International Journal of Current Research and Review
DOI: doi.org/10.31782/IJCRR.2025.172401

Review Article

IJCRR
Section: Healthcare



# Cognitive Dysfunctions in Systemic Inflammatory Diseases: A Systematic Review

**Aleksandra Tlak[1], Katarzyna Bielawska[2], Wiktoria Julia Auguścik[2]**

[1,2]Internal Medicine, Grochowski Hospital, 51/59 Grenadierów Street, 04-073, Warsaw, Poland; [3]Internal Medicine, District Health Center, 44 Batorego Street, 05-400, Otwock, Poland

## ABSTRACT

Cognitive dysfunctions are considered a significant, yet unfortunately often unrecognized, complication of systemic autoimmune diseases. In this systematic review, we have collected and analyzed the available scientific data (using Pubmed and Google Scholar electronic databases) regarding the, epidemiology, pathogenesis, clinical presentation, and management principles of cognitive function disorders in conditions such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), primary Sjögren's syndrome, systemic sclerosis, and ANCA-associated vasculitis. The prevalence of cognitive deficits in autoimmune diseases is high which highlights the scale of clinical challenges. The pathogenesis of these disorders is multifactorial and includes the neuro-inflammatory effects of systemically circulating cytokines, autoimmune neuronal dysfunction induced by autoantibodies, progressive cerebrovascular damage, as well as the indirect impact of chronic pain, depression, fatigue, and medication side effects on cognitive functions. Specific disease entities are characterized by distinct profiles of cognitive dysfunction. Effective therapeutic interventions for the described disorders include the implementation of immunomodulatory therapies, treatment of co-existing depression and pain, and the implementation of neuropsychological rehabilitation programs. An interdisciplinary approach with simultaneous involvement of rheumatologists, neurologists, and neuropsychologists is essential in the treatment process of cognitive function disorders. Future research directions should focus on attempts to identify biomarkers specific for co-existing cognitive dysfunctions, validation of diagnostic tools, and assessment of the impact of modern immunologic therapies and non-pharmacological interventions on cognitive functions, which would allow improving quality of life for patients.

**Key Words:** Autoimmune diseases, Cognitive dysfunction, Neuroinflammation, Neuropsychological assessment, Inflammatory diseases, Rheumatology

## INTRODUCTION

Systemic inflammatory diseases of autoimmune origin are a significant clinical challenge for modern medical diagnostics, extending far beyond issues directly related to damage to internal organs and joints. Autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis, primary Sjögren's syndrome, or ANCA-associated vasculitis significantly affect the functioning of the central nervous system, particularly in the cognitive sphere. Cognitive dysfunctions, defined as objectively measurable impairments in processes such as attention, memory, executive functions, or information processing speed, are a common, yet still rarely recognized complication of these conditions. The spectrum of cognitive function disorders is broad and includes both subtle impairments in concentration or memory and serious deficits that can sometimes prevent adherence to therapeutic recommendations, occupational activity, and even independent functioning, thereby making the patient dependent on caregivers. The chronic, often fluctuating nature of these disorders leads to a significant reduction in quality of life. Although the number of scientific evidences is steadily increasing, cognitive deficits are still rarely subjected to routine assessment in rheumatology clinical practice, resulting in a lack of appropriate therapeutic interventions. In this systematic review, we have synthesized and subsequently analyzed the currently available scientific literature on the epidemiology, risk factors, pathogenesis, diagnostic methods, and clinical consequences of cognitive dysfunctions in selected systemic autoimmune diseases.

