Cognitive Dysfunction in Systemic Lupus Erythematosus: Immunopathology, Clinical Manifestations, Neuroimaging and Management

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ABSTRACT

Cognitive dysfunction (CD) is a common yet often clinically subtle manifestation that considerably impacts the health-related quality of life in patients with systemic lupus erythaematosus (SLE). Given the inconsistencies in CD assessment and challenges in its attribution to SLE, the reported prevalence of CD differs widely, ranging from 3 to 88%. The clinical presentation of CD in SLE is non-specific and may manifest concurrently with overt neuropsychiatric illness such as psychosis or mood disorders or as isolated impairment of attention, working memory, executive dysfunction or processing speed. Despite the lack of standardized and sensitive neuropsychological tests and validated diagnostic biomarkers of CD in SLE, significant progress has been made in identifying pathogenic neural pathways and neuroimaging. Furthermore, several autoantibodies, cytokines, pro-inflammatory mediators and metabolic factors have been implicated in the pathogenesis of CD in SLE. Abrogation of the integrity of the blood-brain barrier (BBB) and ensuing autoantibody-mediated neurotoxicity, complement and microglial activation remains the widely accepted mechanism of SLE-related CD. Although several functional neuroimaging modalities have consistently demonstrated abnormalities that correlate with CD in SLE patients, a consensus remains to be reached as to their clinical utility in diagnosing CD. Given the multifactorial aetiology of CD, a multi-domain interventional approach that addresses the risk factors and disease mechanisms of CD in a concurrent fashion is the favourable therapeutic direction. While cognitive rehabilitation and exercise training remain important, specific pharmacological agents that target microglial activation and maintain the BBB integrity are potential candidates for the treatment of SLE-related CD.

Keywords: Systemic lupus erythematosus; Lupus; Cognitive; Neuropsychiatric; Imaging; Glucocorticoids
Cognitive dysfunction is often clinically subtle in patients with SLE.

While the American College of Rheumatology (ACR) neuropsychological battery is the gold standard for evaluation of cognitive function in SLE patients, computerized tools such as the Automated Neuropsychological Assessment Matrix (ANAM), which do not require long assessment time and clinical psychologists to administer, have been increasingly used for research and clinical purposes.

The pathogenesis of SLE-related cognitive dysfunction likely involves a two-hit mechanism which comprises the breach of the blood-brain barrier integrity where peripherally produced neurotoxic autoantibodies can access the central nervous system.

Functional neuroimaging consistently demonstrates disrupted and compensatory neural networks in patients with SLE, rendering this imaging modality promising if properly validated.

Specific pharmacological agents that target microglial activation and maintain BBB integrity are potential candidates for the treatment of SLE-related cognitive dysfunction.

INTRODUCTION

The study of neuropsychiatric (NP) manifestations in systemic lupus erythematosus (SLE) has evolved considerably since its inception in the 1960s. Initially thought to be a single entity known as “lupus cerebritis”, we now recognize a diverse range of NP manifestations from overt neurological or psychiatric dysfunction, such as stroke or psychosis, to more subtle and subclinical conditions including mild to moderate mood disorders and cognitive dysfunction (CD) [1]. Importantly, CD, defined as a significant deficit in any of the cognitive domains of simple or complex attention, reasoning, executive skills, memory, visual-spatial processing, language and psychomotor speed [2], afflicts 3% to 88% of SLE patients [3–6]. Reasons on the wide variation in the reported prevalence of CD in SLE include: (1) lack of consensus in screening tools for the identification of CD in SLE—the current gold standard is the American College of Rheumatology (ACR) battery, which is limited by cost and time burden, making it more feasible for use in research rather than clinical settings; (2) difficulty in attributing CD to SLE; (3) lack of validated diagnostic biomarkers of CD; (4) the heterogeneous study populations of SLE patients in observational studies [7–12].

Up to 50% of SLE patients with overt NP disease with stroke and seizures have been reported to manifest CD [11]. However, cognitive deficits may also occur in the absence of active systemic disease of SLE and other major NP events, with 30% of SLE patients having isolated impairment of attention, working memory, executive function or processing speed [11, 13, 14]. Other factors which have been associated with CD in SLE include depression status, longer disease duration, regular glucocorticoid use and the presence of anti-neuronal and anti-phospholipid antibodies (aPLs), structural brain alterations, traditional cardiovascular risk factors, physical inactivity and vitamin D deficiency [15–23]. The overall clinical course of CD is favourable, with longitudinal studies describing a stable, improving or fluctuating course, but rarely with progression to frank dementia [9, 23–25]. The radiological...
features potentially related to CD on conventional neuroimaging are varied and inconsistent and include periventricular hyperintensities and cerebral atrophy [26]. Functional magnetic resonance imaging (fMRI), although not being routinely used in clinical practice, allows specific anatomical localization to areas of pathology at the fusiform gyrus, pre-frontal cortex, parietal regions, supplementary motor area and caudate body [27]. To date, there are no consensus guidelines for the treatment of CD in SLE; hence, a multipronged individualized approach involving a combination of non-pharmacological and pharmacological methods is prudent. This review is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors therefore ethical approval was not required.

CD negatively impacts patients’ socio-economic function, employment and health-related quality of life (HRQoL). A retrospective study involving over 800 SLE patients showed that those with severely impaired cognition were twice as likely to be unemployed compared to those with intact cognition, while patients often report CD as one of the most distressing symptoms that detracts from HRQoL [28, 29]. CD in SLE has also been associated with lower household income, poor job sustainability and significant work disability [28, 30, 31]. As such, an in-depth discussion of SLE-related CD is relevant and timely, and this review aims to bring into focus the immunopathology, clinical manifestations, neuroimaging modalities and up-to-date potential treatment options available for CD in patients with SLE.

Immunopathology

The pathogenesis of central nervous system (CNS) manifestations of SLE is complex and not well understood. Implicated mechanisms include blood-brain barrier (BBB) disruption, autoantibody production and effects of pro-inflammatory mediators, leading to injury of the cerebral vessels and disturbance of neuronal function [32]. Nevertheless, factors that mimic NPSLE, including drugs, metabolic abnormalities, haemodynamic instability and infections, must be thoroughly excluded before attributing NP events to SLE [18, 33]. The proposed pathogenesis of CD in SLE is depicted in Fig. 1.

