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Holly Dai Shan April 9, 2021

Association of depression and cognitive functioning in patients with systemic lupus erythematosus (SLE) in a metropolitan Atlanta cohort

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An abstract of
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Abstract

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Significance: Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease with health consequences that can be debilitating for patients, regardless of gender or age. Cognitive dysfunction is a common obstacle for patients with SLE but is often ignored in a clinical setting. Preliminary studies have found depression is associated with such symptoms; however, few studies explore the association between depression and SLE-induced cognitive functions. Insights from such studies serve to improve and expand the quality of care for SLE.

Objective: To examine whether there are associations between depression and performance on cognitive tests measuring episodic memory, working memory, processing speed, attention, inhibition control, and cognitive flexibility in a cohort of patients from metropolitan Atlanta with SLE.

Participants: 50 participants with SLE were recruited from the Georgians Organized Against Lupus (GOAL) cohort (Mean age: 49.0 ± 12.4).

Measures: Depression was measured with the Patient-Reported Outcomes Measurement Information System (PROMIS) questionnaire; both t-scores and dichotomized scores (no vs. any symptoms of depression) were used. Cognitive performance was measured at the same visit using the NIH Toolbox Fluid Cognition Battery, CLOX Drawing task, and Trail Making B task.

Results: No statistically significant associations were found between PROMIS depression scores and any of the cognitive function measures. There were slight associations between higher PROMIS depression scores and worse performance on cognitive tests (Pearson's r correlation coefficients were all negative and had magnitudes <0.1; Linear regression beta coefficients were all negative and had magnitudes <2). All participants with any depressive symptoms had lower scores on all but one cognitive function test compared to participants with no depressive symptoms.

Conclusions: In this cohort of SLE patients, depression was not associated with cognitive function. This may indicate that other factors play a role in cognitive decline in the setting of SLE.

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Table of Contents

Introduction and Background

Systemic lupus erythematosus (SLE) is a relapsing-remitting chronic inflammatory disease caused when the immune system attacks its own tissues. As an autoimmune disease, SLE causes organ and cell deterioration through tissue-binding autoantibodies and immune complexes which increases the production of antibodies against a variety of nuclear antigens (Rose & Mackay, 1992). It is a multi-system disease that can affect many systems and organs, including the nervous, vascular, and renal systems. In many ways, SLE is a "model" autoimmune disease since both cellular and humoral reactivity to multiple soft tissues may cause injury to every organ in the body (Vasilesios et al., 2006). Diagnosis requires a combination of clinical features and the presence of at least one relevant immunological abnormality. The European League Against Rheumatism and American College of Rheumatology uses a multiphase methodologic approach to classify SLE which includes 10 additive criteria (Table 1) along with an entry criterion of antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (Aringer et al., 2019). SLE is a difficult disease to diagnose as there is variation between and within individuals; signs and symptoms vary from each patient and may change over time. Observable symptoms of SLE include fatigue, joint pain, skin rashes, mouth sores, hair loss, and weight changes, which all intersect with other disease presentations, making it more difficult to diagnose correctly. There is no cure, and treatments are currently focused on improving quality of life with lifestyle modifications (sun protection and diet) or medication (anti-inflammatories, immunosuppressants, and steroids).

Epidemiology of SLE

Historically thought to be a rare disease of young women, SLE is now known to affect women and men of all ages, with an overall U.S. prevalence of up to 72.8/100,000 (Izmirly et al., 2021). This disease afflicts 1 to 12 people per 5000 worldwide (Ghodke-Puranik & Nieworld, 2015) which makes it a rare disease overall, but one of the most common autoimmune disorders. The etiology of SLE remains mysterious, and 90% of patients diagnosed are women of childbearing age. SLE patients are at an increased risk for co-morbidities such as atherosclerotic disease, osteoporosis, avascular necrosis, and various infections (Gordon et al., 2018).

SLE differs in incidence and prevalence in groups of patients from different racial and ethnic backgrounds. Both genetic and environmental components of ethnicity influence the expression and outcomes of SLE, including disease activity, damage accumulation, and mortality. Studies suggest that ethnic factors influence outcomes of SLE more than geographic or non-genetic factors (Stojan & Petri, 2018). SLE is more frequent and more severe in non-white populations such as Hispanic and Black populations. In the United States, the prevalence of SLE in Black populations is three times greater compared to white populations and two times greater compared to Hispanic populations (Lim et al., 2014; Dall'Era et al. 2017). In the state of Georgia, SLE prevalence among women is nine times greater than men, and it is three times greater among black individuals than white individuals (Lim et al., 2014), which is the same as the national average. Black individuals with SLE in an Atlanta cohort presented with symptoms at an earlier age compared to white individuals (39.4 vs. 45.4) and the only patients diagnosed under the age of 12 were black women (Lim et al., 2014). Black women with SLE are especially vulnerable, as they have the highest standardized mortality ratio, with deaths occurring sooner

after diagnosis, and at a mean of 13 years younger than their white counterparts (Tselios et al., 2019). Based on 2000-2010 Medicaid data, Black individuals have a 1.14-fold higher risk of cardiovascular events and stroke compared to white individuals with SLE (Stojan & Petri, 2018). The same study revealed a 2.2-fold reduced risk of myocardial infarctions in Hispanic or Asian individuals compared to white individuals with SLE. Overall, more research into how SLE affects minority populations is needed to optimize health care access to marginalized communities.

Depression and Cognitive Impairment in SLE

Many SLE patients, even those who are young, have syndromes that are often associated with geriatric patients including depression and cognitive impairment (Flacker, 2003). Depression is characterized by a negative cognitive bias and maladaptive emotion regulation (Kircanski et al., 2012). It is a mood disorder that creates a persistent feeling of sadness and loss of interest. Depressive symptoms include a prolonged sad mood, diminished interest or pleasure, changes in appetite, sleep disorders, fatigue, feelings of worthlessness or guilt, concentration problems, and recurrent thoughts of death with or without a plan to commit suicide. A diagnosis of major depressive order requires five or more of these symptoms to be present during the same two-week period and the patient must have clinically significant distress (American Psychiatric Association). Depressive symptoms may be severe enough to cause issues with day-to-day activities such as work, social relationships, and completing simple tasks.