## METHODOLOGY

This systematic review was designed according to the recommendations of scientific methodology. In the process of

**Corresponding Author:**
**Aleksandra Tlak,** Internal Medicine, Grochowski Hospital 51/59 Grenadierów Street, 04-073,Warsaw, Poland.
Email: ola.tlak@gmail.com

**ISSN:** 2231-2196 (Print) **ISSN:** 0975-5241 (Online)
**Received:** 01.11.2025 **Revised:** 26.11.2025 **Accepted:** 17.12.2025 **Published:** 29.12.2025

searching the available scientific literature, the following electronic databases were utilized: PubMed and Google Scholar. To gather the most comprehensive material possible, various combinations of phrases and keywords were used during the development of this work. The basic search strategies included the following keywords: "systemic inflammatory diseases" or "autoimmune diseases" or "rheumatic diseases"; "cognitive dysfunction" or "cognitive impairment"; "neuropsychology"; "cognition"; "systemic lupus erythematosus" or "rheumatoid arthritis" or "Sjögren's syndrome"; as well as "inflammation" and "cognition" and "autoimmunity". The inclusion criteria for this work were as follows: 1) original studies (prospective, retrospective, cross-sectional, cohort) and systematic reviews and meta-analyses with documented high methodological quality; 2) publications in English published between 2015 and 2025; 3) studies conducted in an adult patient population diagnosed with a systemic autoimmune disease according to generally accepted classification criteria; 4) research papers in which the objective assessment of patients' cognitive functions constituted a key or significant research objective. Case reports, letters to the editor, low-quality review articles, articles with insufficient data, publications before 2015, experimental studies on animal models, and research papers published in languages other than English were excluded from the analysis. After the initial search for publications meeting the above criteria, selected research papers were qualified for full-text assessment and then included in this systematic review. Works that passed the selection process were thoroughly evaluated in terms of the quality of the applied methodology, sample representativeness, adequacy of neuropsychological assessment tools, and reliability of statistical analysis. The data collected in this way underwent qualitative synthesis, with the extraction of the most crucial information concerning prevalence, postulated pathophysiological mechanisms, characteristic of cognitive profiles, available diagnostic methods, and clinical consequences of cognitive dysfunctions in autoimmune diseases.

## Epidemiology of Cognitive Dysfunctions

It is estimated that the prevalence of cognitive dysfunctions among patients with systemic inflammatory diseases is significantly higher than in the general population.[1] However, precise estimation of the frequency is difficult due to the heterogeneity of generally used definitions, significant differences in neuropsychological test methodologies, and the lack of standardized cut-off points. Despite the above limitations, the collected data clearly indicate the scale of the problem, which affects a significant part of this clinical population. In systemic lupus erythematosus (SLE), cognitive impairments are the best documented, with estimates of their frequency ranging from 12% to as high as 87% of patients.[2] This range is so broad precisely because of methodological differences. In rheumatoid arthritis (RA), the prevalence of cognitive dysfunction is estimated at 30–71%.[3] In primary Sjögren's syndrome, systemic sclerosis, and ANCA-associated vasculitis, the problem of cognitive function disorders has been studied to a slightly lesser extent, but available data indicate their significant frequency.[4]

## Risk Factors for Developing Cognitive Dysfunctions

Risk factors for the development and progression of cognitive dysfunctions in autoimmune diseases are varied and include both disease-specific variables and general factors. The first category includes: long disease duration, high disease activity, elevated markers of systemic inflammation, presence of specific antibodies, history of neuropsychiatric incidents, co-existing depression, anxiety, chronic pain and fatigue, as well as multimorbidity burden, polypharmacy ( including long-term glucocorticoid therapy). The second category includes low level of education, female gender, older age.[1,3,5] Chronic pain, being a frequent accompanying symptom in RA and many other rheumatic diseases, acts as a constant "distracting" stimulus that consumes significant attention and working memory resources, impairing the performance of other cognitive tasks.[3] Depression and anxiety are also phenomena with a high prevalence in the population of patients with autoimmune diseases. They are associated with impairments in concentration, memory, and executive functions, creating a vicious cycle with cognitive dysfunction.[6] Research clearly indicates the additive effect of both the direct consequences of inflammatory processes and co-existing psychosocial and somatic factors in the final clinical picture of cognitive dysfunction. It is currently believed that it is the accumulation of these factors, more than a single cause that determines the risk of development and severity of cognitive deficits.

