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Cognitive and Emotional Abnormalities in People with Systemic Lupus Erythematosus

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by

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ABSTRACT

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Systemic lupus erythematosus (SLE) is a multi-system autoimmune disorder characterized by the production of autoantibodies (ABs). Approximately 30-50% of patients produce ABs directed against N-Methyl-D-aspartic acid receptors (NMDARs). Previous research with animals has identified these ABs as being associated with amygdala damage and a deficit in fear conditioning. People with SLE can have damage to the amygdala. This study aimed to determine if emotional processing deficits occur in people with SLE and to associate such deficits, if they exist, with anti-NMDAR AB presence, length of disease, cognition, and mood. Fifty-eight (11 AB+, 24 AB-, 23 healthy) women participated in tasks used to assess emotional facial recognition, attention to emotional stimuli, and emotional learning, and underwent cognitive testing, including measures of working memory, processing speed, executive functioning, language, visuospatial processing, and memory. Lupus patients were slower than healthy participants in identifying emotional faces, and measures of processing speed and executive functioning proved to be significant predictors of recognition of emotional faces and speeded reactions to emotional pictures. Thus, the results do not provide robust evidence for the existence of emotional processing deficits in people with lupus. The results are discussed within the context of the complex neuroanatomical system involved in cognition and affective processing. Future studies aimed at identifying dysfunction in the cognitive-affective control network are necessary to elucidate dysfunction in this patient group.

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CHAPTER I

INTRODUCTION

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 (ABs). SLE occurs in approximately 1 out of 1,000 people (Manson & 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, Gordon, Palmer, & Bacon, 1995). However, approximately 15-20% of SLE patients begin to have symptoms during childhood, and this early disease onset is associated with more severe disease outcomes, including renal involvement and seizures (Livingston, Bonner, & Pope, 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, with the most common clinical manifestation being arthritis (Alonso et al., 2012).

Previous research has established the presence of a subset of anti-double-stranded deoxyribonucleic acid (anti-dsDNA) ABs that cross-react with *N*-Methyl-D-aspartic acid receptors (NMDAR) in 30-50% of patients with SLE (Gonzalez-Albo & DeFelipe, 2000; Hanly, Walsh, & Sangalang, 1992; Omdal et al., 2005; Ozawa, Kamiya, & Tsuzuki, 1998). Once anti-NMDAR ABs have gained access to the brain parenchyma, they 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 affected; however, changes in many other brain regions also occur in association with SLE, most notably in white matter tracts throughout the brain (Huerta, Kowal, DeGiorgio, Volpe, & Diamond, 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 ABs and loss of hippocampal neurons with resulting impairment in memory (for review see Bruns & 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 ABs (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 research is to explore emotional processing deficits within SLE; I selected emotional deficits that typically arise when amygdala functioning is impaired. Specifically, I targeted deficits in interpreting emotional expressions, remembering emotional events, and attending to emotional features. A secondary aim is to determine if these deficits are associated with anti-NMDAR AB presence. I 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, Begum, & Isenberg, 2003). SLE patients also often

suffer from constitutional symptoms of widespread pain and fatigue, fevers, and weight loss

related to inflammatory processes (Tench, McCurdie, White, & D'Cruz, 2000). Nervous system

involvement in lupus, referred to as neuropsychiatric SLE (NP-SLE) represents a collection of 19

syndromes that affect the central and peripheral nervous systems. I will focus this review of the

literature 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. Others have found higher rates of renal disease, leucopenia, arthritis, and anti-DNA ABs

in patients with childhood onset SLE (Hersh et al., 2010; Webb, 2011). In contrast, those with

adult onset SLE were more likely to have Raynaud's phenomenon (skin discoloration in distal

extremities possibly caused by decreased blood supply), pleuritis (lung inflammation), and

Sjorgren's syndrome (an autoimmune disease that affects the exocrine glands). Greater

frequencies of renal and central nervous system (CNS) involvement may be the most severe

disease-related symptoms for those with childhood onset SLE compared with adult onset disease

(Muscal & Brey, 2010; Papadimitraki & 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. Steroidal treatments, however, can produce psychiatric or cognitive side-effects, such as agitation, changes in mood, and slowed cognitive processing. 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 (NP-SLE)

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 NP-SLE (Liang et al., 1999). As shown in Table 1, these can be broadly grouped into syndromes associated with peripheral nerve disorders, such as mononeuropathy and myasthenia gravis, and those associated with CNS disorders. Within the CNS, some NP-SLE 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 & 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). While CNS involvement in children with SLE is more prevalent than in adults (Papadimitraki & Isenberg, 2009), research has failed to produce evidence for greater cognitive impairment in childhood when compared to age matched controls (Williams et al., 2011).

Micro-infarcts caused by vascular abnormalities and/or accumulated atherosclerotic disease can exacerbate cognitive dysfunction caused by SLE, and these vascular changes may be associated with disease activity. Several studies have found an association between neuropsychiatric manifestations and antiphospholipid ABs (Denburg, Carbotte, & Denburg, 1987b; Long, Denburg, Carbotte, Singal, & Denburg, 1990), particularly in patients with stroke and cognitive dysfunction (Denburg, Carbotte, & Denburg, 1997; Hanly, Hong, Smith, & Fisk, 1999). For instance, Hanly and colleagues (1999) found increased deficits in processing speed and executive functioning in SLE patients positive for anticardiolipin ABs, as compared to those patients negative for those ABs. Antiphospholipid ABs are associated with hypercoaguable states and the mechanism for antiphospholipid-related cognitive decline is attributed to recurrent micro-ischemia.

Treatment of NP-SLE is tailored to the clinical syndrome and driven by our limited knowledge of underlying pathogenic mechanisms. For vascular disease related to antiphospholipid ABs, anticoagulation is used to reduce clotting in the prevention of stroke or micro-ischemia. 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 these variables. Notable cognitive impairment occurs in attention and concentration, working memory, visuospatial skills, and memory (Denburg, Carbotte, & Denburg, 1987a; Emori et al., 2005; Glanz, Schur, Lew, & Khoshbin, 2005; Glanz et al., 1997; Kozora, Ellison, & West, 2004; Loukkola et al., 2003; Monastero et al., 2001; Shucard et al., 2004). Moreover, cognitive impairment 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 NP-SLE than healthy controls, as well as with grey matter damage (Kozora et al., 2011; Steens et al., 2004). Furthermore, although SLE patients with and without overt neuropsychiatric symptoms display cognitive impairment, those with NP-SLE display more pronounced deficits (Monastero et al., 2001). Table 2 shows the comparison of cognitive performance of patients with NP-SLE and SLE to healthy controls across studies for a variety of neuropsychological measures.

Attention and processing speed. Attention and processing speed are cognitive functions that influence performance on other cognitive tasks (Chiaravalloti, Christodoulou, Demaree, & DeLuca, 2003; Sheppard, 2008). Patients with SLE often report problems with attention and processing speed (Vogel, Bhattacharya, Larsen, & Jacobsen, 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 NP-SLE 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 NP-SLE 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, Lee, Safford, & Shucard, 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. The authors also found that SLE patients were less accurate as the working memory

load increased. 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

NP-SLE 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).

