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Cognitive dysfunction in pediatric systemic lupus erythematosus: current knowledge and future directions

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Abstract

Cognitive dysfunction (CD) is a neurologic complication of pediatric systemic lupus erythematosus (SLE) that remains poorly understood and understudied, despite the potential negative effects of CD on long-term socioeconomic status and quality of life. Data regarding the prevalence and risk factors for CD in pediatric SLE as well as the optimal screening, treatment, and long-term outcomes for CD are lacking. In this review, we present current knowledge on CD in pediatric SLE with a focus on the application to clinical practice. We discuss the challenges in diagnosis, clinical screening methods, potential impacts, and interventions for this complication. Finally, we discuss the remaining gaps in our knowledge of CD in pediatric SLE, and avenues for future research efforts.

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Keywords

Cognitive dysfunction; cognitive impairment; pediatric systemic lupus erythematosus; neuropsychiatric lupus; autoimmune disease

Background

Systemic lupus erythematosus (SLE) manifests as a diverse range of clinical phenotypes characterized by widespread immunologic dysfunction of both the innate and adaptive immune systems. Multiple pathways are involved in this systemic inflammation, including dysregulated B and T cell responses. B cells produce antibodies that help fight off infections and T cells are responsible for attacking infected cells, among other roles. The dysregulation of both these cell types that play important roles in the immune system leads to a loss of immune tolerance against self-antigens, abnormal inflammatory signaling, and impaired clearance of immune complexes (a complex formed from an antibody and its target). This results in a broad range of autoantibody formation, autoreactive immune cells, inflammation, and immune complexes depositing in tissues, all of which may cause tissue damage in multiple organ systems throughout the body. Clinically, this may present as arthritis, oral ulcers, glomerulonephritis, pleuritis, pericarditis, photo-sensitive rashes, cytopenias, or neuropsychiatric symptoms (Aringer et al., 2019). Treatment of the disease may involve glucocorticoids, hydroxychloroquine, anti-proliferative medications (such as mycophenolate, azathioprine, or cyclophosphamide), or monoclonal antibodies (such as rituximab or belimumab). Glucocorticoids are used mostly in disease flares with a goal of tapering off once the disease flare has remitted and the other steroid-sparing immunotherapies have taken effect (Ameer et al., 2022).

SLE affects over 3 million persons globally (Tian et al., 2023), with approximately 15–20% of cases representing pediatric onset SLE (Charras et al., 2021). Demographically, there is a higher incidence and prevalence of pediatric SLE among Black, Hispanic, Native American, and Asian/Pacific Islander populations compared to non-Hispanic White populations and a gender ratio (female:male) of between 4.5 and 5:1 (Hiraki et al., 2009; Pineles et al., 2011). Organ damage occurs early in pediatric onset SLE, and this damage can accrue over decades. This leads to greater impairment for individuals with pediatric-onset SLE and substantial negative effects on long-term health-related quality of life (QoL) (Groot et al., 2019), academic achievement, disability level, and employment (Groot et al., 2021).

Neurologic or psychiatric disorders resulting from SLE are termed neuropsychiatric systemic lupus erythematosus (NPSLE). This is a heterogeneous disease group with 19 distinct syndromes, including cognitive impairment or cognitive dysfunction (CD) – a significant impairment in one or more cognitive domains. These terms are often interchangeable and will be referred to as CD throughout this review (Santos et al., 2021). CD in SLE may result from direct neuroinflammation, ischemia or microvascular disease, or breakdown of the blood–brain barrier (BBB) leading to penetration of systemic inflammatory cells and mediators into the brain (Hanly et al., 2022; Kamintsky et al., 2020; Levy et al., 2009), with associations noted with mood disorders and chronic steroid use

as well (Bingham et al., 2021; McLaurin et al., 2005). Self- or parent-reported cognitive concerns are very common in the pediatric SLE population (Sibbitt et al., 2002), yet CD remains understudied and poorly understood. As childhood and adolescence is a critical neurodevelopmental period (Larsen & Luna, 2018), the evaluation, impact, and treatment of CD in pediatric patients with SLE (pediatric SLE) is a topic of considerable interest.

The purpose of this narrative review is to present what is currently known about CD in pediatric SLE, with a focus on clinical practice and application. We will discuss the formal neuropsychological testing, targeted batteries, and screening tests that have been evaluated or recommended for use in the pediatric SLE population. Where able, we compare and interpret the diagnostic accuracy or effect size of these tests (correlation coefficient [r], Cohen's d [d], or Hedge's g [g]) (Cohen, 1960; Ialongo, 2016; Pines et al., 2023; Schober et al., 2018), and note significant relationships (at least $p < .05$). We review the cognitive deficits seen most often in pediatric SLE on neuropsychological testing and their potential long-term academic, social, and economic impacts. Interventions that may modify these impacts or outcomes are also discussed. Finally, we summarize the gaps in knowledge of CD in pediatric SLE and highlight needed areas of future research. While also of great importance, the extensive and ongoing basic science investigations evaluating the heterogenous pathophysiology of this disorder are not detailed in depth here (Mizrachi et al., 2022; Seet et al., 2021).

Neuropsychological testing

In 1999, an international, multidisciplinary committee of experts organized by the American College of Rheumatology (ACR) defined 19 potential neuropsychiatric syndromes of NPSLE in adults, including CD as one manifestation, and recommended a 1-hour targeted neuropsychological battery for evaluation of CD in SLE (ACR-SLE battery) (The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes, 1999). However, some of the measures in this battery are not suitable for use in pediatric population, either due to the measures being designed for adults or a lack of pediatric normative data (Ross et al., 2010). Therefore, a separate standardized core battery specific for pediatric patients with SLE was proposed in 2010 by members of the Neurocognitive Lupus Workgroup of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) (Ross et al., 2010). This battery (the CARRA Neurocognitive Battery) addresses concerns regarding length and cost of traditional comprehensive neuropsychological evaluation (2.5–3 hours compared to >6 hours) which can limit access to neuropsychological evaluations, as well as recommending measures that are validated for use in pediatric populations, focusing on aspects of cognition known to be most affected in pediatric SLE.

The CARRA Neurocognitive Lupus Workgroup chose this specific battery to ensure appropriate assessment of the domains thought to be most informative in persons with pediatric and adult SLE – attention, executive function, visuospatial and visuoconstructive skills, memory, and psychomotor processing speed (Ross et al., 2010). A comparison of the measures included in each battery and the corresponding primary cognitive domains

evaluated by each measure is provided in Table 1. Of note, updated versions of most of the neuropsychological measures in the CARRA Neurocognitive Battery are now available.

