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REVIEW

Cognitive and Emotional Abnormalities in Systemic Lupus Erythematosus: Evidence for Amygdala Dysfunction

Philip Watson · Justin Storbeck · Paul Mattis · Meggan Mackay

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Abstract Systemic lupus erythematosus (SLE) is a multi-system autoimmune disorder characterized by the production of autoantibodies. Approximately 30–50 % of patients produce autoantibodies directed against *N*-Methyl-D-aspartic acid receptors (NMDARs). Once they have gained access to brain tissue, these autoantibodies bind to the NR2A subunit of the NMDARs and synergize with glutamate to cause excitatory, non-inflammatory cell death or alter neuron function. Both humans with SLE and animal models of SLE have shown structural and functional damage to the amygdala. The amygdala is a brain region important for processing the emotional relevance of stimuli in the environment. It also serves to modulate perception, attention, and memory to facilitate the processing and learning of relevant stimuli. Research has linked amygdala damage to deficits in emotional memory and emotional behavior. Individuals with SLE often exhibit emotional dysregulation, such as lability and depression; however, the behavioral impact of possible amygdala dysfunction has yet to be studied in this population. The purpose of this review is to 1) examine possible associations between SLE, anti-NMDAR antibodies, amygdala damage, and emotional processing deficits and 2) to identify the clinical, social, and treatment implications for individuals with SLE who suffer from deficits in emotional processing.

Keywords Systemic lupus erythematosus · Lupus · Neuropsychology · Cognition · Amygdala · Emotion

P. Watson (✉) · J. Storbeck
The Graduate Center and Queens College,
City University of New York,
Flushing, NY, USA
e-mail: philip.watson@qc.cuny.edu

P. Mattis · M. Mackay
The Feinstein Institute for Medical Research,
Manhasset, NY, USA

Systemic lupus erythematosus (SLE, lupus) is a multi-system autoimmune disorder, characterized clinically by periods of disease remission and flare that can affect any organ system, including the brain. On a molecular level lupus is characterized by an inflammatory process directed against the self and led by autoantibodies. SLE occurs in approximately 1 out of 1000 people (Manson and Rahman 2006). It presents ten times more often in women than in men and approximately three to four times more often in people of African, Asian, Hispanic and Caribbean ancestry than in those of European descent. The initial symptoms typically emerge during the second through the fourth decades of life. (Cervera et al. 2003; Johnson et al. 1995). However, approximately 15–20 % of SLE patients begin to have symptoms during childhood, and pediatric disease onset is associated with more severe disease and worse outcome (Livingston et al. 2011). Late onset SLE (after age 50 years) is typically reported as rare, but one study found the prevalence to be 39.3 % of all SLE cases (Alonso et al. 2012).

Previous research has established the presence of a subset of anti-double-stranded deoxyribonucleic acid (anti-dsDNA) autoantibodies that cross-react with *N*-Methyl-D-aspartic acid receptors (NMDAR) in 30–50 % of patients with SLE (Gonzalez-Albo and DeFelipe 2000; Hanly et al. 1992; Omdal et al. 2005; Ozawa et al. 1998). Once they have gained access to the brain parenchyma, these autoantibodies bind to the NR2A and NR2B subunits of the NMDA receptor and synergize with glutamate to cause an excitatory, non-inflammatory cell death of neurons that is mediated by excessive influx of calcium through the open receptor (DeGiorgio et al. 2001). As NMDARs are most abundant in the hippocampus and amygdala, these structures are often severely affected, although many other brain abnormalities also occur in association with SLE (Huerta et al. 2006; Kowal et al. 2004). Cognitive dysfunction occurs commonly in lupus patients with reported prevalence between 50 % and 80 %, but the mechanisms responsible remain unclear. Animal studies have demonstrated a clear causal association

between anti-NMDAR autoantibodies and loss of hippocampal neurons with resulting impairment in memory testing (for review see Bruns and Meyer 2006; Kowal et al. 2006). Additionally, animal models have also revealed emotional and behavioral deficits associated with neuronal loss in the amygdala mediated by anti-NMDAR autoantibodies (Huerta et al. 2006). Depression and anxiety are extremely common in SLE; however, research examining emotional processing deficits linked to amygdala damage in people with SLE has been limited. The goal of this review is to evaluate the published literature on SLE with regard to amygdala function; specifically, deficits in processing emotional information, remembering emotional events, demonstrating appropriate modulation of cognitive processes (e.g., attention and memory) during an emotional or stressful event, and possible associations with anti-NMDAR autoantibodies. We suggest that if such deficits are observed, assessment and intervention for emotional processing deficits should be implemented as routine treatment for people with SLE.

Clinical Presentation of SLE

SLE affects a variety of organ systems and can produce wide-ranging symptoms that frequently masquerade as other diseases; SLE is known as one of the "great imitators" because of its propensity to mimic other disorders. Lupus related pathology classically presents as rashes, arthritis, photosensitivity, renal disease, hematologic cytopenias, and serositis but other organ systems are frequently involved (Sultan et al. 2003). SLE patients also often suffer from constitutional symptoms of widespread pain and fatigue, fevers, and weight loss related to inflammatory processes (Tench et al. 2000). Nervous system involvement in lupus, referred to as neuropsychiatric SLE (NPSLE) represents a collection of 19 syndromes that affect the central and peripheral nervous systems. We will focus this review on the neuro-cognitive and psychiatric presentations of SLE.

Childhood onset SLE has been associated with a number of symptom-related differences as compared to adult onset SLE, and onset in childhood is often associated with more severe outcomes (Hersh et al. 2010; Hersh et al. 2009). For instance, in a meta-analysis of differences in clinical manifestations between children and adults with SLE, Livingston and colleagues (2011) found that those with childhood onset were more likely to have malar rash, ulcers, renal involvement, seizures, and lymphadenopathy, among other symptoms, than those with adult onset. Moreover, others (Hersh et al. 2010; Webb, 2011) have found higher rates of renal disease, anti-DNA autoantibodies, arthritis, and leucopenia in patients with childhood onset SLE. In contrast, those with adult onset SLE were more likely to have Raynaud's phenomenon, pleuritis, and Sjorgren syndrome. Greater frequencies of renal and central nervous system (CNS) involvement may be the most severe differences for those with childhood onset SLE compared with adult onset disease (Muscal and Brey 2010; Papadimitraki and Isenberg 2009).

Treatment goals for SLE patients are to reduce the number and severity of disease flares to prevent organ damage. To that end, pharmacological treatment with immunosuppressive and disease-modifying anti-rheumatic drugs is employed. Typically, steroidal and non-steroidal anti-inflammatory medications are used for their immediate anti-inflammatory properties in acute disease flares. Other immunosuppressive medications are added for their steroid sparing effects and to reduce the body's auto-inflammatory response. Therapy is tailored to individual patients and supportive measures, such as kidney transplant for end stage renal disease or the use of anti-psychotic medication in conjunction with immunosuppression for lupus psychosis, are employed as needed.

Neuropsychiatric SLE (NPSLE)

A subset of patients with SLE will develop nervous system symptoms and both the central and peripheral nervous systems can be affected (van Dam 1991). In 1999, the American College of Rheumatology (ACR) outlined 19 specific symptoms associated with NPSLE (Liang et al. 1999). These can be broadly grouped into syndromes associated with peripheral nerve disorders, such as mononeuritis multiplex and myasthenia gravis, and those associated with CNS disorders. Within the CNS, some NPSLE syndromes are related to focal vascular compromise such as stroke and headache but more diffuse pathophysiology such as cognitive dysfunction, mood disorders, psychosis, acute confusional state, and seizures also occur. The prevalence of neuropsychiatric manifestations in SLE varies widely, ranging from 17 % to 66 % (Bruns and Meyer 2006) and typically presents within the first few years of the SLE diagnosis. Cognitive dysfunction has been found in up to 80 % of patients with SLE; however, attribution to SLE is often difficult given the confounding influences of medications, depression, anxiety, and co-morbid disease on cognitive function (Ainiala et al. 2001; Wekking 1993). Micro-infarcts caused by vascular abnormalities and/or accumulated atherosclerotic disease can exacerbate cognitive dysfunction caused by SLE. While CNS involvement in children with SLE is more prevalent than in adults (Papadimitraki and Isenberg 2009), research has failed to produce evidence for greater cognitive impairment in children with SLE as compared to matched controls (Williams et al. 2011).