       Visuospatial processing. Isolated visuospatial processing skills have been difficult to

evaluate in SLE patients. 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, or 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 NP-SLE 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 NP-SLE 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).

Motor. Motor slowing has been found in people with SLE and NP-SLE: 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.

Memory. Memory is the most commonly impaired cognitive process in people with SLE

and NP-SLE, which is consistent with hippocampal changes associated with the disease (Kozora

et al., 2011). 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). However, empirical findings on memory impairment in this group have been inconsistent in that not all studies have documented memory impairment in people with SLE.

In summary, SLE patients demonstrate impairment in multiple cognitive domains, and the degree of impairment worsens in the context of NP-SLE. Selective impairment in attention and processing speed can be accounted for by reductions in corpus callosum volume and other white matter abnormalities; however, 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 & 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, Chesney, and Criswell (2009) reported that 47% of their SLE cohort had 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 27% of SLE patients 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.

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 & 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, Bechara, Damasio, Tranel, & Cacioppo, 2007).

As mentioned earlier, structural and connectivity changes in the amygdala has been associated with SLE pathology. The amygdala has been extensively implicated in depression pathology and it is frequently found to be smaller than normal in chronically depressed people (Caetano et al., 2004; Hastings, Parsey, Oquendo, Arango, & Mann, 2004). In people with depression the amygdala is generally more active during rest and when viewing negatively valenced stimuli (Sheline et al., 2009; Siegle, Steinhauer, Thase, Stenger, & Carter, 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 been associated with a reduction of glial cells within the amygdala and with a lower glia/neuron ratio (Bowley, Drevets, Ongur, & Price, 2002). Furthermore, the reduced glia/neuron ratio has been associated with a specific reduction of oligodendrocytes, the glial cells that produce myelin (Hamidi, Drevets, & Price, 2004). Thus, the diffuse white matter abnormalities common in SLE (Appenzeller et al., 2007; Appenzeller, Rondina, Li, Costallat, & Cendes, 2005; Appenzeller, Vasconcelos Faria, Li, Costallat, & Cendes, 2008) may represent reduction of oligodendrocytes and contribute to the occurrence of mood disorder in this group.

Additionally, SLE patients with depression have demonstrated decreased cerebral blood flow in the frontal and temporal regions (Giovacchini et al., 2010). This finding highlights the integration of distinct neuroanatomical regions in mood regulation, and implicates frontal regions in the circuitry of mood. Frontal areas, including the orbitofrontal cortex and anterior cingulate cortex, have been implicated in the regulation of mood and response to emotional stimuli, and have been shown to regulate amygdala responding (Ochsner et al., 2004). Thus, in SLE there may be a disruption in the system-wide neural circuitry of mood and emotion regulation involving the frontal cortex and amygdala.

Psychosis manifests in up to 8% of SLE patients (Bruns & Meyer, 2006). Psychotic symptoms are usually limited to hallucinations and delusions (Pego-Reigosa & 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 & Isenberg, 2008). Phenylcyclohexylpiperidine (PCP), a glutamate receptor antagonist that binds to the NMDA receptor, produces hallucinations and paranoia (Olney, Newcomer, & Farber, 1999). Thus,

reactivity of anti-NMDAR ABs 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 ABs. Those ABs directed against nuclear antigen,

antinuclear ABs (ANA), are considered highly sensitive for SLE, and 98% of lupus patients have

a positive serum test for ANA (Worrall, Snaith, Batchelor, & Isenberg, 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 (i.e., low

concentration in blood serum) 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-double stranded DNA (dsDNA) ABs are directed against dsDNA, and they are a

subset of ANA that are more specific to SLE. Approximately 60% of lupus patients have anti-

dsDNA ABs and their presence is frequently associated with renal disease (ter Borg, Horst,

Hummel, Limburg, & Kallenberg, 1990). Anti-dsDNA ABs are one of the only ABs associated

with SLE whose serum titers fluctuate with disease flares. Interestingly, these ABs 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 ABs have been shown to bind to renal antigens including heparin sulfate and α

actinin and laminin (for review see Hanrotel-Saliou, Segalen, Le Meur, Youinou, &

Renaudineau, 2011). Within the brain, anti-NMDAR ABs are a subset of anti-dsDNA ABs that

cross-react with the NR2A subunits of NMDA glutamate receptors and have been shown to

cause excitotoxic or apoptotic cell death in vitro and in vivo (Choi & Rothman, 1990; DeGiorgio et al., 2001; Kowal et al., 2004).

Anti-NMDAR ABs have been eluted from the brains of lupus patients with known cognitive dysfunction. These ABs are toxic to neurons in culture and when injected in a mouse brain (DeGiorgio et al., 2001). Importantly, non-autoimmune mice immunized to produce anti-NMDAR ABs do not experience any adverse effects of these ABs unless the blood brain barrier (BBB) is disrupted. Researchers have observed that an intact BBB prevents damage to neuronal tissue. However, a pharmacologically opened BBB allows antibody access to the brain resulting in neuronal tissue damage. The region of the brain affected most by the anti-NMDAR ABs is a function of the agent used to permeabilize the BBB. In the mouse model, for example, lipopolysacharide (LPS; which 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, Giles, & Rahman, 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 ABs that promote clotting and thrombus formation within blood vessels (Tincani, Andreoli, Chighizola, & Meroni, 2009). Therefore, vascular deterioration is certainly present in the brain and likely affects the BBB, which would provide a pathway for the entrance of ABs 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 ABs 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 ABs in serum results in greater

neuropsychiatric deficits (Fragoso-Loyo et al., 2008; Omdal et al., 2005), while other studies

have failed to demonstrate associations between serum levels of anti-NMDAR ABs and

neuropsychiatric deficits in SLE patients (Hanly, Robichaud, & Fisk, 2006; Harrison, Ravdin, &

Lockshin, 2006; Lapteva et al., 2006). However, correlations between serum levels of anti-

NMDAR ABs may be unreliable because an intact BBB would prohibit the transition of ABs

from blood serum to brain tissue. In agreement with the animal model, several studies have

demonstrated significant associations between anti-NMDAR ABs in the cerebrospinal fluid

(CSF) of SLE patients with active NP-SLE symptoms compared to those without NP-SLE

symptoms (Arinuma, Yanagida, & Hirohata, 2008; Fragoso-Loyo et al., 2008; Yoshio, Onda,

Nara, & Minota, 2006). Measures of AB level in CSF would provide a more accurate indication

of AB presence within the brain parenchyma. These studies did not specifically assess cognitive

function as patients were assessed at the time of increased NP-SLE symptomotology. Other ABs

have been implicated in brain disease in lupus. ABs directed against phospholipid, α tubulin, and

ribosomal P have also been shown to bind to neurons resulting in altered neuronal function or

neuronal death, which has been associated with cognitive, sensory, and behavioral deficits

(Caronti, Pittoni, Palladini, & Valesini, 1998; Kent, Alvarez, Ng, & Rote, 2000; Matus et al.,

2007; Ndhlovu et al., 2011). Further, these antibodies have been found to react with myelin and

with an antigen associated with choroid plexus (Kent et al., 2000), suggesting diffuse cerebral involvement of AB reactivity.