A clinically meaningful level of CD in SLE has been debated, with multiple definitions proposed or utilized based on neuropsychological test scores or function (see Table 2). An ACR committee proposed a standard definition in 2007, including recommended definitions for “cognitive impairment” (focal and multifocal), “cognitive decline,” and a “clinically important response,” using standardized scores from the ACR-SLE battery, as well as a self-reported measure of cognition, the Cognitive Symptom Inventory (CSI) (Mikdashi et al., 2007). The committee provided these recommendations for adults with SLE but did not give recommendations for children with SLE.

The development of these standardized core neuropsychological batteries for adult and then pediatric SLE has provided benefits to both clinical practice and research. In clinical practice, these targeted batteries likely allow more persons with SLE to have neuropsychological testing performed by decreasing time and cost of evaluations. The development and endorsement of these batteries by major rheumatology professional organizations gives a “gold standard” of neuropsychological testing for research studies to use and compare against. However, as discussed in the following sections, difficulties remain in the interpretation of studies researching cognition in pediatric SLE.

Prevalence of CD

The reported prevalence of CD in SLE is highly variable – in pediatric SLE, studies have reported a prevalence of CD between 18 and 71% (Brunner et al., 2007; dos Santos et al., 2010; Frittoli et al., 2016, 2022; Gitelman et al., 2013; Kısaarslan et al., 2023; Lapa et al., 2017; Muscal et al., 2010; Papero et al., 1990; Santos et al., 2021; Vega-Fernandez et al., 2015; Williams et al., 2011). This variability between studies is likely due to several factors, including differences in the specific formal neuropsychological measures utilized, the definitions of CD used, and the composition of the pediatric SLE population studied.

Although the CARRA Neurocognitive Battery remains most standard for assessment of CD in research studies for pediatric SLE, many studies have utilized only parts of the full battery or created custom study batteries, depending on their needs and resources. Only about half of the published research studies on CD in pediatric SLE published since 2010 that utilized neuropsychological measures have included the full CARRA Neurocognitive Battery (Brunner et al., 2014; DiFrancesco et al.,2013, 2020; Gitelman et al., 2013; Jones et al., 2015; Nowling et al., 2021; Vega-Fernandez et al., 2015; Zelko et al., 2012). This has limited the ability to compare studies directly, especially when a custom battery is created using testing not included in the CARRA Neurocognitive Battery.

The CARRA Neurocognitive Lupus Workgroup, in developing their recommended core neuropsychological battery for pediatric SLE, did not specifically comment on definitions of CD. Therefore, recent studies have used variable definitions for CD in pediatric SLE (Table 2), differing in the number of affected domains and in the degree of impairment required. A standard definition has not yet been agreed upon, although variations of the definitions

utilized by Brunner et al. (2007, 2013) have been used most often in subsequent studies. Additionally, a definition of a clinically meaningful and reliable change index score for this population has yet to be determined (Guilmette et al., 2020).

A study by Williams et al. (2011) sought to compare several of the definitions for CD directly. Using an adapted ACR-SLE battery, they found CD in 34.1%, 7.3%, and 63.4% of their pediatric cohort using the definitions by Brunner et al. (2007), the ACR (Mikdashi et al., 2007), and Muscal in 2010 (Muscal et al., 2010), respectively. It should be noted that another study utilizing the Brunner criteria identified 36.6% of healthy controls as meeting the definition of cognitive impairment (Frittoli et al., 2016). This wide variation and lack of specificity demonstrate the need for a standardized and consistently applied definition for CD in pediatric SLE research to be developed, as studies on the sensitivity and specificity of paraclinical evaluations and outcomes of CD would vary greatly depending on the definition chosen.

The clinical differences between SLE patient populations at different sites of care may also be a contributor to variability in these estimates of prevalence. One study in adult SLE utilized the same neuropsychological measures at two separate academic centers in different regions of the United States. Despite using the same measures and definitions of CD, and with similar participant demographics and education levels, there was a significant difference in the prevalence of CD between the two sites (24% vs 60%). The study attributed this to site-specific differences in disease duration and medical complications (Kozora et al., 2012).

This study highlighted the potential lack of generalizability of prevalence estimates for single-site studies, given the potential differences between the patient demographics, disease course, co-morbidities, and the variable approaches to disease-related testing and treatment at different centers. Direct comparison between research studies may also be difficult with the variable batteries and definitions of CD used in these studies. Unfortunately, these factors are not just fundamental for determining the prevalence of CD, but also for all other observational or interventional studies evaluating CD in pediatric SLE.

Neuropsychological deficits in persons with pediatric SLE

There is conflicting information on whether CD occurs at higher rates in persons with pediatric SLE compared to a demographically similar population. Given that the demographics of the pediatric SLE population are different than the populations sampled for norming of most neuropsychological measures, the use of demographically well-matched healthy individuals to serve as controls or comparisons is important for evaluation of this question (Borgia et al., 2023; Conrad et al., 2023; Malik & Norman, 2023). The most common method for obtaining comparison groups for the pediatric SLE population has been the “best friend” method (the patient identifies a friend of similar age and gender to serve as the control) or healthy siblings to help ensure a closer match on socioeconomic or environmental factors. Using this, three studies found no difference between their pediatric SLE cohort and demographically matched controls (Frittoli et al., 2016; Williams et al., 2011; Zelko et al., 2012), compared to one study identifying a significant difference in CD

prevalence between pediatric SLE (33.3%) and matched controls (6.7%) by their definition (Mostafa et al., 2010). Another study noted a higher prevalence of moderate or severe CD in pediatric SLE (12.5%) compared to matched controls (5%), although this difference was not evaluated statistically (Brunner et al., 2013). Studies that matched controls only on age or age/gender more consistently found a significant difference between prevalence rates (Nowling et al., 2021; Vega-Fernandez et al., 2015), suggesting the importance of other demographic factors. Together, this highlights the need for appropriate demographically matched controls for research evaluating the impact of the SLE disease process itself on prevalence, and that socioeconomic or environmental factors may also be contributing to CD in this population. From a clinical standpoint, it is also important to consider selection of appropriate measures and norms, where available, for patients from diverse backgrounds.

