design, in patients with schizophrenia. These associations will be modeled using linear regression with performance on each task (continuous variables) as the primary outcome (dependent) variable. The relationships will also be modeled using the following relevant covariates: age, sex, race, smoking status.

Characteristics of the Study Sample

Forty-three patients with schizophrenia or schizoaffective disorder, between the ages of 18 and 65 years old, were recruited from the Atlanta Veterans Affairs Medical Center. Psychiatric diagnosis was confirmed by the Structured Clinical Interview for

DSM-IV, Axis-1. In order to control for potential other sources of increased inflammation that might confound the relationship between inflammatory markers and psychomotor performance, subjects were excluded if they had a heart attack or heart failure within 6 months of screening, antibiotic use within 60 days of screening, hospitalizations within 60 days of screening, or any condition requiring treatment with steroids within 60 days of screening. Other exclusion criteria included a history of neurologic disease, head trauma, CNS infection, seizure disorder, intellectual disability, active substance abuse within three months of testing (confirmed by interview as well as urine drug screen on day of testing), HIV infection, autoimmune disorder diagnosis, or clinically significant visual or hearing impairment. Informed consent, as approved by both the Emory University Institutional Review Board and the Atlanta VAMC Research and Development Committee, was provided by all subjects.

Primary Dependent Variables: Psychomotor Speed Tasks

The FTT is a motor task in which subjects are instructed to repeatedly press a key in a specified length of time, in this case 60 seconds. The FTT was performed with both the dominant and non-dominant hands. The higher the number of taps, the better the psychomotor performance (61). The TMT is a subscale of the MATRICS Consensus Cognitive Battery (MCCB) wherein subjects draw a line connecting consecutively numbered circles placed randomly on the page. This visuomotor task is timed with the primary variable being time to complete the task. A higher time on the task reflects slower performance (21). Lastly, the SC task is also an MCCB subscale visuomotor task where subjects have to fill in consecutive boxes with numbers that correspond to

nonsense symbols they find on a key. The primary outcome measure is the correct number of coded symptoms completed in 90 second. As such, the higher the number of correct boxes reflects better psychomotor performance on the task (21).

Primary Independent Variables: Inflammatory markers

Subjects provided blood samples for inflammatory markers (taken on the day of neurocognitive testing), which were collected in chilled EDTA-coated tubes and spun at 2000 x *g* for 15 minutes at 4°C. Plasma was collected and stored at -80°C for batched analysis at a later time. The following inflammatory markers were measured: IL-6, IL-1beta, IL-10, MCP-1, TNF as well as the soluble receptors IL-6sr, IL-1RA, and TNFR2. These markers were assayed in duplicate using high sensitivity multiplex bead-based assays (R&D Systems) and analyzed on a MAGPIX CCD imager (Luminex) as previously described (58). All samples were processed in the same batch and included high and low technical replicates in addition to control plasma on each plate. Mean inter- and intra-assay coefficients of variation (CV) were reliably <10%. No immune markers were below the limits of assay detection, although three subjects did not have enough sample volume for MCP-1, IL-6sr, IL-1RA, and TNFR2 assays, and were not used in the analyses.

Sample-size and power considerations/calculations

The sample used for the study was a sample of convenience and was thus not powered a priori to detect associations between variables. As such, we performed a

post-hoc power analysis to determine how much power we had in our analyses to detect true associations.