In summary, SLE results in an overproduction of ABs, including those that target NMDARs (i.e., anti-NMDAR ABs). Disruption of the BBB allows anti-NMDAR ABs, along with other ABs, 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. However, access to particular brain regions by ABs may be dependent on psychological, environmental, and neurovascular states. For instance, periods of high stress is associated with increased epinephrine release. In animal models, epinephrine has been used to create BBB permeability in the area of the amygdala but not the hippocampus. Thus, periods of high stress in humans with SLE may result in specific amygdala-dependent deficits but not in hippocampal-related deficits. 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 ABs exhibit impaired fear learning; however, the full impact of these ABs 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; Appenzeller, Carnevalle, Li, Costallat, & Cendes, 2006; Appenzeller et al., 2005; Emmer, van der Grond, Steup-Beekman, Huizinga, & van Buchem, 2006; Muscal et al., 2010). Critically, the degree of volumetric loss in the brain has been associated with serum presence of ABs 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 ABs 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, Karlson, Feskanich, Stampfer, & Costenbader, 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 & 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 ABs, 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 pre-frontal cortex (PFC), the inferior parietal region, hippocampus, and the anterior

cingulate cortex of patients with SLE (Komatsu et al., 1999; Kozora et al., 2011). Moreover,

SLE patients with neuropsychiatric manifestations are more likely to have global diminished

regional blood flow and metabolism, indicating that abnormal neural functioning has

consequences on behavior. However, increased regional cerebral activation in response to

specific cognitive tasks has been observed in SLE subjects compared to healthy controls,

suggesting that compensatory processing is needed to complete a task (DiFrancesco et al., 2007;

Mackay et al., 2011). These findings suggest that abnormal brain metabolism and activation

patterns associated with compensation are associated with this disease.

Specific amygdala pathology has also been demonstrated in animal models of SLE and

imaging studies of people with SLE. In the mouse model of anti-NMDAR AB-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 ABs. 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 in the hippocampus of SLE

patients with and without the ABs. A study that examined amygdala response to fear faces using

functional MRI observed reduced amygdala activation to fear faces in lupus patients with long

term disease compared to those recently diagnosed (Mackay et al., 2011). Thus, there is data

demonstrating that SLE is associated with anatomical changes within the amygdala, and these

changes may be associated with cognitive and behavioral abnormalities and with anti-NMDAR

ABs as 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 ABs and hippocampus neuronal loss have been causally

associated with impaired learning and memory (Huerta et al., 2006). Kowal and colleagues

(2004) immunized mice to produce anti-NMDAR ABs and treated with LPS to disrupt the BBB.

Immunized mice 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 ABs commonly found in SLE is related to impaired learning in mice.

Studies aimed at examining behavioral deficits in emotional processing have found that

mice expressing the anti-NMDAR ABs 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 ABs showed less freezing behavior than controls when presented with the CS, suggesting a deficit in fear conditioning (see Figure 2). This deficit in fear conditioning was associated with neuronal loss in the amygdala.

Animal models have also been used to study the effects of ABs 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 ABs 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). Thus, in addition to cognitive consequences of disease activity, SLE also produces robust effects on psychiatric health. However, it is unclear if anti-NMDAR ABs have a direct impact on mood abnormalities in people with SLE.

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 (Armony & Dolan, 2002). The amygdala is a paired structure composed of groups of nuclei located in the medial temporal lobes. As shown in Figure 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). The medial prefrontal cortex and amygdala are reciprocally connected, and as such emotional processes can influence executive processes and executive processes can influence emotional processes (Armony & 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).

Given the amygdala's connections to multiple brain areas, it not surprising that the

amygdala is critically involved in the detection of threatening, novel, and emotionally and

motivationally relevant stimuli; these processes direct perceptual and attentional resources to

such stimuli (Attar, Muller, Andersen, Buchel, & Rose, 2010; Blair, Morris, Frith, Perrett, &

Dolan, 1999; Sander, Grafman, & Zalla, 2003; Whalen et al., 2001; Zaretsky, Mendelsohn,

Mintz, & Hendler, 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. Likewise, control

mechanisms are in place, via the PFC, to down-regulate emotional responses by the amygdala

that may be situationally inappropriate (e.g., fleeing from a snake in a cage in a zoo).

Recognition of Emotional Expressions

The amygdala is involved in processing emotional stimuli, such as emotional faces.

Positron emission tomography (PET) and functional MRI (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, Angstadt,

Jelsone, Nathan, & Phan, 2006; Morris et al., 1996; Phillips et al., 1997; Reinders, den Boer, &

Buchel, 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, Somerville, Johnstone, Alexander, & Whalen, 2003), and happiness (Somerville, Kim, Johnstone, Alexander, & Whalen, 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, Tranel, Damasio, & Damasio, 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 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; Whalen et al., 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, Morris, McGlone, Abbott, & Mattingley, 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, Brammer, David, & Fu, 2008). While fearful and humorous stimuli differ in valence, they are similarly highly arousing. Thus, the arousal-level 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, Chua, & Dolan, 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, Braver, & Raichle, 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, Gatenby, Gore, LeDoux, & Phelps, 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 &

Jung, 2006; Vuilleumier, Richardson, Armony, Driver, & Dolan, 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, Armony, Driver, & Dolan, 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 & Dolan,

2002; Catani, Jones, Donato, & Ffytche, 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, Atkinson, Andersson, & Vuilleumier, 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, Bradley, Fitzsimmons, & Lang, 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, Armony, Driver, & Dolan, 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, Smilek, & Merikle, 2001; Fox,

2002; Ohman, Flykt, & Esteves, 2001). Moreover, emotional distracters inhibit detection of non-

emotional targets (Fenske & 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 & 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 & Langton, 2006). Moreover, trials in which emotional stimuli are presented result in greater amygdala activation along with faster behavioral responses (Carlson, Reinke, & Habib, 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 & Blanchette, 2004; Williams, Mathews, & MacLeod, 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 & 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 & 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 & Davis, 2001), and the amygdala is vital for the acquisition (Helmstetter & Bellgowan, 1994) and expression of conditioned fear (Helmstetter & 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, Merino, & Sandi, 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, Markowitsch, & Bartel, 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, Babinsky, Markowitsch, and McGaugh

(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 one month later (Cahill et al., 1996;

Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000; S. B. Hamann, Ely, Grafton, & Kilts, 1999).

Interestingly, this memory enhancement effect is independent of hippocampal function

(Buchanan, Tranel, & Adolphs, 2005; S. B. Hamann, Cahill, McGaugh, & Squire, 1997; S. B.

Hamann, Cahill, & Squire, 1997). Similarly, retrieval of memories of emotional items involves

activation of the amygdala (Dolcos, LaBar, & Cabeza, 2005; Sharot, Delgado, & Phelps, 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 & 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, Baron-Cohen, and Tranel (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, Tranel, and Damasio (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, Strange, O'Doherty, & Dolan, 2002). The amygdala is also involved in making quick, automatic evaluations of motivationally relevant stimuli, which influences subsequent behavior (Cunningham et al., 2004; Cunningham, Van Bavel, & Johnsen, 2008). These quick evaluations also apply to social entities such as racial classification, which is dependent on an array of social contexts (Cunningham, Johnson, Gatenby, Gore, & Banaji, 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 ABs, which may have significant psychosocial implications for lupus patients (Hochberg & 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 ABs and amygdala dysfunction demonstrated by the mouse model, we suggest the presence of emotional processing abnormalities in the lupus population. 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 ABs

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 ABs and disruption of the BBB, we would expect these types of symptoms to

emerge later in the disease process.