Depression is the most frequent psychiatric symptom in SLE patients (Iverson, 2002). Presentations of depression and anxiety are often the earliest symptoms to manifest in SLE (Gao

et al., 2009). Structural damage in areas related to mood regulation (hippocampus, amygdala, basal ganglia, frontal cortex) has been associated with depression, and neuronal damage caused by SLE may lead to depression (Soares et al., 2003). The strong negative effects characterized by depression are frequently accompanied by daily fatigue and pain that many SLE patients report (Petri et al., 2013). However, clinical tests have not been developed to satisfactorily correlate fatigue and pain to severity of disease, so it is difficult to estimate patient discomfort and create appropriate, timely treatments (Jump et al., 2005). Negative illness perception has been found to significantly increase the incidence of depression in SLE patients which may influence other aspects of a patient's life including social relationships and work (Nowicka-Sauer et al., 2018). Furthermore, depressed SLE patients may be more likely to cancel medical appointments, stop taking medications, develop eating and sleeping disorders, and stop exercising which are all essential to maintain health with a chronic disorder. The reported prevalence of depression is quite variable in SLE patients; studies report anywhere from 10-75% of patients with depressive symptoms (Palangi et al., 2003). This can be attributed to the lack of formal depression assessments given to SLE patients during medical visits of diagnosis.

Depression is closely related to cognition, as it influences a negative appraisal of stimuli. Cognition refers to the mental processes involved in gaining knowledge and comprehension. Domains of cognition are higher-level functions of the brain and include language, perception, and planning. Mental capacity in adults is characterized by fluid and crystallized intelligence (Cattell, 1943). Crystallized intelligence is the ability to use skills and knowledge acquired from prior learning (Horn, 1969) such as driving a car or reading a book. Fluid cognition includes episodic memory (ability to remember objects, people, or events experienced at specific time and

places), working memory (ability to mentally maintain and manipulate information over brief periods of time), processing speed (how quickly one can take in and use information), attention and inhibitory control (ability to focus on relevant stimuli in the presence of irrelevant stimuli), and cognitive flexibility (ability to shift thoughts and adapt behavior to new conditions). Fluid intelligence is more studied in the context of depression-influenced cognition in psychiatric disorders (Keyes et al., 2017). Every cognitive process has a profound influence on how we perceive and interact with the world, and cognitive decline is a great concern for many disease outcomes including SLE.

Cognitive Impairments Specific to SLE

SLE patients frequently exhibit neuropsychiatric symptoms including dysfunctions and mental disorders (Saito et al., 2017). SLE-induced cognitive disorders are most likely associated with brain disease, but precise mechanisms remain to be elucidated. Cognitive impairment in patients with SLE is often described as a "lupus fog" and has been reported in up to 50% of patients (Hanly et al., 1994), and 80% of patients present with cognitive impairments after 10 years of diagnosis (Petri et al., 2010). Lupus fog is defined as "the loss of intellectual functions such as thinking, remembering, and reasoning of sufficient severity to interfere with daily functioning" by the American College of Rheumatology (ACR). The ACR ad hoc committee defined 19 neuropsychiatric SLE features (Table 2) categorized as either central or peripheral nervous system, and focal (American College of Rheumatology, 1999). Because cognitive impairment is included as one of the neuropsychiatric syndromes for classification of SLE, it creates a tautological problem in studies that are focused on finding frequency of cognitive impairment. Further, neuropsychological assessment is not routine in SLE, and impairment encompasses a wide range of disturbances. The ACR report recognized that classification of SLE-related psychiatric

disorders and cognitive deficits is difficult and further study is needed. In the last two decades, significant strides have been made to create more comprehensive tests for neuropsychiatric syndromes related to SLE, but much remains unknown about the causes (Moulton et al., 2017).

Around 10% of patients with SLE have severe cognitive impairments with a significant impact on functional outcome and employment (Panopalis et al., 2003). Deficits that include attention, memory, and processing speed can easily affect employment status along with social bonds and self-esteem (Benedict et al., 2008). Common cognitive impairments of lupus include impaired performances in sustained attention, difficulties in visuospatial working memory, and learning tasks (Hanly et al., 2010). Executive functions such as tasks measuring cognitive flexibility and planning abilities were worse in patients with cognitive impairment compared to neurotypical SLE patients (Calderon et al., 2014). Preliminary studies of the ongoing, population-based Georgians Organized Against Lupus (GOAL) cohort of 60 SLE patients, along with objective data of a pilot study, showed a high prevalence of cognitive symptoms by self-report and objective measurement (Plantinga et al., 2017). Plantinga et al. found that cognitive performance in patients in the GOAL pilot was average for episodic and working memory while below average for cognitive flexibility, processing speed, and attention/inhibitory control compared to healthy individuals of the same age, sex, race, ethnicity, and education level.

Both depression and cognitive issues are potentially highly prevalent in the SLE patient population and therefore probably have similar underlying pathophysiological processes (Geda et al., 2006). The existing literature is conflicting, and there are no widely accepted explanations for this association. Monastero et al. found that depression was the only clinical variable associated with cognitive dysfunction while Kozora et al. found that such dysfunction could not be

explained by depression alone. Lupus-prone mice exhibited significant depression-like behavior early in their courses despite normal cognitive functions, indicating that depression precedes neuropsychiatric damage in SLE (Gao et al., 2009). Only SLE patients with longstanding diseases have been studied for cognition, which may explain why little is known about the prevalence of depression and the association with cognitive functions in newly diagnosed patients (Petri et al., 2010). There are many debates about the causes of depression in SLE, and whether it is associated with cognitive dysfunction (Kozora et al., 2007). This makes defining the role of depression essential to elucidate the pathophysiology of SLE cognition and the development of therapies.

The association of depression and cognition in SLE patients is unclear, although studies do report a high prevalence of both symptoms. Depression has been found to influence cognitive decline in non-SLE patient populations and could potentially play a similar role for SLE patients. If mood-related factors can influence lupus fog, treatment methods should be adjusted accordingly. This paper aims to explore whether the degree of depressive symptoms is associated with level of cognitive functioning within a cohort of SLE patients in metropolitan Atlanta.

Hypothesis

If depression significantly influences the cognitive outcomes in SLE patients, then higher PROMIS depression scores will be associated with lower cognitive scores from the NIH Toolbox Fluid Cognition measures (Picture Sequence, List Sorting, Pattern Comparison Processing Speed, Flanker Inhibitory Control, Dimensional Change Card Sort) CLOX scores, and Trail

Making time. Additionally, patients with any depressive symptoms will have lower scores on cognitive tests compared to patients with no depressive symptoms.