Analytic Plan

Descriptive statistics including means and standard deviations for independent and dependent variables were calculated for the sample. To determine which inflammatory measures were associated with psychomotor task performance, stepwise, backward linear regression analyses were performed including all inflammatory markers as independent variables in the models. Each of the psychomotor tasks was analyzed separately to determine similarities and differences in the contribution of inflammatory markers to each task. Normality assumptions for all variables (both dependent and independent) were tested using standard tests (Shapiro-Wilks), and natural log transformations were applied to non-normally distributed variables. The multivariate model (model 1) tested for each task was:

$$\textit{psychomotor task performance} = b_0 + b_1(\textit{IL-6}) + b_2(\textit{TNF}) + b_3(\textit{IL-10}) + b_4(\textit{IL-1b}) + b_5(\textit{MCP1}) + b_6(\textit{IL-1ra}) + b_7(\textit{TNFR2}) + b_8(\textit{sIL-6r})$$

Each model was then adjusted for the following covariates, which have known effects on inflammation: age, sex, race, and smoking (model 2). We did not have complete data for body mass index (BMI), which also has known effects on inflammation, and we therefore further adjusted the model to also account for BMI, albeit in a smaller sample (model 3).

RESULTS

Performance on the psychomotor tasks are presented in **Table 2**. Average scores for the patients with schizophrenia were at least 1 standard deviation below the normative standards on the FTT (both dominant and nondominant hands) and at least 2 standard deviations below the normative means on the TMT and SC. The FTT dominant hand and TMT were found to be non-normally distributed and were log-transformed and used in subsequent analyses. Most inflammatory markers were non-normally distributed, though all were log-transformed and used in subsequent analyses, per convention.

Finger Tapping Tasks

In the model 1, sIL-6r was associated with better motor performance on the finger tapping task with the dominant hand (β = 0.395, p = 0.016, 95% CI 0.118, 1.070), and IL-10 was associated slower performance with the non-dominant hand (β = -0.410, p = 0.012, 95% CI -98.3, -12.8) (**Table 3**). Both findings remained significant after correction for multiple comparisons. After adding relevant covariates to the model (model 2; **Table 3**), sIL-6r was associated with better performance (β = 0.437, p = 0.007, 95% CI 0.194, 1.121) and IL-1RA was associated with slower performance on the FTT with the dominant hand (β = -0.318, p = 0.043, 95% CI -0.306, -0.006). IL-10 was associated with slower performance (β = -0.403, p = 0.011, 95% CI -96.2, -13.2) and sIL-6r was associated with better performance on the FTT with the non-dominant hand (β = 0.357, p = 0.027, 95% CI 13.3, 206.5). Sex was also associated with

performance on the FTT with the dominant hand (β = 0.335, p = 0.033, 95% CI 0.023, 0.519). Exploratory analyses of the effects of sex revealed that men had more total taps (mean = 264.68, s.d. = 56.77) compared to women (mean = 228.24, s.d. = 63.28), though this was not significant different (t = -1.212, p = 0.233). After correcting for multiple comparisons, the association between FTT dominant and IL-1RA was no longer significant. Finally, when BMI was added to the adjusted model (model 3; **Table 3**), sIL-6r remained significant for both the dominant (β = 0.416, p = 0.015, 95% CI 0.13, 1.12) and non-dominant hands (β = 0.349, p = 0.033, 95% CI 9.01, 205.8), and IL-10 remained significantly associated with performance with the non-dominant hand (β = -0.426, p = 0.009, 95% CI -101.2, -15.6). After correcting for multiple comparisons, the association between FTT nondominant and sIL-6r was no longer significant.

Trail Making Task

In model 1, IL-10 was associated with slower performance on the TMT (β = 0.433, p = 0.007, 95% CI 0.123, 0.704) (**Table 3**). This finding remained significant after correction for multiple comparisons. After adding relevant covariates to the model (model 2; **Table 3**), IL-10 remained significant (β = 0.566, p = 0.001, 95% CI 0.245, 0.835), which also remained significant after correction for multiple comparisons. Finally, in model 3 (**Table 3)**, both IL-10 (β = 0.452, p = 0.005, 95% CI 0.143, 0.723) and IL-1b (β = 0.320, p = 0.038, 95% CI 0.083, 2.825) were associated with slower performance. No covariates were significantly associated with performance on the TMT. After correction for multiple comparisons, the association between TMT and IL-1b was no longer significant.

