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REVIEW

Relationship Between Cognitive Impairment and Quality of Life in Systemic Lupus Erythematosus: A Multimodal Neuroimaging Perspective

Qiuping Liu, Min Liu, Qinghua Zou

Department of Rheumatology and Immunology, First Affiliated Hospital of Army Medical University, Chongqing, 400038, People's Republic of China

Correspondence: Qinghua Zou, Email zouqinghua318@tmmu.edu.cn

Abstract: Systemic lupus erythematosus (SLE) is a chronic inflammatory multi-system disorder that affects both central and peripheral nervous systems, leading to diverse neuropsychiatric manifestations. Cognitive impairment represents one of the most prevalent and debilitating neuropsychiatric symptoms in SLE, occurring in up to 80% of patients, with significant long-term clinical consequences. Despite its high prevalence, the underlying pathogenesis remains unclear, and its insidious onset and variable presentation often lead to underdiagnosis in clinical practice. Multimodal MRI techniques offer valuable insights into structural, functional, and metabolic abnormalities across both localized brain regions and global neural networks, facilitating comprehensive assessment of SLE-related cognitive dysfunction. Recent advances in SLE management have emphasized patient quality of life (QoL), and multimodal neuroimaging approaches may elucidate the relationship between cognitive impairment and QoL deterioration. Such strategies could improve early detection, therapeutic intervention, and preventive measures, ultimately enhancing socioeconomic outcomes and QoL for SLE patients with cognitive impairment.

Keywords: systemic lupus erythematosus, cognitive impairment, multimodal magnetic resonance imaging, quality of life

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that frequently involves neuropsychiatric manifestations, including cognitive impairment - one of the most common neuropsychiatric syndromes affecting attention, memory, executive function and other cognitive domains.[1,2] These deficits significantly impair patients' QoL and social functioning.[3] The pathogenesis of SLE-related cognitive dysfunction remains unclear but may involve multiple mechanisms: neuroinflammation, blood-brain barrier disruption allowing autoantibody penetration, ischemia, and microvascular disease.[4–6] These processes can lead to structural and functional CNS abnormalities.[7,8] Notably, cognitive impairment often occurs even without overt neuropsychiatric symptoms.[9] However, emerging evidence suggests early intervention may prevent or reverse cognitive decline.[10,11] Therefore, Effective diagnostic tools and therapeutic strategies can mitigate neuroinflammation-induced structural/functional damage, thereby enhancing cognitive function and QoL in patients.

Currently, there is a lack of sensitive and specific diagnostic tests for SLE-associated cognitive impairment, and neuroimaging techniques cannot fully elucidate its underlying mechanisms. The relationships between cognitive impairment manifestations, neuroimaging findings, and etiopathological processes remain unclear. Additionally, few studies have directly examined the impact of cognitive impairment on SLE patients' QoL, with most focusing on isolated mechanisms. Multimodal MRI provides a comprehensive assessment by detecting brain metabolite abnormalities, microstructural and volumetric changes in gray/white matter (GM/WM), and functional alterations. This approach helps clarify the interplay between brain structure, function, metabolism, and cognitive deficits in SLE.[12,13] This paper reviews the relationship between brain structure, function, and metabolism with cognitive impairment and QoL in SLE patients from a multimodal MRI perspective. It further summarizes the associations between various neuroimaging

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features and cognitive function as well as QoL in SLE patients. The aim is to provide recommendations for successfully assessing cognitive impairment and its progression in SLE using advanced quantitative neuroimaging techniques, as well as suggestions for improving QoL. Furthermore, non-pharmacological interventions targeting these mechanisms are discussed, underscoring the urgent need for biomarkers to enable early detection, treatment, and prevention-ultimately improving patient QoL and reducing socioeconomic burdens.