Autoantibodies

Autoantibodies found in the serum, cerebrospinal fluid (CSF) and neuronal tissues of SLE patients have been postulated to contribute to the pathogenesis of NPSLE [34, 35]. Autoantibodies may be detected in the CSF as a result of passive transfer of peripherally produced autoantibodies across a breached BBB or increased intrathecal production [32]. While a number CSF autoantibodies are associated with diffuse NPSLE manifestations [32], their link with CD is inconsistent [36, 37]. Table 1 summarizes the potential neuropathology and the associated neuropsychiatric manifestations in SLE.

Anti-neuronal Antibodies

Antibodies against the N-methyl-D-aspartate (NMDA) receptor (NMDAR) NR2A/B subunits (anti-NR2A/B antibodies) have been found in the sera of 30–40% of SLE patients and have been inconsistently linked to SLE-related CD [18, 38]. Omdal et al. showed an association between serum anti-NR2A/B antibodies and reduced short-term memory and depressed mood in 57 SLE patients [39], while another cross-sectional study linked serum anti-NR2A/B antibodies with impaired attention and executive function [40]. A longitudinal study by Brunner et al. demonstrated an association between increasing serum anti-NR2A/B antibodies with impaired attention and executive function [41]. However, other studies have failed to draw a similar conclusion. A 5-year longitudinal study of 65 SLE patients demonstrated no relationship between changes in serum anti-NR2A/B antibody levels and cognitive function [42]. By contrast, CSF anti-NR2A/B antibodies are consistently shown to be associated with central and diffuse NPSLE manifestations, specifically CD [43–45]. In addition, CSF anti-NR2A/B antibodies correlate with NPSLE severity, with
the highest titers noted in acute confusion, followed by central diffuse (including CD, mood disorders) and peripheral nerve manifestations (e.g. polyneuropathies) [46]. The discrepant results between CSF and serum anti-NR2A/B antibodies suggest that the serum antibodies alone without their CSF correlates or other surrogate biomarkers of BBB integrity may not be sufficient to induce neurological damage [18].

Anti-ribosomal P (anti-P) antibodies, found in the sera of up to 17% of SLE patients [36], have been reported to be commonly associated with lupus psychosis after this association was first described in the seminal paper by Bonfa et al. [47]. The association between anti-P antibodies and CD, however, remains elusive. A cross-sectional study by Massardo et al. suggested a possible association between anti-P antibodies and deficits in attention and spatial planning abilities [40]. However, a multinational cohort study of 1047 SLE patients that demonstrated a 10-year CD incidence of 6.5% did not reveal a correlation between CD and anti-P antibodies [48]. A point of note is that neuropsychological testing was not systemically performed in all study subjects, rendering the reported incidence of CD potentially inaccurate [40, 48].

Anti-phospholipid Antibodies
aPLs are present in up to 30–40% of SLE patients [49] and have been linked with CD, as evidenced by longitudinal studies which showed a clear correlation between declining cognitive function and persistently elevated aPL levels [50, 51]. A study by Hanly et al. evaluated the aPL profile and cognitive function of 51 female SLE patients at baseline and after a mean follow-up duration of 64 months. While the prevalence of CD did not differ between those with and without persistent aPL positivity, there was a significant correlation between persistent anti-cardiolipin (aCL) immunoglobulin G (IgG) positivity with psychomotor speed reduction as well as persistent aCL immunoglobulin A (IgA) positivity with decreased conceptual reasoning and executive dysfunction [50]. A prospective study of 43 SLE patients which involved serial measurements of aPL and assessment of fronto-subcortical function over 10 years demonstrated a statistically significant association between worsening visuospatial functions with hyperlipidaemia and lupus anticoagulant positivity [9]. However, it is important to note that not all studies agree on the associated risk of aPLs and CD [52]. Regression analysis in a cohort of 98 SLE patients did not reveal any statistical difference in aPL status between patients with and without CD, while a cross-sectional study by Kozora et al. showed high levels of cognitive impairment in the absence of other overt NP disease for both aPL-negative SLE and aPL-positive non-SLE patients [53, 54]. These findings likely reflect the multifactorial causes for CD in SLE, not attributable to aPL status alone [55].

Disruption of the Blood-brain Barrier (BBB)

Typically, immune complex-mediated activation of the complement cascade accounts for end-organ inflammation and damage in SLE [56]. However, the pathway leading to SLE-related CNS manifestations is different because of the presence of the BBB. The BBB serves as a mechanical and functional barrier between the CNS and peripheral blood that protects the former from routine exposure to circulating...
| Antibody                        | Neuropathology                                                                 | Associated NP clinical manifestations                                                                 |
|--------------------------------|--------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| Serum anti-NR2A/B antibodies   | The NR2A/B subunits of NMDA are found in high densities in the hippocampus, a structure linked with memory and learning | Decreased short-term or working memory, learning, depressed mood, attention deficits and impaired spatial planning abilities |
| [18, 38, 57, 58, 149–151]       | Glutamatergic transmission at NMDA receptors is associated with neuronal plasticity in spatial memory, and the dysfunction of which results in emotional and behavioural disorders | Seizures, aseptic meningitis, transverse myelopathy, acute confusion state, anxiety disorder, cognitive dysfunction, mood disorder and psychosis |
| CSF anti-NR2A/B antibodies     | The NR2A/B subunits are subtypes of NMDAR; anti-NR2A/B antibodies are produced extrathecally and required to cross the BBB into the CSF to influence brain function | Low CSF levels cause synaptic alteration and dysfunction; high titers result in mitochondrial stress and apoptosis |
| [40–42, 152]                    | A certain subset of anti-DNA antibodies with cross-reactivity to the pentapeptide consensus sequence Asp/Glu-Trp-Asp/Glu-Tyr-Ser/Gly is capable of binding to NR2A/B subunits, inducing apoptotic neuronal death as another possible mechanism of damage | Equivocal association between serum anti-NR2A/B and CD in SLE. However, stronger association between CSF anti-NR2A/B and CD in SLE has been demonstrated, and CSF anti-NR2A/B have been shown to be directly pathogenic and neurotoxic in mouse models |
Table 1 continued