Symbol Coding

In model 1, no inflammatory markers were associated with performance on the SC (**Table 3**). After adding relevant covariates to the model (model 2; **Table 3**), sIL-6r was associated with better performance on the SC (β = 0.309, p = 0.032, 95% CI 1.793, 37.647). Age was significantly associated with worse performance on the SC (β = -0.502, p = 0.001, 95% CI -0.908, -0.257). Exploratory analyses of the effect of age revealed that older individuals (median split, older group > 53) performed significantly worse on the SC (mean = 33.96, s.d. = 7.83) compared to younger individuals (mean = 43.11, s.d. = 12.78; t = 2.74, p = 0.011). In the younger group, TNF (β = -0.665, p = 0.044, 95% CI -49.6, -0.793) and IL-1b (β = -0.588, p = 0.044, 95% CI -185.3, -3.24) was associated with worse performance on the SC and IL-1ra (β = 0.648, p = 0.031, 95% CI 1.35, 22.9) and TNFR2 (β = 0.679, p = 0.030, 95% CI 1.77, 29.09) was associated with better performance. In the older group, sIL-6r was associated with better performance (β = 0.585, p = 0.004, 95% CI 11.22, 51.92) and IL-10 was associated with worse performance (β = -0.414, p = 0.033, 95% CI -14.3, -0.67). All findings remained significant after correction for multiple comparisons. Finally, in model 3 (**Table 3**), sIL-6r was associated with better performance on the SC (β = 0.308, p = 0.037, 95% CI 1.241, 37.87) and age also was associated with worse performance on the SC (β = -0.513, p = 0.001, 95% CI -0.95, -0.265). Adding BMI to the linear regression models in younger and older groups did not meaningfully change the results of the exploratory analyses of age. All findings remained significant after correction for multiple comparisons.

Principle Component Analysis - Tasks

The four psychomotor tasks were placed in a principle component analysis with varimax rotation, which resulted in two factors. Factor one was made up of the finger tapping tasks with factor loadings of 0.887 and 0.903 for the dominant and nondominant tasks, respectively. This factor was thus referred to as the "motor factor." Factor two was made up of the TMT and the SC tasks with factor loadings of 0.919 and -0.906, respectively. This was thus referred to as the "psychomotor factor." A regression factor score was calculated for each subject for each factor, and this regression factor score was used as the dependent variable in a linear regression analysis using the same approaches as before.

For the motor factor, in the model 1, IL-10 was associated with worse performance (β = -0.355, p = 0.031, 95% CI -1.69, -0.088) while sIL-6r was associated with better performance (β = 0.322, p = 0.049, 95% CI 0.011, 3.649) (**Table 3**). Neither finding remained significant after correction for multiple comparisons. Both inflammatory markers remained significant in model 2 and model 3 (**Table 3**). Sex was also significantly associated with performance in both models 2 and 3. Exploratory analysis of sex revealed that men had better performance based on the motor factor score compared to women, though, the difference was not significant (t = -1.481, p = 0.146). IL-10, sIL-6r, and sex remained significant in model 2 after correcting for multiple comparisons, but only sIL-6r survived correction in model 3.

For the psychomotor factor, in model 1, IL-10 was associated with worse performance (β = -0.420, p = 0.009, 95% CI -1.779, -0.273) while sIL-6r was associated

