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The immunologic etiology of psychiatric manifestations in systemic lupus erythematosus: A narrative review on the role of the blood brain barrier, antibodies, cytokines and chemokines

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ABSTRACT

Introduction: The aim of this narrative review is to provide an overview of the literature on the possible immunologic pathophysiology of psychiatric manifestations of neuropsychiatric systemic lupus erythematosus (NPSLE).

Methods: A systematic search on PubMed was conducted. English studies with full text availability that investigated the correlation between blood-brain barrier (BBB) dysfunction, intrathecal synthesis of antibodies, antibodies, cytokines, chemokines, metalloproteinases, complement and psychiatric NPSLE manifestations in adults were included.

Results: Both transient BBB-dysfunction with consequent access of antibodies to the cerebrospinal fluid (CSF) and intrathecal synthesis of antibodies could occur in psychiatric NPSLE. Anti-phospholipid antibodies, anti-NMDA antibodies and anti-ribosomal protein p antibodies seem to mediate concentration dependent neuronal dysfunction. Interferon-α may induce microglial engulfment of neurons, direct neuronal damage and production of cytokines and chemokines in psychiatric NPSLE. Several cytokines, chemokines and matrix metalloproteinase-9 may contribute to the pathophysiology of psychiatric NPSLE by attracting and activating Th1-cells and B-cells.

Discussion: This potential pathophysiology may help understand NPSLE and may have implications for the diagnostic management and therapy of psychiatric NPSLE. However, the presented pathophysiological model is based on correlations between potential immunologic etiologies and psychiatric NPSLE that remain questionable. More research on this topic is necessary to further elucidate the pathophysiology of NPSLE.

1. Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease. The disease has a prevalence of 81 per 100.000 persons in Caucasians and 212 per 100.000 in black persons. The female to male ratio is 9:1 for both ethnic groups [1]. SLE has a broad variety of

Abbreviations: SLE, Systemic lupus erythematosus; NPSLE, Neuropsychiatric systemic lupus erythematosus; ACR, American College of Rheumatology; CSF, Cerebrospinal fluid; BBB, Blood-brain barrier; MMP-9, Matrix metalloproteinase-9; IL, Interleukin; TNF, Tumour necrosis factor; APL, Anti-phospholipid antibody; aCL, Anti-cardiolipin antibody; ANA, Anti-nuclear antibody; Anti-dsDNA, Anti-double stranded DNA antibody; Anti-Sm, Anti-Smith antibody; Anti-RP, Anti-ribosomal protein p antibody; Anti-NMDA, Anti-N-Methyl-D-Aspartate antibody; IFN-α, Interferon-α; APRIL, A proliferation inducing ligand; MCP-1, Monocyte chemoattractant protein-1; IP-10, Interferon-gamma induced protein-10; Th1-cell, T-helper-1 cell; BAFF, B-cell activating factor of TNF family; IFN-γ, Interferon-γ; PDC, Plasmacytoid dendritic cell; AECA, Anti-endothelial cell antibody; LPS, Lipopolysaccharides

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Table 1
Neuropsychiatric manifestations of SLE according to the American College of Rheumatology (ACR) [2]

Central nervous system - Neurologic	Central nervous system - Psychiatric	Peripheral nervous system
Aseptic meningitis	Acute confusional state	Guillain-Barré syndrome
Cerebrovascular disease	Anxiety disorder	Autonomic neuropathy
Demyelinating syndrome	Cognitive dysfunction	Mononeuropathy
Headache	Mood disorder	Myasthenia gravis
Movement disorder	Psychosis	Cranial neuropathy
Seizure disorder		Plexopathy
Myelopathy		Polyneuropathy

This table shows the neuropsychiatric manifestations of SLE according to the American College of Rheumatology. NPSLE manifestations are divided into central neurologic manifestations, psychiatric manifestations and peripheral nervous system manifestations.

manifestations. Neurologic and psychiatric manifestations are among the least understood. SLE is classified as neuropsychiatric (NPSLE) and consists of 19 neuropsychiatric manifestations (see Table 1), ranging from central neurologic and psychiatric manifestations to peripheral neurologic manifestations [2]. The distinction between the central neurologic and psychiatric manifestations is partially overlapping and somewhat arbitrary. Of these, there are seven mainly neurologic manifestations and five mainly psychiatric manifestations (see Table 1) [2]. The prevalence of NPSLE, based on literature reports, ranges from 27% to 80% in adults with SLE. The broad range illustrates the lack of a clear definition, diagnostic consensus and systematic studies on this subject [3]. Moreover, the prevalence of frequently occurring distinct psychiatric manifestations in SLE patients has not been studied systematically. As a consequence of the lack of diagnostic consensus and the lack of a clear definition, psychiatric manifestations in SLE patients often remains undiagnosed [3]. Importantly, NPSLE patients frequently experience a relevant decrease in health-related quality of life [4–6]. In summary, NPSLE composes a relevant problem that often remains undiagnosed. Thus, understanding the pathophysiology of psychiatric NPSLE is of considerable importance.

Many studies have investigated possible pathophysiological pathways leading to psychiatric manifestations in NPSLE. Studies primarily focused on the role of autoantibodies, cytokines and blood-brain barrier dysfunction. It remains unclear, however, how these elements interact to establish a common pathophysiology.

The aim of this narrative review is to provide an overview of the literature on the possible immunologic etiologies of psychiatric manifestations attributed to SLE. Distinct neurologic manifestations are not considered. Furthermore, this review aims to draw a connection between immunological features of SLE and psychiatric morbidity attributed to SLE based on literature reports.

2. Methods

A PubMed search with the following Mesh terms or words in title/abstract was performed: 'Neuropsychiatric systemic lupus erythematosus' or 'Central nervous system lupus vasculitis' or 'Central nervous system lupus' or 'Central nervous system systemic lupus erythematosus' or 'Lupus meningoencephalitis' or 'NPSLE' and 'Blood-brain barrier' or 'Antibody' or 'Antibodies' or 'Immunoglobulin' or 'Immunoglobulins' or 'Cytokines' or 'Chemokines' or 'Serum' or 'CSF' or 'Cerebrospinal'. No restrictions concerning the date of publication were applied.

2.1. Inclusion criteria

All studies that focused on the association between immunologic aspects and psychiatric NPSLE manifestations were included. Studies that investigated the correlation between immunologic molecules (antibodies, cytokines, chemokines, metalloproteinases, complement) in serum or cerebrospinal fluid (CSF) and psychiatric NPSLE manifestations were included. Moreover, studies that considered the association between markers for blood-brain barrier dysfunction or intrathecal synthesis of antibodies and psychiatric NPSLE manifestations were incorporated. Only studies that focused on adults, studies with full text availability and studies in English were included. References of included articles were scrutinized for relevant additional literature. Included articles were used to extract main pathophysiological elements of psychiatric NPSLE. These elements were identified according to the conclusions and theoretical framework of the included articles. A proposed pathophysiology based on these elements was constructed.

2.2. Exclusion criteria

Non-human studies and studies that merely focused on non-psychiatric NPSLE manifestations were excluded.

3. Results

The search yielded 1158 articles (Fig. 1). After application of the inclusion and exclusion criteria, 125 articles were included. Investigation of the references of these articles yielded 53 more articles, resulting in 178 articles for inclusion.

3.1. The role of the blood brain barrier and intrathecal synthesis of antibodies

A relatively small number of studies (N = 8) focused on the role of the blood-brain barrier (BBB) in the pathophysiology of psychiatric manifestations of NPSLE. Under normal circumstances, the BBB endothelium prevents leukocytes and inflammatory mediators from entering the brain parenchyma and causing inflammation [7]. Consequently, (transient) BBB dysfunction in NPSLE may lead to inflammatory mediators, such as plasma cells, accessing the cerebrospinal fluid and cerebrum and produce intrathecal antibodies [7].