Methods and Materials

Data were taken from the first 50 participants in the ongoing Approaches to Positive, Patient-centered Experiences of Aging with Lupus (APPEAL) cohort study. APPEAL is an ancillary study in which participants are being recruited from the population-based GOAL cohort in metropolitan Atlanta. Initially, GOAL participants were recruited from the existing population-based Georgia Lupus Registry (Lim et al., 2014) and were enriched with additional patients who were receiving treatment for SLE; enrollment of the latter group is going. The Georgia Lupus Registry was designed to collect data on all residents of two Georgia counties, Fulton and Dekalb, which are both in the Atlanta metropolitan area with large black and white populations. GOAL recruitment and data collection details are reported elsewhere (Drenkard et al., 2013). Briefly, participants of GOAL are adults 18 years or older (Hochberg, 1997) with a documented diagnosis of SLE (≥4 revised American College of Rheumatology [ACR] criteria or 3 ACR criteria plus a diagnosis of SLE by an attending board-certified rheumatologist). The inclusion criteria for the APPEAL study are as follows: English-speaking, vision and hearing acuity sufficient to undergo study testing, and the ability to travel to an in-person study visit. The Emory Institutional Review Board approved the APPEAL and GOAL study protocols. All APPEAL participants provided informed consent. A total of 107 GOAL participants were contacted by mail and telephone to obtain the target sample size of 50 participants for in-person visits. Data were obtained from a series of performance tests and questionnaires administered during study visits (from October 2019 to March 2020).

Study Variables

Depression

The Patient-Reported Outcomes Measurement Information System (PROMIS) Depression 8b questionnaire was given to all participants at the time of their visit. This 8-item PROMIS Depression item bank assesses self-reported negative mood, views of self and social cognition, as well as decreased positive affect and engagement. Participants were instructed to answer all items assessing depressive symptoms in the past seven days such as "I felt worthless," "I felt like a failure," or "I felt that nothing could cheer me up," on a scale of 1-5 with 1 being "never" and 5 being "always". Raw scores were then translated into a standardized T-score. T-scores ranged from 37.1 (no depressive symptoms) to 40 (most severe depressive symptoms). Higher scores indicated a greater presence of depressive symptoms. For dichotomous analyses, "no depressive symptoms" were defined as those that did not have any depressive symptoms (T-score = 37.1) on the self-reported PROMIS depression questionnaire, and "any depressive symptoms" (T-score > 37.1) were identified through having at least one symptom of depression from the PROMIS questionnaire.

Cognitive Performance

NIH Toolbox Fluid Cognition Battery

Fluid cognition was assessed in five individual assessments using the NIH Toolbox application (Gershon et al., 2010): The Picture Sequence Memory Test, the List Sorting Working Memory

Test, Pattern Comparison Processing Speed Test, the Flanker Inhibitory Control and Attention Test, and the Dimensional Change Card Sort Test. Raw scores were converted to T-scores, adjusted for age, sex, race/ethnicity, and education. Fully adjusted T-scores (mean = 50, SD = 10) range from 0 to 100, such that 50 is the average score and 40 and 60 are 1 SD below and 1 SD above the mean, respectively. Higher scores indicate better cognitive function. Individual assessment scores were incorporated into a composite adjusted T-score measuring fluid cognition, or overall capacity to reason and solve novel problems.

CLOX Drawing

The CLOX instrument (Royall et al., 1998) was used to score the executive task of clock drawing. Participants were first asked to draw a clock showing 1:45 with no further instructions. All clocks were scored 0-15 (lower scores indicating more impairment) on aspects such as size, number, order of numbers, correct hand size/ position, etc. Drawings were scored by both the interviewer and re-scored by a researcher not involved in study visits; differences were resolved between the research manager and principal investigator.

Trail Making Test B

Trail Making Test B is a test for visual attention and task switching (Reitan, 1971). Participants were instructed to complete the task as quickly as possible without errors and were prompted to correct errors as they performed the task. The time to complete the test was recorded. If the participants continued to work on the test for 5 minutes, they were asked to stop.

Other variables

All data collected was self-reported and included demographic information such as age, race (White, Black Asian, Other), sex assigned at birth (male or female), and years of education.

Statistical Analysis

The primary objective of this study was the evaluate the potential relationship between depression and cognition in SLE patients. We first generated descriptive statistics of the demographic self-reported information. Then, Pearson's correlation coefficients between our exposure, depression, and the outcomes which included all NIH Toolbox cognition test scores along with CLOX scores and Trial B Making times (in seconds) were estimated. Linear regressions were run with cognitive measures as the outcomes and depression scaled per standard deviation (=10 points on a T-score scale). To test for group differences between "any depressive" and "no depressive symptoms," we conducted independent-samples two-tailed T-tests with equal variance. All analyses were performed using Stata v. 16 (College Station, TX) and the statistical significance threshold was set at 0.05.

Results

Table 3 summarizes the demographic characteristics from self-reports of 50 GOAL cohort participants. Results showed that participants were middle-aged (Mean = 50.0 years), predominantly female (84%), predominantly black (90%), and highly educated (68% attended at least some college). All participants resided in the metropolitan Atlanta area.

Figure 1 shows the distribution of PROMIS depression t-scores. Scores were skewed towards having a lower score, which indicates most participants did not experience many depressive symptoms in the past seven days when the data was collected. 19 (38%) of the participants did not have any depressive symptoms.

Table 4. shows Pearson's r partial correlations between cognitive function measures and PROMIS depression t-scores. All correlations were negative, indicating that a higher depression score was associated with lower cognitive performance. However, none of these associations were statistically significant, as $p > 0.05$ in all tests.

Figures 2-8 visualize the associations between cognitive measures and depression T-scores with corresponding regression lines. Despite negative regression lines on all graphs, the spread of data is scattered. Table. 5 displays results of the linear regressions ran on crude associations of cognitive function measures per 10 units of the PROMIS Depression t-scores which is equivalent to one standard deviation. All linear regression coefficients were negative which supports a possible association between greater depressive symptoms and lower cognitive function. The adjusted beta coefficient values were all negative but in a range of no association and the 95% confidence interval indicated that there was no statistically significant linear regression between the variables.

Table 6. reports results of the t-tests between cognitive function measures and the PROMIS Depression t-scores between patients with self-reported depressive symptoms and those without. Patients without depressive symptoms scored higher on every cognitive test except for List Sorting Working Memory. However, none of these differences were significant, as $p > 0.05$ in all tests.

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Discussion

We did not identify statistically significant associations between PROMIS depression scores and cognitive function measures. All correlations and regressions were negative, indicating that a higher PROMIS depression score was associated with a lower cognitive function test score, but the associations were generally weak in magnitude. Although there were no statistically significant differences between the mean values of cognitive function scores between SLE patients with depressive symptoms and those without, patients with depressive symptoms scored lower on all but one cognitive test. Despite the small difference in performance and slight association of depression and cognition, these results suggest that depression is not associated with cognitive function in SLE patients. Thus, an SLE patient's mood may not play a substantial role in their memory, ability to complete tasks, attention, and other functions related to healthy cognition. This underscores the importance of searching for more direct influences of lupus fog.