## Pathophysiological Mechanisms

To understand the pathogenesis of cognitive dysfunctions in systemic inflammatory diseases, it is necessary to first acknowledge their multi-level and multifactorial nature. One single, universal mechanism for all disease entities cannot be distinguished rather, the existence of inter-relationships between numerous processes is postulated, in which the primary role is played by abnormal activation of the immune system and its resulting negative consequences for nervous system functioning. One of the basic mechanisms is the impact of chronic inflammation on brain tissue. In the course of autoimmune disease, there is overproduction of proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6). These cytokines induce changes in the permeability of the blood-brain barrier, thereby disrupting active transport processes across the blood-brain barrier, which directly affects brain tissue. Additionally, proinflammatory cytokines have the

ability to activate microglia, triggering a chronic proinflammatory state in microglia during which further amounts of cytokines, chemokines, and free radicals are released into the environment. Persistent neuroinflammation significantly disrupts synaptic transmission, weakens synaptic plasticity, which in the long term can lead to dysfunction and even loss of brain tissue, particularly in regions critical for cognitive functions such as the hippocampus and prefrontal cortex.[2] In some disease entities, the presence of specific autoantibodies may also be a cause of cognitive function disorders. The best example is systemic lupus erythematosus, where some patients have antibodies with affinity for NMDA receptors (anti-NMDAR). These antibodies bind to NMDA receptors on neurons, leading to their deactivation, resulting in deficits in memory and attention characteristic of SLE.[7] Another important group consists of mechanisms responsible for vascular dysfunction. In diseases such as systemic sclerosis or ANCA-associated vasculitis, characterized by involvement of small and medium-sized blood vessels, the ongoing inflammatory process causes fibrosis in the vessel wall leading to its narrowing, and consequently, impaired blood flow and micro-infarcts. The result of this process is diffuse white matter damage (visible on magnetic resonance imaging as white matter signal abnormalities). The described damage disrupts connections between brain areas critical for cognitive abilities, the clinical consequence of which is slowed thought processes.[4] Finally, considering the pathogenesis of cognitive dysfunctions at the cellular and molecular level, persistent inflammation leads to increased oxidative stress damaging mitochondria, which limits the production of energy necessary for maintaining membrane potentials, signal transmission, and repair processes of nerve cells, thereby contributing to their accelerated aging.

## Cognitive Dysfunctions in Specific Diseases – Profile and Specificity

Although many mechanisms are shared, differences in pathogenetic factors mean that specific disease entities may be characterized by somewhat distinct profiles of cognitive deficits. In systemic lupus erythematosus, the most diverse and often most severe picture is observed. Among the observed deficits, impairments in information processing speed, working memory, attention and complex executive function can be listed, which have great significance for patient independence. The severity of deficits is often correlated with the activity of the ongoing disease process, measured by indices such as SLEDAI, levels of specific autoantibodies, and markers of oxidative stress.[2] Neuroimaging studies reveal structural and functional changes, including reduced gray matter volume in the prefrontal cortex and hippocampus, white matter signal abnormalities (hyperintensity), and disturbances in functional connectivity between key brain networks responsible for attention and executive control. Correlations with disease activity and autoantibody levels have also been demonstrated for the changes observed in imaging studies.[2, 5] A slightly different cognitive profile can be observed in Rheumatoid Arthritis. Impairments in spatial orientation and visuospatial memory come to the fore, while attention deficits and verbal fluency impairments are also common.[3] In RA, the mechanisms responsible for the development of cognitive dysfunction are most strongly linked to systemic inflammation and its somatic consequences.[3] In Sjögren's syndrome, neuropsychological studies revealed executive dysfunction and attention deficits, as well as a subjective sensation of "brain fog".[4, 8] The mentioned deficits may result from both the direct action of autoantibodies on CNS structures and vasculitis leading indirectly to white matter changes. In systemic sclerosis and ANCA-vasculitis, we primarily observe problems with executive functions, which is consistent with the pathogenesis of cognitive disorders in these disease entities related to small vessel damage and subsequent changes in cerebral white matter.[4] A summary of the discussed cognitive dysfunctions in the above disease entities has been collectively presented in a table (Table 1).