Given the difficulties in defining CD, it is also necessary to look not only at differences in prevalence but also at differences in specific cognitive domains between pediatric SLE and control groups. Of the studies above that included demographically matched controls, only two reported their comparison of individual neuropsychological measures or cognitive domains. These were also the studies that found no difference in CD between SLE and demographically matched controls, so in similar fashion, no difference in individual measures or cognitive domains was found either (Williams et al., 2011; Zelko et al., 2012). No study that found a difference in CD between SLE and demographically matched controls compared individual measures or domains. This is in contrast to a recent publication on cognition in adult SLE with age, gender, and premorbid IQ matched controls that showed significantly lower tests in each cognitive domain assessed by the ACR-SLE battery, with moderate to large effect sizes *(d = 0.4–1.21)* (Raghunath et al., 2023).

Focusing just on the pediatric SLE population, Table 3 provides a summary of key articles detailing measures and domains that are significantly different between persons with pediatric SLE with and without CD. These include both studies using formal neuropsychological measures and those from the Pediatric Automated Neuropsychological Assessment Metrics (Ped-ANAM) discussed in greater detail below. As shown by the table, within the pediatric SLE population, there are certain cognitive domains noted to be affected more often in those with CD, including visuospatial or visuoconstructive ability, attention, language processing, processing speed/psychomotor speed, and visual or working memory (Brunner et al., 2007, 2013; Gitelman et al., 2013). A deficit in any of these domains may cause significant academic or social difficulties, especially if unrecognized and unaddressed. Visual and working memory deficits may relate to worse performance in arithmetic (Andersson & Lyxell, 2007). Deficits in attention in early childhood predict high school academic achievement (Lundervold et al., 2017), later development of depression (Rajendran et al., 2013), and social behavioral development (Bellanti & Bierman, 2000). Deficits in processing speed in persons with attention deficit/hyperactivity disorder are associated clinically with academic difficulties, particularly in reading, anxiety, and weaker adaptive and social functioning (Cook et al., 2018). Therefore, in a person with pediatric SLE with new onset of social, academic, mood, or other functional concerns, the underlying cause should be sought, and a neuropsychological evaluation should be considered if appropriate.

Targeted evaluation and screening measures for CD

While the CARRA Neurocognitive Battery represented an important standardization of recommendation for formal neuropsychological evaluations in individuals with pediatric SLE, using it to routinely assess cognitive function of these patients in Rheumatology or Neurology practices is challenging due to the duration of testing (2.5–3 hours), limited timely access to neuropsychological evaluations, and financial considerations (AlE'ed et al., 2017; Cass et al., 2020; Ransom et al., 2020; Salinas et al., 2020). Therefore, there has been interested in determining shorter and more accessible screening methods for patients with pediatric SLE – identifying who may gain the most from comprehensive neuropsychological evaluations and making efficient use of limited neuropsychological resources. This strategy fits in well with proposed prevention-based models of neuropsychological assessments for other pediatric chronic medical diseases – using shorter screening measures for universal monitoring or targeted screening to guide those needing comprehensive evaluations, and identify and intervene prior to functional impairments becoming evident (Hardy et al., 2017). This effort has focused on three categories: self- or parent-reported screening measures, targeted neuropsychological evaluations, and blood or imaging-based biomarkers.

Self- or parent-reported measures of cognition for CD screening

Self- or parent-reported measures of cognition are structured assessments that provide a window into functioning in real-world settings that are not easily obtained from performance-based measures conducted in a controlled environment (Isquith et al., 2013; Silver, 2014). In this way, the information gained from these reported measures is complementary to the formal neuropsychological testing. For screening or monitoring purposes, these questionnaires and rating scales also have the benefits of being brief and easy to administer in clinical settings.

One study evaluated the use of two such questionnaires – the Subjective Awareness of Neuropsychological Deficits for Children (SAND-C) and the Behavioral Rating Inventory of Executive Function (BRIEF) – as screening measures for CD in children with SLE. The ratings on these questionnaires generally correlated weakly and non-significantly *(r < 0.2)* with formal neuropsychological measures, with a few significant moderate correlations noted *(r = 0.26–0.31),* and did not discriminate among persons with different cognitive abilities (Vega-Fernandez et al., 2014).

In adult SLE, other self-reported measures have been evaluated as screening measures for CD against performance-based neuropsychological measures. In one study evaluating the CSI, despite comparing with multiple definitions of cognitive impairment, the area under the receiver operating characteristic (ROC) curve remained close to 0.5, indicating a poor performance of the CSI by itself for screening (Hanly et al., 2012). In another study on the CSI in adult SLE, there was no significant relationship between cognitive symptoms on the CSI with performance-based measures on univariate or multivariable logistic regression models (Raghunath et al., 2022). In a study evaluating the Perceived Deficits Questionnaire-Short Form (PDQ-SF) in adults with SLE, a significant but weak correlation with CD was found *(r = 0.15).* On an ROC analysis, a cut point of ≥10 on the PDQ-SF was determined,

but this had a lower sensitivity (0.55) and a lower negative predictive value (0.87) than performance-based measures (Julian et al., 2012).

These studies demonstrate that while self- and parent-reported questionnaires of cognitive function have several beneficial characteristics for screening purposes, they should not be used alone for screening for CD in SLE. It is important to pair these questionnaires with a thoughtful clinical interview assessing for potential CD or other social-emotional concerns when determining the appropriateness of a referral for a comprehensive or targeted neuropsychological evaluation. Nevertheless, these questionnaires provide relevant information on a person's perceived functioning within a more natural environment than the artificial clinic setting, and so should be considered in complementing information gained from performance-based measures.

Performance-based neuropsychological targeted evaluations for CD screening

The Ped-ANAM is one of the most well-studied targeted screening measures for CD in pediatric SLE. It is a computerized battery of 10 cognitive tests, requiring 30–40 minutes for completion compared to several hours for comprehensive neuropsychological batteries. It may be administered by neuropsychologists, physicians, or other trained personnel. There is a moderate significant correlation between many performance parameters of the Ped-ANAM and other established neuropsychological measures *(r = −0.41–0.74)* (Brunner et al., 2007). A composite cognitive performance score (CPS) composed of all Ped-ANAM test parameters, as well as its subscores (the CPS-Multiscore or the CPS-Primary Component Analysis [PCA]) have been studied as well (Nguyen et al., 2015; Vega-Fernandez et al., 2015). After optimal cutoffs were determined, the area under the ROC curve (AUC) of two validation groups was found to be 0.89 and 0.74 for the CPS-Multiscore (fair to good accuracy) and 0.80 and 0.67 for the CPS-PCA (poor to good accuracy) for detection of moderate-severe CD (Vega-Fernandez et al., 2015). Despite the moderate correlation with formal neuropsychological measures and at least fair accuracy in detecting moderate-severe CD, it has still not gained widespread clinical use in pediatric rheumatology practices. The required presence of a trained proctor, the requirement of a dedicated computer and quiet space within the context of busy outpatient clinical settings, the complexity of and lack of automation of the CPS scoring, and the time required to administer make its application for screening in clinical practice difficult within Rheumatology clinics (CARRA NPSLE Workgroup, personal communications, May 26 2023).