Cognitive Domains That May Be Involved in SLE Cognitive Impairment

Retrospective studies involving over 800 SLE patients demonstrated that severe cognitive impairment doubled unemployment rates compared to cognitively intact patients, with cognitive symptoms frequently reported as among the most distressing QoL concerns.[14,15] Mendelsohn et al's systematic review further confirmed the association between SLE-related cognitive impairment and reduced QoL/social participation.[16] Understanding affected cognitive domains is therefore critical for prevention and treatment. Meta-analyses reveal attention and delayed verbal memory as the most severely impaired functions in SLE patients.[17] Even asymptomatic patients frequently show broad deficits across multiple domains including verbal fluency, attention, visuospatial ability, memory, and executive functioning.[18] Common impairments include: delayed recall, abstract reasoning, verbal fluency, memory, attention, executive function.[19–21] Notably, higher SLE Disease Activity Index (SLEDAI) scores correlate with greater memory impairment, suggesting disease activity influences cognitive severity.[22] Cross-sectional data show Montreal Cognitive Assessment (MoCA) scores associate with visuospatial/abstract deficits, while Mini-Mental State Examination (MMSE) reveals impaired verbal/spatial abilities versus controls.[23] These findings underscore that disease stabilization is essential for preserving cognitive function and improving QoL.

Current Status of Conventional MRI in SLE Cognitive Impairment

Conventional MRI in SLE-related cognitive impairment primarily reveals T2 WM hyperintensities, microhemorrhages, and cerebral atrophy.[24] Studies demonstrate reduced hippocampal volumes in cognitively impaired SLE patients compared to those without cognitive deficits.[15] While conventional MRI effectively detects CNS lesions, particularly acute focal neuropsychiatric manifestations, its utility is limited for diffuse presentations. It cannot accurately quantify white matter damage or characterize underlying pathology, restricting its ability to correlate imaging findings with neuropsychiatric symptoms.[25] Ultimately, conventional MRI fails to establish meaningful connections between morphological changes, clinical manifestations, disease progression, or the pathological mechanisms of SLE-associated cognitive impairment.

Multimodal MRI in SLE Cognitive Impairment

Conventional MRI often fails to detect key pathological mechanisms in SLE-related cognitive impairment, including perfusion abnormalities, neuronal dysfunction, axonal damage, and microstructural alterations caused by vasculitis, immune complex deposition, microglial activation, cytokine-driven inflammation, or thrombosis.[26] Multimodal neuroimaging overcomes these limitations by integrating complementary data: Resting-state functional magnetic resonance (RS-fMR) captures neural activity, while diffusion tensor imaging (DTI) quantifies microstructural damage. No single modality fully elucidates structural, functional, and metabolic changes. However, combining these techniques enables a holistic analysis of brain organization, cognition, and behavior, revealing novel insights through image alignment and data fusion. Advancements in neuroimaging have positioned multimodal approaches as a transformative tool for characterizing brain pathology. This integration improves data consistency, predictive accuracy, and the identification of SLE-associated cognitive and emotional biomarkers. Such comprehensive profiling supports early diagnosis, personalized interventions, and longitudinal monitoring, ultimately enhancing patient outcomes and QoL.

Exploring the Relationship Between Cognitive Impairment and QoL in SLE Based on Structural Brain Changes

Structural alterations are partially causally linked to functional changes in SLE.[27] Structural MRI reveals that whole-brain atrophy, along with reduced corpus callosum and hippocampal volumes, correlates with cognitive impairment,

suggesting progressive cortical thinning across SLE stages.[28] Investigating WM abnormalities may improve understanding of early neuronal pathogenesis in SLE-related cognitive dysfunction. Neuroimaging studies indicate disrupted WM connectivity in SLE, implicating WM damage in disease progression and cognitive deficits.[29] Thus, examining WM abnormalities could elucidate mechanisms of SLE-induced cognitive impairment. DTI noninvasively quantifies cerebral WM microstructure using metrics like mean diffusivity (MD) and fractional anisotropy (FA). This technique effectively identifies SLE-associated structural changes relevant to cognitive assessment. DTI detects microstructural tissue alterations linked to neuropsychiatric symptoms, underscoring its utility in neuropsychiatric lupus imaging.[30]