| Antibody                        | Neuropathology                                                                                                                                                                                                 | Associated NP clinical manifestations                                                                 |
|---------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Serum anti-ribosomal P antibodies [44–47, 149, 153–161] | Anti-P antibodies are directed towards the P proteins (P0, P1, P2) of the 60S ribosomal subunit; these neuronal surface antigens are distributed in brain regions involved in memory, cognition and emotion. Serum anti-P antibodies have been most commonly linked with psychiatric lupus and depression. There are contradictory reports that failed to find a link with NPSLE, however this discrepancy could be due in part to methodological differences. The association between serum anti-P antibodies and CD is more elusive. Murine models have shown a cross-reactivity between anti-P antibodies and neuronal surface P antigen, which is involved in neuronal transmission and memory dysfunction; however, this process remains to be demonstrated in humans.                                                                 | Psychosis, depression, attention deficits and impaired spatial planning abilities                                     |
pathological antibodies, immune complexes, toxins, pathogens and other neurotoxic sub-
stances [11, 56]. BBB disruption may result in altered homeostasis as seen in CNS disorders 
such as Alzheimer’s disease (AD), multiple sclerosis (MS) and stroke [11]. Consequently, a
“two-hit” mechanism, including the presence of pathogenic autoantibodies and a breach in the 
BBB, has been proposed in the pathogenesis of CNS manifestations in SLE [56]. Murine lupus 
models support this mechanism in the development of CD. In an experimental study by

| Antibody                      | Neuropathology                                                                 | Associated NP clinical manifestations                      |
|-------------------------------|-------------------------------------------------------------------------------|----------------------------------------------------------|
| Anti-phospholipid antibodies  | aPLs are directed predominantly towards phospholipid-binding proteins such as β2- | Stroke, seizures, psychomotor speed reduction, decreased conceptual |
| [3, 9, 11, 48, 156, 162–167]  | glycoprotein I, cardiolipin, prothrombin and other autoantigens               | reasoning, executive dysfunction and worsening visuospatial function |
|                               | They exert neuronal damage through direct binding to astrocytes and glial cells, |                                                          |
|                               | overstimulating glutamate receptors, inhibiting cerebral angioegenesis,         |                                                          |
|                               | activating complements and increasing the permeability of nerve terminals |                                                          |
|                               | aPL-mediated thrombosis leads to focal NP manifestations including stroke and |                                                          |
|                               | seizures                                                                      |                                                          |
| Anti-cardiolipin immunoglobulin G (IgG) | positivity was associated with psychomotor speed reduction                  |                                                          |
| Persistent aCL immunoglobulin A (IgA) | positivity was associated with decreased conceptual reasoning and executive dysfunction |                                                          |
| Non-focal, diffuse manifestations, including CD, are likely mediated through an inflammatory | achieved by direct binding of aPLs to brain tissue and endothelium |                                                          |
| Although mouse models have illustrated neurotoxic mechanisms of aPLs, clinical observational studies do not consistently demonstrate association between aPLs and CD in SLE |                                                          |

aPL anti-phospholipid, BBB blood-brain barrier, CD cognitive dysfunction, CSF cerebrospinal fluid, DNA deoxyribonucleic acid, NMDA N-methyl-D-aspartate, NMDAR N-methyl-D-aspartate receptor, NP neuropsychiatric, SLE systemic lupus erythematosus
Kowal et al., mice immunized with the DNA peptide mimotape arrayed as an octamer on a polylysine backbone (MAP-peptide) developed high titers of anti-peptide and anti-DNA antibodies after immunization [57]. Following lipopolysaccharide (LPS) administration which breached the BBB integrity, histopathological examination revealed hippocampal neuronal loss with intense IgG deposition. These changes were not present prior to LPS administration, suggesting that an intact BBB prevented the transport of autoantibodies from the systemic circulation into the brain [57]. Conversely, a breach in the BBB without autoantibodies does not appear to result in neuronal damage. Anti-NMDA and anti-DNA antibodies from the sera of SLE patients were administered to immunized mice, followed by intra-peritoneal LPS [56]. This led to hippocampal neuronal loss in the absence of inflammatory infiltrate, manifesting as persistent memory impairment in the mice. However, administration of autoantibody-depleted sera prior to LPS administration did not result in memory impairment [56]. Increased BBB permeability in SLE may occur because of immune complex deposition, complement and cytokine activation [58–60], which in turn facilitates passive transfer of neurotoxic autoantibodies into the CSF [61]. While serious infections are known to increase BBB permeability, other implicated mechanisms include smoking, hypertension and stress and epinephrine may contribute to the loss of BBB integrity as demonstrated in animal studies [11, 56].

**Inflammatory Mediators**

Pro-inflammatory cytokines have been implicated in the pathogenesis of SLE-related CD and their relevant immunopathological details are summarized in Table 2. Increased levels of pro-inflammatory mediators including interleukin (IL)-1, IL-6, IL-10, interferon (IFN)-γ and transforming growth factor (TGF)-β have been demonstrated in murine lupus models, and these pro-inflammatory cytokines were shown to correlate with memory impairment as assessed by object recognition tests [62]. In humans, serum tumour necrosis factor (TNF)-α levels were found to be independently associated with more depressive symptoms in SLE patients, with depression per se being an important co-morbidity in CD that also predicted significantly poorer cognitive function [18, 63]. Additionally, Kozora et al. found a relationship between elevated serum IL-6 levels and learning deficits in SLE patients [64]. Serum IL-6 has also been reported to play a significant role in the breakdown of the BBB in diffuse NPSLE syndromes, including CD [65].

Matrix metalloproteinases (MMPs) are endoproteinas that work in concert with their endogenous inhibitor, tissue inhibitor of metalloproteinases 1 (TIMP-1), to regulate the integrity of the BBB [26] (see Table 2 for details). Elevated serum MMP-9 and MMP-9/TIMP-1 ratios have been observed in MS, Guillain-Barré syndrome and subacute sclerosing panencephalitis patients [66–68], whereas NPSLE patients, those with CD in particular, have elevated CSF and serum MMP-9 levels [69, 70]. CSF MMP-9 levels also correlate with biomarkers of neuronal and glial degradation in SLE patients, suggesting that increased MMP-9 production is linked to CNS damage in SLE [70].