## Neuropsychological Assessment – Methods and Challenges

Comprehensive diagnosis of cognitive dysfunctions in systemic inflammatory diseases is the basis for appropriate therapeutic management. Considering the lack of a single, specific biomarker for the already initiated process of cognitive impairment in autoimmune diseases, the "gold standard" remains a full, standardized neuropsychological examination conducted by a qualified specialist. In scientific research and clinical practice, various neuropsychological tests are used. Among the most widely used screening tests, allowing for rapid assessment of cognitive functions is the Montreal Cognitive Assessment (MoCA). For more advanced assessment, it may be necessary to use more detailed tests, such as the Trail Making Test (TMT), Victoria Stroop Test (VST), Wechsler Adult Intelligence Scale (WAIS), and Benton Visual Retention Test (BVRT).[7] The lack of standardized, widely accepted and validated tests specifically designed for patients with systemic rheumatic diseases constitutes the main challenge in the field of diagnosing cognitive dysfunctions. Different centers use different test sets, which makes it difficult to compare results between studies and draw reliable conclusions. Another significant difficulty is the influence of numerous confounding factors on test results. Symptoms of depression or anxiety, pain, fatigue on the day of testing, as well as medication side effects can artificially lower test scores, not reflecting an adequate cognitive deficit. Therefore, it is crucial that the examination is conducted under optimized conditions, and its results are interpreted by an experienced specialist: a neuropsychologist or neurologist, taking into account the broad clinical context: the patient's sub-

jective complaints, disease activity, ongoing treatment, and mental state. Periodically, the inclusion of routine cognitive assessment in clinical practice should be considered, especially in patients with long-term, active disease, particularly when they themselves or their close ones report difficulties in daily mental functioning.[3, 5]

### Clinical Significance and Directions of Management

Patients with systemic inflammatory diseases experience negative consequences of cognitive dysfunctions in many aspects of their lives. The effects of the disorders are far-reaching and can lead to difficulties in managing complex therapy, reduced work capacity and safety, increased dependence on family and caregivers, and, as a result, a lowered quality of life and increased risk of developing depression. Therefore, diagnosis and treatment of cognitive dysfunctions is a medical obligation of the therapeutic team. Therapy for the disorders is comprehensive and requires collaboration among a rheumatologist, neurologist, neuropsychologist, psychiatrist, and sometimes an occupational therapist. Its pillars are optimization of treatment for the underlying disease, application of symptomatic and supportive treatment, and implementation of non-pharmacological interventions. The most effective strategy for prevention and treatment of inflammatory-based cognitive dysfunctions is achieving and maintaining deep remission or low activity of the underlying disease. Early and aggressive immunosuppressive treatment aimed at inducing remission in autoimmune diseases has the potential to halt the progression of disorders and, in some cases, even lead to partial improvement of cognitive functions, underscoring the importance of effective control of inflammation.[5] It has been shown that modern disease-modifying drugs, including biological treatment, by effectively suppressing inflammation, can not only protect joints and organs but also potentially stabilize or even improve cognitive functions due to reduced neuroinflammation. Treatment of co-morbid conditions is also important, including effective therapy for depression and anxiety, optimal pain control, and treatment of sleep disorders. Neuropsychological rehabilitation programs, which include individualized cognitive training exercises targeted at specific deficits, can also be beneficial for patients with diagnosed cognitive dysfunctions. Education of the patient and family about cognitive problems is also important, as it can help in the adaptation process and stress reduction. Patients should be encouraged to engage in regular physical activity adapted to their capabilities, which has proven anti-inflammatory and neuroprotective effects. In at-risk patients, periodic screening cognitive testing should be considered, and in the case of abnormal results, in-depth neuropsychological assessment.