Reduced cognitive functioning has been reported since the 1980s, but cognitive assessments remain underused for SLE. Cognitive assessments are not common for check-ups and the cognitive problems SLE patients face in their daily lives are not emphasized for treatment protocols. SLE medical charts do not include cognitive function, nor is it discussed frequently in a clinical setting. Tools are being developed to bridge the gap between cognitive functions and SLE assessments, but results remain tentative (Plantinga et al., 2021). This reveals a gap in SLE treatment, as many studies have reported a high prevalence of lupus fog (Hanly et al., 1994; Palangi et al., 2003; Panopalis et al., 2003; Petri et al., 2010), yet there is little acknowledgment of it during assessment and treatment. Therefore, it is important to understand

causes of SLE cognitive impairment to make a more compelling case to highlight it in a clinical setting as a separate entity from depression, to which clinicians may attribute impairment.

Results suggest cognitive impairment in SLE may not be explained by the presence of depression only. Influential factors of SLE-induced cognitive impairment range from molecular to environmental. Intrinsic disease factors such as antibodies play a role in cognitive impairment (Matus et al., 2007). SLE, but not depression, distinctly is associated with visual memory and spatial working memory (Calderon et al., 2014). Molecular mechanisms can also influence cognitive functions. For example, a subset of anti-dsDNA from SLE patients binds NR2 glutamate receptors in the CNS which allows aAb mediated cognitive impairment and emotional disturbances (DeGiorgio et al., 2001). In mice, it was shown that Antiribosomal aAb could induce depression via targeting neuronal surface protein causing calcium influx and apoptosis (Katzav et al., 2008). Anti-NMDA receptors and anti-Ribosomal aAbs have been linked to certain pathophysiological features of neuropsychiatric SLE. Anti-a-Internexin Autoantibody from SLE induces cognitive damage via inhibiting axonal elongation and promotes neuron apoptosis (Lu et al., 2010). White matter lesions are common findings in SLE patients, regardless of neuropsychiatric symptoms. Underlying causes such as inflammation, ischemia, vasculitis, immune-mediated response, presence of antiphospholipid antibodies, age, and active disease, among other etiologies, have been suggested as the underlying pathology of these lesions (Appenzeller et al., 2008). There are numerous hypotheses on the molecular underpinnings of lupus fog, and future works should consider whether depressed SLE patients are more susceptible to abnormal chemistry compared to SLE patients without depressive symptoms. Results from such studies could inform clinicians and researchers on molecular therapeutic targets for depression in SLE along with providing more insight into causes of lupus fog.

Another potential cause of cognitive impairment in SLE is permanent cerebral damage, which has been attributed to neural injury brought about by SLE-related cerebrovascular system pathology. Early histopathological work revealed evidence of small vessel deterioration in SLE brains (Johnson & Richardson 1968). They found destructive and proliferative changes due to extravasations of fibrin and red blood cells within small vessel walls that likely led to brain thrombosis and hemorrhages. Abnormalities in autoantibody regulation and generation that target neuronal tissue is another likely mechanism of neuronal injury. Large vessels may also be affected by SLE which may lead to transient ischemic attacks or irreversible strokes (Scolding & Joseph, 2002). Taking measurements such as blood pressure to monitor cardiovascular disease risk while still performing cognitive tests following our cohort of patients could reveal associations of cardiovascular disease and cognitive performance.

Sociodemographic factors may also play a role in SLE cognitive outcome. Participants in this study were predominately well-educated Black women, so these results could provide insight into this specific demographic, as there are few studies focused on this intersection of patients. However, the demographics of this cohort made it harder to examine racial or educational differences of SLE cognition. Additionally, the cohort could not be generalized to a broader SLE patient population. The APPEAL pilot study found low socioeconomic status was a risk factor for worse functioning outcomes, although cognitive functioning was not specifically examined (Hoge et al., 2020). Black women are more likely to experience psychosocial stressors known to exacerbate SLE compared to their white counterparts. Such stressors include poverty, unemployment, exposure to violence, and victimization (Nuru Jetter et al., 2009). Racial discrimination for black women may have consequences for acute SLE outcomes and can exacerbate autoimmune inflammatory diseases like SLE (Ronnblom & Elkon, 2010). Therefore, exploring stressors that are unique to well-educated black women could provide more insights to

treat this vulnerable SLE patient population. Metropolitan Atlanta is a unique area where there is a higher portion of black individuals and one of the wealthiest black areas in the country. Georgia has the second largest proportion of black doctors in the country (after Washington DC), with 12% of its doctors being black (AAMC, 2021). Patients have better outcomes when they see a doctor of their own race (Tann, 2002). Since patients in this study were predominately black (90%) and live in an area where they have access to more black doctors, this may have factored into their high fluid cognition scores. As cognitive decline often can only be diagnosed through clinical assessments (Kotagol et al., 2015), patients that complain of such symptoms are more likely to be believed and get treatment accordingly if they have a doctor of the same race. Asking whether the patients saw a doctor of their own race may provide further insight into this racial phenomenon.

Moreover, metropolitan areas have more robust and accessible healthcare systems than rural or poorer cities in the United States. Atlanta is a hub in the south for research, business, and entertainment. Thus, there may be socioeconomic factors influencing results of this study. Examining the wealth of a city, number of healthcare options and employment opportunities between the GOAL cohort and a matched cohort from a rural or less developed city could inform us of environmental factors that affect SLE cognition. To further explore the factors of race and SLE cognitive outcomes, questions that provide insight into racial interactions could also be included in the check-in sessions for the GOAL cohort.

This study has several limitations. The cross-sectional nature of the design prevented us from determining whether depressive symptoms preceded the level of functioning, which would increase causal inference. The sample size was only 50, limiting generalizability. Moreover, there was not a lot of variation in depression, as it was skewed towards participants not having

many depressive symptoms. Recruiting more patients would increase the power of the statistical tests and may reveal more patterns, as there were slight negative associations between depression scores and all cognitive function scores. Expanding the study to include more diverse patients could reveal trends in depression and cognitive function that affect those of different ages, race, socioeconomic level, and gender differently.

Overall, the skewed data and small sample size may have prevented us from seeing an association. The PROMIS depression score only measured depressive symptoms over the last seven days so there was no formal clinical diagnosis of depression which requires a prolonged sadness over 14 days. If we were to formally diagnose patients with depressive symptoms and create a longitudinal study, the results may reveal patterns of cognitive function over time related to depressive symptoms. Furthermore, participants were recruited from the GOAL cohort, which may be subject to healthy volunteer bias, resulting in participants with fewer depressive symptoms and higher cognitive function than the target SLE population.