The Montreal Cognitive Assessment (MoCA) is a quick (< 10 minutes) screening tool in common use for assessment of mild cognitive impairment in adults. It has a strong correlation *(r = 0.79)* with CD on formal neuropsychological testing (Paez-Venegas et al., 2019). When assessed for diagnostic accuracy for CD in adult SLE, however, the AUC varied from 0.66 (poor) to 0.99 (excellent) depending on the study and score threshold used (Paez-Venegas et al., 2019; Papastefanakis et al., 2021; Raghunath et al., 2021; Tayer-Shifman et al., 2022). Regardless, as the MoCA was developed and validated for adults, few studies have attempted to use it in pediatric populations (Mittal et al., 2012; Phabphal & Kanjanasatien, 2011; Pike et al., 2017) and none in children with SLE.

A small pilot study investigated use of the Gordon Diagnostic System in patients with pediatric SLE, a measure used to detect attention deficits during neuropsychological evaluations (Nuruzzaman et al., 2015). They noted that the mean scores for patients with pediatric SLE were consistently in the lowest quartile of normative data; however, additional measures of attention such as caregiver questionnaires were not administered to determine if the patient met formal criteria for an attentional disorder.

Therefore, other than the Ped-ANAM, there are few measures or tools that have been evaluated and validated for screening for CD in pediatric SLE. The use of the Ped-ANAM as a universal monitoring or screening tool may have some limitations for clinical settings; further research is needed into additional measures or methods to improve implementation.

Blood-based biomarkers

Blood-based biomarkers for CD, if validated, could provide easily obtainable and objective screening measures. SLE generates autoantibodies against organs or tissues at high rates and these autoantibodies and the inflammation they induce are often associated with dysfunction in the target organ. Therefore, in biomarker studies of NPSLE or CD, autoantibodies have held a primary focus. These include antibodies against the NR2 subunit of the N-methyl-D-aspartate receptor (anti-NR2), anti-phospholipid antibodies, anti-ribosomal P antibodies, and anti-ganglioside antibodies. Each of these has known antigenic targets within the brain (Cotman & Monaghan, 1989; Cutillo et al., 2020; Dale et al., 2011; Kent et al., 1997; Matus et al., 2007), and both anti-NR2 and anti-ribosomal P antibodies have also been found to alter synaptic transmission and induce cognitive dysfunction in animal models (DeGiorgio et al., 2001; Faust et al., 2010; Segovia-Miranda et al., 2015).

Another approach has been to look at the concentration of brain-derived proteins within the peripheral blood. Certain proteins may be released from neurons or glial cells in the brain into the blood during times of ischemic or inflammatory injury, microglia activation, or increased permeability of the blood–brain barrier, events similar to some of the proposed pathophysiology of CD in SLE. These proteins include the S100 proteins (beta [B] and A8/9) and neutrophil gelatinase associated lipocalin (NGAL), which are found most in astrocytes, and neurofilament light (NfL), a structural neuro-axonal protein found in neurons. They have been evaluated and found to have growing utility as predictive, prog-nostic, and therapeutic biomarkers in a number of autoimmune neurologic or neurodegenerative disorders (Barro et al., 2020; Kammeyer et al., 2022; Langeh & Singh, 2021; Naudé et al., 2021).

Table 4 reviews pertinent findings from studies that have evaluated both these autoantibodies and brain-derived protein biomarkers for CD in pediatric SLE. Unfortunately, findings for each of the candidate autoantibodies and proteins for CD in pediatric SLE individually have been either inconsistent, contradictory, or are still awaiting subsequent confirmatory studies. One study did evaluate a combination of these serum markers of cerebral injury/inflammation (S100A8/9, S100B, NGAL) and serum autoantibodies (anti-NR2 and anti-ribosomal P) in an exploratory analysis. This combination was able to identify CD in pediatric SLE with a sensitivity of 100% and specificity of 76% (Brunner et al., 2014), but this has not been validated in a subsequent study.

In studies of adult SLE, while there are conflicting studies on relevance of the above autoantibodies for NPSLE, there is increasing evidence against their association with CD specifically (Duarte-García et al., 2018; Gulati et al., 2016; Hanly et al., 2022; Harrison et al., 2006; Kozora et al., 2010; Peretti et al., 2012; Tomietto et al., 2007; Yue et al., 2020). Other immunologic markers including serum interleukin-6 have shown only weak or conflicting associations with NPSLE or CD in adult SLE (Barraclough et al., 2021; Duarte-García et al., 2018; Hirohata & Kikuchi, 2021; Kozora et al., 2011). For brain-derived proteins, plasma NfL showed a moderate significant correlation with simple attention *(r = −0.41)* but not other cognitive domains in one study (Zervides et al., 2022); in another, there was no significant association found between plasma NfL and neuropsychological testing when included in a multivariable regression model (Lauvsnes et al., 2022).

Together, we see that blood-based biomarkers do not replace neuropsychological measures for the screening of CD in pediatric SLE. Further research is needed to validate or evaluate several of these biomarkers or combinations of biomarkers and determine their predictive value for CD.

Neurodiagnostic testing

Magnetic resonance imaging (MRI) of the brain, MRI-based spectroscopy, and functional MRI may differentiate CD and non-CD in pediatric SLE. Studies have noted differences in the microstructural or microvascular integrity, microstructural connectivity, metabolite ratios, blood–brain barrier permeability, cerebral white and gray matter volumes, or regional brain activation during certain cognitive tasks between persons with pediatric SLE with and without CD (Arciniegas, 2021; DiFrancesco et al.,2013, 2020; Frittoli et al., 2022; Gitelman et al., 2013; Gulati et al., 2015; Jones et al., 2015; Kilic et al., 2019). While each of these studies contributes toward understanding the pathophysiology of CD in pediatric SLE, they have not been evaluated for their predictive value for CD for an individual. Routine screening by MRI-based techniques may also be limited by cost or availability of the testing.