DTI has demonstrated microstructural abnormalities in neuropsychiatric lupus, particularly through altered FA, MD, and radial diffusivity (RD) values reflecting neuroinflammation.[31] DTI studies consistently demonstrate widespread white matter microstructural alterations in SLE patients, particularly involving the corpus callosum, anterior internal capsule, uncinate fasciculus, and left cingulate gyrus, with these changes emerging early in disease course and showing significant associations with cognitive dysfunction.[32–34] Structural neuroimaging reveals both gray matter volume reduction and white matter integrity loss in cognitively impaired SLE patients, with these changes directly correlating with poorer cognitive performance and reduced QoL.[35,36] Nystedt et al found that decreased FA in the corpus callosum correlated with disease progression, while psychomotor speed showed weak association with right hippocampal FA, suggesting neuronal damage as a potential mechanism for cognitive impairment.[37] Correa et al reported significantly reduced FA alongside increased RD and MD values in SLE patients with cognitive impairment compared to controls, particularly noting external capsule FA reductions associated with white matter abnormalities.[38] The diffuse white matter changes extend beyond memory-related regions to broader cognitive networks, with impaired tracts connecting key structures like the hippocampus, corpus callosum, and cingulate gyrus that are critical for memory, language, attention, and emotional processing, potentially explaining SLE-related cognitive deficits. For instance, visuospatial processing impairments stemming from these abnormalities can significantly impact patients' independence in daily activities and transportation use. Investigating white matter alterations in SLE patients with cognitive impairment is therefore crucial for both understanding disease pathophysiology and developing interventions to improve QoL.

Exploring the Relationship Between Cognitive Impairment and QoL in SLE Based on Functional Brain Changes

RS-fMRI is a blood oxygen level-dependent (BOLD) technique that analyzes regional brain activity through deoxyhemoglobin fluctuations, reflecting spontaneous neuronal activity during rest.[39] This method detects abnormal functional connectivity prior to structural changes or clinical symptom onset.[40] Resting-state network alterations serve as reliable indicators of cognitive and brain function, offering valuable insights into neural activity changes associated with brain disorders.[41,42]

Functional Changes in Localized Brain Regions

Local brain activity reflects the intrinsic properties of the brain tissue activity and is associated with cognitive processes.[43] It is well known that there is a relationship between the frontal lobes and cognitive function. The prefrontal region is the center of frontal control of cognitive functions and mediates is a variety of cognitive functions, including motivation, task setting, monitoring, and behavioral/emotional regulation.[44] Neuroimaging studies, including rs-fMRI, have identified consistent functional abnormalities in the frontal lobes of SLE patients, such as decreased functional connectivity between bilateral frontal lobes and subcortical structures,[45] with these impairments significantly correlating with memory deficits,[46] and reduced QoL.[28] Moreover, inflammatory activity in SLE may exacerbate frontal lobe abnormalities, leading to cognitive symptoms and further diminishing QoL.[47] Therefore, the observation of damage to the frontal regions in SLE cognitive impairment may affect social interactions in patients, resulting from an inability to coordinate their communication with others and leading to reduced social participation and well-being, and ultimately resulting in a lower QoL.

The amplitude of low-frequency fluctuation (ALFF) measures spontaneous neuronal activity at rest. Dynamic ALFF (dALFF) quantifies temporal variability in local brain activity across voxels by analyzing ALFF changes over time,[48] while static ALFF (sALFF) represents its time-averaged counterpart. In SLE with cognitive impairment, increased

sALFF was observed in the right parahippocampal gyrus (compared to SLE patients without impairment) and the left caudate nucleus (compared to healthy controls), indicating disrupted functional connectivity strength and stability.[49] Conversely, dALFF was elevated in the right parahippocampal gyrus in SLE cognitive impairment versus controls, suggesting altered dynamic stability of local activity.[49] These findings imply that abnormal sALFF and dALFF reflect distinct neuropathological pathways affecting cognitive function in SLE. The caudate nucleus plays a key role in cognitive control by regulating motor patterns and target selection.[50] The parahippocampal gyrus serves as the primary cortical input to the hippocampus and is crucial for memory encoding, retrieval, and visuospatial processing.[51] Increased activity in these regions may contribute to cognitive dysfunction in SLE.