Several studies have found an association between neuropsychiatric manifestations and antiphospholipid antibodies

(Denburg et al. 1987b; Long et al. 1990), particularly in patients with stroke and cognitive dysfunction (Denburg et al. 1997; Hanly et al. 1999). For instance, Hanly and colleagues (1999) found increased deficits in processing speed and executive functioning in SLE patients positive for anti-cardiolipin autoantibodies, as compared to those patients negative for those antibodies. Antiphospholipid antibodies are associated with hypercoaguable states and the mechanism for antiphospholipid-related cognitive decline is attributed to recurrent micro-ischemia.

Treatment of NPSLE is tailored to the clinical syndrome and driven by our limited knowledge of underlying pathogenic mechanisms. For vascular disease related to antiphospholipid antibodies, anticoagulation is used. The more severe disturbances of thought and level of consciousness, such as psychosis or acute confusional state, are generally treated aggressively with corticosteroids and immunosuppression. Treatment for mood disorders follows guidelines for non-SLE related mood disorders but treatment for cognitive dysfunction remains problematic, largely due to insufficient understanding of the underlying pathophysiology and problems with ascertainment and attribution.

Cognitive Function and SLE

In addition to the possible influences of mood disorder, infections, metabolic disturbances, and medication on cognitive functioning, SLE patients demonstrate cognitive deficits independent of other variables. Notable impairment occurs in attention and concentration, working memory, visuospatial skills, and memory (Denburg et al. 1987a; Emori et al. 2005; Glanz et al. 2005; Glanz et al. 1997; Kozora et al. 2004; Loukkola et al. 2003; Monastero et al. 2001; Shucard et al. 2004). Furthermore, although SLE patients with and without overt neuropsychiatric symptoms display cognitive impairment, those with NPSLE display more pronounced deficits (Monastero et al. 2001). Table 1 shows the comparison of cognitive performance of patients with NPSLE and SLE to healthy controls across studies for a variety of neuropsychological measures. Cognitive decline in people with SLE has been associated with damage to white matter tracts, particularly the corpus callosum that was found to be smaller in SLE and NPSLE than healthy controls, as well as with grey matter damage (Kozora et al. 2011; Steens et al. 2004).

Attention and Processing Speed Attention and processing speed are cognitive functions that influence performance on other cognitive tasks (Chiaravalloti et al. 2003; Sheppard, 2008). Patients with SLE often report problems with attention and processing speed (Vogel et al. 2011). Performance during formal neuropsychological evaluation confirms these impairments in approximately 20 % of patients (Kozora et al. 2008; Vogel et al. 2011). Slower processing speed in SLE and NPSLE patients is found during simple cognitive (i.e., non-motor) and motor tasks (Glanz et al. 2005; Loukkola et al. 2003). Deficits in these domains appear to be greater for patients with NPSLE than for those with no overt CNS involvement (Loukkola et al. 2003).

Working Memory Deficits in working memory have also been found in people with SLE, as evidenced by impaired performance on letter-number sequencing tasks (Kozora et al. 2008; Shucard et al. 2011; Shucard et al. 2004). To examine working memory deficits independent of attention, Shucard and colleagues (2011) employed an N-back task. As expected, results revealed slower overall processing speed in people with SLE as compared to controls. While both groups had slower reaction times (RT) as the working memory load increased, the SLE group displayed disproportionately greater slowing. This effect remained after the authors controlled for processing speed, indicating that people with SLE suffer from deficits in working memory that cannot be accounted for by a decline in general attentional functioning. Other studies have reported similar deficiencies in working memory, but attribution remains an important issue. Animal models and findings of impaired working memory in recently diagnosed patients suggest that SLE is a causative factor separate from other confounding influences (e.g., Petri 2008). However, more research is required to accurately identify deficits in this domain as working memory is often confounded with other cognitive factors like attention.

Executive Functioning Studies examining executive functioning in people with SLE and NPSLE have produced inconsistent results (Kozora et al. 2008; Monastero et al. 2001), and other studies have not effectively examined the gamut of executive functions (Vogel et al. 2011). That being said, impairments have been noted in response inhibition during a Stroop task and ability to shift cognitive set on the Trail Making Test (Kozora et al. 2008; Loukkola et al. 2003; Vogel et al. 2011).

Motor Motor slowing has been found in people with SLE and NPSLE: this effect has largely been documented with the finger tapping test (Kozora et al. 2004), although other tasks that include a motor component have also shown motor slowing in SLE patients (Kozora et al. 2004; Loukkola et al. 2003). For instance, Glanz and colleagues (2005) found that SLE patients performed worse than controls on the Digit Symbol subtest of the WAIS-R and on the Trail Making Test—part A. While impairment of SLE patients on motor tasks is clearly documented, it should be noted that this is entirely consistent with slowed processing speed, which has also been associated with cognitive impairment in SLE.

Table 1 Comparison of cognitive performance of NPSLE patients (1), SLE patients (2), and healthy controls (3) across studies

	Denburg et al. (1987)	Emori et al. (2005)	Glanz et al. (1997)	Glanz et al. (2005)	Kozora et al. (2004)	Kozora et al. (2008)	Kozora et al. (2011)	Loukkola et al. (2003)	Monastero et al. (2001)
Intelligence									
WAIS-R Verbal IQ	-	-	-	-	NS*	-	-	-	-
WAIS-R Performance IQ	-	-	-	-	1 < 3	-	-	-	-
Attention and Processing Speed									
WAIS-R Digit Span	-	NS	-	-	-	-	-	-	NS
WAIS-R Digit Span Forward	-	-	-	NS	-	-	-	1 < 2 < 3	-
WAIS-R Digit Span Backward	-	-	-	NS	-	-	-	NS	-
Letter-Number Sequencing**	-	-	-	NS	NS	2 < 3	-	-	-
Paced Auditory Addition Test	-	-	-	-	1 < 3	NS	-	-	-
WMS-III Spatial Span Forward	-	-	-	NS	-	-	-	-	-
WMS-III Spatial Span Backward	-	-	-	NS	-	-	-	-	-
Stroop Color-Word Test Word Naming	-	-	-	2 < 3	-	-	-	1 < 2, 3	-
Stroop Color-Word Test Color Naming	-	-	-	2 < 3	-	-	-	-	-
Trail Making Test - Part A	-	1, 2 < 3	-	2 < 3	1, 2 < 3	-	-	NS	NS
WAIS-R Digit Symbol Substitution Test**	1 < 3	NS	2 < 3	2 < 3	1, 2 < 3	NS	-	1 < 2 < 3	-
Executive Functioning									
Controlled Oral Word Association Test	-	-	-	NS	1 < 3	NS	-	NS	NS
Design Fluency	-	-	-	NS	-	-	-	-	-
Ruff Figural Fluency Test	-	-	-	-	NS	-	-	-	-
Trail Making Test - Part B	-	1 < 3	-	2 < 3	1, 2 < 3	NS	-	1 < 2, 3	NS
Stroop Color-Word Test Interference	-	NS	-	NS	1 < 3	NS	-	1 < 2, 3	-
Category Test	-	-	-	-	1 < 3	NS	-	-	-
Wisconsin Card Sorting Test	-	NS	-	-	-	-	-	NS	-
Wisconsin Card Sorting Test Perseverative Errors	-	-	-	-	-	-	-	1 < 2 < 3	-
Raven's Coloured Progressive Matrices	-	-	-	-	-	-	-	-	NS
WAIS-R Similarities	-	NS	-	NS	NS	-	-	NS	-
Motor Functioning									
Finger Tapping Test Dominant Hand	-	-	-	NS	1, 2 < 3	NS	-	-	-
Finger Tapping Test Non-Dominant Hand	-	-	-	NS	2 < 3	NS	-	-	-
Visuospatial Processing									
Facial Recognition Test	-	-	-	NS	-	-	-	-	-
Block Design**	1 < 3	NS	NS	NS	1 < 3	NS	-	NS	-
WAIS-R Object Assembly	-	-	-	NS	NS	-	-	-	-
WAIS Picture Completion	NS	-	-	-	-	-	-	-	-
RCFT Copy	NS	NS	NS	NS	-	-	-	-	1, 2 < 3
Language									
WAIS-R Vocabulary	-	-	-	NS	-	-	-	1 < 2 < 3	-