## DISCUSSION

The collected evidence supports the notion that cognitive impairments are a common and clinically relevant feature of systemic immunological disorders. Variability in their presentation among different disease entities makes accurate diagnosis challenging and requires assessment by experienced specialists, as well as the application of carefully selected neuropsychological testing methods. The treatment of cognitive disorders should encompass both pharmacological and non-pharmacological interventions and should be conducted with the involvement of all members of the therapeutic team. Increasing awareness among patients and healthcare professionals regarding the potential occurrence of cognitive dysfunctions in individuals with autoimmune diseases may translate into a significant improvement in patients' quality of life and enhanced treatment compliance.

### Future Research Perspectives

Despite significant progress made in recent years in understanding cognitive dysfunctions in autoimmune diseases, many key research questions remain unanswered. Among future research directions, efforts should be made to identify sensitive and specific biomarkers (such as specific autoantibodies in cerebrospinal fluid, markers of neuro-inflammation, or advanced parameters in neuroimaging) that would allow for early detection of cognitive dysfunctions and monitoring response to applied therapeutic interventions.[2,5] Important task is also the development and validation of standardized neuropsychological tests with specifications for the rheumatological population, which would account for the presence of potential confounding factors affecting test results, such as pain or depressive symptoms. It is necessary to design long-term, prospective studies that would allow for better insight into the development process of cognitive dysfunctions, factors influencing their progression or regression, and the relationship between inflammation control and the trajectory of cognitive functions. It would also be reasonable to conduct studies focused on assessing the impact of modern immunomodulatory therapies on cognitive functions and changes in neuroimaging, which would directly prove the effectiveness of treatment in this area. Non-pharmacological interventions, such as individualized cognitive training programs, rationalized dietary support, and mindfulness-based interventions require assessment of their effectiveness in future studies. Finally, to enable the inclusion of preventive strategies and a more personalized therapeutic approach, research work is necessary to enable a deeper understanding of gene-environment interactions and the role of cognitive reserve in modifying the risk and course of cognitive deficits in this patient group.

## CONCLUSIONS

Patients with systemic inflammatory diseases are at significant risk for developing cognitive dysfunctions, which constitute an important, though often overlooked, complication of these conditions. The most commonly observed cognitive deficits in autoimmune diseases are impairments in information processing speed, attention, memory, and executive functions. For each disease entity, a characteristic cognitive impairment profile can be distinguished, resulting from the pathogenetic mechanisms dominant in its presentation. The etiology of cognitive dysfunctions is complex and multifactorial, involving the direct action of proinflammatory cytokines and autoantibodies on the central nervous system, as well as secondary vascular damage and the indirect impact of chronic pain, depression, anxiety, and side effects of pharmacotherapy. A necessary condition for the correct diagnosis of cognitive dysfunctions is their assessment using standardized neuropsychological tests, interpreted within a broad clinical context. The foundation of therapeutic management is effective control of inflammation through optimal immunomodulatory therapy, supplemented by comprehensive symptomatic treatment and implementation of non-pharmacological interventions. An interdisciplinary approach, combining the competencies of a rheumatologist, neurologist, neuropsychologist, and psychiatrist, is crucial for improving cognitive functioning and the overall quality of life of this vulnerable patient population. Among further research directions, priority should be given to identify biomarkers, standardize diagnostic methods, and assess the effectiveness of targeted therapeutic interventions.

## ACKNOWLEDGEMENTS

Authors acknowledge the immense help received from the scholars whose articles are cited and included in references of this manuscript. The authors are also grateful to authors / editors / publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed.

### Conflict of Interest:

The authors report no conflicts of interest in relation to this work.

### Source of Funding:

The authors declare that no financial support was received for the conduct of this study or preparation of this manuscript.