with better performance (β = 0.353, p = 0.026, 95% CI 0.249, 3.671) (**Table 3**). IL-10 remained significant after correction for multiple comparisons, whereas sIL-6r did not. IL-10 remained associated with worse performance in both models 2 and 3 while TNFR2 was associated with better performance (**Table 3**). Older age was also associated with worse performance on the psychomotor factor. Exploratory analyses of the effect of age revealed that older individuals (median split, older group > 53) performed significantly worse on the psychomotor factor compared to younger individuals (t = 2.47, p = 0.018). In the younger group, IL-6 (β = -0.621, p = 0.037, 95% CI -3.539, -0.126) and IL-1b (β = -0.563, p = 0.034, 95% CI -13.94, -0.655) were associated with worse performance on the psychomotor factor and IL-1ra (β = 0.942, p = 0.008, 95% CI 0.453, 2.405) was associated with better performance. In the older group, sIL-6r was associated with better performance (β = 0.543, p = 0.002, 95% CI 1.255, 4.745) and IL-10 was associated with worse performance (β = -0.649, p < 0.001, 95% CI -1.782, -0.615). IL-10, TNFR2, and age remained significant in model 2 after correction for multiple comparisons. Adding BMI to the linear regression models in younger and older groups did not meaningfully change the results of the exploratory analyses of age. IL-10, but not TNFR2 or age, remained significant in model 3 after correction for multiple comparisons.

Principle Component Analysis – Inflammatory Markers

In an exploratory analysis, we placed all of the inflammatory markers into a principle component analysis with varimax rotation to see how the different markers

grouped together (**Table 4**). Factor 1 was made up of TNF and IL-10. Factor 2 was made up of IL-6, IL-1beta, and IL-1RA. Factor 3 was made up of sIL-6r and TNFR2.

In exploratory model 1, Factor 1 was associated with worse performance on the FTT nondominant hand (β = -0.358, p = 0.030, 95% CI -35.31, -1.933; **Figure 1**) and in the dominant hand at trend level significance (β = -0.315, p = 0.058, 95% CI -0.163, 0.003). Factor 1 was also associated with worse performance on the TMT in model 1 (β = 0.434, p = 0.005, 95% CI 0.052, 0.266; **Figure 1**). Factor 3 was associated with better performance on the SC (β = 0.388, p = 0.018, 95% CI 0.779, 7.611). Adding potential confounding variables to the models did not meaningfully change the results save for SC where age was associated with worse performance (β = -0.481, p = 0.001, 95% CI -0.877, -0.238) in addition to Factor 3.

Post-hoc Power Calculations

Given the small sample size, post-hoc power was calculated. Effect sizes were calculated and placed in G*power 3.1 to determine the amount of post-hoc power. Power ranged from 0.17 for the SC to 0.81 for TMT. The calculated power for FTT was 0.39 and 0.41 for the dominant and nondominant hands, respectively.

DISCUSSION

A significant association between peripheral inflammatory markers and performance on psychomotor tasks was found in a sample of patients with schizophrenia who had slowed performance relative to normative standards. Increased concentrations of IL-10 and decreased concentrations of sIL-6r were most consistently associated with slowed performance across the four tasks. Moreover, after correcting for multiple comparisons, sIL-6R was associated with better performance on the motor factor whereas IL-10 was associated with worse performance on the psychomotor factor. Taken together, the results indicate that peripheral inflammatory markers were associated with psychomotor performance in patients with schizophrenia and may serve as an important outcome variable for anti-inflammatory treatment trials in patients with schizophrenia.

There have been a few studies that have investigated the relationship between inflammation and psychomotor performance in patients with schizophrenia, though the primary limitation of this literature is either the use of a small number of inflammatory markers and/or a small number of psychomotor tasks. Kogan et al demonstrated relationships between the processing speed domain of the MCCB and TNF as well as IL-12p70 (65). Though we did not find a significant relationship in the primary analyses for TNF, there was a relationship between TNF and symbol coding (one of the processing speed tasks of the MCCB) in younger individuals in the sample. Moreover, in exploratory factor analyses, we found that TNF clustered with IL-10, and this factor

was associated with worse performance on the TMT (the other processing speed item in the Kogan study) and FTT nondominant hand.

Performance on the TMT, but not the SC, was associated with increased C-reactive protein (CRP; >3 mg/L), an acute phase reactant synthesized by the liver in response to peripheral inflammation, in the FACE-SZ (FondaMental Academic Centers of Expertise for Schizophrenia) sample (66, 67). We did not include CRP in our analyses largely due to significant collinearity with many inflammatory markers. Moreover, in our previous study of inflammatory markers and psychomotor slowing in depression, we did not see relationships between CRP and task performance (31), despite seeing individual inflammatory markers that were associated with slower performance, as we saw in this study.