Studies on the correlation between cerebrospinal fluid markers of BBB function in humans (such as Q albumin [8–14], S100B [15], anti-S100B [15]) and psychiatric NPSLE manifestations yielded contradictory results. In these studies with contradictory results, Q albumin was compared between NPSLE patients and SLE patients (without known NPSLE) or patients with a different neurologic disease [8–14]. S100B and anti-S100B levels were determined in SLE patients and correlated to results of neuropsychological tests validated for diagnosing depression and cognitive dysfunction (Beck's Depression inventory, Automated Neuropsychological Assessment Metrics). No correlation with depression or cognitive dysfunction was found [15]. Three studies found disruption of the BBB in a subgroup of patients presenting with neuropsychiatric symptoms according to the ACR classification [8,10,13].

A considerable number of methodologically similar (N = 8) of studies found evidence for the intrathecal synthesis of several different antibodies in NPSLE patients with psychiatric manifestations [8,10,13,14,16–19], while only one study showed no such association [9]. Under normal circumstances, the BBB prevents transport of antibodies and leukocytes from the serum to the CSF. Consequently, impairment of BBB dysfunction is imperative for plasma cells to access the CSF and produce antibodies intrathecally. Research yielded convincing evidence for intrathecal synthesis of antibodies in psychiatric NPSLE, while the evidence for persistent BBB dysfunction is inconsistent. This contradiction may be explained by a transient nature of BBB dysfunction in NPSLE. This is demonstrated by the evidence for BBB dysfunction in studies that featured NPSLE patients presenting with neuropsychiatric symptoms at the time of measuring the Q albumin. Transient BBB dysfunction may also explain the lack of evidence for

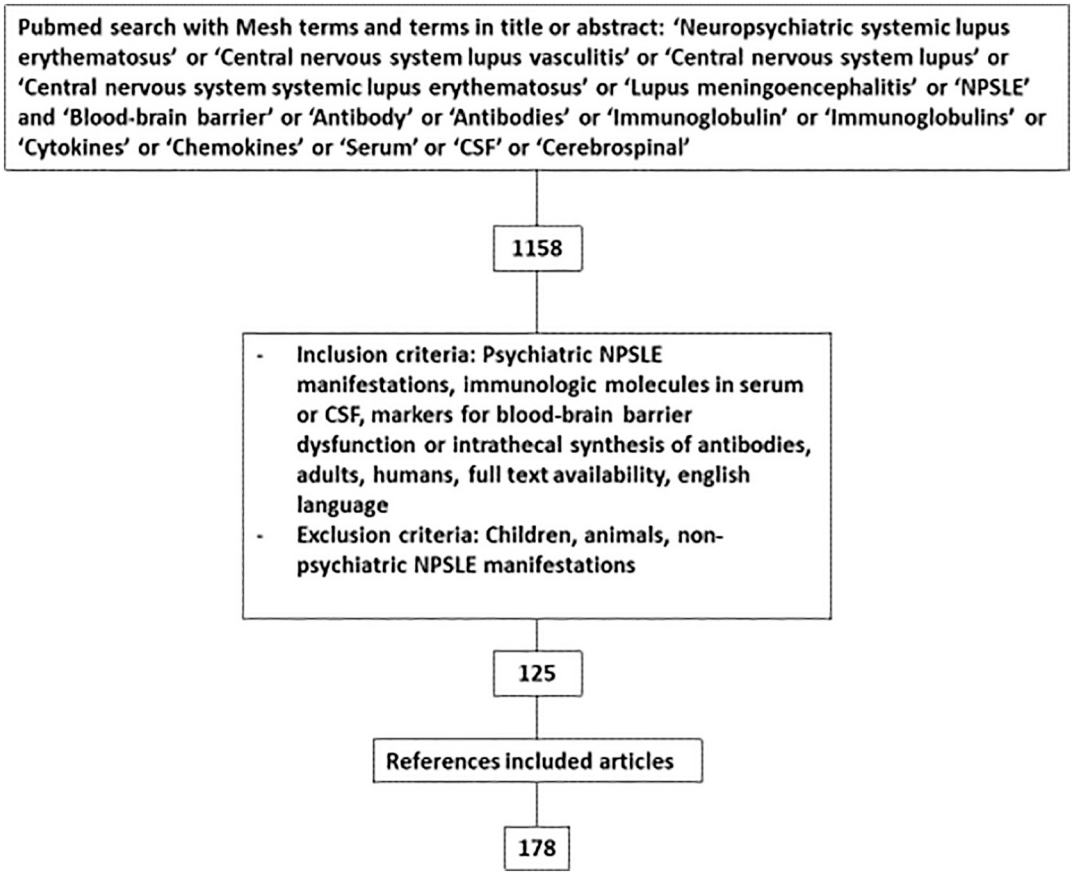

Fig. 1. Search strategy.
This figure shows the search strategy used to find literature on the research topic. 178 articles were included.

BBB dysfunction in methodologically comparable studies. Yet, this contradiction may also be explained by intrathecal synthesis of antibodies in NPSLE by activated plasma cells without (transient) BBB dysfunction.

In psychiatric NPSLE, potential transient BBB dysfunction may be caused by triggers such as infections and stress; in conjunction with fluctuations of serum levels of antibodies and pro-inflammatory cytokines. Antibodies may cause BBB dysfunction by causing a microangiopathy (anti-endothelial cell antibodies) [20], mediating apoptosis (anti-endothelial cell antibodies, anti-ribosomal protein antibodies, anti-U1-70k antibodies) [7,21–24], inducing production of cytokines and leukocyte adhesion molecules (anti-NMDA antibodies, anti-phospholipid antibodies) [22,25] or by damaging astrocytes (anti-glial fibrillary protein antibodies) [26,27]. Likewise, pro-inflammatory cytokines [7,20,22] and matrix metalloproteinase-9 [7,20,22] (MMP-9) induce production of cytokines and leukocyte adhesion molecules by endothelial cells, facilitating the entry of leukocytes and proteins into the CSF [22,28,29]. Activation of the complement system may also be implicated in BBB-dysfunction [30]. Finally, bacterial lipopolysaccharides cause enhanced BBB permeability during infections by stimulating the production of Interleukin(IL)-1 and Tumor necrosis factor (TNF) [29,31], while epinephrine increases the cerebral blood flow and impairs BBB function during stress [16,32].

3.2. Autoantibodies and psychiatric NPSLE manifestations

Many researchers have investigated the role of autoantibodies in the pathophysiology of NPSLE. Several different antibodies may access the CSF, potentially after transient BBB dysfunction, and contribute to the immunologic pathophysiology of psychiatric NPSLE by mediating neuronal dysfunction or apoptosis, dependent of their concentration and location [8,27,31]. These antibodies can be roughly divided into the following categories: anti-phospholipid antibodies (APL), anti-nuclear antibodies (ANA), antibodies against neuronal antigens and anti-endothelial antibodies (AECA). The associations between the most important antibodies and NPSLE that have been demonstrated or refuted in different studies are illustrated in Table 2. Merely antibodies that seem to play an important role in the pathophysiology of psychiatric NPSLE are discussed in the paragraphs below. A complete overview of the associations between antibodies [33–79] and NPSLE is represented in appendix A.

The majority of the studies seem to suggest an association between serum APL, NPSLE and cognitive dysfunction specifically. APL may both induce neuronal dysfunction and thrombosis in NPSLE.

Various studies found a correlation between serum APL, NPSLE [80–86], cognitive dysfunction [80,87–91] and lupus psychosis [92]; while the correlation between serum APL, psychiatric NPSLE manifestations [93–99] and cognitive dysfunction specifically [100] could not be confirmed by different studies. Specifically, antibodies against cardiolipin (aCL) in serum or CSF have been frequently associated with psychiatric NPSLE manifestations [9,10,17,80,83–85,98,99,101–105,110] and cognitive dysfunction in particular [100,105–108]; although various studies (N = 12) showed conflicting results concerning the correlation with psychiatric NPSLE [9,10,17,81,109,111–117].

APL bind to several antigens on negatively charged phospholipids [80,162]. This interaction leads, amongst others, to thrombosis in small blood vessels in the brain [163]. However, APL are also associated with direct neuronal damage by inducing oxidative stress and damage to neuronal cell membranes via β2-glycoprotein. This second mechanism seems to play a more important role in the pathophysiology of psychiatric NPSLE [164–167].