Table 1 (continued)

	Denburg et al. (1987)	Emori et al. (2005)	Glanz et al. (1997)	Glanz et al. (2005)	Kozora et al. (2004)	Kozora et al. (2008)	Kozora et al. (2011)	Loukkola et al. (2003)	Monastero et al. (2001)
WAIS-R Comprehension	-	NS	-	NS	-	-	-	-	-
Information**	NS	-	NS	-	-	-	-	-	-
BDAE Complex Ideational Material	-	-	-	-	NS	-	-	-	-
Peabody Individual Achievement Test – Reading Recognition Test	-	-	-	-	NS	-	-	-	-
Boston Naming Test	-	-	-	NS	-	-	-	NS	-
Category Fluency	-	-	-	NS	1 < 3	NS	-	NS	-
Memory									
Verbal Learning**	-	-	-	NS	NS	2 < 3	2 < 3	NS	-
Verbal Immediate Recall**	-	1 < 3	-	NS	NS	2 < 3	-	NS	1, 2 < 3
Verbal Immediate Cued Recall**	-	-	-	NS	-	-	-	1 < 2 < 3	-
Verbal Delayed Recall**	-	1 < 3	-	NS	-	-	NS	NS	NS
Verbal Delayed Cued Recall**	-	-	-	NS	-	-	-	1 < 2 < 3	-
Verbal Recognition**	-	NS	-	NS	-	-	NS	1<2<3	-
WMS Verbal Paired Associates	-	1, 2 < 3	-	-	-	-	-	-	-
Logical Memory Immediate Recall**	-	-	NS	2 < 3	-	-	-	1 < 3	-
Logical Memory Delayed Recall**	-	-	-	2 < 3	-	-	-	1 < 3	-
Logical Memory Recognition**	-	-	-	NS	-	-	-	-	-
WMS-R Visual Memory Immediate Recall	-	-	-	-	-	-	-	NS	-
WMS-R Visual Memory Delayed Recall	-	-	-	-	-	-	-	1 < 2 < 3	-
Visual Reproduction Immediate Recall**	-	-	2 < 3	NS	-	-	-	-	-
WMS-III Visual Reproduction Delayed Recall	-	-	-	2 < 3	-	-	-	-	-
WMS-III Visual Reproduction Recognition	-	-	-	2 < 3	-	-	-	-	-
RCFT Immediate Recall	-	-	-	-	NS	NS	NS	-	-
RCFT Delayed Recall	1 < 3	NS	-	NS	NS	NS	NS	-	1, 2 < 3
RCFT Recognition	-	-	-	-	-	-	2 < 3	-	-
Benton Visual Retention Test	-	NS	-	-	-	-	-	-	-

* *NS* Not significant

** *Note:* Letter-Number Sequencing = WAIS-III (Kozora et al. 2004, 2008), WMS-III (Glanz et al. 2005). Digit Symbol Substitution Test = WAIS (Denburg et al. 1987a, b), WAIS-R (Emori et al. 2005; Glanz et al. 2005; Kozora et al. 2004, 2008; Loukkola et al. 2003). Block Design = WAIS (Denburg et al. 1987a, b), WAIS-R (Emori et al. 2005; Glanz et al. 1997, 2005; Kozora et al. 2004; Kozora et al., 2008; Loukkola et al. 2003). Information = WAIS (Denburg et al. 1987a, b), WAIS-R (Glanz et al. 1997). Verbal Learning, Verbal Immediate Recall, Verbal Immediate Cued Recall, Verbal Delayed Recall, Verbal Delayed Cued Recall, Verbal Recognition = RAVLT (Emori et al. 2005; Monastero, 2001), CVLT (Glanz et al. 2005; Kozora et al. 2004, 2008; Loukkola et al. 2003), CVLT-II (Kozora et al. 2011). Logical Memory Immediate Recall, Logical Memory Delayed Recall, Logical Memory Recognition = WMS-R (Glanz et al. 1997; Loukkola et al. 2003), WMS-III (Glanz et al. 2005). Visual Reproduction Immediate Recall = WMS (Glanz et al. 1997), WMS-III (Glanz et al. 2005)

Visuospatial Processing Visuospatial skills are largely left intact in people with SLE. Some studies have found deficits in this patient group on tasks that have a visuospatial component (Lapteva et al. 2006; Monastero et al. 2001; Petri et al. 2008; Vogel et al. 2011); however, results have been inconsistent. Moreover, the significant results have been largely based on the Block Design subtest of the WAIS and the Rey-Osterrieth Complex Figure Test, both of which require more than visuospatial processing (i.e., speeded constructional abilities, planning, and organization) to perform effectively. Thus, impaired performance may be due to deficits in other cognitive domains (e.g., processing speed, executive functions) as opposed to visuospatial processing.

Language Language in SLE and NPSLE is generally intact (Glanz et al. 2005; Kozora et al. 2008). However, some

studies have noted deficits. For instance, Kozora and colleagues (2004) have reported poorer verbal fluency in SLE patients compared to controls. Loukkola and colleagues (2003) found that SLE and NPSLE patients performed worse on the WAIS Vocabulary subtest than controls, and they noted trends toward significant differences between these groups in other, untimed, language tasks (i.e., Boston Naming Test).

Memory Memory is the most commonly impaired cognitive process in people with SLE and NPSLE, which is consistent with hippocampal changes associated with the disease (Kozora et al. 2011). However, empirical findings on memory impairment in this group have been inconsistent. Deficits in people with SLE have been reported for verbal and non-verbal information and for immediate and delayed recall (Loukkola et al. 2003; Monastero et al. 2001). For example, impaired delayed recall of the Rey-Osterrieth Complex Figure (non-verbal memory) and the California Verbal Learning Test (verbal memory) has been found in these patient groups compared to healthy controls (Kozora et al. 2011; Monastero et al. 2001).

In summary, SLE patients demonstrate impairment in multiple cognitive domains, and the degree of impairment worsens in the context of NPSLE. Selective impairment in attention and processing speed can be accounted for by reductions in corpus callosum volume and other white matter abnormalities but imaging studies and animal models have also implicated grey matter damage. Deficits in working memory and aspects of executive functions indicate abnormalities specific to frontal areas, whereas, impaired learning and memory point to hippocampal dysfunction.

Psychiatric Syndromes and SLE

NPSLE can also present as mood disturbance. In fact, up to 75 % of patients with SLE have a co-morbid mood or anxiety disorder, with depression being the most common manifestation (Bruns and Meyer 2006). However, it is difficult to ascertain if depression and/or anxiety are a direct product of SLE, the impact of the symptoms of the disorder, medication effects, or psychosocial factors. A study by Bachen et al. (2009) reported that 47 % of their SLE cohort had previously received a diagnosis of Major Depressive Disorder (MDD) and 6 % had been diagnosed with Bipolar I disorder. Forty-nine percent had also been diagnosed with an anxiety related disorder. Of note, the authors found that increased disease activity, as assessed through the Systemic Lupus Activity Questionnaire (SLAQ), was associated with higher probability of having MDD, and with having any mood or anxiety disorder. Similarly, Nery and colleagues (2007) found that out of 71 SLE subjects participating in their study, 19 (27 %) met criteria for MDD or a depressive episode not otherwise specified. Interestingly, depressed patients did not differ from non-depressed patients in disease duration but their disease severity and functional disability were greater. While these results may suggest that the prevalence of psychological dysfunction in SLE results from the stress of having the disease, they may also indicate that increased disease activity produces CNS neurochemical changes that result in mood disturbance.