The goal of this study was to determine whether there was a cross-sectional association between depressive symptoms and level of cognitive functioning in SLE patients. SLE is a complex disease that has a variety of biomarkers, symptoms, and causes. Cognitive assessments are not routine for this patient population and clinicians are not well-versed in how cognitive problems can affect disease management. These initial findings suggest there is no association. Future work should first confirm whether these findings stand with a larger, diverse patient population; then examine these associations in subgroups of interest and collect longitudinal data that allow for measurement of cognitive functioning and depression over time to elucidate the direction of any association. Additionally, it is important to perform more targeted studies to find factors that do influence cognition related to both environmental and biological factors. This

would help create more effective and individualized treatment plans for SLE that address functional outcomes that are important to these patients.

Tables and Figures

Table 1. Additive criteria for SLE diagnosis by the European League Against Rheumatism and American College of Rheumatology

Clinical domains	Immunology domains
Constitutional Fever	**Antiphospholipid antibodies** Anti-cardiolipin OR Anti-β2GP1 antibodies OR Lupus anticoagulant
Hematologic Leukopenia Thrombocytopenia Autoimmune hemolysis	**Complement proteins** Low C3 and/or C4
Neuropsychiatric Delirium Psychosis Seizure	**SLE-specific antibodies** Anti-dsDNA antibody OR Anti-Smith antibody
Mucocutaneous Non-scarring alopecia Oral ulcers Subacute cutaneous OR discoid lupus Acute cutaneous lupus	
Musculoskeletal Joint involvement	
Renal Proteinuria >0.5g/24h Renal biopsy Class II or V lupus nephritis Renal biopsy Class III or IV lupus nephritis	
Serosal Pleural or pericardial effusion Acute pericarditis	

Table 2. Neuropsychiatric symptoms in SLE (American College of Rheumatology, 1999)

Central Nervous System	Peripheral Nervous System
Aseptic meningitis	Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barre Syndrome)
Cerebrovascular Disease	Autonomic Disorder
Demyelinating syndrome	Mononeuropathy, single/ multiplex
Headache	Myasthenia Gravis
Movement disorder (chorea)	Neuropathy, cranial (usually optic neuritis)
Myelopathy (transverse Myelitis)	Plexopathy
Seizure disorder	Polyneuropathy
Acute confusional state	
Anxiety disorder	
Cognitive dysfunction	
Mood disorder	

Table 3. Demographic Summary of Study Participants (n = 50)

Gender	Number of Patients	Percentage of Patients
Male	8	16%
Female	42	84%
Age (Mean Age = 50.0 ± 12.4)		
20-30	6	12%
31-40	6	12%
41-50	11	22%
51-60	18	36%
61-70	9	18%
Education		
Less than high school	4	8%
High school	12	24%
Some college	7	14%
College graduate	11	22%
Post-college degree	16	32%
Race		
White	3	6%
Black	45	90%
Asian	1	2%
Other	1	2%

Table 4. Pearson's r Correlations between Cognitive Function Measures and PROMIS Depression T Scores.

Cognitive Test	Correlation Coefficient	P value
Fluid Cognition	-0.0666	0.649
Picture Sequence Memory	-0.0329	0.822
Flanker Inhibitory Control	-0.0947	0.512
Dimensional Card Sort	-0.0794	0.583
List Sorting Working Memory	-0.0270	0.852
Pattern Comparison Processing Speed	-0.0542	0.708
CLOX	-0.1036	0.478
Trail Making B time	-0.0415	0.774

Table 5. Linear Regressions of Crude Associations of Cognitive Function Measures per 10 units of PROMIS Depression T scores

Cognitive measures (NIH Toolbox adjusted t-scores)	Difference in cognitive score associated with 1 standard deviation higher depression t-score (Beta Coefficient)	95% confidence interval
Fluid Cognition	-.900	-4.85 3.05
Picture Sequence Memory	-.300	-2.99 2.38
Flanker Inhibitory Control	-.876	-3.54 1.79
Dimensional Card Sort	-1.33	-6.20 3.53
List Sorting Working Memory	-.330	-3.89 3.23
Pattern Comparison Processing Speed	-.745	-4.73 3.24
CLOX score	-.219	-.836 .398
Trail Making B Time, seconds	-2.09	-16.7 12.5

Table 6. Results of T-Test of Cognitive Function Measures and PROMIS Depression T Scores of patients with depressive symptoms and patients without depressive symptoms

Cognitive Test	P value	No depressive Symptoms Mean	Any depressive Symptoms, Mean
Fluid Cognition	0.9	45.4	44.9
Picture Sequence Memory	0.9	49.3	49.1
Flanker Inhibitory Control	0.5	42.7	41.1
Dimensional Card Sort	0.5	50.3	47.9
List Sorting Working Memory	0.6	44.5	46.0
Pattern Comparison Processing Speed	0.8	48.8	47.7
CLOX 1	0.6	11.89	11.56
Trail Making B Time, in seconds	>0.9	26.57	26.56