**Complement Activation**

Both the classical and alternative pathways of complement activation have been implicated in the disease process of NPSLE. For instance, C1q activates microglial cells, which continue to release C1q to maintain microglial activation in an autocrine fashion [71]. Also, MRL/lpr mice deficient in a key alternative pathway protein, complement factor B (fB), show reduced apoptosis and expression of extracellular matrix proteins in the brain [72]. While complements may enter the CSF via a breached BBB, intrathecal synthesis of complement 3 and complement 4 has been particularly shown in patients with diffuse NPSLE. Serum complements also directly contribute to diffuse NPSLE by breaching the BBB via aPL-dependent interaction [73].

The neurotoxicity of complement activation products has been demonstrated via their
Table 2 Summary of various inflammatory mediators, metabolic and endocrine factors and their clinical significance

| Molecule                        | Immunopathology                                                                                                                                                                                                 | Clinical significance                                                                                                                                                                                                                                                                                                                                 |
|---------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cytokines                       | Cytokines may function as neuromodulators and inflammatory mediators. SLE patients have increased type I IFN production and increased intrathecal levels of IL-2, IL-8, IL-10. Pro-inflammatory cytokines are produced by neuronal, glial and infiltrating immunocompetent cells following the binding of autoantibodies to neuronal surface antigens to form immune complexes and trigger an inflammatory cascade. Pro-inflammatory cytokines may also be produced by BBB endothelium following surface binding of NR2 glutamate receptors and anti-P antibodies. S100β, a cytoplasmic protein produced by astrocytes, has demonstrated neuromodulatory effects on neurons and glial cells. They are neurotrophic in low levels but overproduction by activated glial cells leads to loss of neuronal cells and increased BBB permeability. | Increased levels of IL-1, IL-6, IL-10, IFN-γ, TGF-β correlate with memory impairment (murine studies). Elevated CSF IL-6 is associated with seizures in SLE. Elevated CSF IFN-α is associated with lupus psychosis. Increased serum IL-6 production is associated with learning deficits in SLE. Higher serum TNF-α levels are independently associated with more depressive symptoms and poorer HRQoL in SLE. |
| Matrix metalloproteinases        | MMPs are endoproteinases that reside in the BBB and are responsible for remodelling and degrading extracellular matrix proteins. They are postulated to breach the BBB integrity via degradation of the basal lamina and disruption of inter-endothelial junctions. MMP-9 is inhibited by TIMP-1, a glycoprotein that forms a complex with MMP-9 to inhibit its proteolytic activity, hence promoting BBB stability. | Cross-sectional studies evaluating serum MMP-9 levels in SLE patients have been heterogeneous, with varying levels of serum MMP-9 levels compared to controls; this discrepancy could be due to different measurement techniques or MMP-9 promoter polymorphisms. In contrast, serum and CSF MMP-9 are more consistently elevated in NPSLE patients, in particular among those with CD. In SLE patients, CSF MMP-9 levels correlate with CSF levels of tau and glial fibrillary acid protein, biomarkers of neuronal and astrocytic degeneration, respectively. |
| Molecule                                | Immunopathology                                                                 | Clinical significance                                                                 |
|-----------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Neutrophil extracellular traps          | NETs are released by activated neutrophils during phagocytosis when they combat pathogens | Lupus mouse models have shown a predominantly neutrophilic infiltrate in leukocyte-endothelial cell interactions in the cerebral vasculature |
| [18, 62, 82, 86, 174–176]               | This process, known as “NETosis”, is a unique form of cell death distinct from necrosis and apoptosis | Other murine studies support the hypothesis that NETs alter the vascular endothelial integrity in SLE |
|                                         | In vitro studies have demonstrated that the histones and proteases released during NETosis are potentially neurotoxic | It is likely that abnormal endothelial cell-immune cell interactions permit access of NETs into the CNS, consequently leading to neuronal damage in SLE, including CD |
|                                         | Autoantibodies in SLE patients against NETs components (e.g. anti-dsDNA, anti-histone) and complement (e.g. C1q) have been identified, protecting them from degradation and allowing for persistence of NETs in circulation |  |
| Vitamin D [21, 177–180]                | 1,25(OH)$_2$D$_3$ promotes chemotaxis and phagocytosis of macrophages which are important for clearance of apoptotic cells | 25(OH)D$_3$ levels are significantly lower in lupus patients, and also contributes to disease activity and morbidity of SLE |
|                                         | 1,25(OH)$_2$D$_3$ inhibits the type I IFN-mediated pathway of monocyte differentiation into dendritic cells | 25(OH)D$_3$ deficiency in SLE patients independently predicts worse cognitive performance |
|                                         | 1,25(OH)$_2$D$_3$ modulates the activation and maturation of dendritic cells, which in turn skews interacting T cells into a more anti-inflammatory from a regulatory state |  |
|                                         | 1,25(OH)$_2$D$_3$ induces apoptosis in activated B cells. 1,25(OH)$_2$D$_3$ inhibits production of plasma cells and memory B cells |  |
|                                         | 1,25(OH)$_2$D$_3$ reduces cellular proliferation and anti-dsDNA immunoglobulin production when incubated with isolated peripheral blood mononuclear cells from lupus patients |  |
potential to induce apoptosis in MRL/lpr mouse models by upregulating cerebral glutamate receptor expression and through increased expression of inducible nitric oxide synthase, tumour necrosis factor receptor 1 (TNFR1) and intracellular adhesion molecule-1 (ICAM-1) [74]. Complement 5a also increases BBB permeability directly by inducing actin fiber rearrangement and cytoskeleton remodelling in endothelial and astroglial cells. In addition, complement 5a (C5a) alters the nuclear factor-κβ-mediated signaling pathway that interferes with the expression of tight junction proteins including claudin-5 and zonula occludens-1 [59]. Indeed, in an autopsy study of brain tissue from 16 deceased NPSLE patients, C4d- and C5b-9-associated microthrombi and diffuse vasculopathy were uniquely found in patients with NPSLE but not in SLE patients without neurological involvement [75]. In another study of 93 patients with NPSLE, serum total hemolytic complement (CH50), complement alternative pathway assay (AP50) and complement 3 were significantly lower in diseased patients compared to controls, particularly in patients with diffuse NPSLE [76].