Similarly, Frydecka et al., found a relationship between IL-6 (but not CRP) and slower performance on both the TMT and SC in a sample of 151 patients with schizophrenia (68). Though we did not find any association with IL-6 in the primary analyses, we did find a relationship between IL-6 and worse performance on the psychomotor factor in the younger individuals. IL-6 has been shown to be associated with psychomotor slowing in our previous study in depression and in healthy individuals given typhoid vaccination (a known inflammatory stimulus) (30). Moreover, IL-6 has been shown to be associated with motor slowing in laboratory animals (69-71).

Interestingly, one of our most consistent findings was that sIL-6r was associated with better performance on the psychomotor tasks. IL-6 signaling is complex and is involved in both “classical” signaling via membrane bound IL-6 receptors, which is thought to be anti-inflammatory in nature, as well as trans-signaling via the sIL-6r, which

is thought to be involved in pro-inflammatory processes (72-74) Both signaling pathways involve the formation of complexes with the gp130 protein, though the soluble form of gp130 that binds the IL-6-sIL-6R complex appears to inhibit trans-signaling thus regulating pro-inflammatory signaling (74, 75). In addition, sIL-6r has been shown to be present at high concentrations regardless of inflammatory states and does not increase significantly during periods of high inflammation (76-78). As such, there are a number of possible interpretations of the sIL-6r data in this study. The concentrations of sIL-6r may not represent increased inflammation and would therefore not be hypothesized to be related to worse performance on the tasks. Without measurement of gp130, it is difficult to interpret how sIL-6r may be binding IL-6 to undergo pro-inflammatory trans-signaling. The relationship of IL-6 and worse psychomotor performance in younger individuals does suggest that pro-inflammatory signaling via IL-6 may play a role in psychomotor slowing in some individuals.

The most consistent marker in this study was IL-10, an anti-inflammatory cytokine. IL-10 has previously been shown to be associated with faster performance on psychomotor tasks in patients with depression and in patients co-infected with HIV and hepatitis C (31, 79). One possibility for the finding of IL-10 being associated with slower performance here is that IL-10 may be acting in a counter-regulatory fashion in response to increased concentrations of pro-inflammatory markers such as TNF (80). Our PCA data showing IL-10 and TNF clustering together supports this possibility. TNF has been shown to be associated with negative symptoms of schizophrenia, which itself may be related to cognitive symptoms, including psychomotor slowing (60, 81). Moreover, concentrations of IL-10 (and TNF) has been consistently shown to be

increased in meta-analyses of inflammatory markers in patients with schizophrenia, which has similarly been thought to be a counter-regulatory mechanism in response to the evidence for multiple pro-inflammatory markers being elevated in patients with schizophrenia (28).

The literature implicates abnormalities in the basal ganglia with motor abnormalities in patients with schizophrenia in addition to other neuropsychiatric disorders (22-25). Increasingly, there is accumulating evidence implicating the basal ganglia and related circuitry as a target for inflammation. For example, patients treated with interferon-alpha for hepatitis or certain cancers, show increased glucose metabolism in the basal ganglia, which is thought to be related to impaired dopamine-mediated inhibition of oscillatory burst activity in basal ganglia nuclei (82, 83). Similarly, healthy individuals given typhoid vaccination show decreased activation in the substantia nigra, a basal ganglia structure involved in motor activity, using functional MRI. This decreased activation was associated with increased IL-6 as well as slowing on a reaction time task (30). Inflammation has also been shown to mediate motor circuits between the dorsal striatum and the ventromedial prefrontal cortex, which has, in turn, been associated with slower performance on the FTT and TMT (58). Finally, patients with treatment resistant depression with high inflammation (CRP > 5mg/L) who were treated with infliximab, a TNF antagonist, showed significant psychomotor improvements compared to placebo (84). To our knowledge, the relationship between inflammation and the basal ganglia has not been confirmed in patients with schizophrenia.