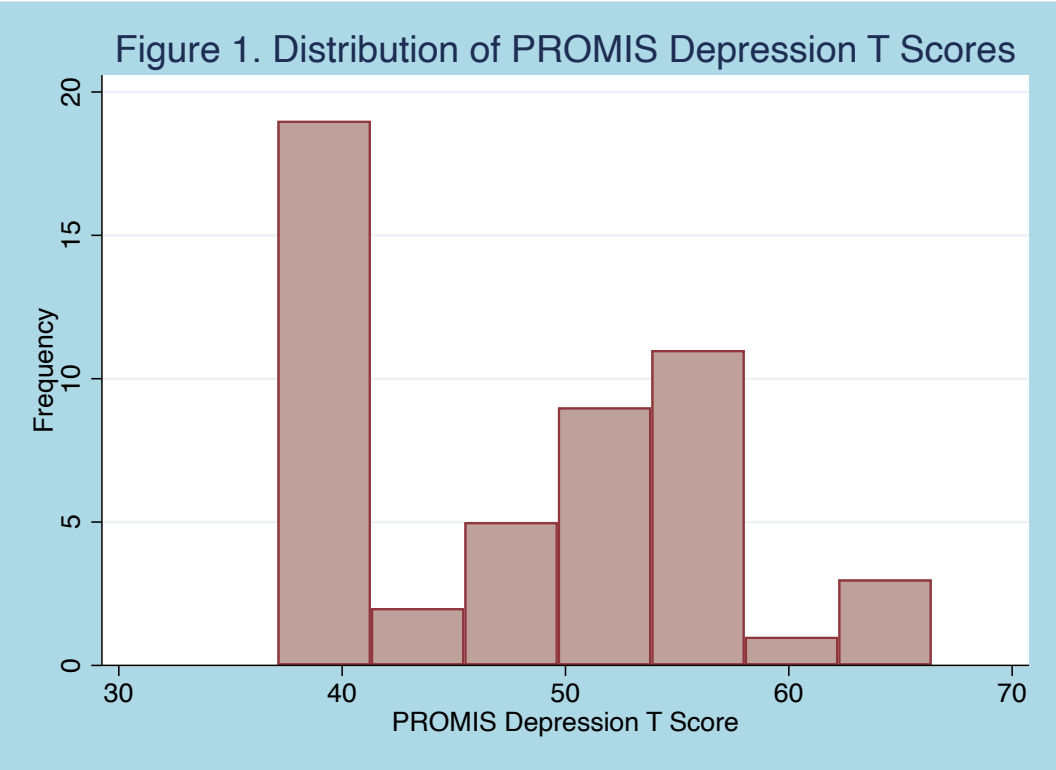

Figure 1. Distribution of PROMIS Depression T Scores

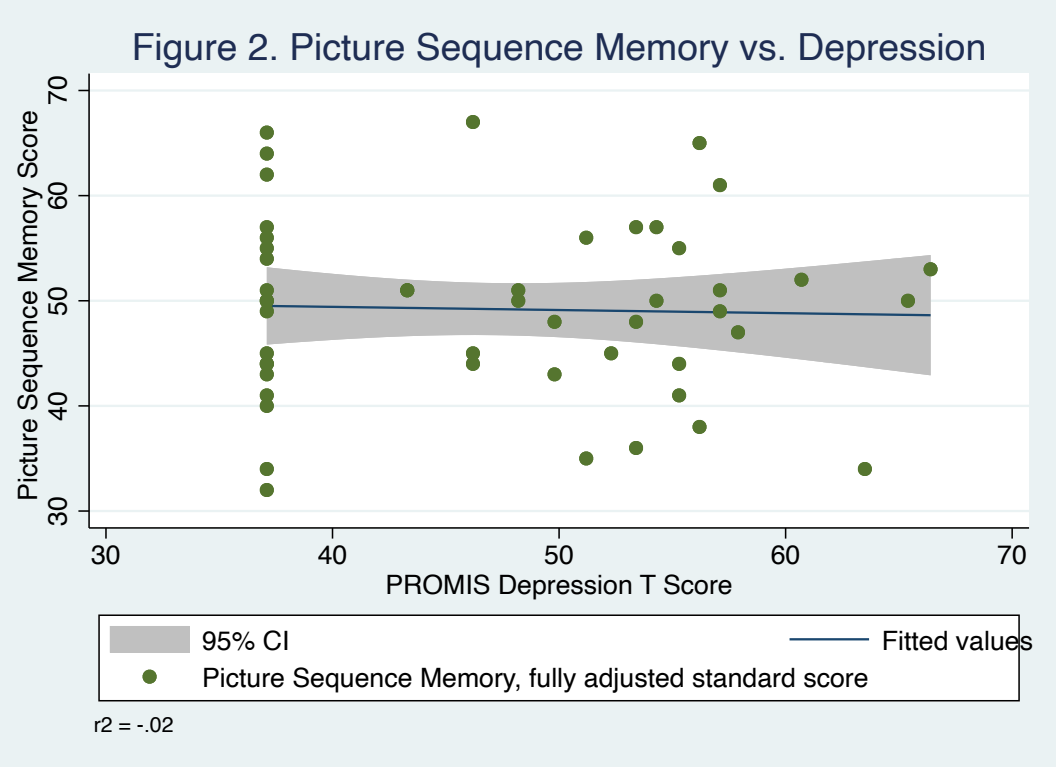

Figure 2. Picture Sequence Memory vs. Depression

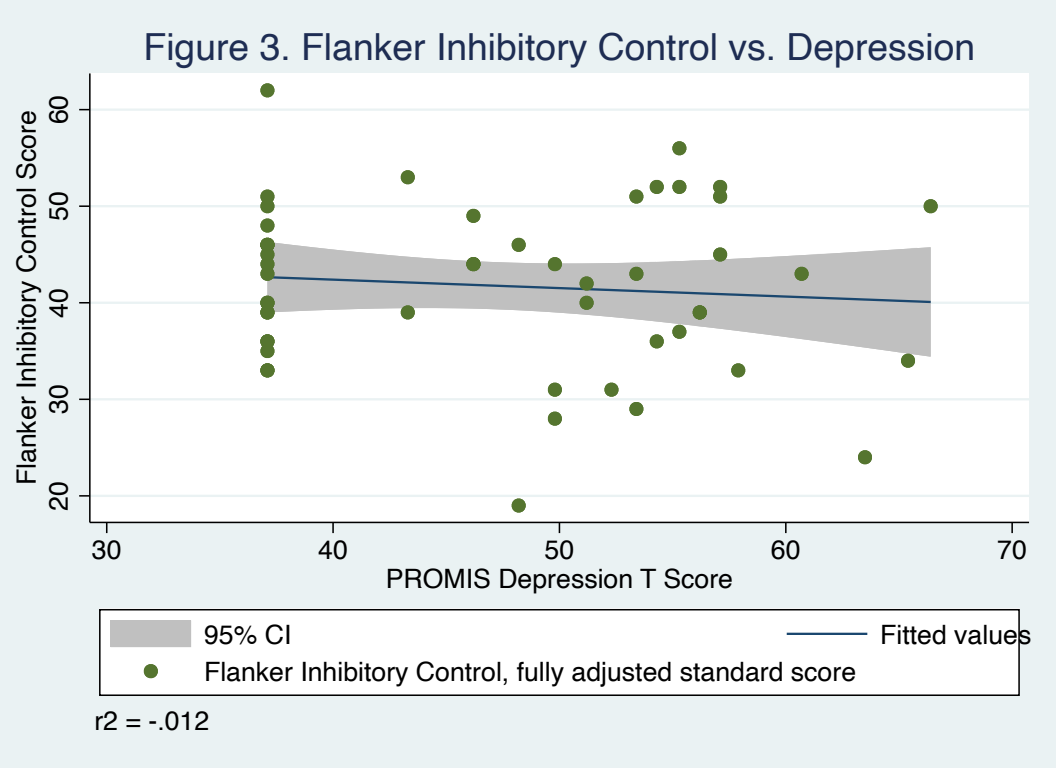

Figure 3. Flanker Inhibitory Control vs. Depression

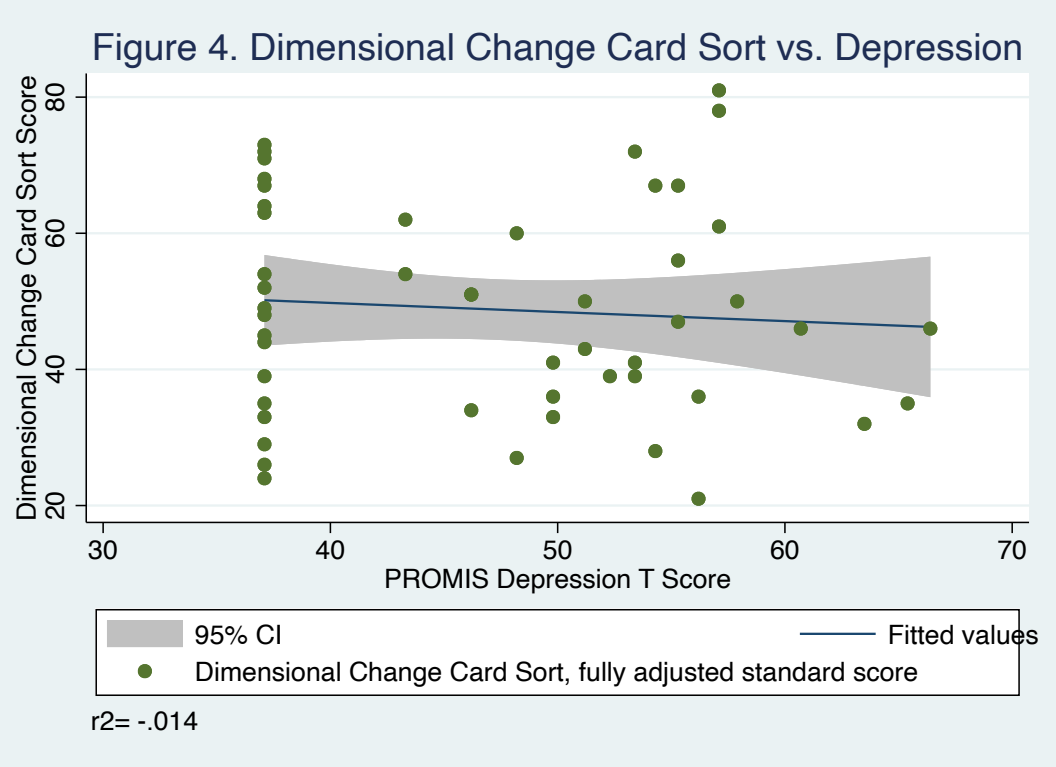