Connectivity and Functional Changes in Brain Networks

Coordinated interactions between brain regions are crucial for normal cognition and behavior.[52] Disruptions in these networks due to neuropsychiatric disorders can lead to cognitive deficits and neurological sequelae.[53] Studying neuronal activity connections may reveal underlying pathophysiological mechanisms. Functional connectivity density (FCD) reflects brain network integration. Zhang et al found reduced FCD-ALFF coupling in the left superior parietal gyrus, postcentral cortex, and bilateral precuneus in SLE patients with cognitive impairment, demonstrating how these combined metrics can synergistically assess brain network disruptions in SLE-related cognitive dysfunction.[54]

The default mode network (DMN) is a set of functionally interconnected brain regions exhibiting high metabolic activity during rest. It serves as the primary hub for resting-state functional connectivity and supports higher cognitive functions including emotional processing, episodic memory retrieval, and self-referential thinking.[55] Key DMN regions comprise the medial prefrontal cortex, posterior cingulate cortex/precuneus, medial temporal lobe, and the hippocampus. The DMN is implicated in the neuropathology of various neuropsychiatric disorders, particularly in SLE-related brain dysfunctions. Studies reveal that SLE patients exhibit DMN impairments across functional, structural, and perfusion domains.[56–58] Given the DMN's extensive structural and functional connectivity throughout the brain, its structural damage has been proposed as a underlying cause of cognitive deficits in SLE.[59–61] Therefore, cognitive impairments likely stem from disrupted connectivity across distributed brain networks rather than isolated regional abnormalities in SLE. These functional disturbances correlate with poorer cognitive performance and reduced QoL by compromising information processing efficiency.

Studies demonstrate that SLE patients exhibit cognitive dysfunction, as evidenced by lower MoCA scores compared to controls.[62] Neuroimaging findings reveal reduced activation in memory-related regions (bilateral caudate nucleus/insula and hippocampus/parahippocampal gyrus) during memory tasks,[62] along with decreased FCD and ALFF values in the posterior cingulate gyrus, precuneus, superior parietal gyrus, and hippocampus-parahippocampal regions.[54] These functional alterations correlate with cognitive test scores, suggesting hippocampal-parahippocampal dysfunction plays a key role in SLE-related cognitive impairment.[63] The observed changes in DMN connectivity further characterize the neural basis of cognitive deficits in SLE.

Exploring the Relationship Between Cognitive Impairment and QoL in SLE Based on Brain Metabolic Changes

Metabolic alterations can precede structural brain lesions. Diffusion-weighted magnetic resonance spectroscopy (DW-MRS) measures metabolite concentrations in glial cells and neuronal axons, revealing specific biochemical properties of brain tissue and detecting early neuronal dysfunction. Therefore, DW-MRS has been widely used in studies related to SLE.[64,65] Studies indicate that abnormal metabolite ratios detected by MRS, particularly choline/creatine (Cho/Cr), may serve as early biomarkers of cognitive impairment in SLE.[64–66] Choline is essential for myelin formation and serves as a biomarker for myelin turnover, with its levels correlating with disease progression and cognitive performance.[67] Progressive myelin damage occurs during SLE progression, and the correlation between Cho/Cr ratios and cognitive scores suggests this may represent the initial neurological damage leading to cognitive dysfunction.[68,69] These observations support the hypothesis that myelin damage may underlie the earliest cognitive impairment in SLE. Therefore, researchers have suggested that myelin damage may underlie the earliest appearance of cognitive impairment in SLE.

Acetylaspartate (NAA), a key neuronal viability marker detectable by MRS, shows reduced levels in SLE patients with CNS involvement.[70,71] These metabolic alterations provide valuable insights into early neural damage and cognitive impairment pathophysiology in SLE. However, the direct correlation between such metabolic changes and QoL remains unclear. While DW-MRS and metabolite analyses elucidate mechanistic aspects of SLE-related cognitive dysfunction, their predictive value for QoL assessment appears limited. This highlights the need for future multimodal studies integrating imaging with clinical variables to better understand how metabolic and microstructural changes collectively impact QoL in SLE patients.