<p align="center">**Specific Aims**</p>

Aim 1. To determine if people with SLE have deficits in processing emotional stimuli.

My goal was to examine the presence and extent of emotional processing deficits in

people with SLE because of the associations between neuronal death in the amygdala and

disruption of neuronal communication (Emmer et al., 2006; Huerta et al., 2006). For instance,

amygdala damage in SLE animal models has produced deficits in processing emotionally

relevant stimuli, and people with non-SLE related amygdala damage have also been associated

with poor emotional processing (Adolphs et al., 1994; Anderson & Phelps, 2001). Therefore, to

examine this goal, I evaluated cognitive processes that rely on proper amygdala function,

including: 1) emotional recognition, 2) attention to emotional stimuli, and 3) emotional learning.

It was hypothesized that people with SLE would have deficits in processing emotionally relevant

stimuli when compared to healthy controls.

Aim 2. To determine the association between emotional processing and autoantibody

presence in people with SLE.

Anti-NMDAR ABs, when the BBB has been compromised, result in neuronal death in

the amygdala and hippocampus in animal models of SLE (Lapteva et al., 2006), and have been

associated with neuropsychiatric and cognitive deficits (Kowal et al., 2004). Therefore, I

hypothesized that the presence of anti-NMDAR ABs in SLE patients would produce

disproportionately greater deficits in emotional processing as compared to patients without circulating ABs.

Aim 3. To examine the influence of disease duration on emotional deficits in people with SLE.

In animal models of SLE, deficits in emotional and cognitive processing only occur in the context of disrupted brain vasculature (Huerta et al., 2006; Kowal et al., 2004). In humans, vascular disruption often results from the presence of ABs aimed at the endothelium, and worsens as the disease progresses (Tincani et al., 2009). The likelihood of ABs accessing and damaging brain tissue becomes greater as vascular abnormalities increase (Huerta et al., 2006; Kowal et al., 2004). Therefore, I hypothesized that disease duration would be positively associated with impaired performance on the emotional and cognitive tasks.

Aim 4. To determine the relationship between emotional processing, cognitive functioning, and affective symptoms in people with SLE.

Cognitive dysfunction has been found in up to 80% of people with SLE (Ainiala et al., 2001), and mood disorders occur in approximately 75% of patients (Bachen et al., 2009; Bruns & Meyer, 2006). Determining the interacting effects of emotional processing deficits, cognitive functioning, and affective symptoms (i.e., depression) is important to understand the etiology of any deficits in emotional processing in people with SLE, and in employing the most effective intervention strategies. I hypothesized that increased deficits in emotional processing will be associated with a corresponding deficit in cognitive and/or affective symptoms.

CHAPTER II

METHODS

Behavioral assessment through experimental and traditional psychometric examination were conducted sequentially on the same day and took approximately 45 – 60 minutes each to complete. Clinical evaluations were done within 2 weeks prior to the behavioral and neuropsychological testing provided the patient's disease activity remained stable in the interim.

Participants

Two groups of patients (those with circulating anti-NMDAR ABs and those without) and a group of healthy controls were recruited. Antibody status in lupus patients was determined via serum analysis of circulating anti-NMDA ABs collected from participants with SLE and healthy participants. Mean AB level of healthy control participants was used to determine AB+ status in the lupus group. Those participants with SLE that had anti-NMDAR AB levels greater than two standard deviations of the mean healthy control level were determined to be AB+. To avoid bias, all investigators involved in the clinical assessments remained blinded to anti-NMDAR autoantibody status until data collection was completed. The healthy control group was matched for gender, age (within 3 years), and education. Testing was performed only during times of stable disease activity and medication use to avoid confounding influences of acute changes in disease activity.

Inclusion and exclusion were as follows for SLE subjects:

Inclusion Criteria: eighteen years of age or older; fulfilled the current American College of Rheumatology revised criteria for the diagnosis of SLE; willing and able to sign informed consent.

Exclusion Criteria: history of neurological disease (e.g., head injury resulting in a loss of consciousness, stroke (secondary to hypertension, atherosclerosis, diabetes), seizure, toxic

exposure, any difficulties at birth, mental retardation); documented transient ischemic attacks within six months of screening; limited fluency with English that in the opinion of the investigator would have limited the subject's performance on neuropsychological testing; history of illicit drug use (e.g., cocaine, cannabis, heroin); increased disease activity within four weeks, as defined by an increase in Systemic Lupus Erythematosus Activity Index (SLEDAI) score by 3 points or more exclusive of points from serologies and unchanged medication; any increase in steroid dose or addition of disease modifying agents within four weeks prior to screening; history of an anxiety disorder, depression, or other psychiatric illness that required medication. Exclusion criteria for healthy controls included: history of autoimmune disease; first-degree relative of a patient with autoimmune disease; history of neurological disease (e.g., head injury resulting in a loss of consciousness, stroke (secondary to hypertension, atherosclerosis, diabetes), seizure, toxic exposure, any difficulties at birth, mental retardation); documented transient ischemic attacks within six months of screening; limited fluency with English that in the opinion of the investigator would have limited the subject's performance on neuropsychological testing; history of illicit drug use (e.g., cocaine, cannabis, heroin).

With the exception of the emotional learning task, 58 female participants were included in the analyses; 35 lupus patients (11 AB+ and 24 AB-) and 23 healthy controls (HC). Sixty-three participants were enrolled in the study and signed consent forms but five of them were excluded following their enrollment. Two potential participants within the lupus group signed consent but could not complete the neuropsychological and behavioral testing due to an increase in disease activity. A third lupus patient was excluded from analysis because her lack of proficiency with the English language prohibited her ability to understand task instructions. An additional five lupus patients were run in the study but were not included in the analysis because

AB data was not able to be analyzed due to error on the part of the laboratory that conducted the

assay. One healthy control was excluded from analysis due to impaired performance across

multiple neuropsychological measures, which suggested impairment in cognitive functioning.

Another healthy control was excluded from analyses because of their high level of education.

Based on the prevalence of anti-NMDAR AB presence in lupus, I expected to obtain an

equal number of AB+ and AB- lupus patients in the study. The proposed goal was to have 20

participants in each group, which would ensure adequate power. However, the study procedures

required the active scientists involved were to remain blind to group assignment, and as a result,

the group size was unequal. The unequal group assignment may impact the resulting statistical

power. Thus, I am reporting the estimated power obtained for each statistical result.

Demographic information is provided in Table 3. As expected, there were significant

differences between groups in level of circulating anti-NMDAR AB such that the SLE AB+

group had higher average levels than the healthy participants and the SLE AB- group ($p < 0.01$).

The SLE AB- group was also found to be older, on average, than the healthy controls ($p. < 0.01$).