A study in adults with SLE found no significant difference in neuropsychological test scores between persons with and without an abnormal electroencephalogram (Waterloo et al., 1999). The cost and limitations for availability of this test would also limit utility in routine screening.

Demographic and clinical factors associated with CD

In persons with pediatric SLE and CD, a significantly lower annual household income has been noted compared to those without CD *(g = 1.22)* (Gitelman et al., 2013). A difference in disease duration has not been seen (Brunner et al., 2007; dos Santos et al., 2010; Gitelman et al., 2013; Zelko et al., 2012). A parent-reported rating of a child's functioning across multiple academic domains (the School Competence scale of the Child Behavior Checklist) showed significant moderate negative correlations with disease activity *(r = −0.55)* and prednisone daily dose in mg *(r = −0.40)* (Zelko et al., 2012). One study also found disease activity to be significantly but weakly correlated with CD *(r = 0.33)* (de Amorim et al., 2022); however, other studies evaluating CD have found no significant difference in disease

activity, systemic damage, or daily prednisone dose between those with and without CD (Brunner et al., 2007; dos Santos et al., 2010).

In adult SLE, a number of disease-related factors have been found to be associated with the presence of CD, including a longer disease duration, prior or concurrent central nervous system involvement (NPSLE), a higher disease activity at onset or at baseline, chronic steroid use, and a higher level of medical complications of SLE (Duarte-García et al., 2018; Kozora et al., 2012; Maneeton et al., 2010; McLaurin et al., 2005; Mikdashi & Handwerger, 2004; Teixeira Santos et al., 2023; Tomietto et al., 2007). Potentially modifiable factors including obesity, low exercise capacity, physical inactivity, diabetes, and hypertension are also associated (Duarte-García et al., 2018; Katz et al., 2012; Kozora et al., 2015; McLaurin et al., 2005; Murray et al., 2012; Tomietto et al., 2007), as are other demographic factors including less education, lower socioeconomic status, and increasing age (Duarte-García et al., 2018; McLaurin et al., 2005; Teixeira Santos et al., 2023; Tomietto et al., 2007).

In the general population, depression is known to have a negative association with cognitive performance in both adolescents and adults (Wang et al., 2023). Depression and anxiety are very common in pediatric SLE, with at least one mood disorder occurring in 20–50% (Knight et al., 2016; Sibbitt et al., 2002). The impact of mood disorder on CD is of special interest as these may be treated and improved (Cunningham et al., 2019). However, the specific impact of mood on cognition within the pediatric SLE population has not received much attention.

Within adult SLE populations, self-reported cognitive symptoms are well associated with mood disorders. In one study, cognitive symptoms on the CSI showed greater association with history of depression or anxiety (*Odds ratio [OR]: 3.17; 95% Confidence Interval [CI] 1.30,7.72])* or current mood symptoms *(OR: 1.17; 95% CI 1.08,1.26)* than with objective neuropsychological testing on multivariable logistic regression models. Another study also found a significant positive association of depression or anxiety symptoms with cognitive symptoms on the CSI in a multivariable linear regression model (Hanly et al., 2012). In each of these two studies, the relationship between the mood disorder and symptoms with cognitive symptoms was greater than the association of cognitive symptoms with performance-based cognitive testing.

Associations of depression with objective cognitive performance within adult SLE populations are also noted, although the degree of the association varies. One study found a significant yet weak negative correlation *($r = -0.29$)* of Frontal Assessment Battery (FAB) scores with Beck's Depressive Inventory (Maciel et al., 2016). A study looking at patients recently diagnosed with SLE in the previous 9 months found that those with depression had significantly poorer performance on multiple ANAM throughput measures (throughput is a measure of correct answers per minute), even when the multivariable regression model was adjusted for age, sex, ethnicity, education, and prednisone dose (Petri et al., 2010). Another study comparing otherwise healthy adults with depression to adults with SLE and depression, those with both SLE and depression scored worse on an index of cognitive impairment based on the ACR-SLE battery *($g = 0.92$)*, demonstrating that other factors than depression alone impact cognition within the SLE population (Kozora et al., 2007).

While much research has been done into demographic and clinical factors associated with CD in adult SLE, there is little on this in pediatric SLE. Unfortunately, this also extends to potentially modifiable disease-specific and lifestyle factors as well as comorbid mood disorders. The risk factors for CD in both pediatric and adult SLE should be evaluated and considered at clinical encounters, to help identify those for whom targeted screening may be beneficial.

Potential impacts of CD

As discussed earlier, the cognitive domains most affected in SLE are associated with significant academic, social, and behavioral challenges in the general population; the few studies on the impact of CD in pediatric SLE have focused most on academics and quality of life. One study found that pediatric SLE patients with CD had lower school grades in mathematics than those without, with a small significant effect *(g = 0.38)* (Frittoli et al., 2016); another found that academic achievement was globally depressed in a cohort of children with SLE, with an average reading comprehension estimated to be 5 years behind grade-level (Wyckoff et al., 1995). Moderate to strong significant correlations *(r = −0.46, −0.54)* are also found between parent reported executive functioning (BRIEF) and parent reported School Competency on the Child Behavior Checklist. Deficits in executive function in pediatric SLE are moderately to strongly correlated with poorer quality of life, especially for fatigue-related quality of life *(r = 0.53)* (El Tal et al., 2022). Another study found a lower quality of life among persons with SLE and CD compared to those without *(g = 0.77),* using one definition of CD, but not for others (Williams et al., 2011). The prevalence of CD in adults with pediatric onset SLE remains high and is associated with greater difficulties with conducting or adhering to their treatment (Teixeira Santos et al., 2023).

In adult SLE, the presence of CD has been associated with likelihood of unemployment *(OR: 5.12, 95% CI 3.1–6.3)* (Appenzeller et al., 2009) and work disability *(OR: 14.44, 95% CI 3.01–68.20)* (Utset et al., 2006). A systematic review of studies in adult SLE found associations of the presence of CD with lower health-related quality of life and social role participation (Mendelsohn et al., 2021).

Given these associations with long-term outcomes, once CD is diagnosed in a person with pediatric SLE, interventions must be considered to potentially improve these outcomes.