Other Neuroimaging Changes

Dynamic contrast-enhanced MRI (DCE-MRI) quantifies contrast agent extravasation into brain parenchyma, measuring blood-brain barrier (BBB) leakage rates at a voxel-wise level. Research demonstrates that hippocampal BBB disruption, as detected by DCE-MRI, is significantly associated with cognitive impairment in SLE patients, particularly affecting working memory, sustained attention, and spatial functioning.[72] Hanly et al further linked these cognitive deficits to BBB leakage in SLE, suggesting that permeability allows inflammatory mediators or autoantibodies to infiltrate the CNS, potentially inducing neuronal injury.[73] Such BBB dysfunction drives neuroinflammation and neuronal damage, exacerbating cognitive decline and reducing QoL.[74]

Magnetization transfer imaging (MTI) exploits the interaction between free and bound water protons, leveraging differences in proton mobility across macromolecules to generate contrast. This technique enables quantitative assessment of brain damage in various pathologies. Early studies suggest MTI is sensitive to mild brain injury and may serve as a prognostic marker for cognitive dysfunction.[75] In SLE, MTI detects reduced magnetization transfer ratios in patients with cognitive impairment, reflecting demyelination and axonal damage that correlate with cognitive deficits and diminished QoL.[76] Additionally, MTI shows promise in monitoring disease activity and therapeutic responses in SLE-related neuropsychiatric disorders.[77]

Arterial spin labeling (ASL) is a non-contrast perfusion imaging technique that quantifies cerebral blood flow (CBF) using magnetically labeled arterial water protons. This method enables assessment of cerebral perfusion abnormalities in various neurological and psychiatric conditions. Existing evidence suggests CBF may serve as a biomarker for early cognitive impairment.[78] In SLE, ASL could help identify cerebral perfusion abnormalities preceding cognitive dysfunction, potentially revealing pathogenic mechanisms and enabling early diagnostic intervention.

The pathophysiology of cognitive impairment in SLE is multifactorial, involving immune dysregulation, vascular pathology, neurotransmitter dysfunction, and other mechanisms. Given this complexity, single neuroimaging modalities often fail to fully capture the underlying pathological changes. Multimodal neuroimaging combining structural MRI, functional MRI, and diffusion tensor imaging reveals structural abnormalities, functional connectivity alterations, neural activity changes, and metabolic disturbances in systemic lupus erythematosus patients. This approach enhances diagnostic accuracy and may detect subclinical abnormalities before overt cognitive symptoms emerge, facilitating early intervention to mitigate disease impact. The literature reports that multimodal MRI, integrating structural, functional, and perfusion parameters, combined with machine learning, can effectively predict cognitive function.[79] The study emphasizes that the combination of machine learning and multimodal MRI provides new perspectives for early identification and mechanistic research of CD in SLE patients. Additionally, multimodal neuroimaging aids in elucidating the pathophysiological mechanisms of SLE-related cognitive impairment, guiding personalized treatment strategies, rehabilitation programs, and psychosocial support to improve patient outcomes. Longitudinal imaging before and after treatment allows clinicians to monitor structural, functional, and metabolic recovery, optimizing therapeutic adjustments for faster cognitive restoration.

Despite its advantages, multimodal neuroimaging faces several challenges. In DTI, eddy currents induced by rapid gradient switching can distort white matter tractography, while magnetic field inhomogeneities further compromise measurement reliability. The lack of standardized imaging protocols across institutions limits comparability of data, and semi-quantitative metrics often fail to reflect subtle microstructural changes with sufficient reproducibility. Post-processing algorithms, reliant on oversimplified models, may also introduce biases, affecting data validity.