However, there no group differences in education or disease duration.

Measures

Emotional recognition

Emotion recognition is associated with amygdala functioning, particularly for expressions

of fear. Human lesion studies have consistently found impairment in emotion recognition

following amygdala damage (Adolphs, Tranel, Damasio, & Damasio, 1995; Adolphs et al., 1999;

Anderson & Phelps, 2000; Broks et al., 1998), and recognition of fear faces leads to amygdala

activation in brain imaging studies with healthy individuals (Phillips et al., 1998; Whalen et al.,

2001). Thus, I hypothesized that an emotion recognition task could be used to assess the degree

of impairment in recognizing emotional faces in SLE patients, and I expected the severity of

impaired recognition to positively correlate with the presence of anti-NMDAR ABs and disease duration.

Stimuli. Stimuli consisted of pictured faces displaying each of the six emotions (anger, disgust, fear, happiness, sadness, and surprise) and a neutral expression. Seventy pictures were selected from a standardized series of emotional faces (Ekman, 1976); 10 pictures were selected from each of the seven emotion categories, five for males and five for females. Each face measured 3.16 x 4.5 inches and was displayed centrally on a computer screen. The response options (numbers 1 – 7, each one associated with an emotion (anger, disgust, fear, happiness, sadness, surprise) or neutral) were displayed at the bottom of the screen along with the pictured face. The entire stimulus remained on the screen until a response was made.

Procedure. Participants sat in front of a computer screen at a viewing distance of 60 cm. Practice trials were given so that participants could become familiar with the recognition task. Following any questions from the participants, the experimental trials began. Participants were instructed to identify the emotional expression displayed on the screen by pressing a corresponding button (numbers 1-7) on the keyboard. Accuracy served as the primary dependent outcome but RT was also recorded.

Emotionally modulated attention

Visual search tasks are used to investigate attentional bias toward particularly salient stimuli. A typical visual search task consists of an array of stimuli presented on a screen. The goal of the participant is to determine the presence or absence of a target stimulus from among the distracting items. Emotional target items are often attended to faster than neutral targets (Calvo & Marrero, 2009; Frischen, Eastwood, & Smilek, 2008). The amygdala has been implicated in modulating attentional biases through feedback projections to both early and late

visual cortical areas. When the amygdala is damaged the feedback system is impaired and

emotional stimuli no longer bias attention (Lane et al., 1999; Vuilleumier, 2005). I hypothesized

that a reduced attentional bias toward emotional stimuli would be present in people with SLE

and would be greater for the AB+ group.

Stimuli. Emotional and non-emotional stimuli were selected from the International

Affective Picture System (IAPS; Cuthbert, 2008). Thirty negative, 30 positive, and 15 neutral

pictures were selected based on the standardized ratings. A one-way ANOVA was conducted and

the emotional picture sets differed in valence, $F(2, 72) = 262.25$, $p < 0.01$, $\eta^2 = 0.88$. Post-hoc

results revealed that the positive, negative, and neutral picture sets all differed from one another

with respect to valence, all p's < 0.01. The emotional picture sets also varied with respect to

arousal, $F(2, 72) = 20.67$, $p < 0.01$, $\eta^2 = 0.37$. The positive and negative sets had similar arousal

ratings, $p = 0.98$; however, the neutral picture sets were less arousing than both the positive, $p <$

0.01, and the negative, $p < 0.01$, sets.

Pictures were displayed in a circular fashion around a central point. On target present

trials, one of these pictures was different from the others; on target absent trials, all of the

pictures were the same. Demonstration trials were used to ensure proper understanding of task

instructions. Practice trials were also administered to allow for familiarization with the task.

Procedure. Participants sat in front of a computer screen at a viewing distance of 60 cm.

Practice trials were given so that participants could become familiar with the testing procedures.

Following any questions from the participants, the experimental trials began. Participants were

instructed to identify the presence or absence of a target stimulus by pressing either the "Z" key

or the "?" key. RT and accuracy were measured.

Emotional Learning

A fear-inducing unconditioned stimulus (US) elicits a startle response, which can be associated with an otherwise benign or conditioned stimulus (CS). In healthy individuals, following several pairings of the US and CS, the CS alone will cause a startle response. Research has demonstrated that fear-related responses and fear conditioning are dependent on amygdala functioning (Kim & Jung, 2006). Amygdala lesions or pharmacological inhibition of the amygdala prevents fear conditioning (Guarraci, Frohardt, Falls, & Kapp, 2000; J. J. Kim, Rison, & Fanselow, 1993). Moreover, amygdala dysfunction has been identified using fear conditioning in populations such as Urbach-Wiethe disease, Alzheimer's disease, and epilepsy (Bechara et al., 1995; S. Hamann, Monarch, & Goldstein, 2002; LaBar, LeDoux, Spencer, & Phelps, 1995). I expected that SLE patients would demonstrate impairment in conditioned fear learning, and that this impairment would increase with presence of anti-NMDAR ABs and disease duration.

Stimuli. Three phases of fear conditioning were presented. 1) During the habituation phase, red and green rectangles were presented independently and encompassed the entire computer screen. This phase allowed participants to become familiar with the stimuli and habituate to them. 2) In the acquisition phase, participants were again presented with red and green rectangles; however, one of the rectangles was paired with 100db of white noise presented through headphones (CS+ trials). The white noise served as the US. 100dB of sound was selected because it can reliably produce a startle response without causing damage to the ear (Spoendlin & Brun, 1973); the US was presented for two seconds. Trials were randomly presented during this phase to allow for CS presentation without concurrent US presentation (CS- trials). Comparison of physiological response during the CS- trials and trials in which the opposing rectangle appeared are used in the analysis to examine the extent of emotional learning.

3) The extinction phase was presented to reduce the relationship between the CS and the US by presenting CS- trials.

  Procedure. Participants were seated in front of a computer screen at a viewing distance of 60 cm. Participants were instructed to make an association between the color of the stimulus presented and the sound heard through the headphones. Left orbicularis oculi muscle electromyogram (EMG) eye blink reflexes were recorded with electrodes placed above and below the left eye, along with a ground electrode placed behind the left ear. Galvanic skin response (GSR; skin conductance response (SCR)) was recorded with electrodes placed on the left index and middle fingers. The Biopac MP36R system was used to record the physiological responses, and the data were processed using the Biopac Acquisition data processing software. Prior to placement of the electrodes, the skin was cleaned with an alcohol pad in order to ensure stability of the electrode and optimal recording of the electrical signal.

  The data were coded prior to analysis. For the eye blink EMG amplitude data, two research assistants working independently coded each trial for inclusion in analysis. Trials were included if eye blinks had normalized by 20 ms post stimulus onset. Data were recorded in a temporal window from 20 ms to 150 ms post stimulus onset. For the SCR data, two research assistants coded the temporal window at 0.5 s to 5 s post stimulus onset, and only trials with a minimum 0.02 microSiemens within that time window were included for analysis (Delgado, Jou, Ledoux, & Phelps, 2009).

Neuropsychological Testing

  Cognitive functions were measured using ACR recommended battery of neuropsychological tests. The tests included in this battery can be used to estimate intelligence and to assess a variety of cognitive functions, including working memory, processing speed,

executive functioning, motor skills, and verbal and non-verbal memory. I worked one-on-one with all of the participants and administered the neuropsychological measures.