The amygdala has been extensively indicated in depression pathology and it is frequently found to be smaller than normal in chronically depressed people (Caetano et al. 2004; Hastings et al. 2004). In people with depression the amygdala is generally more active during rest and when viewing negatively valenced stimuli (Sheline et al. 2009; Siegle et al. 2002; Surguladze et al. 2005). In contrast to the exaggerated reaction of the amygdala to negative stimuli, activation is blunted in response to positively valenced stimuli (Suslow et al. 2010). Moreover, there is greater glucose metabolism in the left amygdala of depressed individuals, as compared to healthy people (Drevets et al. 2002).

Depression has also been associated with a reduction of glial cells within the amygdala and with a lower glia/neuron ratio (Bowley et al. 2002). Furthermore, the reduced glia/neuron ratio has been associated with a specific reduction of oligodendrocytes, the glial cells that produce myelin sheath (Hamidi et al. 2004). The myelin sheath allows for rapid communication between neurons by insulating axons, and neuronal communication is disrupted if the myelin sheath is damaged. The diffuse white matter abnormalities that have been a consistent finding on neuroimaging studies in SLE patients (Appenzeller et al. 2007, 2005, 2008) may represent similar reductions of oligodendrocytes and contribute to the occurrence of mood disorder in this group. SLE patients with depression have also demonstrated decreased cerebral blood flow in the frontal and temporal regions (Giovacchini et al. 2010) suggesting alternative pathologic mechanisms. Pertinent to our interests, serum titers of anti-NMDAR antibodies have correlated with depression (Lapteva et al. 2006; Omdal et al. 2005).

Disturbances in emotion regulation are a common clinical observation in the SLE patient group (Langosch et al. 2008). Studies of emotional regulation have associated emotional lability with SLE (Himelhoch and Haller 1996). For instance, Langosch and colleagues (2008) found that 47 % of people with SLE exhibited clinically significant emotional lability that was unrelated to disease duration, medication, or psychiatric variables. Event-related potential (ERP) data has suggested that people with high emotional lability are more responsive to external stimuli. Thus, people with SLE may have disproportionate emotional lability due to increased sensitivity to external stimuli (Berntson et al. 2007).

Psychosis manifests in up to 8 % of SLE patients (Bruns and Meyer 2006). Psychotic symptoms are usually limited

to hallucinations and delusions (Pego-Reigosa and Isenberg 2008). One study that examined psychosis in the lupus population found the co-morbidity of psychosis and other neuropsychiatric symptoms to be high; depression occurred in 90 % of study participants, and cognitive dysfunction was found in 70 % (Pego-Reigosa and Isenberg 2008). Phenylcyclohexylpiperidine (PCP), a glutamate receptor antagonist that binds to the NMDA receptor, produces hallucinations and paranoia (Olney et al. 1999). Thus, reactivity of anti-NMDAR autoantibodies in SLE patients suggests a reasonable mechanism for the presence of psychotic features.

Mechanisms for Disease

Effects of Autoantibodies on Neuronal Tissue in SLE

SLE results in an overproduction of autoantibodies. Antibodies directed against nuclear antigen, antinuclear autoantibodies (ANA), are considered highly sensitive for SLE and 98 % of lupus patients have a positive serum test for ANA (Worrall et al. 1990). However, the presence of ANA is not specific to SLE as many other diseases, such as rheumatoid arthritis, Sjögren's syndrome, and scleroderma, also result in ANA overproduction. Low titers of ANA are also detected in 5–10 % of a healthy female population. ANA per se are not considered pathogenic; their presence in high titers is indicative of an immune system that has lost tolerance to self. Subsets of ANA are associated with specific organ pathology, including the brain.

Anti-dsDNA autoantibodies are a subset of ANA that are directed against dsDNA, and are more specific to SLE than ANA. Approximately 60 % of lupus patients exhibit anti-dsDNA autoantibodies and their presence is frequently associated with renal disease (ter Borg et al. 1990). Anti-dsDNA autoantibodies are one of the only autoantibodies associated with SLE whose serum titers fluctuate with disease flares. Interestingly, these autoantibodies have been eluted from affected tissue (e.g., kidney, skin, brain), and their pathologic affects are thought to be secondary to antigenic specificities that are different from dsDNA. For example, subsets of anti-dsDNA autoantibodies have been shown to bind to renal antigens including heparin sulfate and α actinin and laminin (for review see Hanrotel-Saliou et al. 2011). Anti-NMDAR autoantibodies are a subset of anti-dsDNA autoantibodies that cross-react with the NR2A subunits of NMDA glutamate receptors in the brain and have been shown to cause excitotoxic or apoptotic cell death in vitro and in vivo (Choi and Rothman 1990; DeGiorgio et al. 2001; Kowal et al. 2004).

Anti-NMDAR autoantibodies have been eluted from the brains of lupus patients with known cognitive dysfunction and are toxic to neurons in culture and when injected into mouse brain (DeGiorgio et al. 2001). Importantly, non-autoimmune mice immunized to produce anti-NMDAR antibodies do not experience any adverse effects of these antibodies unless the blood brain barrier (BBB) is disrupted. Researchers have observed that an intact BBB prevents damage to neuronal tissue but a pharmacologically opened BBB allows antibody access to the brain, resulting in neuronal tissue damage and the region of the brain affected most by the anti-NMDAR antibodies is a function of the agent used to permeabilize the BBB. For example, in the mouse model, lipopolysacharide (LPS) that mimics infection results in antibody deposition in the hippocampus and functional impairment on memory tasks. Conversely, the use of epinephrine, which mimics stress, results in antibody deposition in the amygdala and impaired emotional learning (Huerta et al. 2006; Kowal et al. 2004). It is known that BBB permeability in humans is altered in response to insults such as hypertensive episodes, nicotine, infection, stress, and alcohol. In addition, vasculopathy and cerebral infarcts occur often in SLE patients leading to endothelial cell disruption and impairment of the BBB (Hanly et al. 1992; Narshi et al. 2011). In fact, up to 49 % of SLE patients show vascular deterioration in the brain (Luyendijk et al. 2011), and many people with SLE also suffer from anti-phospholipid syndrome, a disorder associated with autoantibodies that promote clotting and thrombus formation within blood vessels (Tincani et al. 2009). Therefore, vascular deterioration is certainly present in the brain and likely affects the BBB, which would provide a pathway for the entrance of antibodies into brain parenchyma. Deterioration of vasculature seems to occur over time as the disease progresses, which is consistent with the finding that cognitive dysfunction becomes greater later in the course of the disease (Appenzeller et al. 2007).

Direct connections between the presence of serum anti-NMDAR autoantibodies and neuropsychiatric deficits in human studies have been mixed, and the mouse model that relies on breach of the BBB for pathologic effects of the antibody to occur predicts this. Several studies have observed that a higher presence of anti-NMDAR autoantibodies in serum results in greater neuropsychiatric deficits (Fragoso-Loyo et al. 2008; Lapteva et al. 2006; Omdal et al. 2005), while other studies have failed to demonstrate associations between serum levels of anti-NMDAR autoantibodies and neuropsychiatric deficits in SLE patients (Hanly et al. 2006; Harrison et al. 2006; Lapteva et al. 2006). However, correlations between serum levels of anti-NMDAR autoantibodies may be unreliable because an intact BBB would prohibit the transition of antibodies from blood serum to brain tissue. In agreement with the animal model, several studies have demonstrated significant associations between anti-NMDAR antibodies in the cerebrospinal fluid of SLE patients with active NPSLE symptoms

compared to those without NPSLE symptoms (Arinuma et al. 2008; Fragoso-Loyo et al. 2008; Yoshio et al. 2006). These studies did not specifically assess cognitive function as patients were assessed at the time of NPSLE flares. Other autoantibodies have been implicated in brain disease in lupus. Autoantibodies directed against phospholipid, α tubulin, and ribosomal P have also been shown to bind to neurons resulting in altered neuron function or death and in cognitive, sensory and behavioral deficits (Caronti et al. 1998; Kent et al. 2000; Matus et al. 2007; Ndhlovu et al. 2011).