Potential for Non-Pharmacological Interventions in Improving the QoL in SLE Patients with Cognitive Impairment

Enhanced QoL is both a key outcome of effective disease management and a critical measure in cognitive function research.[80] With QoL now recognized as a primary endpoint in SLE management, achieving timely, effective, and safe QoL improvement has become essential.[81] Unlike the progressive cognitive decline seen in neurodegenerative diseases, SLE-related cognitive impairment may fluctuate, with potential for improvement or stabilization.[10,82,83] This suggests the condition may be reversible or controllable through proper disease activity management and prevention of cumulative damage. Ceccarelli et al's 10-year longitudinal study found 50% of SLE patients showed cognitive and QoL improvements, with only 10% experiencing deterioration,[10] demonstrating that appropriate disease management can mitigate SLE-related cognitive deficits. These findings underscore the importance of preventing disease flares and chronic impairment development. Additional studies indicate memory loss may also be stabilized or reversed, highlighting the need for effective prevention and intervention strategies.[84]

First, strengthening primary care teams is essential for consistent and effective patient management through interventions like frequent follow-ups, personalized services, and long-term prescriptions. Memory and attention impairments can lead to forgetfulness and reduced learning capacity, negatively impacting self-confidence, self-care, and treatment adherence.[85,86] Thus, effective disease management during follow-up is critical. Second, EULAR guidelines highlight physical activity, exercise, and training as key non-pharmacological interventions for SLE, indirectly benefiting cognition by reducing fatigue and improving overall health.[87] Community-based recreational and exercise programs can enhance mood, mobility, social engagement, and support. Regular exercise improves cognitive function by enhancing vascular physiology and neurovascular coupling.[88] Conversely, inadequate exercise and social support may worsen physical and psychological stress, reducing QoL.[89] Additionally, cognitive training enhances executive function, memory, problem-solving, and daily living skills, improving QoL.[90,91] Lifestyle management through cognitive training is a cost-effective approach to mitigating cognitive impairment's impact on well-being.[92]

Sleep deprivation is well-established to impair QoL and cognitive function, while adequate sleep supports memory consolidation.[93] Napping demonstrates significant benefits for cognitive perception, learning abilities, motor skills, and procedural memory,[94] with specific improvements in language processing, visuospatial abilities, and decision-making.[95] These findings highlight the importance of sleep management in maintaining patient QoL during follow-up care. Growing evidence also supports dietary interventions for cognitive improvement in neurological disorders like multiple sclerosis and Alzheimer's disease,[96] emphasizing the need to incorporate cognitive rehabilitation strategies into the daily routines of SLE patients with cognitive impairment.

In summary, the management of chronic diseases like SLE with cognitive impairment requires balancing effective treatment with minimizing drug toxicity, while exploring safer therapeutic approaches. Acupuncture has emerged as a valuable complementary therapy due to its safety, efficacy, and lack of adverse effects.[97] Evidence suggests acupuncture may improve cognitive symptoms by enhancing cerebral blood flow, preserving blood-brain barrier integrity, promoting glucose metabolism, and protecting white matter structure.[98] However, neuroimaging research on SLE-related cognitive impairment remains preliminary, and acupuncture's role specifically in SLE cognitive dysfunction is underexplored. This gap highlights the urgent need for further investigation to develop effective interventions. Currently, evidence supporting non-pharmacological approaches is limited. More rigorous basic and clinical studies are warranted to validate their therapeutic potential.

Conclusion

Multimodal MRI approaches, combining structural, functional, and perfusion metrics, have shown promise in predicting cognitive function and QoL in SLE patients. These findings underscore the value of multimodal neuroimaging in elucidating the complex interplay between brain abnormalities, cognitive dysfunction, and QoL in SLE. The mechanisms of cognitive impairment in SLE are complex and likely multifactorial, requiring further large-scale studies to elucidate them. Such research could facilitate timely, personalized treatment and significantly improve patients' QoL. This review underscores the need for future clinical and research efforts to refine diagnostic and follow-up strategies for SLE-related

cognitive impairment, enabling early detection and tailored interventions to optimize neurodevelopment, mental status, and long-term prognosis.

Data Sharing Statement

The data on which the review is based were accessed from a repository and are available for downloading through the following link: PubMed.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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