1) <u>North American Adult Reading Test (NAART)</u>: The NAART is a word-reading task that can be used to estimate intelligence. The task consists of 50 English language words that vary in frequency of use. Participants are asked to read each word out loud and the number of words they incorrectly pronounce is recorded.

2) <u>Wechsler Adult Intelligence Scale – 3rd Edition (WAIS-III) Letter-Number Sequencing Subtest</u>: The letter-number sequencing task is used as a measure of verbal working memory. Participants are asked to repeat a series of randomly presented numbers and letters, but are asked to say the numbers first, from the lowest to the highest number, and then say the letters in alphabetical order. The sequences increase in length up to 8 digits and the raw score is the number of correct sequences.

3) <u>Symbol Digit Modalities Test</u>: The Digit Symbol test is a measure of psychomotor speed, which requires subjects to transcribe figure-coded numbers on to a blank figure-coded grid. The total Digit Symbol score corresponds to the total number of items completed correctly within 90 seconds.

4) <u>Trail Making Test, Parts A & B (TMT)</u>: The TMT is used as a measure of visual scanning, attention, processing speed, and rapid sequencing. In Part A, participants are required to quickly draw lines connecting randomly arranged numbers (1-25) in proper sequence. In Part B, participants quickly sequence numbers and letters in alternating order (i.e., 1-A-2-B…etc.). Errors are corrected immediately and time to finish is recorded.

5) <u>Stroop Color and Word Test</u>: The Stroop is a measure of attention, concentration, and behavioral inhibition under distracting conditions, and performance is sensitive to frontal lobe

dysfunction (Lezak, Howieson, & Loring, 2004). In the Stroop task, stimuli are presented as lists

on a sheet of paper, and participants identify the name or color of the stimulus. There are three

conditions. In the first condition, printed color names (Red, Blue, Green) are presented in black

ink and participants are asked to read as many colors as they can in 45 seconds. In the second

condition, a string of XXXs is presented in varying colors (Red, Blue, Green) and participants

are asked to name the color of the ink. In the third condition, color names are presented in

incongruous color inks (e.g., Red printed in green ink); participants are asked to name the color

of the ink. Subjects are given feedback on each incorrect trial by the examiner saying, "No," and

participants are required to provide the correct answer before continuing to the next trial. The

number of trials completed in 45 seconds is recorded. Additionally, an interference effect is

calculated by dividing the product of the scores on the first and second conditions by the sum of

those scores and then subtracting that from the score on the third condition

(i.e., $3rd - \frac{1st \times 2nd}{1st + 2nd}$).

      6) <u>Finger Tapping Test (FTT)</u>: The FTT is a measure of motor speed and can be used to

measure lateral differences in motor functioning. Participants are required to tap a specialized

tapper and counter as rapidly as possible for 10 seconds using their index finger. Five trials are

administered for each hand, and the mean number of taps per hand is calculated.

      7) <u>Controlled Oral Word Association Test (COWAT)</u>: This test measures the

spontaneous production of words to a category letter. Participants are asked to say as many

words as they can that begin with a specific letter in one minute; they are asked to avoid saying

proper names. Three trials are given, each with a different category letter (i.e., F-A-S). The total

number of correct non-repetitious responses is recorded.

8) <u>Animal Naming</u>: Animal naming is similar to COWAT but adds the component of providing a semantic category from which words can be produced. Participants are asked to say as many animals as they can in one minute and the number of correct non-repetitious answers are recorded.

9) <u>California Verbal Learning Test – 2nd Edition (CVLT-II)</u>: The CVLT-II is used as a measure of verbal memory. It consists of a 16-item word list encompassing four semantic categories, which is read by an examiner. Five trials are administered and participants are asked to recall the words from the list after each trial. An interference list is then read once by the examiner and participants are asked to recall words from the interference list. Recall of words from the primary list is again measured following the interference trial, and then following the provision of semantic cues (i.e, "Tell me the words from the first list that are animals). Delayed free recall and cued recall is recorded after 20-minutes, during which other tasks are administered. A recognition trial is also given to measure discriminability between target and distractor words. A forced-choice recognition trial is given approximately 10-minutes after the recognition trial.

10) <u>Rey-Osterrieth Complex Figure Test</u> (ROCFT): This task examines visual-spatial constructional ability and visual memory. Participants are asked to copy a complex geometrical figure onto a blank sheet of paper. Following a 20-minute delay, during which other tasks are given, they are asked to draw the figure from memory. Scoring criteria is used to calculate the raw score and is based on the accuracy and placement of each component of the figure.

Anti-NMDAR Autoantibody

Blood was drawn by one of two research assistants to determine the presence of the anti-NMDAR AB. The assays were performed in the Center for Autoimmune and Musculoskeletal

Diseases laboratory at the Feinstein Institute for Medical Research using an ELISA with the

DWEYS consensus sequence as the substrate. Briefly, the antigen was adsorbed onto high

binding, half-area 96 well plates (Costar #3690, Corning, NY) at 15 μg/ml in 0.1 M NaHCO$_3$ pH

8.6, overnight at 4° C. The serum was tested at 1:100 dilution in 0.2% BSA/PBS at 37° C for 1 hr

following 1 hr blocking with 1% BSA/PBS also at 37° C. The bound antibodies were detected

with AP-labeled goat anti-human-IgG (SouthernBiotech, Birmingham, AL) followed by AP

substrate (SIGMA, St. Louis, MO). Persons involved with data acquisition remained blind to

participant AB status until after data collection period had ended.

Mood Assessments

The Beck Depression Inventory – second edition (BDI-II; measures self-reported

presence of current depressive symptoms) and State-Trait Anxiety Inventory (SAI/TAI;

measures self-reported state and trait levels of anxiety) were used to assess self-reported mood

(Beck, Steer, & Brown, 1996; Gladman et al., 1997; Rahman, Gladman, Urowitz, Hallett, &

Tam, 2001; Stoll, Seifert, & Isenberg, 1996).

<div align="center">

Procedure

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Screening

After signing informed consent, participants were screened for entry into the study and

given a study ID number. The screening visit for SLE patients included a complete history and

physical examination conducted by a rheumatologist. Identification of ACR criteria, date of

diagnosis, other co-morbid illnesses, blood, and history of CNS disease was also collected and

documented. Current disease activity and stability of symptoms was determined at that time.

Testing

Cognitive and behavioral testing was conducted within two weeks of the screening in

order to ensure disease stability. For all participants, demographic information, including level of

education, zip code, occupation, and ethnicity was documented. The testing procedures began

with collection of demographic information, including self-report of cognitive dysfunction, and

then the neuropsychological testing. Following a short break, the behavioral testing was

administered, beginning with the Emotional Recognition task, then the Visual Search task, and

ending with the Fear Conditioning task. A measure of spatial memory was administered between

the Visual Search task and the Fear-Conditioning task but was not included as part of the

analysis on emotional processing. The session ended upon completion of the self-report health

assessments.

CHAPTER III

RESULTS

Aim 1. To determine if people with SLE have deficits in processing emotional stimuli.