Interventions for CD

The best intervention or combination of interventions for CD in pediatric SLE is still unknown. Given the heterogeneous potential etiologies of CD in SLE (Bingham et al., 2021; Hanly et al., 2022; Kamintsky et al., 2020; Levy et al., 2009; McLaurin et al., 2005), evaluation for specific etiologies is important and may point toward appropriate interventions. For example, depression and anxiety may impact cognition, with treatments including cognitive behavioral therapy (Cunningham et al., 2019) and/or psychiatric medication. Attentional disorders, sleep disorders, thyroid or other endocrinologic disease, or adverse effects of medications are additional factors that should be evaluated for and can be addressed and treated if found (Kabasakalian & Finney, 2009). Evaluation and

examination with a neurologist for symptoms and signs of other NPSLE syndromes may be performed; depending on the result of this consultation, there may be consideration of additional neurodiagnostic testing for inflammatory, ischemic, or genetic etiologies. If no comorbid condition with a specific known treatment is found to be contributing, then there is consideration of supportive care with cognitive or school supports, lifestyle modifications, or a trial of immunotherapy.

Academic and cognitive supports

Cognitive and school supports are some of the most common and well-recognized interventions for children with CD (Grigorenko et al., 2020). In children with attention, executive dysfunction, or working memory deficits, a number of interventions have been advanced to help improve function. This includes the use of physical activity, mindfulness training, computer-based or therapist-delivered cognitive interventions, or school-based accommodations (Diamond & Lee, 2011; Holmes et al., 2009; Janz et al., 2019; Robinson et al., 2014). However, the efficacy and sustainment of benefits over time for some of these, in particular the therapist or computer-based cognitive training or interventions, are debated (Melby-Lervåg & Hulme, 2013; Simons et al., 2016).

There are few studies on these supports within SLE. In one study funded by the software developer, adults with SLE and CD regularly used a video-game style computerized training for 4 weeks. There was greater improvement in visuomotor speed and cognitive flexibility/sequencing by Trail-making tests A and B *(d = 0.58, 0.62)* at the end of the 4 weeks in the persons who had done the training (Kozora et al., 2022). However, it is not known if these improvements persisted after the study and training were stopped, and if the impact extended outside the video game to real-world functioning. A pilot study of an 8-week psychoeducation group intervention improved metamemory *(d = 1.33)* and cognitive symptoms *(d = 4)* for adults with SLE and subjective CD (Harrison et al., 2005). Cognitive rehabilitation, a systemic process of assessing cognitive deficits and providing specific retraining or support of these cognitive domains, has been shown effective in multiple diseases with non-progressive acquired brain damage, similar to some of the possible pathophysiologies of CD in SLE, although further studies investigating the generalizability of these skills is needed (Chung et al., 2013).

Lifestyle modifications

Improving diet and increasing exercise are known to be important factors in supporting optimal cognitive function for children in the general population (Jirout et al., 2019; Martin et al., 2005). While this has not been specifically investigated in children with SLE, in adult women with SLE who did not regularly exercise, 12 weeks of combined moderate-intensity aerobic exercise and resistance training was associated with improvement on one measure of executive function (go-no go reaction time), but not the other (Stroop Color and Word Test) (Kao et al., 2021). Diet is known to impact cognition in a number of neurologic disorders, with increasing interest in dietary interventions for diseases including multiple sclerosis (MS), Alzheimer's, and other neurodegenerative or neuroinflammatory diseases that have CD as a common symptom impacting QoL (Francis & Stevenson, 2018).

Role of immunotherapy

There have been very few studies investigating the utility of immunotherapy for the treatment of isolated CD in pediatric SLE. A series of 53 pediatric patients with either isolated severe CD (definition in Table 2 by Lim et al. 2013) or psychosis with associated CD who were treated with high-dose steroids and a second-line immunotherapy showed improvement in their CD afterward – with persistent CD only noted in 15% after treatment (Lim et al., 2013). However, the median systemic SLE disease activity in this study was above the threshold already used for intensification of immunotherapy (Yee et al., 2011), and there was no control group for comparison. For pediatric or adult persons who have CD concurrently with major NPSLE syndromes, treatment with immunotherapies focused on the treatment of NPSLE is likely to be beneficial, which may include glucocorticoids, cyclophosphamide, or rituximab (Barile-Fabris et al., 2005; Lim et al., 2013; Tokunaga et al., 2007). The pathophysiology of CD in pediatric SLE is likely heterogeneous, and the presence of CD may or may not always correlate with overall SLE disease activity status (Brunner et al., 2007; de Amorim et al., 2022; dos Santos et al., 2010; Muscal et al., 2010). Thus, the role of immunotherapy for the treatment of isolated CD in quiescent SLE remains unknown.

Future directions

This review highlights the many gaps in our knowledge of CD in pediatric SLE, which may be addressed in ongoing or future research studies focused on the evaluation, definition, screening, biomarkers, interventions, and outcomes for CD.

Study quality and validation of findings

A large proportion of the studies reviewed had limitations that affected generalizability or validity of their findings. Many were single center, with small group sizes, and focused on a topic whose findings were not repeated for confirmation by other research groups. Even when repeated, heterogeneity in the populations, diagnostic testing, and statistical tests used made direct comparisons difficult. The overall low number of articles on this topic in the medical literature makes assessment for publication bias difficult. Some used an extensive number of statistical tests to look at relationships with individual NPTs, without correcting for multiple comparisons, or provided insufficient data to determine effect sizes. Future studies will benefit from the use of multicenter research networks to ensure adequate group sizes and generalizability. Standardization of tests and procedures, well-documented hypothesis-driven analyses, and replication of results in other studies will assist in ensuring the validity of findings.

Defining CD

Part of the difficulty in comparing studies on CD in pediatric SLE is due to differences in the measures used or in the chosen definition of CD. This makes evaluation of new diagnostics, treatments, or outcomes difficult. A consensus evidence-based definition for CD in children and adolescents is needed to standardize future research studies and complement the current endorsed gold standard for neuropsychological evaluation in pediatric SLE, the CARRA Neurocognitive Battery. A meaningful definition of CD or change in cognition may not be

binary, as used in some of the studies previously discussed, but a spectrum of dysfunction or change. These may be developed using the standardization developed by the American Academy of Clinical Neuropsychology (Guilmette et al., 2020). The analysis of clustering of scores on neuropsychological testing may yield subpopulations to phenotype and develop definitions from as well and has been performed in adults with SLE (Raghunath et al., 2023).

Neuropsychological measures do not define impairment in isolation (Guilmette et al., 2020). How a person is functioning or how that functioning has changed in day-to-day life may be as important to know as their scores on performance-based measures and may be more meaningful to patients or their families. Self- or parent-reported rating scales or questionnaires on cognitive symptoms, academic performance, required academic supports, and psychosocial function may be methods to help identify impairments in real-world settings of significance to patients and their families, knowing that the variability and confounders that real-world settings provide can make interpretation more challenging. The relationship of long-term psychosocial, economic, or quality of life outcomes to a certain definition of CD may also be of interest in assessing the meaningfulness of a definition, although a number of confounders and changes in cognition over time may make this also difficult to use.