ANA are directed against nuclear antigens and, amongst others,

Table 2
Antibodies and their associations with NPSLE

Antibody	Medium	Studies that found an association with NPSLE (no. of patients)	Studies that found no association with NPSLE (no. of patients)
APL	Serum	Ho et al. 2016 (5539) [80] Borowoy et al. 2012 (1253) [81] Mok et al. 2012 (252) [82] Mikdashi et al. 2004 (130) [83] Sanna et al. 2003 (323) [84] Mok et al. 2001 (518) [85] Toubi et al. 1995 (196) [86] Murray et al. 2012 (694) [87] Tomietto et al. 2007 (52) [88] McLaurin et al. 2005 (123) [89] Leritz et al. 2002 (56) [90] Jacobson et al. 1999 (27) [91] Appenzeller et al. 2008 (528) [92]	Kozora et al. 2012 (43) [93] Kellner et al. 2010 (58) [94] Kamen et al. 2008 (184) [95] Shimojima et al. 2005 (62) [96] Houman et al. 2004 (100) [97] Afeltra et al. 2003 (61) [98] Abdul-Sattar et al. 2013 (84) [99] Hanly et al. 1999 (51) [100]
aCL	Serum	Ho et al. 2016 (5539) [80] Mikdashi et al. 2004 (130) [83] Sanna et al. 2003 (323) [84] Mok et al. 2001 (518) [85] Afeltra et al. 2003 (61) [98] Abdul-Sattar et al. 2013 (84) [99] Hanly et al. 1999 (51) [100] Love et al. 1990 (1000) [101] Baraczka et al. 2004 (13) [102] Karassa et al. 2000 (128) [103] Sabbadini et al. 1999 (114) [104] Conti et al. 2012 (58) [105] Zandman-Goddard et al. 2007 (-*) [106] Peretti et al. 2012 (31) [107] Menon et al. 1999 (45) [108]	Jedryka-Goral et al. 2000 (15) [9] Martinez-Cordero et al. 1997 (32) [10] Lai et al. 2000 (31) [17] Borowoy et al. 2012 (1253) [81] Hanly et al. 2011 (1047) [109] Hanly et al. 2015 (1827) [110] Fragoso-Loyo et al. 2008 (96) [111] Conti et al. 2004 (51) [112] Yoshio et al. 1995 (70) [113] Pereira et al. 1992 (50) [114] Hanly et al. 1992 (10) [115] Costallat et al. 1990 (66) [116] Hanly et al. 1993 (70) [117]
	CSF	Martinez-Cordero et al. 1997 (32) [10] Lai et al. 2000 (31) [17] Baraczka et al. 2004 (13) [102]	Jedryka-Goral et al. 2000 (15) [9] Fragoso-Loyo et al. 2008 (96) [111] Pereira et al. 1992 (50) [114]
Anti-RP	Serum	West et al. 1995 (66) [18] Abdel-Nasser et al. 2008 (68) [23] Ho et al. 2016 (5539) [80] Borowoy et al. 2012 (1253) [81] Mok et al. 2012 (252) [82] Baraczka et al. 2004 (13) [102] Hanly et al. 2011 (1047) [109] Yoshio et al. 1995 (70) [113] Hanly et al. 2008 (412) [118] Brey et al. 2002 (128) [119] Jönsen et al. 2003 (44) [120] Watanabe et al. 1996 (144) [121] Mahler et al. 2006 (947) [122] Tzioufas et al. 2000 (178) [123] Arnett et al. 1996 (394) [124] Schneebaum et al. 1991 (269) [125] Karimifar et al. 2013 (100) [126] Unterman et al. 2011 (1439) [127] Briani et al. 2009 (219) [128] Massardo et al. 2002 (138) [129] Isshi et al. 1998 (87) [130] Georgescu et al. 1997 (336) [131] Isshi et al. 1996 (75) [132] Nojima et al. 1992 (91) [133] Bonfa et al. 1986 (59) [134] Bonfa et al. 1987 (2) [135]	Shimojima et al. 2005 (62) [96] Afeltra et al. 2003 (61) [98] Hanly et al. 2015 (1827) [110] Fragoso-Loyo et al. 2008 (96) [111] Conti et al. 2004 (51) [112] Hanly et al. 1992 (10) [115] Tikly et al. 1996 (111) [136] Winfield et al. 1978 (25) [137] Yoshio et al. 2005 (70) [138] Pradhan et al. 2015 (120) [139] Jarpa et al. 2011 (83) [140] Nery et al. 2008 (71) [141] Karassa et al. 2006 (1537) [142] Gerli et al. 2002 (149) [143] Asero et al. 1988 (324) [144] Yalaoui et al. 2002 (100) [145] Kozora et al. 1996 (51) [146] Teh et al. 1993 (62) [147] Bai et al. 2016 (149) [148] Almeida et al. 2002 (60) [149] Teh et al. 1992 (116) [150]
	CSF	Baraczka et al. 2004 (13) [102] Yoshio et al. 2005 (70) [138] Hirohata et al. 2007 (72) [151] Golombek et al. 1986 (31) [152]	Fragoso-Loyo et al. 2008 (96) [111] Isshi et al. 1998 (87) [130] Isshi et al. 1996 (75) [132]
Anti-NMDA	Serum	Gono et al. 2011 (107) [153] Lapteva et al. 2006 (60) [154] Omdal et al. 2005 (57) [155]	Gulati et al. 2016 (57) [15] Kozora et al. 2010 (43) [32] Ho et al. 2016 (5539) [80] Sanna et al. 2003 (323) [84] Kozora et al. 2012 (43) [93] Houman et al. 2004 (100) [97] Hanly et al. 2011 (1047) [109] Fragoso-Loyo et al. 2008 (96) [111] Hanly et al. 2008 (412) [118] Hanly et al. 2006 (65) [156] Arinuma et al. 2008 (56) [157] Harrison et al. 2006 (93) [158]

(*continued on next page*)

Table 2 (*continued*)

Antibody	Medium	Studies that found an association with NPSLE (no. of patients)	Studies that found no association with NPSLE (no. of patients)
			Steup-Beekman et al. 2007 (51) [159] Husebye et al. 2005 (109) [160]
	CSF	Hirohata et al. 2014 (81) [8] Fragoso-Loyo et al. 2008 (96) [111] Arinuma et al. 2008 (56) [157] Yoshio et al. 2006 (80) [161]	

This table shows the studies that advocated or refuted the association between several antibodies in serum and/or cerebrospinal fluid and NPSLE. The number of patients that participated in the different studies is represented in parentheses. APL = Anti-phospholipid antibodies, aCL = Anti-cardiolipin antibodies, Anti-RP = Anti-ribosomal protein antibodies, Anti-NMDA = Anti-N-methyl-D-aspartate antibodies, CSF = Cerebrospinal fluid, NPSLE = Neuropsychiatric systemic lupus erythematosus, * = Narrative review.

consist of anti-double stranded DNA (anti-dsDNA), anti- Ro, anti-La, anti-Smith (anti-Sm) and anti-ribosomal protein (anti-RP). Studies on the association between these antibodies and NPSLE have yielded conflicting results. However, more convincing evidence concerning the association between anti-RP in serum/CSF, depression and psychosis suggests a role for anti-RP in the pathogenesis of these NPSLE manifestations by mediating concentration dependent neuronal dysfunction or apoptosis.

Several studies demonstrated a correlation between anti-RP in serum or CSF, psychiatric NPSLE [18,23,80,102,113,118,122,23,138,151] and more specifically depression [23,80,120,124–126] and lupus psychosis [80–82,109,119–121,124–135,152]. An important number of studies (N = 20) could not confirm the association between anti-RP in serum or CSF and psychiatric NPSLE as a group [81,82,96,98,111,112,115,132,134,137,139–147,151], though considerably fewer studies disputed the association between serum anti-RP, depression [110,148–150] and psychosis [113,136,149,150]. Accordingly, anti-RP might be associated with psychiatric NPSLE. Yet, evidence remains inconsistent.