### Authors' Contribution:

**Aleksandra Tlak:** conceptualization, methodology, formal analysis, data curation, review and editing.

**Katarzyna Bielawska:** conceptualization, methodology, formal analysis, data curation, review and editing.

**Wiktoria Julia Auguścik:** conceptualization, methodology, formal analysis, data curation, review and editing.

## REFERENCES

1. Gwinnutt JM, Toyoda T, Barraclough M, Verstappen SMM, Hornberger M, MacGregor A. Cognitive impairment in the immune-mediated inflammatory diseases compared with age-matched controls: Systematic review and meta-regression. Semin Arthritis Rheum. 2023 Feb;58:152131 https://www.sciencedirect.com/science/article/abs/pii/S0049017222001822
2. de Sousa DC, Sobreira EST, Feitosa WLQ, Aires TMPM, Araújo LPP, Silva ALC et al. Cognitive dysfunction in systemic lupus erythematosus is associated with disease activity and oxidative stress: a comparative study with rheumatoid arthritis for identifying biomarkers. BMC Neurosci. 2023 Dec 13;24(1):66 https://link.springer.com/article/10.1186/s12868-023-00839-8
3. Pigłowska-Juhnke A, Stanisławska-Kubiak M, Kalmus P, Waszczak-Jeka M, Samborski W, Mojs E. Cognitive Impairment in Rheumatoid Arthritis: The Role of Pain, Inflammation, and Multimorbidity in Neuropsychological Outcomes. Biomedicines. 2025 Jul 11;13(7):1699 https://www.mdpi.com/2227-9059/13/7/1699
4. Camard M, Urbain F, Noel N. Cognitive impairment in systemic autoimmune and inflammatory diseases: A narrative review focused on ANCA-associated vasculitis, sarcoidosis, Sjögren's syndrome, systemic sclerosis, and Behçet's disease. Autoimmun Rev. 2025 Nov 28;24(11):103899 https://www.sciencedirect.com/science/article/abs/pii/S1568997225001600?via%3Dihub
5. Myasoedova E, Sattui SE, Lee J, O'Brien JT, Makris UE. Cognitive impairment in individuals with rheumatic diseases: the role of systemic inflammation, immunomodulatory medications, and comorbidities. Lancet Rheumatol. 2024 Dec;6(12):e871-e880 https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(24)00190-5/abstract
6. Callhoff J, Berger K, Albrecht K, Strangfeld A; NAKO Investigators. Depression, anxiety and cognitive function in persons with inflammatory rheumatic diseases: cross-sectional results from the German National Cohort (NAKO). RMD Open. 2024 Oct 23;10(4):e004808 https://rmdopen.bmj.com/content/10/4/e004808
7. Oláh C, Schwartz N, Denton C, Kardos Z, Putterman C, Szekanecz Z. Cognitive dysfunction in autoimmune rheumatic diseases. Arthritis Res Ther. 2020 Apr 15;22(1):78 https://link.springer.com/article/10.1186/s13075-020-02180-5
8. Manzo C, Martinez-Suarez E, Kechida M, Isetta M, Serra-Mestres J. Cognitive Function in Primary Sjögren's Syndrome: A Systematic Review. Brain Sci. 2019 Apr 15;9(4):85 https://www.mdpi.com/2076-3425/9/4/85

**Table 1: A Summary of Cognitive Dysfunction in Selected Autoimmune Diseases**

| Disease | The spectrum of cognitive impairments | Mechanisms | References |
|---|---|---|---|
| Systemic Lupus Erythematosus | impairments in information processing speed, working memory, attention and complex executive functions | inflammatory cytokines, autoantibodies, oxidative stress | de Sousa et al., 2023 |
| Rheumatoid Arthritis | impairments in visuospatial memory, spatial orientation, attention, verbal fluency | inflammatory cytokines | Pigłowska-Juhnke et al., 2025 |
| Sjögren's syndrome | executive dysfunction and attention deficits, „brain fog" | microangiopathy, autoantibodies | Camard, 2025 Manzo, 2019 |
| Systemic sclerosis | executive dysfunction | microangiopathy | Camard, 2025 |
| ANCA-vasculitis | executive dysfunction | microangiopathy | Camard, 2025 |