**NETosis and Neutrophil Extracellular Traps**

Over a decade ago, a new form of active cell death process in neutrophils was described and termed as “NETosis” [77]. Activated neutrophils undergo NETosis to release NETs, a unique form of cell death that is distinct to necrosis and apoptosis [18]. NETs are fibrous structures consisting of chromatin backbones with diameters of ~17 nm with attached globular domains with diameters of ~50 nm [78, 79]. The proteome of NETs includes: (1) locally elevated concentrations of antimicrobial proteins (e.g. citrullinated histones, myeloperoxidase and neutrophil elastase) to promote the clearance of microbes; (2) modified neoantigens to serve as autoantigens (e.g. LL-37); (3) active MMP-9 that mediates endothelial dysfunction [80–82]. Active MMP-9 is externalized on NETs at

Table 2 continued

| Molecule | Immunopathology | Clinical significance |
|----------|-----------------|----------------------|
| Neuropeptides [26, 181–183] | Other than cholinergic neurons, there is evidence that various neurotransmitters are involved in cognition, and these include neuropeptides that have been implicated as modulators of cognitive processes | Altered learning and memory functions in lupus mice have been associated with decreased hypothalamic levels of calcitonin gene-related peptide, substance P and neuropeptide Y |
| Neuropeptides are widely distributed through the brain and participate in several physiological processes including pain sensation, memory, regulation of mood and neuroendocrine functions | Lupus mice have demonstrated enhanced vasopressin and reduced CRF gene expression in the hypothalamus and amygdala; CRF levels were also found to be inversely related to behavioural performance in stress-sensitive tasks |
| | Increased serum levels of vasopressin and calcitonin-gene related peptide have been observed in SLE patients with CD |

*BBB* blood-brain barrier, *CD* cognitive dysfunction, *CNS* central nervous system, *CRF* corticotropin-releasing factor, *dsDNA* double-stranded deoxyribonucleic acid, *HRQoL* health-related quality of life, *IFN* interferon, *IL* interleukin, *MMP* matrix metalloproteinase, *NET* neutrophil extracellular trap, *SLE* systemic lupus erythematosus, *TGF* transforming growth factor, *TIMP* tissue inhibitor of matrix metalloproteinase.
significantly higher levels by a distinct proinflammatory subset known as low-density neutrophils [83, 84]. Another related protein is lipocalin-2, an acute phase reactant protein that is found in close association with MMP-9 in the granules of neutrophils [85]. Lipocalin-2 was recently described to be hyperexpressed within the brain of murine NPSLE and CSF of human NPSLE and appears to be relatively specific for human NPSLE compared to patients with other neurological diseases [85]. LCN2 expression that codes for lipocalin-2 is also significantly increased in low-density neutrophils (Dr. S.H. Tay, personal communication).

Neutrophil extracellular traps have been shown to be associated with SLE-related CD. Mouse models mimicking CD in SLE have shown increased leukocyte-endothelial cell interactions in the cerebral vasculature, of which the predominant cell type of infiltrating leukocytes was neutrophils [62]. NETs also influence the endothelial integrity in SLE, with murine studies demonstrating the correlation between endothelial dysfunction and activation of MMP-2 by MMP-9 present in NETs, whereas inhibition of MMP-2 activation restored endothelial function and reduced NET-induced vascular cytotoxicity [82]. Ultimately, the process leading to CD in SLE involves abnormal endothelium-immune cell interactions that permit access of neutrophils and therefore NETs into the CNS, resulting in neuronal damage [18, 86]. The immunopathology of NETs in SLE is summarized in Table 2.

Metabolic and Endocrine Factors

Vitamin D displays a variety of immunoregulatory actions [87] (see Table 2). Specific to CNS manifestations, vitamin D has been proposed to promote neuron survival, with murine studies suggesting that it suppresses oxidative pathways in the brain by reducing free radical formation and inhibiting β-amyloid accumulation, which has been implicated in AD [88]. A cross-sectional study by Tay et al. demonstrated that 25(OH)D₃ deficiency independently predicted worse cognitive performance in SLE patients even after adjusting for demographics, anxiety, cumulative steroid dose, disease duration, disease activity and disease-related damage [21].

Finally, the neuropeptides vasopressin, corticotropin-releasing factor (CRF), calcitonin gene-related peptide, substance P and neuropeptide Y have all been linked with lupus-related neurobehavioural manifestations in both animal and human studies [26]. Table 2 summarizes these associations.

Clinical Manifestations

Most SLE patients with CD have subtle or subclinical deficits [8, 14, 89]. SLE-related CD may occur in the absence of active systemic lupus or major NP events, although patients with overt NPSLE tend to have more profound cognitive impairment [8, 13]. CD most commonly presents in the form of deficits in attention and working memory, or a compromise in the daily function of SLE patients [8, 22, 90]. Other affected domains include psychomotor slowing, executive dysfunction, deficits in free recall of recently learned information, impaired visuospatial constructional skills, language fluency and difficulty in performing cognitive tasks [8, 91, 92]. While the constellation of memory impairment, deficits in information-processing speed and language preservation is reminiscent of subcortical white-matter dementia, a dominant and characteristic pattern of cognitive deficit in SLE has yet to emerge [18, 26]. The clinical course of CD in SLE is variable, but the overall prognosis appears to be favourable. A prospective cohort study of 70 SLE patients by Hanly et al. reported CD in 21% at baseline and observed resolution of CD at 1 year of follow-up in the majority, with only 12% demonstrating persistent CD [24]. Likewise, a longitudinal study of 43 SLE patients by Ceccarelli et al. reported improvement in CD in 50% of patients over a 10-year observation period [9]. However, a large prospective cohort study of 655 SLE patients by Touma et al. described a persistently low but stable cognitive performance in patients with CD, with or without depressive symptoms over 7 years of follow-up [23]. These variations may be accounted for by different sample sizes, follow-up periods or NP
assessment tools used to detect CD, but nonetheless, progression to frank dementia remains uncommon [18, 23, 93].

SLE-related disease damage is associated with CD. Higher damage accrual, as evaluated by the Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index (SDI), has been found to be related to poorer performances in the spatial recognition and continuous performance tests in SLE patients [93]. A 10-year longitudinal study of 43 SLE patients revealed a correlation between CD and SLE damage accrual [9, 10]. Conversely, a longitudinal study of 99 SLE patients by Mimica et al. did not show a relationship between CD and lupus damage accrual, although the follow-up duration was shorter and a different cognitive assessment test was used [2, 9]. Hyperlipidaemia has been associated with impaired memory, executive function and abstract reasoning, while lupus anticoagulant positivity was correlated with worsening visuospatial functions over time [9]. In addition, depression, fatigue and pain have been associated with CD in lupus patients [26, 94].