Anti-RP are directed against different ribosomal proteins and induce concentration dependent neuronal dysfunction or apoptosis by increasing intracellular calcium release and disruption of protein synthesis [80,168]. Anti-RP may induce apoptosis in neurons by binding to ribosomal protein like antigens on the neuronal cell surface; consequently stimulating intracellular calcium release [169]. Moreover; Anti-RP may cause apoptosis by binding to a variant of ribosomal proteins on the neuronal cell surface, penetrate the neuron and inhibit protein synthesis [170,171]. Interestingly, low concentrations of anti-RP caused impairment of neuronal function (synaptic transmission), whereas high concentrations of anti-RP induced apoptosis [169,172].

Antibodies in NPSLE can be directed against several extra- and intracellular neuronal antigens. Convincing evidence suggests an important role for anti-neuronal antibodies in both serum and CSF in the pathophysiology of psychiatric NPSLE manifestations by mediating diffuse neuronal damage and impairment of synaptic transmission. Particularly, anti-NMDA antibodies in CSF seem to be well associated with psychiatric NPSLE manifestations [8,111,157,159].

Nevertheless, only three studies found an association between serum anti-NMDA with psychiatric NPSLE manifestations [153–155]; while a vast number of studies contradicted the correlation between serum anti-NMDA, psychiatric NPSLE manifestations [32,80,84,97,109,111,118,156–160] and more specifically depression [80,93,118,158] and cognitive dysfunction [15,93,118,154,156,158].

Anti-neuronal antibodies contribute to the pathophysiology of psychiatric NPSLE by mediating (concentration dependent) diffuse neuronal damage and impairing synaptic transmission. Anti-neuronal antibodies cause diffuse neuronal damage by directly binding to antigens on the neuronal cell surface [27,80]. Anti-NMDA antibodies are anti-dsDNA antibodies that interact with glutamate receptors [140,173–175]. Anti-NMDA antibodies activate glutamate receptors and induce an intracellular increase of sodium and calcium, causing neuronal apoptosis by activating caspase 3 [176,177]. Furthermore, anti-NMDA causes neuronal apoptosis by modifying mitochondrial activity [178,179]. Again, Low concentrations of anti-NMDA seem to impair synaptic transmission, while high concentrations seem to cause neuronal apoptosis [8,31,173].

3.3. Cytokines, chemokines, matrix metalloproteinase-9, complement and NPSLE

Although not as extensively studied as antibodies, interest in the significance of cytokines and chemokines in NPSLE has been growing recently. IL-6 in CSF is convincingly associated with psychiatric NPSLE and may be produced by neurons, endothelial cells and glial cells (induced by Interferon-α (IFN-α)). A proliferation inducing ligand (APRIL) may also be correlated with NPSLE, although research is scant. Both IL-6 and APRIL stimulate B-cell activation and survival and may play an important role in the synthesis of antibodies in psychiatric NPSLE. Despite of contradictory evidence; IFN-α (produced by plasmacytoid dendritic cells after endocytosis of immune complexes) may play a pivotal role in the pathogenesis of diffuse NPSLE manifestations by inducing microglial engulfment of neurons, direct neuronal damage and production of other pro-inflammatory cytokines and chemokines by microglia (IL-6, IL-8, Monocyte chemoattractant protein-1 (MCP-1), Interferon-gamma induced protein-10 (IP-10)). IL-10 production by neurons or glial cells may be important by regulating the immune response in NPSLE, in conjunction with peripherally produced TNF-α. Chemokines IL-8, MCP-1 and IP-10 seem to be well correlated with psychiatric NPSLE and may contribute to the pathophysiology by mediating a T-helper-1 (Th1) cell response. IL-8 may be produced by neurons, glial cells or endothelial cells; while MCP-1 and IP-10 may be produced by microglia. Few studies on the association between MMP-9 (involved in T-cell migration), complement (involved in mediating BBB dysfunction and microglial engulfment of neurons) and psychiatric NPSLE have been conducted.

IL-6 is a cytokine that is involved in B-cell activation [180]. IL-6 in CSF was associated with psychiatric NPSLE manifestations by a significant number of studies [8,12,14,19,29,152,181–189], while only two studies could not confirm this association [28,120]. Research on the correlation between serum IL-6 and psychiatric NPSLE provided inconclusive results [93,183,186]. Antibodies stimulate the production of IL-6 by endothelial cells and neurons [8,185]. Moreover, IFN-α may stimulate the production of IL-6 by microglia [190].

Santer et al. demonstrated a significant association between IFN-α in CSF and NPSLE [180]. Yet, additional studies on the correlation between IFN-α in CSF or serum and psychiatric NPSLE manifestations yielded contradictory results [14,19,93,94,120,191–194]. Increased levels of IFN-α in the CSF of NPSLE patients may be the result of

plasmacytoid dendritic cell activation by immune complexes consisting of anti-neuronal antibodies and neuronal antigens [190]. IFN-α seems to cause damage by activating microglia in the CSF [195,196]. IFN-α stimulates the microglial engulfment of neuronal cells; a process in which microglial cells internalize neuronal cell components. Degradation of these neuronal cell components causes damage to neuronal cells and may cause apoptosis [195]. Antibodies against neuronal cells and complement may be important in the initiation of this process [196]. Furthermore, IFN-α may impair brain function by altering levels of neurotransmitters and generating toxic metabolites [190]. Finally, IFN-α may mediate damage by secondary release of cytokines and chemokines, such as IL-6 and IP-10 [190].

Several studies showed an association between IL-10 in both serum [197] and CSF [29,182,192,197] and NPSLE, although these results were disputed by different studies [28,120,181,183]. IL-10 could be produced by neurons and glial cells [185,191]. IL-10 has an inhibitory effect on macrophages and regulates the immune response [190].

Only one study found a significant association between APRIL in CSF and psychiatric NPSLE, yet not between B-cell activating factor of TNF family (BAFF) in CSF and psychiatric NPSLE [12]. BAFF and APRIL are important factors in the survival of B-cells [25]. The mechanism behind a potential elevation of these cytokines in the CSF has not been identified. Interestingly; Belimumab, a monoclonal antibody against BAFF, has been associated with an increased risk of psychiatric adverse effects such as depression and anxiety [198]. Elaborate research on the effect of Belimumab on psychiatric NPSLE manifestations has not been conducted yet. Research on this topic could be relevant for the identification of a possible correlation between BAFF and psychiatric NPSLE manifestations.

Studies on the correlation of TNF-α in both serum and CSF with psychiatric NPSLE showed conflicting results [19,28,120,181–183,187,197]. Peripherally produced TNF-α may cause damage in the central nervous system [197]. However, TNF-α may have a protective effect in SLE; as displayed by the induction of SLE in some rheumatoid arthritis patients treated with anti-TNF-α-therapy [199,200]. Research on the effect of Anti-TNF-α therapy on psychiatric NPSLE manifestations has not been conducted. Again, research on this topic may be important to elucidate a possible protective role for TNF-α in psychiatric NPSLE.

Interferon-γ (IFN-γ), produced by Th1-cells [190], in serum and CSF was associated with psychiatric NPSLE by a single study [197]; though a majority of studies refuted this association [28,93,120,181]. Few studies showed a correlation between IL-1β in CSF [185] respectively serum [183], transforming growth factor β in serum [27] and psychiatric NPSLE. No association between CSF or serum levels of IL-1β [19,28,93], IL-2 [28,120,181,187], IL-4 [28,136,197], IL-12 [28], IL-17 [28] and psychiatric NPSLE was found.

Four studies found a significant association between IL-8 in CSF and NPSLE [28,29,152,184], while only two studies contested this association [14,183]. IL-8, unlike many other interleukins, is a chemokine that is involved in leukocyte chemotaxis [201,202]. IL-8 may be produced by neuronal and glial cells [185,191] after induction by immune complexes [190] or by endothelial cells after binding of antibodies [8].