In summary, SLE results in an overproduction of autoantibodies, including those that target NMDARs (i.e., anti-NMDAR autoantibodies). Disruption of the BBB allows anti-NMDAR autoantibodies, along with other autoantibodies, to access brain tissue and cause neuronal death or dysfunction. As the NMDARs are found in highest density in the hippocampus and amygdala, these structures may be particularly vulnerable to this process. NMDARs play an important role in long-term potentiation (vital for learning and memory; Sakimura et al. 1995) and antibody-associated cell death within the hippocampus can lead to cognitive dysfunction in mice (DeGiorgio et al. 2001). Additionally, mice whose amygdala has been targeted by anti-NMDAR autoantibodies exhibit impaired fear learning; however, the full impact of these antibodies on behaviors associated with amygdala functioning in humans is still unclear.

Neuro-Anatomical Changes Associated with SLE

Neuroimaging studies in SLE patients have demonstrated abnormalities in a variety of structures, including white and gray matter. The most commonly reported abnormalities on conventional MRI include cerebral atrophy, periventricular white matter hyperintensities, infarcts, and hemorrhage. More sophisticated volumetric studies have shown reductions in hippocampus, corpus callosum, cerebellum, cerebral cortex, and amygdala (Appenzeller et al. 2007, 2006, 2005; Emmer et al. 2006; Muscal et al. 2010). Critically, the degree of volumetric loss in the brain has been associated with the presence of autoantibodies and disease duration for individuals with SLE, and greater volumetric loss has been positively associated with more severe cognitive impairment (Appenzeller et al. 2007). These volumetric findings suggest that disease duration is an important factor in determining cognitive functioning and may also be an important factor in determining emotional dysfunction.

As mentioned, antiphospholipid autoantibodies associated with SLE can cause vascular deterioration and negatively impact brain tissue. Indeed, SLE is associated with a risk of stroke that is two-times greater than in the general population (Hak et al. 2009). In people with SLE, deterioration of neural structures due to cerebral micro-infarcts is found diffusely in the brain and affects both gray and white matter (Luyendijk et al. 2011). Moreover, vascular deterioration in the white matter of SLE patients has been repeatedly associated with accumulated disease-associated damage, including neuropsychiatric manifestations (Ainiala et al. 2005; Appenzeller et al. 2008; Castellino et al. 2008).

One of the most abundant neuro-anatomical changes in people with SLE is diffuse white matter abnormalities (for review see Kozora and Filley 2011). For example, Luyendijk and colleagues (2011) examined structural brain images of 74 patients with SLE and found that 36 of them (49 %) had white matter hyper-intensities (WMHI); moreover, all of the participants who had WMHI also exhibited neuropsychiatric manifestations. Similarly, Jung and colleagues (2012) found significant correlations between white matter abnormalities and cognitive deficits in people with SLE, and to a greater extent those patients with neuropsychiatric symptoms. It is not clear whether white matter lesions are representative of direct targeting of myelinated axons by inflammatory molecules or autoantibodies, vascular insults, or diminished white matter tracts resulting from grey matter lesions.

Functional neuroimaging studies have also demonstrated altered regional response patterns in SLE subjects. Within specific brain regions, diminished regional blood flow has been found in the posterior cingulate cortex (Oda et al. 2005), and reduced metabolism has been found in the prefrontal cortex, the inferior parietal region, hippocampus, and the anterior cingulate cortex of patients with SLE (Komatsu et al. 1999; Kozora et al. 2011). Additionally, increased regional cerebral activation in response to specific cognitive tasks has been observed in SLE subjects compared to healthy controls (DiFrancesco et al. 2007; Mackay et al. 2011). These findings suggest that abnormal brain metabolism and activation patterns are associated with this disease. Moreover, SLE patients with neuropsychiatric manifestations are more likely to have diminished regional blood flow and metabolism, indicating that abnormal neural functioning has consequences on behavior.

Specific amygdala pathology has also been demonstrated in animal models of SLE and imaging studies of SLE subjects. In the mouse model of anti-NMDAR antibody-mediated brain disease, Huerta et al. (2006) found greater neuronal loss in the lateral amygdala when compared to control mice. Figure 1 shows the reduction of neurons in the amygdala in animals that were immunized to produce anti-NMDAR antibodies. In humans, Emmer and colleagues (2006) employed diffusion weighted imaging (DWI) to examine structural integrity within the amygdala of patients with SLE. They found that SLE patients with severe cognitive dysfunction had more abnormalities (suggestive of cytotoxic edema) within the amygdala than healthy controls. Moreover, the severity of the abnormalities in the amygdala correlated with serum anti-NMDAR antibody titers. However, the study did not find abnormalities

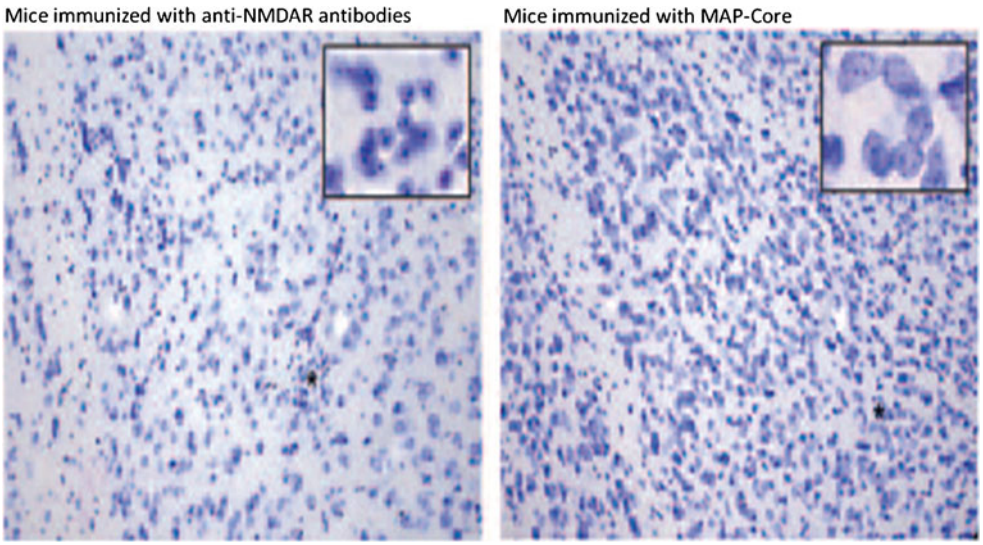

Fig. 1 Mice immunized with anti-NMDAR antibodies show shrunken amygdala neurons that possess clumped nuclei. These neurons also show a marker of neurodegeneration. Mice immunized with MAP-core show normal amygdala neurons. Figure reproduced from Huerta et al. (2006) Copyright (2006) National Academy of Sciences, USA

in the hippocampus of SLE patients with and without the autoantibodies. A recent study demonstrated loss of amygdala function on functional MRI in response to fearful faces stimuli in lupus patients with long term disease compared to those recently diagnosed (Mackay et al. 2011). Thus, there is data demonstrating that human SLE is associated with anatomical changes within the amygdala, and these changes may be associated with cognitive and behavioral abnormalities and with anti-NMDAR autoantibodies as clearly shown in the mouse model.

Behavioral Abnormalities Associated with SLE Pathology

Behavioral deficits associated with brain pathology have been found in animal models of SLE. Specifically, anti-NMDAR antibodies and hippocampus neuron loss have been causally associated with impaired learning and memory (Huerta et al. 2006). Kowal and colleagues (2004) in the non-autoimmune mice immunized to produce anti-NMDAR antibodies and treated with LPS to disrupt the BBB took a disproportionally longer time searching for a known submerged platform in murky water, as compared to control mice. In addition, when platform locations were moved, it took longer for the immunized mice to learn the new locations of platform. Therefore, the presence of antibodies commonly found in SLE is related to impaired spatial learning in mice.