Screening

The signs of CD are often subtle [95]. Self-reported measures of perceived cognitive impairment correlate poorly with objective assessment in SLE patients and may be confounded by anxiety, depression and fibromyalgia [89, 96]. Hence, an objective and sensitive screening test that reliably detects CD in SLE is paramount. A comprehensive neuropsychological battery such as the ACR-SLE battery is the gold standard for the evaluation of cognitive function in SLE patients but up to an hour is required to complete the test [11]. This screening tool has been validated against a more comprehensive 4-h battery and demonstrated good agreement in detecting CD in SLE [97]. The clinical utility of these formal neuropsychological batteries is, however, limited because of the long administration time, fatigue on prolonged testing, practice effect and the lack of trained personnel to conduct the assessment. Therefore, these batteries are reserved for research, standardization in clinical trials and confirming the diagnosis [30].

Simpler tools to detect CD in SLE have been validated. These include the Automated Neuropsychological Assessment Metrics (ANAM), Montreal Cognitive Assessment (MoCA), Hopkins Verbal Learning Test-Revised (HVLT-R) and Controlled Oral Word Association Test (COWAT), all of which have been shown to facilitate rapid and efficient screening [12, 98]. The ANAM is a 30–45 min computerized battery of tests developed by the US military to assess the effects of combat on cognitive function. It has been validated against the ACR-SLE battery with good correlation, demonstrating a sensitivity of 78–80% and specificity of 70% [99]. The MoCA is a one-page, performance-based questionnaire designed as a highly sensitive and specific screening tool to identify mild cognitive impairment in the elderly [100]. It was evaluated against the ANAM for its performance in identifying CD in a cohort of 44 SLE patients and had sensitivity of 83% and specificity of 73% when the standard cut-off score of 26 was used [101]. Another cross-sectional study by Chalhoub et al. compared 78 SLE patients with age- and sex-matched healthy individuals and rheumatoid arthritis (RA) patients, assessing them for CD using ANAM and MoCA. Not only did the MoCA display a good correlation with ANAM, it also showed sensitivity of ≥90% compared to RA patients (at the cut-off score of 28) and ≥83% compared to healthy controls (at the cut-off score of 26) in identifying CD [102]. It should be noted, however, that ANAM and MoCA may fail to identify subtle cognitive impairment and may be subject to practice effects [98, 103].

The HVLT-R and COWAT are independent neuropsychological tests that assess specific domains (verbal learning and memory and verbal fluency, respectively) and are also a part of the neuropsychological battery [12]. They have both been used broadly as screening tools for CD in SLE and other clinical populations because of their brevity and accessibility.

The HVLT-R is a brief 12-item word list learning and memory test, assessing verbal learning efficiency, ability to access newly learned information and retention [53]. This
has been validated against a comprehensive cognitive battery and found to be of sufficient reliability for the detection of CD in SLE [104]. While its low administrative and respondent burden may be attractive for clinical use, it only evaluates verbal learning and memory; other tests may be necessary for a comprehensive assessment of cognition. The controlled oral word association test (COWAT) evaluates verbal fluency (phonemic and semantic) and executive function. This test consists of three trials for which participants generate words beginning with specific letters under timed conditions. Caution though should be taken when administering the COWAT as a stand-alone tool for CD assessment as the results are highly influenced by education and age and only valid for participants fluent in the language of administration [12]. The ANAM, MoCA, HVLT-R, and COWAT have psychometric evidence for reliability, validity and responsiveness generally and in rheumatic disease (including SLE). The strengths and weaknesses with respect to comprehensiveness, administrative burden and degree of evidence per psychometric property of each of these tests should be taken into account prior to the selection of assessment tools for CD in SLE [12].

**Neuroimaging**

Neuroimaging is pivotal in unraveling pathophysiological mechanisms pertaining to CD in SLE and monitoring treatment response. Conventional structural magnetic resonance imaging (MRI) demonstrated lower hippocampal volumes in SLE patients with CD compared to those without [29]. The presence of periventricular hyperintensities, infarcts, haemorrhages, cerebral atrophy and small focal lesions has been reported in patients with SLE but their associations with SLE-related CD have not been consistently shown [26].

**Diffusion Tensor Imaging and Magnetization Transfer Imaging**

Structural neuroimaging such as diffusion tensor imaging (DTI) and magnetization transfer imaging (MTI) measures the integrity of white matter tracks which cannot be readily visualized on conventional MRI [105]. DTI is based on the principle of isotropy, which refers to the unrestricted movement of proton-containing molecules in free water. Low fractional anisotropy (FA) indicates damaged white matter, which may be due to decreased axonal density, number, diameter or myelination [29]. Decreased FA in the external capsule has been reported in SLE patients with CD [106–108]. MTI quantifies the exchange of magnetization between macromolecule-bound proteins in myelin and water protons in biological tissues by generation of a magnetization transfer ratio (MTR). A lower magnetic transfer peak height value is indicative of demyelination and has been seen in SLE patients with CD [109]. Because of the lack of standardized interpretation guidelines, MTI is not currently used for clinical purposes.

**Dynamic Contrast-enhanced MRI**

Studies on the role of BBB dysfunction in SLE-related CD have been furthered by technical advances in neuroimaging. The use of dynamic contrast-enhanced MRI (DCE-MRI) allows quantification of contrast extravasation into the brain parenchyma and calculation of cross-BBB leakage rates for every voxel of the brain [110]. Multiple T1-weighted images obtained before, during and after contrast administration allow evaluation of blood flow and permeability between the intra- and extravascular extracellular space [111]. Significant associations between the extensive abrogation of the BBB involving especially the hippocampal region and concurrent cognitive impairment have been found in SLE patients with impairment of working memory, sustained attention and spatial function, without previous history of CNS compromise [111]. Volumetric comparison of brain structures has additionally revealed that SLE patients with extensive BBB leakage had significantly smaller cerebral grey matter volumes compared to controls, further establishing the role of BBB as a potential diagnostic and therapeutic target [110]. Larger studies are necessary to validate these results.
**Magnetic Resonance Spectroscopy**

Metabolic changes may be evident before structural lesions appear, and myelin injury underlies the earliest CD in SLE [26]. CD has been shown to correlate with abnormalities in the choline/creatine ratio on magnetic resonance spectroscopy (MRS). The ratio of these cell-specific metabolites is used as an index of white matter integrity; choline is essential to neuronal membranes and myelin, while creatinine is a stored phosphate used as a reference. An elevated choline/creatine ratio represents increased membrane turnover due to demyelination, ischaemia and/or gliosis [29].