To address this aim, I conducted analyses comparing performance on each behavioral between healthy controls and participants with lupus. Bonferroni corrections were used to reduce the potential for type I error. In general, the results did not suggest a robust deficit in processing emotionally relevant stimuli in people with SLE. However, there was evidence to suggest that lupus patients may be slowed in their processing of the subtleties of the facial expression of emotion. A summary of the results is shown in Table 4.

Emotional Recognition

A mixed 2 x 2 (Face Emotion [emotional, neutral] x Group [HC, lupus patients]) factorial ANOVA on percent of accurate responses (Figure 4) showed a main effect of face emotion, $F(1, 56) = 12.68$, $p < 0.01$, $\eta^2 = 0.19$, such that neutral faces were responded to with greater accuracy than emotional faces. There was no main effect of group, $F(1, 56) = 2.71$, $p = 0.11$, $\eta^2 = 0.05$ (observed power = 0.37), and, critically, the Face Emotion x Group interaction was not significant, $F(1, 56) = 0.24$, $p = 0.63$, $\eta^2 = 0.004$ (observed power = 0.08). As this was an a priori analysis, a Bonferroni correction was not applied.

I found a similar pattern of results as that reported above when I split face emotion by the specific emotions (Anger, Fear, Disgust, Happiness, Neutral, Sadness, Surprise); there was a main effect of face specific emotion after a Bonferroni correction was applied ($p \leq 0.017$), $F(6, 56) = 27.27$, $p < 0.01$, $\eta^2 = 0.33$, but no main effect of group, $F(1, 56) = 2.05$, $p = 0.16$, $\eta^2 = 0.04$ (observed power = 0.29), and no interaction, $F(6, 56) = 0.43$, $p = 0.86$, $\eta^2 = 0.01$ (observed power = 0.18).

Although accuracy was the primary dependent measure of this task, the RT data was assessed for a potential speed, accuracy trade-off. A mixed 2 x 2 (Face Emotion [emotional, neutral] x Group [HC, lupus patients]) factorial ANOVA revealed no main effect of face emotion, $F(1, 56) = 2.40$, $p = 0.13$, $\eta^2 = 0.04$ (observed power = 0.33). There was a main effect of group, $F(1, 56) = 6.06$, $p = 0.02$, $\eta^2 = 0.10$ (observed power = 0.79), in which the healthy controls were faster in responding; however, this result did not meet the more stringent criteria after applying a Bonferroni correction ($p \leq 0.017$). Figure 5 shows a significant interaction, $F(1, 56) = 7.86$, $p = 0.01$, $\eta^2 = 0.12$ (observed power = 0.79), such that healthy controls were faster than the lupus patients in responding to neutral faces, but there were no differences between the groups when responding to emotional faces.

When I analyzed the effect on RT separated by the emotion of the faces (Anger, Fear, Disgust, Happiness, Neutral, Sadness, Surprise) in a 7 (emotion of face) x 2 (group) ANOVA, I found a significant main effect of emotion, $F(6, 56) = 17.32$, $p < 0.01$, $\eta^2 = 0.24$, and a trend for a main effect of group, $F(1, 56) = 2.90$, $p = 0.09$, $\eta^2 = 0.05$ (observed power = 0.39; Figure 6), although this trend is less powerful once the Bonferroni correction is considered ($p \leq 0.017$). The interaction was at the cutoff level for significance before the Bonferroni correction was applied, $F(1, 56) = 2.10$, $p = 0.05$, $\eta^2 = 0.04$ (observed power = 0.12). Independent measures t-tests revealed significantly faster responding by the healthy controls for neutral faces, $t(56) = 3.00$, $p = 0.004$ (remains significant after Bonferroni correction of ($p \leq 0.007$), but not for any of the emotional faces.

Both groups exhibited a non-significant inverse relationship between emotional recognition accuracy and RT to emotional faces (HC: $r = -0.12$, $p = 0.57$; lupus patients: $r = -0.25$, $p = 0.15$), suggesting no speed-accuracy tradeoff.

Emotionally modulated attention

Prior to analysis, incorrect trials were eliminated and the RT data were log transformed in order to normalize the data. Additionally, outliers greater than three standard deviations above the mean for each individual participant were replaced with values equal to the cutoff (i.e., three standard deviations). A mixed 2 x 2 (Group [HC, lupus patient] x Target Emotion [emotional, neutral]) factorial ANOVA showed that healthy controls were significantly faster in their overall responding than lupus patients, $F(1, 56) = 5.19$, $p = 0.03$, $\eta^2 = 0.09$ (observed power $= 0.61$). There was no significant main effect of target emotion, $F(1, 56) = 1.11$, $p = .30$, $\eta^2 = 0.02$ (observed power $= 0.18$), and no interaction, $F(1, 56) = 0.37$, $p = 0.55$, $\eta^2 = 0.01$ (observed power $= 0.09$; Figure 7). The Bonferroni correction was not applies, as this was an a priori analysis.

I next analyzed the target pictures according to their specific affective properties (Valence and Arousal). The 2 x 5 (Group [HC, lupus patients] x Target Emotion (negative, high arousal; negative, low arousal; positive, high arousal; positive, low arousal; neutral]) factorial ANOVA revealed significantly faster overall responding by HCs, $F(1, 56) = 4.94$, $p = 0.03$, $\eta^2 = 0.08$ (observed power $= 0.59$), although this was not statistically significant once the Bonferroni correction was applied at $p \leq 0.017$. There was no main effect of target emotion, $F(1, 56) = 1.76$, $p = 0.14$, $\eta^2 = 0.03$ (observed power $= 0.53$), or interaction , $F(1, 56) = 0.39$, $p = 0.82$, $\eta^2 = 0.01$ (observed power $= 0.14$).

Following the technique of Salemink, van den Hout, & Kindt (2007), I calculated quantitative measures of orienting to emotional targets and disengaging from emotional distractors. The orienting index was calculated by subtracting RT on trials with an emotional target (E) and neutral distractors (N) from trials with a neutral target and neutral distractors (i.e.,

orienting index = N, N – E, N). The disengaging index was calculated by subtracting RT on trials

with a neutral target and neutral distractors from RT on trials with a neutral target and emotional

distractors (i.e., disengaging index = N, E – N, N). Moreover, these two factors were calculated

independently for each target emotion (i.e., negative, high arousal; negative, low arousal;

positive, high arousal; positive, low arousal). Separate independent measures t-tests for each of

these factors revealed no significant differences between groups (all p values > 0.05). I also

conducted one-sample t-tests for each factor to test for difference from zero. No significant

differences were found in the lupus group (all p values > 0.05). In the healthy control group, all

factors were not significant, with the exception of the orienting to positive stimuli factor, $t(22) =$

-2.10, $p = 0.05$, but this was not significant after the Bonferroni correction of $p \leq 0.005$.

Emotional learning

I analyzed emotional learning under two dependent measures, max eye-blink response

and square root of the average SCR. As shown in Figure 8, a 2 x 2 (Condition [CS-, CS+] x

Group [HC, lupus patient]) ANOVAs on each of the dependent measures revealed no main

effects and no interaction effects, (all p values > 0.05; all η^2 < 0.01; observed power for each

result < 0.1).