A few studies demonstrated an association between MCP-1 in CSF and NPSLE [28,181,203,204]. MCP-1 is a chemokine that attracts monocytes and T-cells. MCP-1 binds the CCR2-receptor, which is only expressed in T-cells after induction by IL-2 [203,205]. Again, the production of MCP-1 by microglia may be induced by the activity of immune complexes [190].

Three studies showed a correlation between IP-10 in CSF and NPSLE [181,204,206], although one study could not confirm this association [28]. IP-10 mainly attracts Th1-cells and is secreted by monocytes and fibroblasts after stimulation by IFN-γ [207]. The production of IP-10 may be promoted by immune complexes and IFN-α [180]. Interestingly, one study found a significantly higher IP-10/MCP-1-ratio in NPSLE patients than in SLE patients without NPSLE [204]. Both chemokines may be implicated in the pathogenesis of psychiatric NPSLE by initiating a Th1-cell response [207].

Few studies on the correlation between RANTES [28,181], monokine induced by IFN-γ [181], fractalkine [208,209], kallikrein [183], kininase-2 [183] and psychiatric NPSLE manifestations have been conducted with inconclusive results.

One study demonstrated an association between CSF levels of MMP-9, psychiatric NPSLE and markers for neuronal/astrocytic damage [210]; while a different study found an association between serum levels of MMP-9 and psychiatric NPSLE [211]. MMP-9 is an endoproteinase [212,213] that is secreted by macrophages, T-cells and endothelial cells [213] and may be induced by IL-6 and IL-8 [210]. MMP-9 may contribute to the pathogenesis of psychiatric NPSLE by stimulating T-cell migration [213].

The role of the complement system in NPSLE has not been investigated extensively. Two studies showed a correlation between C3 and C4 levels in serum and psychiatric NPSLE manifestations [121,214], although four different studies did not support this association [94,103,108,126]. As mentioned previously, complement may contribute to the pathophysiology of psychiatric NPSLE manifestations by facilitating microglial engulfment of neuronal cells and by inducing BBB dysfunction.

4. Conclusion: integration of elements into a pathophysiologic model for psychiatric NPSLE

In summary, potential (transient) BBB dysfunction in NPSLE may be caused by triggers such as infections or stress; in conjunction with fluctuations in serum levels of antibodies (APL, anti-RP, AECA), cytokines (TNF-α, IL-1β), MMP-9 and complement. BBB dysfunction may allow antibodies such as APL, anti-NMDA and anti-RP to access the CSF and mediate neuronal dysfunction (impairment of synaptic transmission and/or mitochondrial metabolism) or apoptosis, dependent of their concentration. However, as mentioned earlier, intrathecal synthesis of antibodies in NPSLE could also occur without (transient) BBB dysfunction. Ensuing neuronal cell damage, antibodies in the CSF may form immune complexes with neuronal antigens.

Immune complexes may be endocytosed by plasmacytoid dendritic cells, which produce IFN-α. IFN-α may play a pivotal role in the pathogenesis of diffuse NPSLE manifestations by inducing microglial engulfment of neurons (possibly facilitated by antibodies and complement), direct neuronal damage and production of different pro-inflammatory cytokines and chemokines by microglia (IL-6, IL-8, MCP-1, IP-10).

Chemokines IL-8 (produced by endothelial cells and neuronal cells after binding of antibodies and by microglia), MCP-1 and IP-10 (both produced by microglia) mediate a cellular immune response in psychiatric NPSLE by attracting Th1-cells. This cellular immune response is further induced by IL-2 (produced by neurons after binding of antibodies) and MMP-9 (produced by several different cells after induction by Il-6 and IL-8), which stimulates T-cell migration.

Cytokines IL-6 (produced by endothelial cells and neuronal cells after binding of antibodies and by microglia) and APRIL (possibly produced peripherally) stimulate B-cell activation and survival, consequently inducing intrathecal synthesis of antibodies.

IL-10 (produced by neurons after binding of antigens) and TNF-α (possibly produced peripherally) may be important in the pathophysiology of psychiatric NPSLE by regulating the immune response.

An overview of the immunologic pathophysiology of psychiatric NPSLE is represented in Fig. 2.

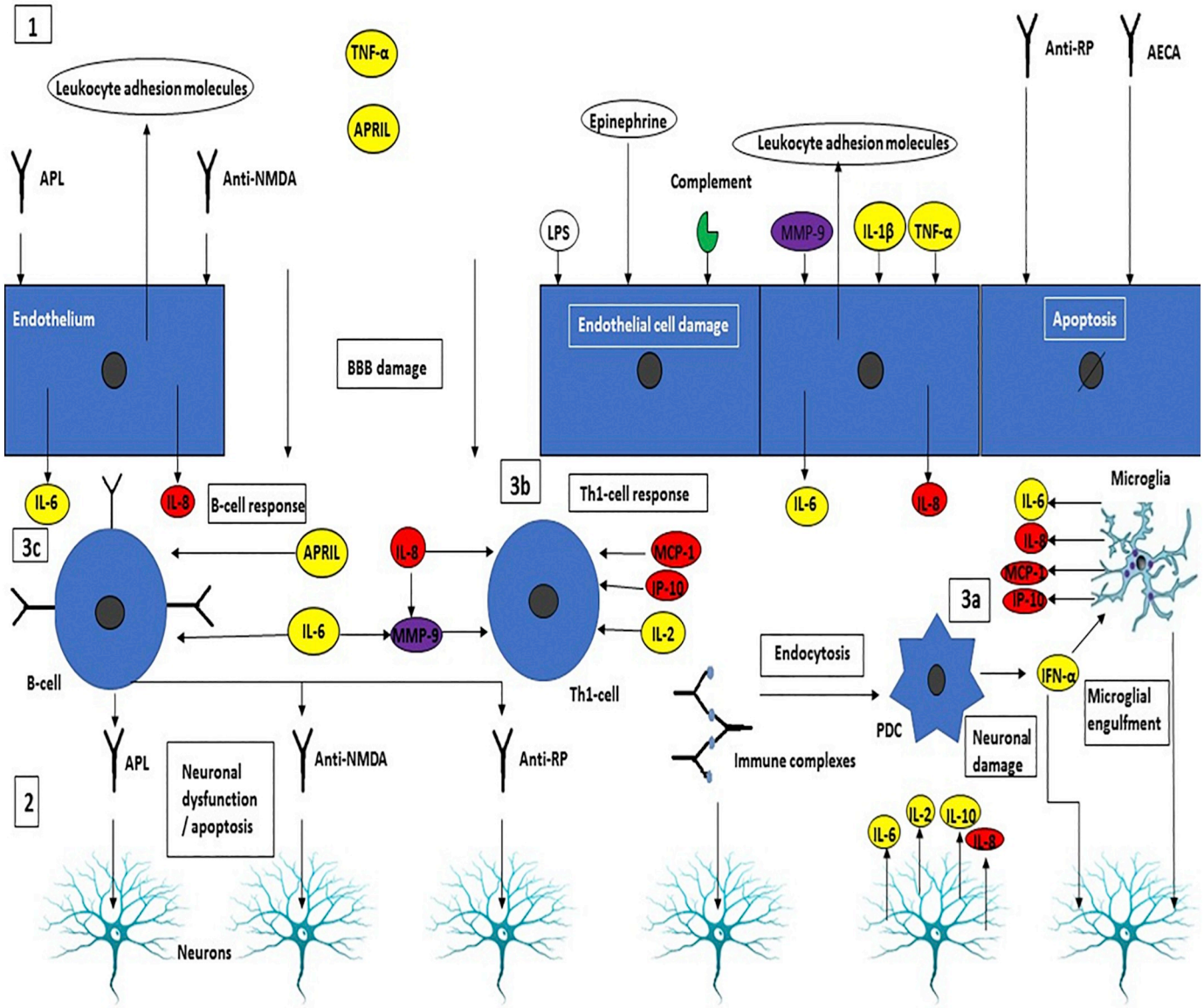

Fig. 2. A potential pathophysiology for psychiatric NPSLE manifestations.