**Positron Emission Tomography**

CD may be detected via the assessment of microglial activity. In vitro studies reveal BV2 microglial activation as evidenced by increased MHC II and CD86 expression following exposure to SLE sera [112]. In addition, anti-DNA antibody-mediated microglial activation was shown to contribute to CNS damage and spatial memory impairment in a murine lupus model [113]. Positron emission tomography (PET) tracers targeting the 18-kD translocator protein (TSPO) have shown that TSPO is expressed on the outer mitochondrial membrane of microglia and is markedly upregulated in response to brain injury and inflammation [29]. While a potential link between altered TSPO distribution in the hippocampus and cerebellum has been described in SLE patients with CD [114], more evidence is needed to validate its utility, given the technical challenges and radiation exposure.

**Functional Magnetic Resonance Imaging**

The severity of cognitive dysfunction often does not correlate with the damage shown on structural brain imaging [27]. The development of functional neuroimaging is a major step forward to reliably assess the working brain. Functional magnetic resonance imaging (fMRI) of the brain is a non-invasive imaging technique that measures changes in blood flow either at rest or while performing cognitive tasks, utilizing deoxyhemoglobin as an endogenous contrast agent to identify areas of increased perfusion. fMRI records blood oxygen level-dependent (BOLD) signals as a measure of neuronal metabolism, providing an indirect assessment of neuronal activity. This modality can be used to inform the functional connectivity of brain regions and the loss of connectivity may be indicative of pathology. A disturbance to the anatomic areas corresponding to working memory and executive function has been the most well-replicated finding. Increased BOLD signals during cognitive tasks have been found in the fusiform gyrus, prefrontal cortex, parietal regions, supplementary motor area and caudate body [27].

While task-based fMRI has been adopted to identify brain regions that are functionally involved in specific cognitive task performance, resting state fMRI is used to explore the intrinsically functional segregation or specialization of brain regions to elucidate the organization and origination of cognitive functioning [115]. Studies that combined task-based and resting-state fMRI showed altered cerebral functions in patients with SLE-related CD. SLE patients with CD may maintain cognitive performance through compensatory cortical reorganization and recruitment of regions where function is preserved [116, 117]. Hou et al. found that SLE disease activity positively correlated with functional connectivity strength in the frontal-parietal cortex in SLE patients [118], suggesting patients with SLE employ additional mechanisms to maintain cognitive performance.

fMRI has been instrumental in highlighting the impact of mood on cognitive performance. In a study by Barraclough et al. that utilized fMRI to evaluate brain responses to working memory and emotional processing tasks revealed significant interference in emotional tasks in patients with SLE compared to healthy subjects [22]. SLE patients had fewer task negative BOLD signals in the left transverse temporal gyrus and right superior temporal gyrus, areas that are part of the default mode network (DMN). The DMN is largely inactive during cognitive tasks and active during self-reflection [119]. Poor attenuation of the DMN in SLE patients implies an inability to inhibit self-reflective processes which potentially impedes performance of cognitive tasks that do not
usually have an emotional component. Additionally, when presented with sad faces, patients with SLE had a greater response in the frontal regions compared with healthy controls, despite both groups scoring within normal ranges on the depression scales [119, 120].

While fMRI may be an emerging investigative tool, studies published to date have low participant numbers and mostly do not account for confounders such as medication use, socioeconomic status, intelligence quotient and the presence of mood disorders [121]. The signal-change generation by shifts in cognitive states or tasks is relatively small, and to detect them, numerous MRI acquisitions and long scanning sessions may be required. The use of fMRI is further limited by the lack of clear standards for interpreting haemodynamic responses as indirect measures of neuronal activity.

While a multi-modal imaging study of CD in SLE may capitalize on the high sensitivity and temporal resolutions of different but complementary tools to better characterize CD in SLE, further clarity as to how these imaging modalities augment clinical management is required (Fig. 2).

**Management**

While severe CD occurs in 3–5% in SLE patients, most who have a mild-to-moderate degree of CD run a benign course [28]. To date, there is no consensus guideline on the management of SLE-related CD. Owing to the multifactorial aetiology of SLE-related CD and variable involvement of cognitive domains, a multi-pronged, individualized approach involving a systematic appraisal of potential mimics and confounders as well as management of modifiable vascular risk factors for CD is warranted. See Fig. 3 for the proposed approach to CD in SLE patients.
Clinical history remains fundamental in recognizing CD in SLE patients. Besides characterizing the nature, magnitude and course of cognitive changes, history should always encompass a review of medical conditions that could affect cognition including vascular disease risk factors (such as hypertension and diabetes mellitus), pre-existing neurological disorders (such as stroke) and the use of medications that impair cognition (e.g. sleep aids and anxiolytics such as benzodiazepines; analgesics such as codeine-containing agents; anticholinergics such as tricyclic antidepressants and bladder antimuscarinics). The cognitive examination ought to identify the presence, severity and nature of cognitive impairment (e.g. memory versus language) and should incorporate cultural, linguistic and educational factors and consider mood symptoms or disorders that may confound the manifestations of CD [122]. Monastero et al. found that severity of depression was the only clinical factor that significantly predicted CD in SLE patients, highlighting the importance of assessing and treating depression in these patients [123].

**Non-pharmacological Interventions**

The utility of non-pharmacological interventions cannot be overstated. Engagement in regular physical activity has been linked to a decreased risk of cognitive decline, dementia and AD in numerous longitudinal studies [124–126]. Regular exercise has been shown to improve cognitive function through beneficial adaptations in vascular physiology and improved neurovascular coupling [127]. However, a pilot study demonstrated that SLE patients had lower exercise capacity than healthy controls, with poorer performance in memory, attention and visuoconstruction in those with lower diffusing capacity for carbon monoxide [128].

However, varying recommendations on physical activity abound because of the unclear dose-response relationship between exercise and cognition. In general, the risk of cognitive deterioration may be ameliorated with > 30 min of moderate-intensity aerobic exercise 5 days a week or vigorous-intensity aerobic exercise for a minimum of 20 min, 3 days every week [129].