There are several strengths of this study, including a hypothesis-driven approach in addition to a large panel of inflammatory markers and multiple psychomotor tasks, which has not been the case of previous studies in patients with schizophrenia. This approach has allowed us to look at differences in task domains (motor vs psychomotor) as well as clusters of inflammatory markers with our exploratory PCA data. Patients were medically cleared to avoid potential confounding illnesses and/or medications that might impact the immune system. Another strength is that we performed corrections for multiple comparisons in order to reduce type 1 error.

There are also several important limitations to this study. Though we were able to compare psychomotor performance with published normative control data, there are no normative cutoff values for inflammatory markers (other than CRP, which we did not include in our analyses). We do not know whether this constitutes a highly inflamed group of patients with schizophrenia, though meta-analyses do suggest that inflammatory marker concentrations are elevated in patients with schizophrenia, including individuals with chronic illness. Data from healthy controls was not included in this analysis for comparison purposes. Furthermore, we only examined concentrations of the proteins of the indicated inflammatory markers and not their biological activity. This may lead to an over or under-estimation of the relationship of the various markers and psychomotor performance.

Another limitation is the small sample size and subsequent concerns regarding power to detect significantly meaningful associations between inflammatory markers and psychomotor deficits. The sample used in this study was a sample of convenience and our a priori power calculation suggested that we were underpowered to detect true

associations Our post-hoc power analysis suggested that we may have been appropriately powered for the associations with the trail making test, though underpowered for the other tasks. Future work should seek to recruit a large enough sample to adequately power the study.

The statistical approach of this study is correlational in nature and thus, we cannot assume that there is a casual relationship between inflammation and psychomotor slowing in patient with schizophrenia. Future work using animal models or interventional human studies where inflammation is either induced or blocked would allow for a better understanding of causal contributions of inflammation to psychomotor deficits in patients with schizophrenia.

In summary, this study provided evidence for associations between peripheral inflammation and psychomotor abnormalities in patients with schizophrenia. These deficits are well described in individuals with schizophrenia and these data are consistent with a growing literature demonstrating that inflammation may target the basal ganglia leading to psychomotor slowing. Much of this work has been studied in patients with depression and future studies should extend these results to determine whether this might be a transdiagnostic phenomenon. Future work using neuroimaging approaches, for example, should seek to replicate findings from the depression literature that have shown that motor circuits may be sensitive to inflammation that is, in turn, associated with psychomotor slowing. Taken together, these data indicate that psychomotor speed may be a relevant outcome variable for studies targeting the immune system, such as those that may test anti-inflammatory treatments in patients

with neuropsychiatric disorders, such as schizophrenia, that are characterized by increased inflammation.

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Table 1.
Sociodemographic, clinical, and immune characteristics of the study sample (N = 43).

Variable	means (SD)/percentage	median (range)
Age (years) (±SD)	51.47 (9.35)	
Sex (% male)	90.7%	
Race (% black)	95.3%	
Smoking (% smokers)	55.8%	
BMI* (±SD)	31.60 (5.43)	
PANSS Total Score	58.37 (11.73)	
PANSS Positive Symptom Scale	15.30 (4.38)	
PANSS Negative Symptom Scale	16.67 (5.76)	
PANSS General Symptom Scale	26.40 (5.68)	
IL-6 (pg/ml) (±SD)	3.27 (0.89)	3.15 (1.82-5.93)
TNF (pg/ml) (±SD)	4.03 (1.33)	3.84 (1.41-7.52)
IL-1 beta (pg/ml) (±SD)	0.58 (0.06)	0.58 (0.47-0.75)
IL-10† (pg/ml) (±SD)	0.49 (0.25)	0.40 (0.28-1.53)
sTNFR2* (ng/ml) (±SD)	2330.95 (1258.67)	2077 (1101-8199)
sIL-6R‡ (ng/ml) (±SD)	39639.93 (8315.45)	37783 (26035-61006)
IL-1RA* (ng/ml) (±SD)	508.89 (289.01)	439.39 (198.56-1641)
MCP-1* (pg/ml) (±SD)	172.99 (16.77)	169.66 (150.22-218.61)