Screening for CD

Once a meaningful definition of CD is created, routine and efficient identification of those with CD through universal monitoring, screening, or targeted/comprehensive evaluations becomes even more important. Evidence exists on the utility of Ped-ANAM for screening patients with pediatric SLE for CD. However, given its time requirements and poor adoption, either dissemination and implementation research into methods for improving general adoption or development of more rapid and easily accessible measures are needed. Similarly, evaluation of the biological mechanism of CD in pediatric SLE and new biomarkers of neuronal or glial injury, alone or in combination with other biological or clinical measures, may be useful in improving diagnosis and follow-up management of CD.

Interventions for CD

There is a paucity of data on interventions that may help with CD in pediatric SLE, and intervention trials with control groups are desperately needed. School accommodations and interventions as well as therapies are recommended for cognitive difficulties in children in general. Drawing from adult studies of SLE and other neuroinflammatory or neurodegenerative disorders such as MS, there may be modifiable lifestyle factors, such as diet or exercise that could improve CD and general health. A subset of patients with pediatric SLE and CD, especially with severe CD, may respond to increased immunotherapy.

Centrally acting angiotensin-converting enzyme inhibitors have been shown to decrease inflammation, microglial activation, and Type I interferon levels in animal mice models of lupus, along with increasing serotonin levels (Nestor et al., 2018; Nocito et al., 2020). For this reason, a phase II trial is currently investigating the role of lisinopril in improving

cognitive function in adult patients with SLE (National Library of Medicine [NLM], NCT04486118). Memantine, an NMDA, 5-HT-3 (serotonin), and nicotinic cholinergic receptor antagonist were not beneficial for improving cognitive dysfunction in adult patients with SLE in a randomized clinical trial (Petri et al., 2011), although it is now being evaluated in a subset of patients with a genetic mutation in the NMDA receptor (NLM, NCT03527472).

Outcomes of CD

Little is known about how CD in pediatric SLE will relate to eventual long-term academic, socioeconomic, and QoL outcomes in adulthood. Longitudinal studies would be useful for answering this question, and in determining if early interventions are able to improve these trajectories into adulthood. One ongoing study funded by the Centers for Disease Control and Prevention and administered by the CARRA network (*Improving Pediatric Lupus Care and Outcomes through the Childhood Arthritis and Rheumatology Research Alliance Lupus Registry*) seeks to answer some of these questions through longitudinal Ped-ANAM assessments.

Conclusions

CD may have long-term negative effects for persons with pediatric SLE, but this co-morbidity remains poorly understood and understudied. The development and evaluation of new biomarkers, screening measures, targeted evaluation batteries standardized definitions, and interventions for CD in pediatric SLE may each help address the gaps in knowledge that are currently prominent. Multi-center longitudinal studies are key to ensuring generalizability and assessing outcomes.

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Table 1.

Primary cognitive domains assessed in the ACR-SLE and CARRA Neurocognitive batteries.

Cognitive Domain	ACR-SLE Battery (ACR, 1999)	CARRA Neurocognitive Battery (Ross et al., 2010)
Intelligence Quotient (IQ)	North American Adult Reading Test	Wechsler Abbreviated Scale of Intelligence (WASI): Two-Subtest Form
Psychomotor speed	Digit Symbol Substitution Test	Wechsler Intelligence Scale for Children (WISC)-IV Subtests: Coding and Symbol Search
	Trail-Making Test – Part A	
	Stroop Color and Word Test	
Processing speed and attention		Conners' Continuous Performance Test II (CPT-II)
Executive function/ complex attention	Trail-Making Test – Part B	Delis-Kaplan Executive Function System (D-KEFS) Color-Word Interference Test
	Wechsler Adult Intelligence Scale (WAIS)-III: Letter-Number Sequencing	
Visual-spatial processing	Rey-Osterrieth Complex Figure Test – Copy	
Visual memory	Rey-Osterrieth Complex Figure Test – Immediate and Delayed Recall	Wide Range Assessment of Memory and Learning (WRAML)-2 Screening subtests: Picture Memory, Design memory
Verbal memory	California Verbal Learning Test	WRAML-2 Screening Subtests: Story Memory, Verbal Learning
		WISC-IV Subtests: Digit Span and Letter-Number Sequencing
Verbal fluency	Controlled Oral Word Association Test (F-A-S)	
	Animal Naming	
Fine motor	Finger Tapping	
Academic skills mastery	Not addressed	Woodcock-Johnson III Tests of Achievement Subtests: Letter-Word Identification, Reading Fluency, Calculation and Math Fluency
Behavior	Not addressed	Child Behavior Checklist: Parent Form

ACR-SLE = American College of Rheumatology – Systemic Lupus Erythematosus; CARRA = Childhood Arthritis and Rheumatology Research Alliance; IQ = Intelligence Quotient; WASI = Wechsler Abbreviated Scale of Intelligence; WISC = Wechsler Intelligence Scale for Children; CPT = Continuous Performance Test; D-KEFS = Delis-Kaplan Executive Function System; WAIS = Wechsler Adult Intelligence Scale; WRAML = Wide Range Assessment of Memory and Learning.

Table 2.

Definitions of cognitive dysfunction, impairment, decline, or change used in studies of persons with SLE.

ACR 2007 (Mikdashi et al., 2007)	
Cognitive impairment	A score of ≥2.0 standard deviation (SD) below the mean (Z-score of ≤ −2) in the domains of attention, memory, and psychomotor speed
Focal	One or more measures are impaired within one domain
Multifocal	Measures within two or more domains are impaired
Cognitive decline	A score 1.5–1.9 SD below the mean in a domain
Clinically important response	1) Improvement of ≥1.0 SD in a key domain, OR 2) A ≥ 1.0SD change in the Cognitive Symptom Inventory
Muscal et al. (2010)	
Neurocognitive impairment	Two or more tests, spanning two or more cognitive domains, with scores > 1.5 SD below the mean
Brunner et al. (2007)	
Neurocognitive dysfunction	1) At least one averaged domain score ≥ 2.0 SD below the mean, OR 2) At least two averaged domain scores between 1.0 and 2.0 below the mean
Brunner et al. (2013)	
Mild to moderate CD	1) One averaged domain Z-score ≤ −2, OR 2) One or two averaged domain Z-scores ≤ −1
Moderate to severe CD	1) More than one averaged domain Z-score ≤ −2, OR 2) More than two averaged domain Z-scores ≤ −1
Lim et al. (2013)	
Cognitive dysfunction	1) Significant self-reported or observed difficulties in concentration or memory, significantly impairing a patient's ability to perform academically, AND 2) Improvement in CD (i.e., return to previous performance level) following SLE-specific treatment (i.e., immunosuppressive therapies), AND 3) CD was thought not to be due to fatigue or drug use, and was out of proportion to that expected from mood disorders
Mostafa et al. (2010)	
Cognitive dysfunction	Using the Wechsler Intelligence Scale for Children (WISC)-III, 1) a difference between the verbal and performance IQ is >15, OR 2) individual subtests < 7, OR 3) full-scale IQ < 70