Cognitive rehabilitation is a complementary therapeutic approach that involves intensive retraining of cognitive organization and memory skills by occupational therapists [130, 131].
It comprises psychoeducational intervention (cognitive behaviour therapy), the use of memory aids, prioritization, time optimization and cognitive training exercises [122]. Ruminations that ensue from delayed acceptance of the diagnosis of SLE may interfere with cognitive function [132]. Psychoeducation, with the aim of addressing these cognitive errors in SLE patients with self-perceived CD, may improve memory self-efficacy, memory function and ability to perform daily activities that require cognitive function [133]. Memory aids in the form of written reminders or smartphones also help our patients to better manage their activities of daily living. Prioritizing tasks is vital for patients with SLE-related CD, allowing them to focus on one task before proceeding with the next. Time optimisation involves engaging cognitively challenging tasks in the early part of the day and more relaxed tasks towards the end of the day. Cognitive training exercises (e.g. chess) may enhance executive function and problem-solving skills [122].

Pharmacological Interventions

Systemic Glucocorticoids Despite emerging evidence of immune-mediated mechanisms, the insidious nature of CD and its potential occurrence independent of systemic activity of SLE has shifted the risk-benefit assessment away from immunosuppressive therapy. While a small, prospective, double-blind placebo-controlled trial showed that the use of low-moderate doses of glucocorticoid (0.5 mg/kg) for 28 days resulted in improvement of cognition and mood in five of eight patients with mild SLE [134], several observational studies have failed to demonstrate concordance regarding the impact of glucocorticoid use on cognition in SLE patients [15, 16, 135, 136]. Both short- and long-term glucocorticoid use has been associated with deficits in declarative and verbal memory deficits in some studies [15, 137].

The mechanistic impact of glucocorticoids, in particular the dose, on neurocognitive function in SLE patients remains largely unclear. Glucocorticoids interact and interfere with neuronal receptors through the genomic and non-genomic pathways in the prefrontal cortex, hippocampus and basolateral amygdala, where memory and learning functions are mediated [138, 139]. Short-term therapy with high-dose glucocorticoids is associated with hippocampal atrophy and declarative memory deficits on structural neuroimaging [140]. Teo et al. showed that a daily prednisolone dose of higher than 9 mg had an independent adverse impact on mathematical processing in patients with SLE, which is an indicator of poorer working memory [141]. Another study that evaluated the impact of long-term use of moderate doses of prednisolone on executive function showed that SLE patients had lower cognitive flexibility and poorer decision-making ability compared to healthy controls [142]. Taken together, corticosteroids do not appear to be effective to treat CD in patients with SLE. Indeed, glucocorticoids may worsen CD especially in long-term use.

NMDAR Antagonist Acetylcholinesterase inhibitors were the first group of drugs approved in the US for the treatment of AD. These drugs inhibit the brain acetylcholinesterase, thereby increasing acetylcholine at the synaptic clefts. In a meta-analysis which involved ten randomized, double-blind, placebo-controlled trials of a 6-month duration of drug exposure, acetylcholinesterase inhibitors were found to be associated with a 2.4-point slower decline in a cognition outcome measure that ranged from 0 to 70 [143]. While this improvement is equivalent to about 6 months of cognitive decline from natural history studies of AD dementia, whether this magnitude of change is clinically important remains uncertain [144]. The efficacy of anticholinesterase inhibitors is similar amongst the individual drugs (donepezil, rivastigmine, galantamine) [145]. Unfortunately, acetylcholinesterase inhibitors have not been assessed in any randomised controlled trial involving SLE patients with CD.

As neurodegeneration in AD progresses, further cognitive and functional decline invariably occurs. Memantine, an NMDAR antagonist, may be considered for patients with moderate to severe dementia. As with acetylcholinesterase inhibitors, the modest effect of memantine in slowing cognitive decline in AD was evaluated.
in 51 SLE patients with CD. This 12-week trial failed to demonstrate a significant improvement in cognitive performance with memantine use in SLE patients compared to placebo, even though the trial was likely underpowered [146]. Future well-designed studies on acetylcholinesterase inhibitors to treat CD in SLE are eagerly awaited.

**Anticoagulation/Antiplatelet Therapy** While no clinical trial has assessed the benefit of anticoagulation or antiplatelet therapy in SLE patients with CD in the absence of thromboembolic phenomena, observational studies have reported some utility with antiplatelets [15, 147]. In a 3-year prospective study assessing predictors of CD in 123 SLE patients, regular use of low-dose aspirin improved cognitive function as gauged by the ANAM total score in SLE patients of all ages with or without aPLs compared to those not taking aspirin [15]. The beneficial impact of aspirin on cognitive function improvement was particularly evident in older patients who also had cardiovascular risk factors, particularly diabetes [15].

**C5a Receptor Blockade** The abrogation of the BBB as a pathogenic mechanism of SLE-related CD has prompted much interest and research into the preservation of its integrity. C5a receptor blockade ameliorates BBB disruption and attenuates behavioural abnormalities in MRL/lpr lupus prone mice [72], revealing a potential therapeutic target for CD. Rho-kinase inhibitors have also shown promise in reducing BBB permeability in in vitro human models [148], but have yet to be evaluated in the context of SLE.

**CONCLUSION**

CD has a substantial impact on the HRQoL of patients with SLE. The ascertainment of CD in SLE is, however, challenging. The current knowledge regarding the pathogenesis of CD in SLE remains elusive although it is likely an interplay of multifactorial aetiologies. The lack of specific serum, CSF and radiological biomarkers contributes to the difficulty in achieving accurate diagnosis of and monitoring for CD in patients with SLE. The current standard of practice encompasses eliciting a good clinical history of impaired functioning, supported by objective assessment via comprehensive neuropsychological testing. A multi-modal approach to diagnostic imaging allows for better characterization of CD in SLE, as it capitalizes on the high sensitivity and temporal resolutions of complementary imaging techniques. While several potential treatment strategies appear promising, much work remains to explore and validate clinically relevant biomarkers and end points for clinical use. Further efforts to elucidate interventions that are effective and sustainable in different geographic, economic and cultural settings should be undertaken. Future clinical studies will require well-defined cohorts with diligent adjustment for confounding variables, including coexisting neurological and psychiatric disease, medications, comorbidities and psychosocial factors.

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