SD: standard deviation; BMI: body mass index; PANSS: Positive and Negative Syndrome Scale; IL-6: interleukin 6; TNF: tumor necrosis factor alpha; IL-1 beta: interleukin 1 beta; IL-10: interleukin 10; sTNFR2: soluble tumor necrosis factor receptor 2; sIL-6R: soluble interleukin 6 receptor; IL-1RA: interleukin 1 receptor antagonist; MCP-1: monocyte chemoattractant protein 1.
*n=40; ‡n=41; †n=42

Table 2.
Mean (±SD) and Median (range) measures of psychomotor speed in the study sample (N = 43).

Variable	Mean (SD)	Median (range)
FTT (taps; dominant)	261.29 (57.59)	271.33 (98 – 371)
FTT (taps; nondominant)	235.02 (51.95)	241.33 (114 – 343)
TMT (seconds)	50.26 (20.52)	46 (23 – 121)
SC (boxes correct)	38.00 (11.17)	37 (15 – 65)

SD: standard deviation; FTT: finger tapping task; TMT: trail making task; SC: symbol coding

Table 3.
Variables associated with psychomotor speed in patients with schizophrenia

	Model 1			Model 2			Model 3		
	β (95% CI)	un-corrected p	corrected p	β (95% CI)	un-corrected p	corrected p	β (95% CI)	un-corrected p	corrected p
FTT Dominant									
sIL-6r	0.395 (0.118,1.070)	0.016	0.048	0.437 (0.194, 1.121)	0.007	0.037	0.416 (0.13, 1.12)	0.015	0.048
IL-1RA	-	-	-	-0.318 (-0.306, -0.006)	0.043	0.052	-	-	-
sex	-	-	-	0.335 (0.023, 0.519)	0.033	0.044	-	-	-
FTT Non-Dominant									
IL-10	-0.410 (-98.3, -12.8)	0.012	0.048	-0.403 (-96.2, -13.2)	0.011	0.037	-0.426 (-101.2, -15.6)	0.009	0.048
sIL-6r	-	-	-	0.357 (13.3, 206.5)	0.027	0.044	0.349 (9.01, 205.8)	0.033	0.051
TMT									
IL-10	0.433 (0.123, 0.704)	0.007	0.048	0.566 (0.245, 0.835)	0.001	0.009	0.452 (0.143, 0.723)	0.005	0.04
IL-1b	-	-	-	-	-		0.320 (0.083, 2.825)	0.038	0.051
SC									
sIL-6r	-	-	-	0.309 (1.793, 37.647)	0.032	0.044	0.308 (1.241, 37.87)	0.037	0.051
age	-	-	-	-0.502 (-0.908, -0.257)	0.001	0.009	-0.502 (-0.908, -0.257)	0.001	0.016
Motor Factor									
IL-10	-0.355 (-1.69, -0.088)	0.031	0.062	-0.347 (-1.629, -0.110)	0.026	0.044	-0.343 (-1.670, -0.074)	0.033	0.051
sIL-6r	0.322 (0.011, 3.649)	0.049	0.064	0.396 (0.481, 4.017)	0.014	0.039	0.393 (0.407, 4.078)	0.018	0.048
sex	-	-		0.332 (0.079, 1.948)	0.034	0.044	0.332 (0.046, 1.983)	0.041	0.051