Figure 4. Dimensional Change Card Sort vs. Depression

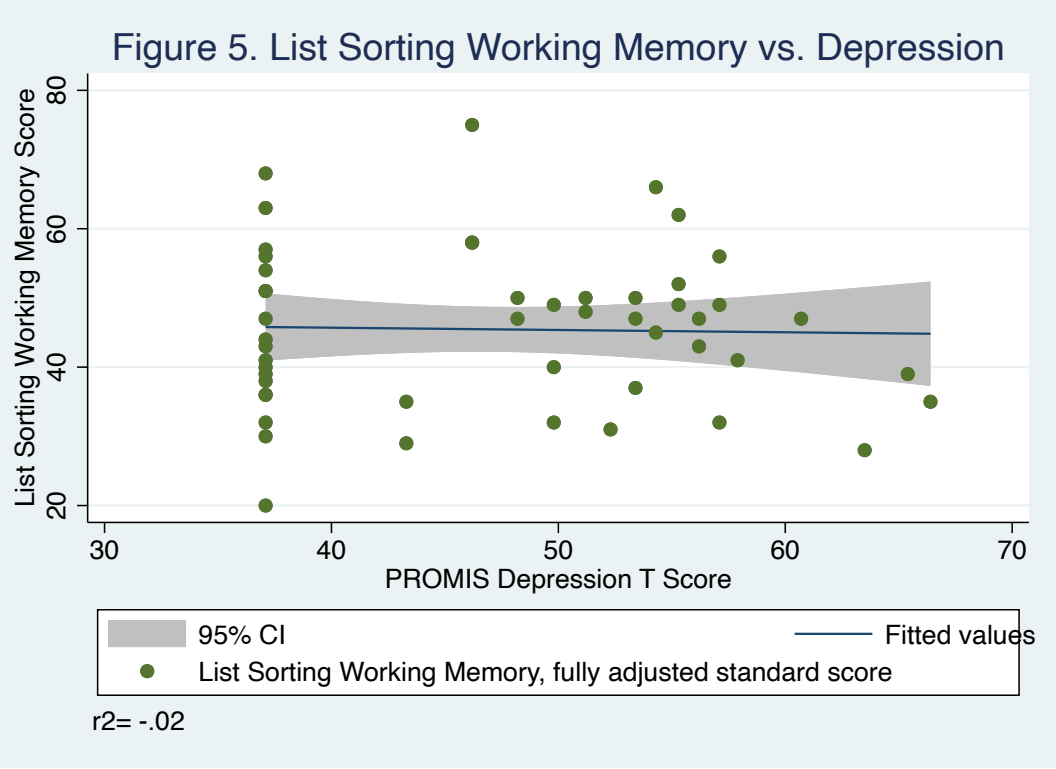

Figure 5. List Sorting Working Memory vs. Depression

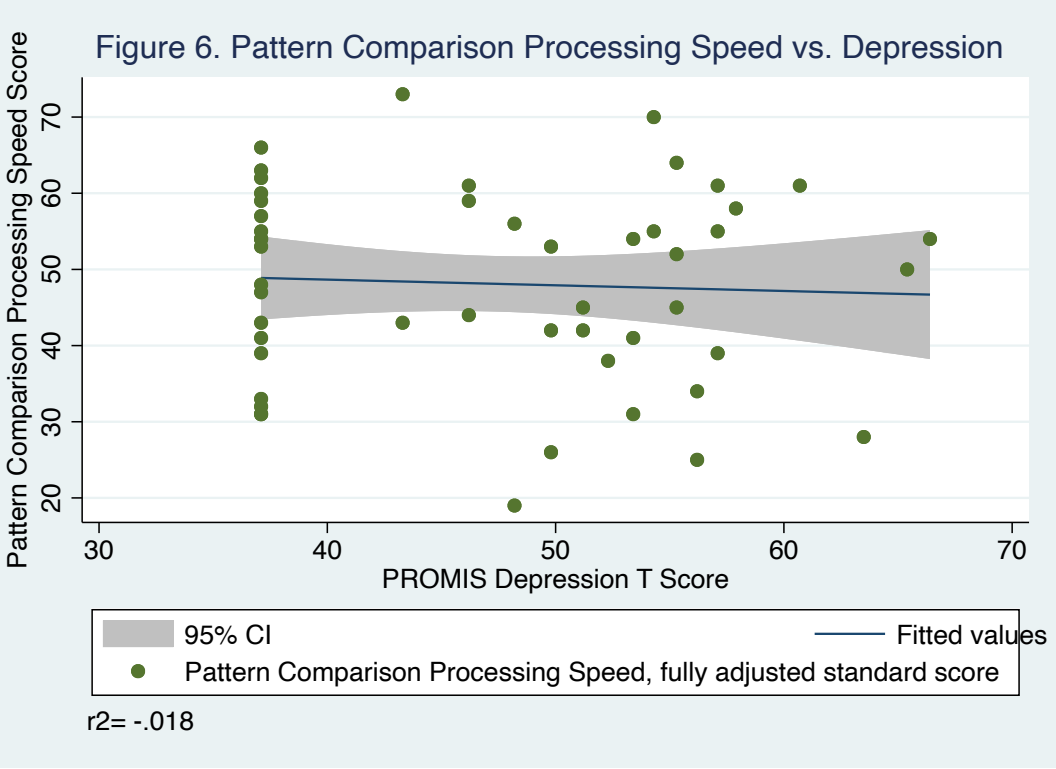

Figure 6. Pattern Comparison Processing Speed vs. Depression

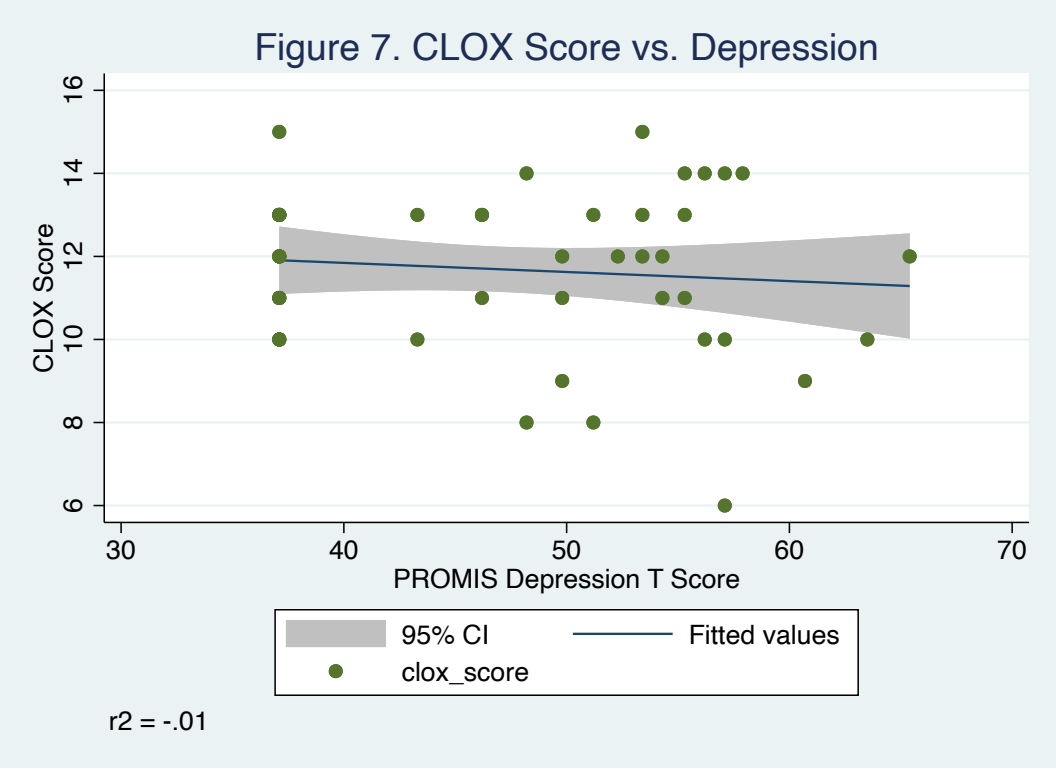

Figure 7. CLOX Score vs. Depression