Studies aimed at examining behavioral deficits in emotional processing have found that mice expressing the anti-NMDAR antibodies and treated with epinephrine have impaired emotional learning, which is reliant on proper amygdala functioning (Huerta et al. 2006). Fear-conditioning paradigms are used to examine emotionally based learning. In this task, a tone (conditioned stimulus, CS) is often paired with an electric foot shock (unconditioned stimulus, US), which elicits a fear response (freezing). Several pairings of the CS and US typically result in freezing when the CS is presented alone. However, the immunized mice with circulating anti-NMDAR antibodies showed less freezing behavior than controls when presented with the CS, suggesting a deficit in fear conditioning (see Fig. 2). This deficit in fear conditioning was associated with neuronal loss in the amygdala.

Researchers have also used animal models to study the effects of other autoantibodies on depression and anxiety (Katzav et al. 2008; Lapter et al. 2009). For instance, Katzav and colleagues (2008) found that mice injected with anti-P antibodies displayed more depressive-like behavior than control mice, as measured by the absence of escape-oriented behavior during a forced swimming test. Lupus-prone mice (NZB/NZW mice) demonstrate infiltration of the hippocampus with inflammatory cells, immunoglobulin, complement and a variety of pro-inflammatory molecules. This pathology is characterized phenotypically by behaviors consistent with anxiety symptoms in a variety of behavioral tests (e.g., open field test) (Lapter et al. 2009).

Emotional Processing, Cognitive Functions, and the Amygdala

The amygdala is involved in the processing of emotional stimuli and modulates emotionally relevant social behavior and cognitive functions. The amygdala is a paired structure composed of groups of nuclei located in the medial temporal lobes. As shown in Fig. 3, the amygdala has vast connections throughout the brain (Pessoa 2008). The amygdala has reciprocal connections with the hippocampus, and can modulate memory function (Cahill et al. 1996; McGaugh 2004). Reciprocal cortical connections to the prefrontal cortex suggests that amygdala function can influence prefrontal cortical processes (e.g., executive processes) and be regulated by

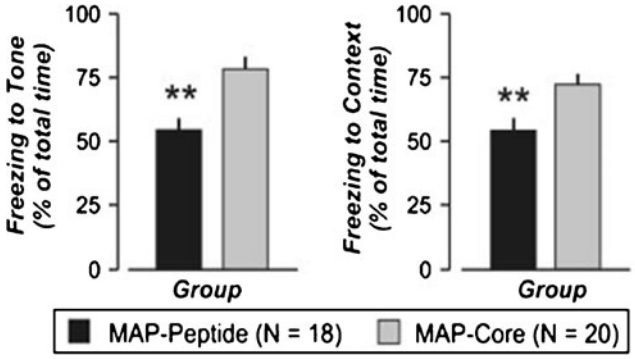

Fig. 2 Mice immunized with MAP-Peptide to imitate SLE showed an impairment in emotional learning when compared to mice immunized with MAP-Core. Figure reproduced from Huerta et al. (2006) Copyright (2006) National Academy of Sciences, USA

executive processes (Armony and Dolan 2002). The amygdala also has afferent and efferent connections with sensory cortical areas, and receives direct projections from the thalamus, indicating that it influences the processing of sensory information (Vuilleumier 2005). As the amygdala is intimately involved in the processing of fear stimuli and the initiation of fear responses, it has many connections with neural areas involved with the fight-or-flight response, including the brainstem, hypothalamus, basal forebrain, and striatum.

General Function

The amygdala is critically involved in the detection of threatening, novel, and emotionally relevant stimuli in order to direct perceptual and attentional resources to such stimuli (Attar et al. 2010; Blair et al. 1999; Sander et al. 2003; Whalen et al. 2001; Zaretsky et al. 2010). For example, a threatening stimulus, such as a snake, is more likely to receive our attention than a non-threatening stimulus. The amygdala receives input from the thalamus and sensory cortices that allows it to integrate sensory information. Its output connections with brain regions involved with attention, motivation, and movement allow it to modulate behavior based on the initial evaluation of the environment.

Recognition of Emotional Expressions

The amygdala is involved in processing emotional stimuli, such as emotional faces. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have shown that the amygdala is active during the processing of emotionally expressive faces. Fear faces most consistently elicit the greatest amount of activation (Breiter et al. 1996; Fitzgerald et al. 2006; Morris et al. 1996; Phillips et al. 1997; Reinders et al. 2005; Whalen et al. 2001; Yang et al. 2002), but the amygdala is also responsive to faces expressing various emotional expressions, including anger (Whalen et al. 2001), sadness (Yang et al. 2002), surprise (Kim et al. 2003), and happiness (Somerville et al. 2004).

Some of the first evidence for the involvement of the amygdala in processing emotional expressions was with individuals who had sustained amygdala damage. Such individuals demonstrated increased difficulty recognizing fearful expressions when compared to other types of emotional expressions (Adolphs et al. 1994; Broks et al. 1998). Initial work identifying the involvement of the amygdala in the recognition of fear expressions has been supported with functional brain imaging in healthy participants. For instance, Morris and colleagues (1996) observed increased

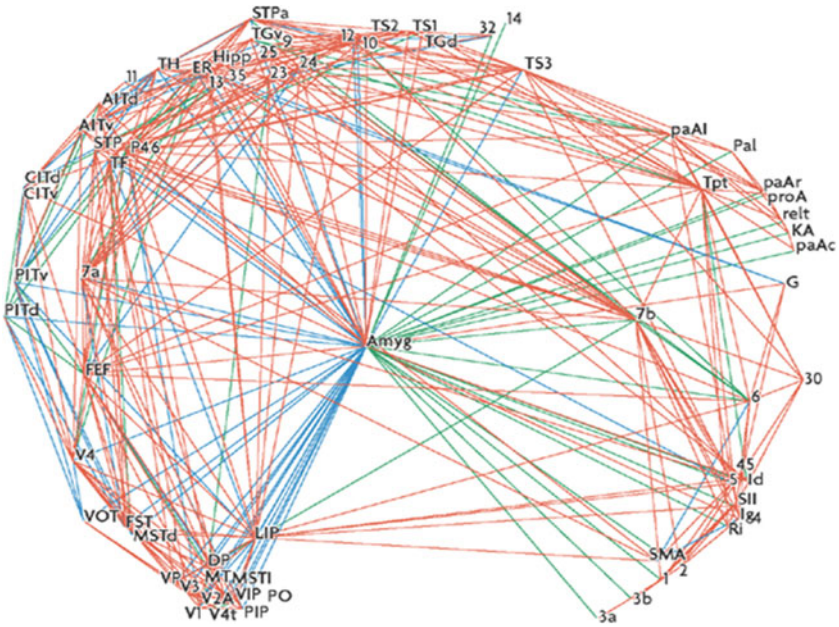

Fig. 3 Cortical connections of the amygdala show widespread afferent and efferent connections throughout the brain. Reprinted by permission from Macmillan Publishers Ltd: [Nature Reviews Neuroscience] (Pessoa, L. (2008). On the relationship between emotion and cognition. *Nat Rev Neurosci, 9*(2), 148-158.), copyright (2008)

metabolic activity in the amygdala while participants viewed fear faces as compared to happy faces. Other research has also observed that the amygdala is more active for fear faces compared to both happy and angry faces (Whalen et al. 1998, 2001). One hypothesis to explain this effect posits that the ambiguity associated with fear requires more processing from the amygdala to determine the cause of the fear (Whalen et al. 2001). To support this conclusion, Whalen and colleagues (2001) observed that angry faces elicited activation in the ventral amygdala, while fearful faces elicited activation in both the ventral and dorsal amygdala.