Psycho-motor Factor									
IL-10	-0.420 (-1.779, -0.273)	0.009	0.048	-0.401 (-1.719, -0.238)	0.011	0.037	-0.399 (-1.756, -0.200)	0.015	0.048
sIL-6sr	0.353 (0.249, 3.671)	0.026	0.062	-	-		-	-	
TNFR2	-	-		0.358 (0.130, 1.439)	0.020	0.043	0.348 (0.084, 1.430)	0.029	0.051
age	-	-		-0.361 (-0.065, -0.007)	0.016	0.039	-0.346 (-0.067, -0.004)	0.026	0.051

FTT: finger tapping task; TMT: trail making task; SC: symbol coding; sIL-6r: soluble interleukin 6 receptor; IL-1RA: interleukin 1 receptor antagonist; IL-10: interleukin 10; IL-1b: interleukin 1 beta; TNFR2: tumor necrosis factor receptor 2

Corrected p values based on Benjamini Hochberg < 0.05.

*adjusted for age, sex, race, smoking

**adjusted for age, sex, race, smoking, BMI

Table 4.
Loading factors for principle component analysis (varimax rotation) of inflammatory markers.

Marker	1	2	3
TNF	0.858		
IL-1beta		0.669	
IL-6		0.772	
IL-10	0.851		
MCP1			
sIL-6r			0.762
IL-1RA		0.746	
TNFR2			0.766

IL-6: interleukin 6; TNF: tumor necrosis factor alpha; IL-1 beta: interleukin 1 beta; IL-10: interleukin 10; sTNFR2: soluble tumor necrosis factor receptor 2; sIL-6R: soluble interleukin 6 receptor; IL-1RA: interleukin 1 receptor antagonist; MCP-1: monocyte chemoattractant protein 1.

Figure 1.

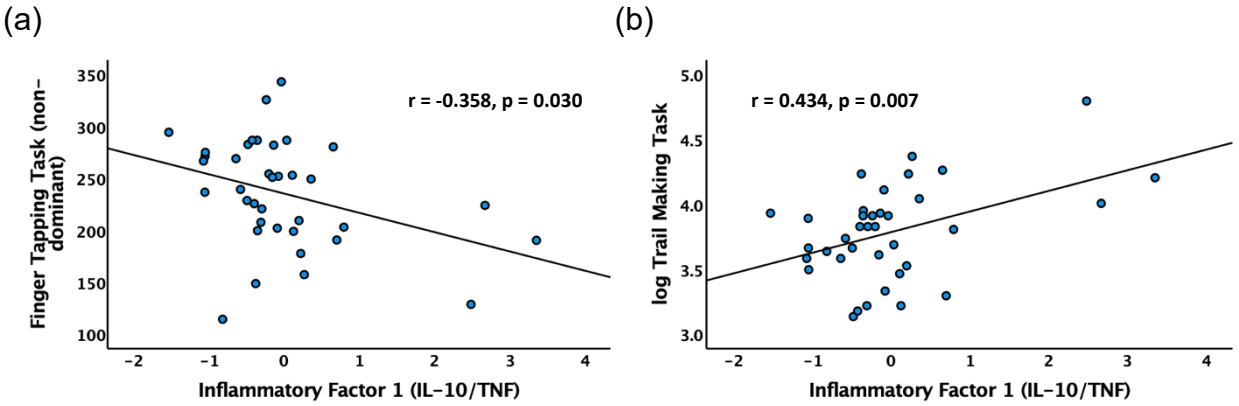

Fig. 1. Relationship between Inflammatory Factor 1 (IL-10 and TNF) and (a) Finger Tapping Task (non-dominant hand) and (b) Trail Making Task. The inflammatory factor 1 was negatively associated with performance on the finger tapping task and was positively associated with performance on the trail making task. Both reflect an association between inflammatory factor 1 and psychomotor slowing on the tasks. (a) Inflammatory factor 1 and number of taps on the FTT were negatively correlated (r = -0.358, p = 0.030). (b) Inflammatory factor 1 and time of the TMT were positively correlated (r = 0.434, p = 0.007).