This figure shows a potential pathophysiology for psychiatric NPSLE manifestations. Cells are represented in blue, antibodies in black, cytokines in yellow ovals, chemokines in red ovals, MMP-9 in purple ovals, complement in green and other molecules/substances in white ovals. Processes that occur in the pathophysiology of psychiatric NPSLE manifestations are represented in white boxes. The pathophysiology is represented in three steps. The first step in the pathophysiology is potential (transient) dysfunction of the blood-brain barrier (1). Anti-RP and AECA could mediate direct damage to endothelial cells and cause apoptosis. APL and anti-NMDA may induce cytokine/chemokine (IL-6 and IL-8) and leukocyte adhesion molecule production in endothelial cells. MMP-9 and cytokines iL-1β and TNF-α may have a similar effect. Substances such as complement, LPS and epinephrine may cause dysfunction of the blood brain barrier. However, as mentioned earlier, intrathecal synthesis of antibodies may very well occur without (transient) BBB dysfunction.

After the blood-brain barrier is compromised, antibodies gain access to the CSF (2). APL, anti-NMDA and anti-RP directly bind to neurons and induce neuronal dysfunction (impairment of synaptic transmission and/or mitochondrial metabolism) or apoptosis, dependent on the concentration of the antibodies. Neurons are stimulated to produce cytokines and chemokines (IL-2, IL-6, IL-8, IL-10). Following neuronal cell damage, antibodies form immune complexes with neuronal antigens; which contribute to the diffuse neuronal damage/dysfunction in the brain.

Immune complexes are endocytosed by plasmacytoid dendritic cells, which produce IFN-α (3a). IFN-α has a direct toxic effect on neurons and stimulates microglial engulfment of neurons. Microglial engulfment is further facilitated by antibodies and complement (not shown in figure). Furthermore, IFN-α enhances microglial cytokine and chemokine production (IL-6, IL-8, MCP-1, IP-10).

Chemokines IL-8, MCP-1 and IP-10 attract Th1-cells from the serum, which enter the CSF via the compromised blood-brain barrier (3b). Th1-cells mediate the cellular immune response in NPSLE. This response is further enhanced by IL-2 and MMP-9. MMP-9 enhances T-cell migration and may be produced by several different cells (stimulated by IL-6 and IL-8).

IL-6 and APRIL (possibly peripherally produced) enhance B-cell activation and survival (3c). Consequently, antibodies are produced intrathecally and further aggravate neuronal damage/dysfunction.

IL-10 (produced by neurons after binding of antigens) and TNF-α (possibly produced peripherally) may be important in the pathophysiology of psychiatric NPSLE by regulating the immune response.

Th1-cell = T-helper-1-cell, PDC = plasmacytoid dendritic cell, APL= anti-phospholipid antibodies, anti-RP = anti-ribosomal-protein antibodies, AECA = anti-endothelial cell antibodies, TNF-α = Tumor necrosis factor α, APRIL = a proliferation-inducing ligand, IL-1β= Interleukin-1β, IL-6 = Interleukin-6, IL-2 = Interleukin-2, IL-10 = Interleukin-10, IFN-α= Interferon-α, IL-8 = Interleukin-8, MCP-1 = Monocyte chemoattractant protein-1, IP-10 = Interferon-gamma inducible protein-10, MMP-9 = Matrix metalloproteinase-9, BBB = Blood-brain barrier, LPS = Lipopolysaccharides.

5. Discussion

In NPSLE with mainly psychiatric manifestations, transient BBB dysfunction may be caused by different mechanisms and may be imperative for antibodies to access the CSF. This hypothesis is advocated by studies that show BBB dysfunction in SLE patients presenting with neuropsychiatric symptoms, while evidence for persistent BBB dysfunction is sparse. However, the literature on this topic is scarce. Furthermore, evidence for intrathecal synthesis of antibodies in NPSLE is convincing. Thus, intrathecal synthesis of antibodies by plasma cells in NPSLE may very well occur without transient BBB dysfunction. Besides, transient BBB dysfunction could also be the consequence of the immune reaction in NPSLE following intrathecal synthesis of antibodies; explaining the BBB dysfunction in NPSLE patients with psychiatric symptoms.

For the majority of the antibodies conflicting evidence on the correlation with NPSLE manifestations was found. Different factors may contribute to this contradiction. First, the conflicting evidence concerning the association between antibodies and NPSLE may be explained by the large variety of antibodies involved. The number of antibodies and other factors that possibly play a role in the pathogenesis of NPSLE in individual patients is significant. Thus, it may be difficult to find a significant correlation between a single antibody and psychiatric NPSLE manifestations. Second, the role of certain antibodies in the pathogenesis of NPSLE may be different in individual patients as displayed by the observation that several studies found associations between different antibodies and different NPSLE manifestations; while groups of studies that were combined rarely demonstrated any association. Furthermore, the lack of consistent evidence may be explained by the large variety of the clinical phenotype of NPSLE and the absence of a clear definition and diagnostic consensus concerning NPSLE manifestations.

Interestingly, anti-neuronal antibodies (anti-NMDA particularly) in the CSF were convincingly associated with NPSLE. The most plausible explanation for this phenomenon is that anti-neuronal antibodies directly damage neurons by binding to them. Concerning APL and anti-RP, research on the correlation between these antibodies in CSF and NPSLE is more scarce and the evidence is less convincing.

Again, no significant association with NPSLE could be found for many cytokines or chemokines. Factors similar to those in antibodies may explain this phenomenon. In other words, there is a large variety of cytokines and chemokines that contribute to inflammation in the brain. Accordingly, it is difficult to find a significant correlation between a single cytokine or chemokine and NPSLE. Furthermore, different inflammatory pathways with different cytokines and chemokines may be more or less important in different NPSLE patients. This is displayed by the fact that many different studies found an association between cytokines or chemokines and NPSLE, while studies that are combined fail to demonstrate a significant association.

According to the pathophysiological model for psychiatric NPSLE, neuronal dysfunction (impairment of synaptic transmission and/or mitochondrial metabolism) caused by antibodies and further enhanced by cytokines may be the specific hallmark of psychiatric NPSLE manifestations. However, it remains unclear why specific antibodies or cytokines mediate specific psychiatric manifestations such as lupus psychosis or depression and why neuronal dysfunction specifically causes psychiatric symptoms. This question provides an interesting topic for additional research.

This potential pathophysiology may help understand NPSLE and may have implications for the diagnostic management and therapy of psychiatric NPSLE manifestations. Diffuse neuronal dysfunction via impairment of synaptic transmission and/or mitochondrial metabolism seems to be the main pathophysiologic mechanism in psychiatric NPSLE manifestations. However, neuronal dysfunction possibly occurs on a microscopic level and may be nearly impossible to demonstrate by using routine imaging techniques (such as MRI). Thus, the value of conventional imaging techniques for the diagnosis of psychiatric NPSLE manifestations may be limited. Yet, neuronal dysfunction may be identified with more advanced imaging techniques such as PET-MRI or functional MRI. The diagnostic value of these advanced imaging modalities for the diagnosis of psychiatric morbidity attributable to NPSLE provides an interesting topic for further research. Determining CSF levels of antibodies or cytokines such as APL, anti-RP, anti-NMDA, IL-6 and IFN-α may be helpful in diagnosing psychiatric NPSLE manifestations. Although, this investigation is invasive and the CSF levels of the antibodies and cytokines mentioned above were infrequently correlated with psychiatric NPSLE manifestations. Thus, the diagnostic value of CSF levels of antibodies and cytokines in NPSLE remains unclear.

Furthermore, the limited availability of accurate diagnostic instruments to diagnose or exclude psychiatric symptoms and to attribute these symptoms to NPSLE may have implications for the therapeutic management of these manifestations. When SLE patients present with psychiatric symptoms and these symptoms are suspected to be attributable to NPSLE, it may be indicated to start immunosuppressive therapy or increase the dosage of immunosuppressive therapy; after excluding diseases in the differential diagnosis of NPSLE such as infections, anti-phospholipid syndrome with multiple infarcts, lymphoma, sarcoidosis or medication. After all, it may be difficult to reliably attribute these symptoms to neuropsychiatric involvement of SLE. Nevertheless, a higher dosage of immunosuppressive therapy may provoke adverse effects in NPSLE patients such as opportunistic infections or bone marrow depression. This hypothetical statement provides an interesting topic for discussion. Furthermore; specific antibodies, cytokines, chemokines or other molecules that have been convincingly associated with specific psychiatric manifestations may be new potential targets for therapy.