The amygdala appears to be preferentially responsive to negatively perceived facial expressions, suggesting that it is sensitive to the valence of a stimulus. Evidence shows that people who interpret a surprised face as negative have greater amygdala activation than those who interpret the face as positive; moreover, positively judging a face correlates with increased activation in the medial prefrontal cortex, which sends inhibitory projections to the amygdala (Kim et al. 2003). The net effect of that inhibition is reduced, but observable, amygdala activation in response to positively valenced facial expressions (Williams et al. 2004).

The amygdala also seems to be sensitive to the arousal, or intensity, of a stimulus. For instance, Adolphs and colleagues (1999) examined a patient with bilateral amygdala damage and found that, while she was impaired in recognizing the arousal of emotional faces, words, and sentences, she was able to identify the valence of the stimuli. Moreover, a meta-analysis of amygdala response to emotional stimuli found that the amygdala was most responsive to fearful stimuli but was closely followed by humorous stimuli (Costafreda et al. 2008). While fearful and humorous stimuli differ in valence, they are similarly highly arousing. Thus, the arousal of a stimulus may be as important to amygdala activation as valence.

Considering the evidence discussed above, it is not surprising that negatively valenced stimuli elicit the greatest amount of amygdala activation, as negatively valenced stimuli are often more arousing than positively valenced stimuli (Lane et al. 1999; Morris et al. 1998; Robinson 1998). While the arousing nature of a stimulus is important to amygdala activation, negative stimuli consistently elicit amygdala activation and robust behavioral findings. The synergistic effect of a highly arousing negative stimulus (i.e., fear) produces the most robust findings.

Regulation of Cognitive Functions by the Amygdala

Emotional and cognitive processes have largely been studied as separate entities. However, the importance of understanding the interacting effects of emotion and cognition on behavior is becoming clearer (Gray et al. 2002; Pessoa 2008, 2011). The amygdala plays an important modulatory role in cognitive processing. Perception, attention, learning, and memory are cognitive processes that are modulated by the amygdala, and by emotion more generally (LaBar et al. 1998; Lang et al. 1998; Vuilleumier 2005). Moreover, the amygdala may play a vital role in increasing attention to emotional relevant stimuli and bringing such information into conscious awareness (Kim and Jung 2006; Vuilleumier et al. 2004).

Attention

Emotionally relevant stimuli elicit greater activation in sensory regions of the brain than neutral stimuli (Lang et al. 1998). For example, emotionally salient scenes, as compared to neutral scenes, elicit greater activation in the lateral occipital lobe, part of the visual cortex (Lane et al. 1999). Similarly, emotional faces, as compared to neutral faces, elicit greater activation in the fusiform face area, which is intimately involved in the processing of faces (Vuilleumier et al. 2001). The specific role that the amygdala plays in the heightened activation of sensory areas to emotional stimuli remains somewhat unclear. However, there are strong neural connections between the amygdala and visual cortex (Armony and Dolan 2002; Catani et al. 2003), which suggests that the amygdala can modulate basic visual processing. In further support of this claim, brain imaging studies have observed strong positive correlations between amygdala activation and visual cortex activation to emotionally salient stimuli (Peelen et al. 2007). Moreover, the strength of the positive relationship between the amygdala and the visual cortex increases as the affective arousal of the stimuli increases (Sabatinelli et al. 2005).

The amygdala can increase attention to broad visual features, and it may also facilitate processing of specific features necessary for identifying emotional expressions. For instance, the amygdala may be able to quicken the processing of emotionally salient visual information by increasing attention to low spatial frequencies (Vuilleumier et al. 2003). To examine this, Vuilleumier and colleagues (2003) presented neutral and emotional faces and manipulated the spatial frequency of the presented faces such that either only the broad features (low spatial frequency) or the fine details (high spatial frequency) of the faces were displayed. They found heightened activation in the thalamus, superior colliculus, and amygdala during the presentation of low spatial frequency fear faces. Interestingly, this pattern of activation was not seen for high spatial frequency faces. These data implicate 1) the existence of a pathway that relays core visual information to the amygdala to allow for fast processing of relevant information and 2) that the amygdala sends this information, via feedback connections,

to the visual cortex to enhance visual processing of relevant emotional stimuli. The existence of such a pathway provides a method for faster attention to and processing of emotional stimuli compared to non-emotional stimuli.

The amygdala's role in speeding perceptual processing may modulate where attention is focused in a visual scene. Many studies demonstrate that emotionally relevant stimuli more readily capture attention than neutral stimuli (for review see Vuilleumier 2005). In visual search tasks, in which a target item must be selected out of distracting items, emotionally salient targets are routinely detected faster than non-emotional ones (Eastwood et al. 2001; Fox 2002; Ohman et al. 2001). Moreover, emotional distracters inhibit detection of non-emotional targets (Fenske and Eastwood 2003). Visual search tasks rely on the goals of the observer to deploy attention to the appropriate area or stimulus, and executive control by the observer allows for the focus of attention to one stimulus and for the rejection of distracting stimuli (Posner and Petersen 1990). Therefore, in a complex scene involving a variety of items, attention can be quickly directed toward those stimuli that hold emotional value while non-relevant distracting stimuli can be ignored, and it seems that the amygdala facilitates this process. Similarly, in a dot probe task, individuals are faster at processing the number of dots at a specific location when those dots are preceded by an emotionally relevant stimulus compared to a non-emotional stimulus (Cooper and Langton 2006). Moreover, trials in which emotional stimuli are presented result in greater amygdala activation along with faster behavioral responses (Carlson et al. 2009). Thus, the amygdala becomes active in response to emotionally relevant stimuli and facilitates the direction of attention toward such stimuli.

In addition to modulating the processing of visuospatial stimuli, the amygdala is involved in modulating attention for emotionally relevant verbal information. For instance, emotional and neutral words can be presented within the context of a Stroop paradigm, and emotional words slow down responses to naming the font color of the word (Richards and Blanchette 2004; Williams et al. 1996). A similar effect occurs during the attentional blink task, which typically presents a series of words at a rate of 10–15 per second. Two target stimuli are presented in the series. The second target stimulus cannot be detected if it is presented in close temporal proximity to the first target, resulting in an 'attentional blink.' Therefore, the observer must disengage from the first target in order to detect the second. The attentional blink phenomenon dampens when the second of two target words is emotionally relevant (Anderson 2005). That is, engagement in the second target can occur much faster following the first if the second target is emotionally relevant. However, people with amygdala damage fail to detect a second emotional target faster than a second neutral target, suggesting that they are not processing the emotional meaning of the word in the same way as people with intact amygdala functioning (Anderson and Phelps 2001). Moreover, fMRI data has shown that reduction in the attentional blink for emotional words is associated with amygdala activation (Schwabe et al. 2011). Thus, the amygdala facilitates attention for verbal information in the same way that it does for visual information.

Learning

The amygdala is vital to emotional learning, as shown in fear conditioning paradigms (for review of neural circuits related to fear conditioning see Kim and Jung 2006). Fear conditioning tasks (as described above) are often used to assess emotional learning. The association linking the emotionally salient US to the CS depends on amygdala functioning (Shi and Davis 2001). That is, the amygdala is vital for the acquisition (Helmstetter and Bellgowan 1994) and expression of conditioned fear (Helmstetter and Bellgowan 1994). Bechara and colleagues (1995) highlighted the importance of amygdala functioning in emotional learning by examining fear conditioning in one patient with selective bilateral amygdala damage and another with selective hippocampal damage. While the patient with hippocampal damage demonstrated an intact fear-response, the patient with amygdala damage failed to exhibit the expected response. Thus, the amygdala is critical in associating an otherwise benign stimulus with an emotionally aversive event.

Functional brain imaging further supports the role of the amygdala in emotional learning. In humans with a non-traumatized amygdala, there is increased blood flow to the amygdala when undergoing fear conditioning (LaBar et al. 1998). As the intensity of the US increases, the association between the CS and the US becomes stronger. Thus, fear responses to the CS become more pronounced as the strength of the US increases (Cordero et al. 1998).