Note: CLOX scoring scale only goes to 15 points, so many participants scores of the PROMIS Depression T -score and CLOX score overlapped, so it appears that there are less points on the scatter plot.

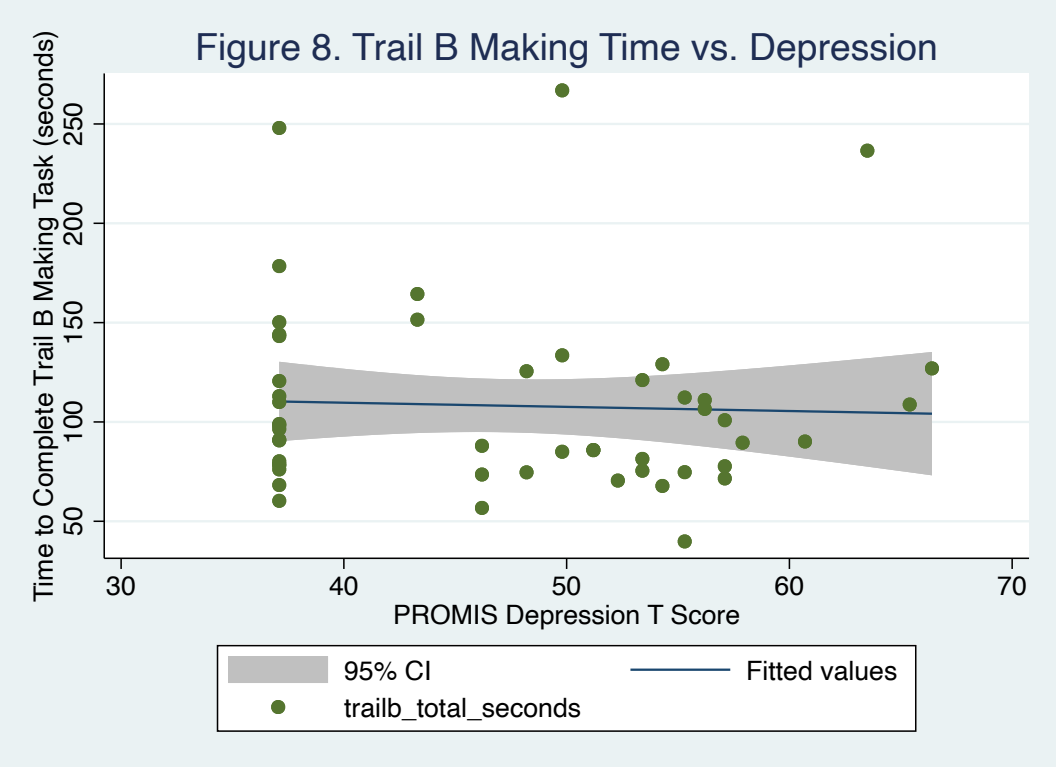

Figure 8. Trail B Making Time vs. Depression

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