Importantly, the pathophysiological model of NPSLE described above is based on correlations between antibodies, cytokines, chemokines, other molecules and NPSLE that remain questionable. Particularly the associations of cytokines, chemokines, MMP-9 and complement with NPSLE have not been studied extensively. Likewise, BBB-dysfunction has not been studied broadly. Especially BBB dysfunction in NPSLE patients with active disease provides an interesting topic for more research. Moreover, the role of various antibodies (in CSF in particular) in NPSLE has not been investigated sufficiently. Furthermore, it remains unclear how neuronal dysfunction via impairment of synaptic transmission leads to neuropsychiatric symptoms. Likewise; there is few literature on the areas of the brain that are affected by antibodies, although anti-RP have been shown to target hippocampal neurons [169,172]. More research on these topics is necessary to convincingly elucidate the role and interconnection of these individual components in the pathophysiology of psychiatric NPSLE manifestations.

Declaration of Competing Interest

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Beside the authors, there were no other contributors to this research paper.

Appendix

Appendix A: Complete overview of antibodies and their associations with NPSLE

Antibody	Medium	Studies that found an association with NPSLE (no. of patients)	Studies that found no association with NPSLE (no. of patients)
APL	Serum	Ho et al. 2016 (5539) [80] Borowoy et al. 2012 (1253) [81] Mok et al. 2012 (252) [82] Mikdashi et al. 2004 (130) [83] Sanna et al. 2003 (323) [84] Mok et al. 2001 (518) [85] Toubi et al. 1995 (196) [86] Murray et al. 2012 (694) [87] Tomietto et al. 2007 (52) [88] McLaurin et al. 2005 (123) [89] Leritz et al. 2002 (56) [90] Jacobson et al. 1999 (27) [91] Appenzeller et al. 2008 (528) [92]	Kozora et al. 2012 (43) [93] Kellner et al. 2010 (58) [94] Kamen et al. 2008 (184) [95] Shimojima et al. 2005 (62) [96] Houman et al. 2004 (100) [97] Afeltra et al. 2003 (61) [98] Abdul-Sattar et al. 2013 (84) [99] Hanly et al. 1999 (51) [100]
Lupus anticoagulans	Serum	Syuto et al. 2009 (68) [33] Jouhikainen et al. 1993 (37) [34] Denburg et al. 1997 (75) [35] Ho et al. 2016 (5539) [80] Mikdashi et al. 2004 (130) [83] Sanna et al. 2003 (323) [84] Mok et al. 2001 (518) [85] Love et al. 1990 (1000) [101]	Chapman et al. 2003 (-*) [36] Borowoy et al. 2012 (1253) [81] Afeltra et al. 2003 (61) [98] Abdul-Sattar et al. 2013 (84) [99] Hanly et al. 2011 (1047) [109] Hanly et al. 2015 (1827) [110]
aCL	Serum	Ho et al. 2016 (5539) [80] Mikdashi et al. 2004 (130) [83] Sanna et al. 2003 (323) [84] Mok et al. 2001 (518) [85] Afeltra et al. 2003 (61) [98] Abdul-Sattar et al. 2013 (84) [99] Hanly et al. 1999 (51) [100] Love et al. 1990 (1000) [101] Baraczka et al. 2004 (13) [102] Karassa et al. 2000 (128) [103] Sabbadini et al. 1999 (114) [104] Conti et al. 2012 (58) [105] Zandman-Goddard et al. 2007 (-*) [106] Peretti et al. 2012 (31) [107] Menon et al. 1999 (45) [108]	Jedryka-Goral et al. 2000 (15) [9] Martinez-Cordero et al. 1997 (32) [10] Lai et al. 2000 (31) [17] Borowoy et al. 2012 (1253) [81] Hanly et al. 2011 (1047) [109] Hanly et al. 2015 (1827) [110] Fragoso-Loyo et al. 2008 (96) [111] Conti et al. 2004 (51) [112] Yoshio et al. 1995 (70) [113] Pereira et al. 1992 (50) [114] Hanly et al. 1992 (10) [115] Costallat et al. 1990 (66) [116] Hanly et al. 1993 (70) [117]
	CSF	Martinez-Cordero et al. 1997 (32) [10] Lai et al. 2000 (31) [17] Baraczka et al. 2004 (13) [102]	Jedryka-Goral et al. 2000 (15) [9] Fragoso-Loyo et al. 2008 (96) [111] Pereira et al. 1992 (50) [114]
Anti-β2-glycoprotein	Serum	Ho et al. 2016 (5539) [80] Baraczka et al. 2004 (13) [102]	Kozora et al. 2012 (43) [93] Zandman-Goddard et al. 2007 (-*) [106] Hanly et al. 2011 (1047) [109] Fragoso-Loyo et al. 2008 (96) [111] Conti et al. 2004 (51) [112] Hanly et al. 2008 (412) [118] Brey et al. 2002 (128) [119]
	CSF	Baraczka et al. 2004 (13) [102]	Fragoso-Loyo et al. 2008 (96) [111]
ANA	Serum	Karassa et al. 2000 (128) [103] Peretti et al. 2012 (31) [107]	Ho et al. 2016 (5539) [80] Shimojima et al. 2005 (62) [96] Sabbadini et al. 1999 (114) [104] Zandman-Goddard et al. 2007 (-*) [106] Fragoso-Loyo et al. 2008 (96) [111] Tikly et al. 1996 (111) [136]
	CSF		Fragoso-Loyo et al. 2008 (96)[111]
Anti-dsDNA	Serum	Mikdashi et al. 2004 (130) [83] Peretti et al. 2012 (31) [107]	Miguel et al. 1994 (49) [37] Ho et al. 2016 (5539) [80] Borowoy et al. 2012 (1253) [81] Kellner et al. 2010 (58) [94] Shimojima et al. 2005 (62) [96] Hanly et al. 1999 (51) [100] Sabbadini et al. 1999 (114) [104] Zandman-Goddard et al. 2007 (-*) [106] Menon et al. 1999 (45) [108] Hanly et al. 2011 (1047) [109] Fragoso-Loyo et al. 2008 (96) [111] Conti et al. 2004 (51) [112] Jönsen et al. 2003 (44) [120] Watanabe et al. 1996 (144) [121] Tikly et al. 1996 (111) [136] Winfield et al. 1978 (25) [137] Hanly et al. 2006 (65) [156]