SLE = systemic lupus erythematosus; ACR = American College of Rheumatology; SD = standard deviation; CD = cognitive dysfunction; WISC = Wechsler Intelligence Scale for Children; IQ = Intelligence Quotient.

Table 3.

Summary of neuropsychological measures significantly different in persons with pediatric SLE with and without CD.

Study	Comparison	Measures with Lower Performance in CD*	Cognitive Domains
		Pediatric SLE	
Brunner et al. (2007)	CD vs non-CD	Formal Neuropsychological Measures *RCFT – copy (mean Z-score: −1.59 vs 0.63)* *RCFT – immediate recall (mean Z-score: −1.08 vs −0.19)*	Visuoconstructive ability, visual memory
		Ped-ANAM, accuracy *Mathematical processing (g = 1.03)* *Continuous performance test (g = 1.09)*	Arithmetic, attention, processing speed, working memory
Brunner et al. (2013)	Mild CD vs non-CD Moderate-severe CD vs non-CD	No significant difference Ped-ANAM, accuracy *Spatial processing (g = 2.91)* *Continuous performance test (g = 1.66)* *Matching to sample (g = 1.84)* *Code substitution (g = 1.61)* *Code substitution delayed (g = 2.28)* *Logical relations (g = 2.06)*	Spatial analysis, attention, working memory, short-term memory, visuospatial discrimination, language processing
Gitelman et al. (2013)	CD vs non-CD**	Formal Neuropsychological Measures *Wechsler Intelligence Scale for Children (WISC)-IV: Digit Span, Letter-Number Sequencing, Coding, and Symbol Search* *Conners' Continuous Performance Test (CPT)-II* *Delis-Kaplan Executive Function System (D-KEFS): Inhibition vs Color Naming Contrast Score* *Wechsler Abbreviated Scale of Intelligence (WASI): Block Design* *Kaufman Assessment Battery for Children-II: Block Counting and Gestalt Closure*	Working memory *(mean Z-score:-1.02 vs −0.15)* Psychomotor speed *(mean Z-score: −1.07 vs 0.23)* Visuoconstructive ability *(mean Z-score −1.28 vs −0.16)*

g = Hedge's g, a variant of Cohen's d determining effect size for unequal size samples.

*All comparisons between groups showed statistically significant differences in performance (at least $p < .05$).

**Cognitive domains Z-scores were compared and significantly different between groups in this study; neuropsychological measures used for these domains in the study are included for reference.

SLE = systemic lupus erythematosus; CD = Cognitive dysfunction; NPSLE = neuropsychiatric SLE; RCFT = Rey Complex Figure Test; Ped-ANAM = Pediatric Automated Neuropsychological Assessment Metrics; WISC = Wechsler Intelligence Scale for Children; CPT = Continuous Performance Test; D-KEFS = Delis-Kaplan Executive Function System; WASI = Wechsler Abbreviated Scale of Intelligence.

Table 4.

Summary of blood-based biomarkers studied for CD in pediatric SLE.

Biomarker	Study	Pertinent Findings
Autoantibodies		
Anti-Ribosomal P	dos Santos et al. (2010)	No association of presence of antibody with CD
	Brunner et al. (2014)	Borderline difference between levels in CD vs non-CD ($p = .05$) Fair diagnostic potential of level ≥ 1 in predicting CD, AUC = .7** Performance on working memory*, processing speed*, and visuoconstructive ability** testing negatively associated with log-transformed antibody levels on adjusted mixed-effect models
	Mostafa et al. (2010)	No significant (sig) difference in odds of antibody positivity between CD vs non-CD
	Nowling et al. (2021)	Exploratory analysis: worse verbal memory and attention if antibody positive
Anti-NR2	Ruth et al. (2013)	Positive correlation of levels with CPT-II reaction time, $r = .54$* No other significant NPT correlations No sig difference between levels in SLE vs JIA
	Brunner et al. (2014)	Positive correlation of levels with processing speed (domain z-score), $r = .26$* No sig correlation with other cognitive domains No sig difference between levels in CD vs non-CD
	Nowling et al. (2021)	No significant correlation of levels with individual NPTs Higher median levels in SLE compared to JIA*
Anti-phospholipid	Brunner et al. (2014)	No significant correlation of levels with individual NPTs No sig difference between levels in CD vs non-CD
	dos Santo et al. (2010)	No association of presence of antibodies with CD
	Mostafa et al. (2010)	No sig difference between odds of antibody positivity between CD and non-CD
Anti-ganglioside M1	Mostafa et al. (2010)	Odds of antibody positivity significantly elevated in CD compared to CD (OR: 36)**
Proteins associated with neurologic injury or inflammation		
S100B	Brunner et al. (2014)	No sig difference in levels between CD and non-CD No significant correlation with performance in any cognitive domain
	Lapa et al. (2017)	Significant association between levels and CD (OR: 3.7)*
S100A8/A9	Brunner et al. (2014)	No significant correlation with performance in any cognitive domain No sig difference in levels between CD and non-CD
NGAL	Brunner et al. (2014)	Negative correlation of levels with processing speed* No significant correlation with other cognitive domains No sig difference in levels between CD and non-CD
NfL	Not yet evaluated	

*Significant at $p < .05$

**Significant at $p < .01$.

SLE = systemic lupus erythematosus; CD = Cognitive dysfunction; AUC = area under the curve; sig = significant; NR2 = N-methyl-D-aspartate subunit 2; CPT = Continuous Performance Test; NPT = neuropsychological test; JIA = juvenile idiopathic arthritis; OR = odds ratio; NGAL = neutrophil gelatinase-associated lipocalin; NfL = neurofilament light.