Memory

Evidence shows that the amygdala modulates memory for emotional events (see McGaugh 2004 for review). Neuropsychological studies show that patients with amygdala lesions lack the normal enhancement of memories for emotional stimuli (Markowitsch et al. 1994; Siebert et al. 2003). Urbach-Weithe disease is a genetic disorder that can affect a multitude of systems, including vocal cords, skin, and the brain. Symptoms can vary drastically between patients, and some rare cases have resulted in very specific bilateral calcification of the amygdaloid complexes. Cahill, et al. (1995) found that a patient with Urbach-Weithe disease that specifically affected the amygdala did not display a normal memory enhancement for emotional aspects of a

story despite reporting a normal emotional reaction to the story (see Hurlemann et al. 2007 for similar finding). Neuroimaging studies also provide support for the amygdala being involved in the modulation of long-term memory for emotional stimuli. Greater amygdala activation during the encoding of emotional items predicts better memory for those items up to 1 month later (Cahill et al. 1996; Canli et al. 2000; Hamann et al. 1999). Interestingly, this memory enhancement effect is independent of hippocampal function (Buchanan et al. 2005; Hamann et al. 1997; Hamann, Cahill, and Squire 1997). Similarly, retrieval of memories of emotional items involves activation of the amygdala (Dolcos et al. 2005; Sharot et al. 2004). Overall, the amygdala is involved with modulating long-term memory for emotional events.

The Amygdala and Social Behavior

Humans are social beings that have adapted to live with others (Beckes and Coan 2011). Humans live in complex social societies and social interactions are quite common and critical for survival. The amygdala's role in facilitating our cognitive resources to detect and attend to emotionally relevant stimuli, such as facial expressions, suggests a role for it in interpreting and eliciting appropriate social behavior. For instance, Adolphs et al. (2002) found that people with bilateral or unilateral amygdala damage were less accurate in recognizing social facial expressions than brain injured controls. Moreover, they showed a specific deficit to facial expressions often displayed in social situations (e.g., guilt, admiration, flirtatiousness) compared to facial expressions less common to social situations (e.g., happiness, anger).

The amygdala has also been implicated in social behaviors other than simple emotional recognition. Adolphs et al. (1998) found that people with amygdala damage are impaired in their judgments of others' trustworthiness and approachability. Moreover, amygdala activation in healthy individuals has been associated with making such judgments (Winston et al. 2002). The amygdala is also involved in making quick, automatic evaluations of motivationally relevant stimuli, which influences subsequent behavior (Cunningham et al. 2004, 2008). These quick evaluations also apply to social entities such as racial classification, which is dependent on an array of social contexts (Cunningham et al. 2003; Hart et al. 2000). Therefore, the implications of amygdala damage on social behavior may extend to SLE and may even limit SLE patients' ability to make appropriate social evaluations based on affective feelings or cues. The psychosocial impact of SLE has been studied fairly extensively but it is not clear which aspects of the disease itself, the medications used to treat disease, or reactive mood disorders are responsible for the negative impact of SLE on individual development and environment. We suggest that impaired amygdala function that is mediated by anti-NMDAR autoantibodies, which may have significant psychosocial implications for lupus patients (Hochberg and Sutton 1988; Segui et al. 2000).

Implications for People with SLE

Given the importance of the amygdala in emotional processing, the frequency of emotional and behavioral deficits in SLE patients, and the causal relationship between anti-NMDAR autoantibodies and amygdala dysfunction demonstrated by the mouse model, we suggest that amygdala dysfunction may be related to the emotional and behavioral deficits seen in SLE patients. Thus, we would expect to see a reduction in the perception of, attention to, and memory for emotionally or motivationally relevant items on specific testing in SLE patients with anti-NMDAR autoantibodies compared to those without. The behavioral implications of these impairments would impact patients' emotional and psychosocial functioning, resulting in affective distress and difficulty functioning in social environments. As our model of neurological involvement depends on the presence of autoantibodies and disruption of the BBB, we would expect these types of symptoms to emerge later in the disease process.

Future Directions

Emotional processing is an important human function because it allows us to navigate through information and events that are most relevant to us. Impaired emotional processing can have a severe impact on our cognitive and social functioning, and on our health. The establishment of deficits in emotional processing in people with SLE begins with the process of developing appropriate assessments and outcome measures. The American College of Rheumatology (ACR) has established a recommended neuropsychological assessment battery for SLE patients ("The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes," 1999); however, this battery does not assess emotional processing. Therefore, an important aspect of overall cognition may be overlooked in a patient group that may have severe deficits in this area. Routine examination of emotional processing may be warranted in people with lupus, and such an examination can be easily implemented into a standard neuropsychological battery. There are several measures of emotional processing that can be used, such as the Florida Affective Battery (Bowers et al. 1999) or the Social Cognition subtests that are part of the Advanced Clinical Solutions package (Pearson 2009). These tests measure social perception and communication skills by

assessing the ability to recognize and name facial affect, prosody, and interactions between people. Thus, these tasks are sensitive to behaviors supported by proper amygdala functions and could be used to evaluate the extent to which deficits in psychosocial behavior may be affecting a person's daily functioning.

Future studies aimed at understanding the role of the amygdala in SLE disease pathology are needed in order to characterize the exact nature and extent of its involvement. The amygdala facilitates the perception, attention, recognition, and memory of emotionally relevant items in our environment. In people with amygdala dysfunction, we would expect to see an attenuation of these processes. Implications for these attenuated functions can result in general cognitive deficits such as limiting attention to and memory for salient events. Socially, individuals with SLE may have reduced capacity for identifying, evaluating, and recognizing emotional expressions and avoiding aversive situations, which could negatively impact their social relations and increase risk for social withdrawal, depression, and poor decision-making.

For clinicians treating lupus patients, it will be important to establish the presence of emotional deficits because such deficits may be an important diagnostic factor in determining the presence of NPSLE and cognitive deficits. The caveat will be attribution of emotional dysfunction to SLE and not to the confounding influences of medications, reactive depression and anxiety, or metabolic and hormonal influences. In addition to establishing appropriate functional assessments of emotional response and function, neuroimaging studies should also be employed to determine amygdala size and function so that a causal relationship between anti-NMDAR autoantibody, amygdala dysfunction and emotional impairment can be established in human disease. Emotional deficits that are clearly associated with anti-NMDAR antibodies and amygdala dysfunction will highlight the need for therapeutic intervention. Very importantly, development of the appropriate assessments and outcome measures will also provide us with the tools necessary for an interventional trials designed to test efficacy of neuroprotective agent(s). Furthermore, the interaction of the amygdala with other brain regions will likely emerge as an important factor in modulating emotional and motivation behaviors in this group. Specifically, changes in the pre-frontal cortex may impact amygdala functioning and affect emotional control and behavior.

Conclusions

In this review, we have characterized the pathophysiology and clinical presentation of SLE, including recent evidence suggesting abnormal amygdala function associated with this disease. Further, we characterized the role of the amygdala in emotional and non-emotional cognitive functioning. The implications of this review point to a specific pattern of deficits that may exist in people with SLE. Previous research in animal models has demonstrated neuronal loss in the amygdala that is associated with a specific neurotoxic autoantibody and a deficit in emotional learning. In humans with SLE, neural imaging has shown abnormalities in the amygdala. Thus, there is sufficient evidence to suggest that the amygdala is adversely affected during the course of SLE. However, it remains unknown the extent to which these abnormalities translate into functional behavioral deficits observable in this patient group. While cognitive functioning and emotional lability have been studied in people with SLE, the behaviors that are specific to amygdala dysfunction have yet to be documented in this patient group.

In conclusion, there is sufficient evidence to suggest that most SLE patients have amygdala damage and may have an associated deficit in emotional processing. Further research is necessary in order to establish and characterize the nature of such deficits. Structural and functional brain imaging studies will help to associate any behavioral deficits that do exist with amygdala damage, and could be used to examine the relationship between neurotoxic anti-NMDAR antibodies, amygdala damage, and abnormalities in mood, cognition, and other brain regions. Importantly, this line of research will allow for better assessments and interventions to be developed in order to help people with SLE cope with their disease.

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