Anti-Ro	Serum	Borowoy et al. 2012 (1253) [81] Mikdashi et al. 2004 (130) [83] Tikly et al. 1996 (111) [136]	Miguel et al. 1994 (49) [37] Ho et al. 2016 (5539) [80] Shimojima et al. 2005 (62) [96] Conti et al. 2004 (51) [112]
Anti-La	Serum	Karassa et al. 2000 (128) [103]	Ho et al. 2016 (5539) [80] Borowoy et al. 2012 (1253) [81] Shimojima et al. 2005 (62) [96] Tikly et al. 1996 (111) [136]
Anti-histone	Serum	Sun et al. 2008 (144) [38]	
Anti-Sm	Serum	Tikly et al. 1996 (111) [136] Winfield et al. 1978 (25) [137]	Miguel et al. 1994 (49) [37] Singh et al. 1991 (276) [39] Ho et al. 2016 (5539) [80] Borowoy et al. 2012 (1253) [81] Kellner et al. 2010 (58) [94] Shimojima et al. 2005 (62) [96]
Anti-70kda-U1-ribonucloprotein	Serum	Katsumata et al. 2013 (106) [24]	Miguel et al. 1994 (49) [37]
Anti-RP	Serum	West et al. 1995 (66) [18] Abdel-Nasser et al. 2008 (68) [23] Ho et al. 2016 (5539) [80] Borowoy et al. 2012 (1253) [81] Mok et al. 2012 (252) [82] Baraczka et al. 2004 (13) [103] Hanly et al. 2011 (1047) [109] Yoshio et al. 1995 (70) [113] Hanly et al. 2008 (412) [118] Brey et al. 2002 (128) [119] Jönsen et al. 2003 (44) [120] Watanabe et al. 1996 (144) [121] Mahler et al. 2006 (947) [122] Tzioufas et al. 2000 (178) [123] Arnett et al. 1996 (394) [124] Schneebaum et al. 1991 (269) [125] Karimifar et al. 2013 (100) [126] Unterman et al. 2011 (1439) [127] Briani et al. 2009 (219) [128] Massardo et al. 2002 (138) [129] Isshi et al. 1998 (87) [130] Georgescu et al. 1997 (336) [131] Isshi et al. 1996 (75) [132] Nojima et al. 1992 (91) [133] Bonfa et al. 1986 (59) [134] Bonfa et al. 1987 (2) [135]	Shimojima et al. 2005 (62) [96] Afeltra et al. 2003 (61) [98] Hanly et al. 2015 (1827) [110] Fragoso-Loyo et al. 2008 (96) [111] Conti et al. 2004 (51) [112] Hanly et al. 1992 (10) [115] Tikly et al. 1996 (111) [136] Winfield et al. 1978 (25) [137] Yoshio et al. 2005 (70) [138] Pradhan et al. 2015 (120) [139] Jarpa et al. 2011 (83) [140] Nery et al. 2008 (71) [141] Karassa et al. 2006 (1537) [142] Gerli et al. 2002 (149) [143] Asero et al. 1988 (324) [144] Yalaoui et al. 2002 (100) [145] Kozora et al. 1996 (51) [146] Teh et al. 1993 (62) [147] Bai et al. 2016 (149) [148] Almeida et al. 2002 (60) [149] Teh et al. 1992 (116) [150]
	CSF	Baraczka et al. 2004 (13) [102] Yoshio et al. 2005 (70) [138] Hirohata et al. 2007 (72) [151] Golombek et al. 1986 (31) [152]	Fragoso-Loyo et al. 2008 (96) [111] Isshi et al. 1998 (87) [130] Isshi et al. 1996 (75) [132]
Anti-neuronal	Serum	Kang et al. 2008 (44) [40] Weiner et al. 2000 (38) [41] Alosachie et al. 1998 (326) [42] Ochola et al. 1995 (24) [43] Hanson et al. 1992 (20) [44] Klein et al. 1991 (91) [45] Hanly et al. 1989 (20) [46] Denburg et al. 1987 (70) [47] Danon et al. 1986 (54) [48] How et al. 1985 (54) [49] Bresnihan et al. 1979 (15) [50] Wilson et al. 1979 (20) [51] Tin et al. 2005 (100) [52] Ho et al. 2016 (5539) [80]	Hanly et al. 1992 (10) [115] Hanly et al. 1993 (70) [117] Isshi et al. 1998 (87) [130] Pradhan et al. 2015 (120) [139]
	CSF	Kelly et al. 1987 (36) [11] West et al. 1995 (66) [18] Kang et al. 2008 (44) [40] Alosachie et al. 1998 (326) [42] Zhang et al. 2007 (67) [53] Bluestein et al. 1981 (45) [54] Ho et al. 2016 (5539) [80] Isshi et al. 1998 (87) [130]	

Anti-NMDA	Serum	Gono et al. 2011 (107) [153] Lapteva et al. 2006 (60) [154] Omdal et al. 2005 (57) [155]	Gulati et al. 2016 (57) [15] Kozora et al. 2010 (43) [32] Ho et al. 2016 (5539) [80] Sanna et al. 2003 (323) [84] Kozora et al. 2012 (43) [93] Houman et al. 2004 (100) [97] Hanly et al. 2011 (1047) [109] Fragoso-Loyo et al. 2008 (96) [111] Hanly et al. 2008 (412) [118] Hanly et al. 2006 (65) [156] Arinuma et al. 2008 (56) [157] Harrison et al. 2006 (93) [158] Steup-Beekman et al. 2007 (51) [159] Husebye et al. 2005 (109) [160]
	CSF	Hirohata et al. 2014 (81) [8] Fragoso-Loyo et al. 2008 (96) [111] Arinuma et al. 2008 (56) [157] Yoshio et al. 2006 (80) [161]	
Anti-gangliosides	Serum	Galeazzi et al. 2000 (448) [55] Hirano et al. 1988 (232) [56] Pereira et al. 1992 (50) [114] Costallat et al. 1990 (66) [116]	Weiner et al. 2000 (38) [41] Martinez et al. 1992 (60) [57] Endo et al. 1984 (31) [58] Ho et al. 2016 (5539) [80]
	CSF	Pereira et al. 1992 (50) [114]	
Anti-lymphocytes	Serum	Long et al. 1990 (98) [59] Silva et al. 1996 (93) [60] Denburg et al. 1994 (115) [61] Lenert et al. 1996 (87) [62] Temesvari et al. 1983 (34) [63]	Magelhaes et al. 2007 (138) [64] Ho et al. 2016 (5539) [80] Hanly et al. 1992 (10) [115] Hanly et al. 1993 (70) [117] Winfield et al. 1978 (25) [137]
Anti-GAPDH	Serum	Delunardo et al. 2016 (67) [65]	
Anti-GABA RB	Serum	Tsuchiya et al. 2014 (88) [66]	
	CSF	Tsuchiya et al. 2014 (88) [66]	
Anti-neurofilaments	Serum	Robbins et al. 1988 (56) [67] Lu et al. 2010 (67) [68]	
	CSF	Lu et al. 2010 (67) [68]	
Anti-MAP-2	Serum	Williams et al. 2004 (100) [69]	
Anti-GFAP	Serum	Sanna et al. 2000 (68) [26]	Conti et al. 2004 (51) [112]
	CSF	Trysberg et al. 2003 (99) [70]	
AECA	Serum	Song et al. 2000 (41) [71] Conti et al. 2004 (51) [112]	Conti et al. 2012 (58) [105]
Anti-Nedd-5	Serum	Margutti et al. 2005 (51) [72]	Conti et al. 2012 (58) [105]
Anti-TPI	Serum	Watanabe et al. 2004 (16) [73]	
	CSF	Sasajima et al. 2006 (12) [74]	
Anti-rab guanosine	Serum	Kimura et al. 2010 (7) [75]	
Anti-APEX nuclease-1	Serum	Katsumata et al. 2011 (106) [76]	
Anti-aquaporin-4	Serum		Zavada et al. 2013 (76)[77] Wandinger et al. 2010 (48) [78]
Anti-VH4-34	Serum	Bhat et al. 2002 (95) [79]	

This table shows the studies that advocated or refuted the association between several antibodies in serum and/or cerebrospinal fluid and NPSLE. The number of patients that participated in the different studies is represented in parentheses. APL = Anti-phospholipid antibodies, aCL = Anti-cardiolipin antibodies, ANA = Anti-nuclear antibodies, Anti-dsDNA = Anti-double stranded DNA antibodies, Anti-Sm = Anti-Smith, Anti-RP = Anti-ribosomal protein antibodies, Anti-NMDA = Anti-N-methyl-D-aspartate antibodies, Anti-GAPDH = Anti-glyceraldehyde 3-phosphate dehydrogenase antibodies, Anti-GABA RB = Anti-gamma-aminobutyric receptor B antibodies, Anti-MAP-2 = Anti-microtubule-associated protein-2 antibodies, Anti-GFAP = Anti-glial fibrillary acidic protein, AECA = Anti-endothelial cell antibodies, Anti-TPI = Anti-triosephosphate isomerase antibodies, Anti-APEX nuclease-1 = Anti-apurinic/apyrimidinic endonuclease-1 antibodies, CSF = Cerebrospinal fluid, NPSLE = Neuropsychiatric systemic lupus erythematosus, * = Narrative review

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