Aim 2. To determine the association between emotional processing and autoantibody presence in people with SLE.

To address this aim, I compared performance on the behavioral measures between lupus

patient positive for the anti-NMDAR AB and those negative for the antibody. Again, Bonferroni

corrections were applied to reduce the potential for type I error. The healthy control group was

included in the analysis only for the emotional learning task. The analyses for Aim 2 did not

show emotional processing deficits to be dependent on the presence of anti-NMDAR AB in

lupus. A summary of the findings for Aim 2 is provided in Table 5.

Emotional Recognition

A mixed 2 x 2 (Face Emotion [emotional, neutral] x Group [AB-, AB+]) factorial ANOVA on percent of accurate responses showed a main effect of face emotion, $F(1, 33) = 5.79$, $p = 0.02$, $\eta^2 = 0.15$ (observed power = 0.64), such that neutral faces were responded to with greater accuracy than emotional faces. There was no main effect of group, $F(1, 33) = 0.26$, $p = 0.60$, $\eta^2 = 0.01$ (observed power = 0.08), and the Face Emotion x Group interaction was not significant, $F(1, 33) = 1.40$, $p = 0.25$, $\eta^2 = 0.04$ (observed power = 0.21; Figure 9). As this was an a priori analysis, a Bonferroni correction was not applied.

I again found a similar pattern of results when I analyzed the separate face emotions; there was a main effect of face emotion, $F(6, 33) = 17.23$, $p < 0.01$, $\eta^2 = 0.34$ (after Bonferroni correction of $p \leq 0.017$; observed power = 1.0), but no main effect of group, $F(1, 33) = 0.04$, $p = 0.85$, $\eta^2 = 0.001$ (observed power = 0.05), and no interaction, $F(6, 33) = 1.75$, $p = 0.11$, $\eta^2 = 0.05$ (observed power = 0.48).

I also analyzed the RT data. A mixed 2 x 2 (Face Emotion [emotional, neutral] x Group [AB-, AB+]) factorial ANOVA revealed no main effects of face emotion, $F(1, 33) = 1.06$, $p = 0.31$, $\eta^2 = 0.03$ (observed power = 0.17), or group, $F(1, 33) = 0.98$, $p = 0.33$, $\eta^2 = 0.03$ (observed power = 0.16). The interaction effect was also not significant, $F(1, 33) = 0.44$, $p = 0.51$, $\eta^2 = 0.01$ (observed power = 0.10). When I analyzed the effect for the specific emotional faces with the Bonferroni correction of $p \leq 0.017$, a significant main effect of emotion was found, $F(6, 33) = 8.75$, $p < 0.01$, $\eta^2 = 0.21$ (observed power = 1.0), but there was no main effect of group, $F(1, 33) = 1.83$, $p = 0.19$, $\eta^2 = 0.05$ (observed power = 0.26). The interaction effect was also not significant, $F(1, 33) = 0.39$, $p = 0.89$, $\eta^2 = 0.01$ (observed power = 0.16). However, as shown in Figure 10, I analyzed group (HC, AB-, AB+) differences in RT for each face using independent

measures one-way ANOVAs; the Bonferroni correction was applied at $p \leq 0.007$. The healthy

control group was included in this analysis in order to determine if AB presence within the lupus

group had an effect on performance in comparison to normal functioning. Post-hoc analysis

revealed significantly faster responding by healthy controls than the AB- group for neutral faces

($p = 0.004$). Other results were significant at the 0.05 level but not with the Bonferroni

correction. These included faster responding by healthy controls than AB- participants for fear

faces ($p = 0.04$) and a trend toward faster responding for surprised faces ($p = 0.06$). While no

effects were shown between healthy controls and the AB+ group, there was a trend toward faster

responding by healthy controls for neutral faces ($p = 0.09$). Within the lupus groups the AB+

group responded significantly faster to happy faces than the AB- group ($p = 0.03$).

Within the lupus group, bivariate Spearman's correlations showed a significant positive

relationship between AB level and accuracy for surprised faces, $r = 0.37$, $p = 0.03$, but this

statistical significance does not hold after the Bonferroni correction of $p \leq 0.007$. No other

relationships reached significance. No significant correlations were found for the RT data, (all p

values > 0.05).

Emotionally modulated attention

A mixed 2 x 2 (Group [AB-, AB+] x Target Emotion [emotional, neutral]) factorial

ANOVA on log RT data showed no significant main effects of group, $F(1, 33) = 0.28$, $p = 0.60$,

$\eta^2 = 0.01$ (observed power = 0.08), or target emotion, $F(1, 33) = 0.04$, $p = 0.85$, $\eta^2 = 0.001$

(observed power = 0.05), and no interaction effect, $F(1, 33) = 0.13$, $p = 0.72$, $\eta^2 = 0.004$

(observed power = 0.06; Figure 11).

I also analyzed log RT to target pictures according to their specific affective properties.

The 2 x 5 (Group [AB-, AB+] x Target Emotion [negative high, negative low, neutral, positive

high, positive low]) factorial ANOVA also showed no significant main effects of group, $F(1, 33)$

$= 0.25$, $p = 0.62$, $\eta^2 = 0.01$ (observed power $= 0.08$), or target emotion, $F(1, 33) = 0.42$, $p = 0.80$,

$\eta^2 = 0.01$ (observed power $= 0.14$), and no interaction effect, $F(1, 33) = 1.37$, $p = 0.25$, $\eta^2 = 0.01$

(observed power $= 0.42$).

Factors were created for orienting and disengaging to emotional pictures that varied with

respect to valence and arousal. Separate independent measures one-way ANOVAs were

conducted with group (HC, AB-, AB+) as the independent variable for each of these factors.

These revealed no significant differences between groups (all p values > 0.05). I also conducted

one-sample t-tests for each factor to test for difference from zero. No significant differences were

found in the AB- or the AB+ groups (all p values > 0.05).

I conducted bivariate Spearman's correlations between AB level and RT to target stimuli

(emotional, neutral, negative high, negative low, positive high, positive low) and did not find any

significant relationship in the RT (all p values > 0.05).

Emotional learning

I analyzed group differences in emotional learning. The healthy control group was

included to determine if performance within either of the lupus groups was different from the

performance of the controls. The mixed 2 x 3 (Condition [CS-, CS+] x Group [HC, AB-, AB+])

factorial ANOVAs on max eye-blink or SCR did not produce any significant main effects or

interaction effects (all p values > 0.05; all $\eta^2 < 0.03$; observed power for each < 0.3; Figure 12).

**Aim 3. To examine the influence of disease duration on emotional processing deficits in
people with SLE.**

The analyses used to address this aim centered on assessing for the existence of

relationships between lupus disease duration and performance on behavioral measures. Disease

duration ranged from one year to 34 years. The distribution was slightly positively skewed

(skewness = 1.03; kurtosis = 0.72), possibly due to a floor effect. Measures of center were as

follows: mean = 12.09, median = 11, mode = 10. The findings that resulted from the analyses to

determine the contribution of disease duration suggested that, in general, differences in

emotional processes are not impacted by disease duration. However, there was further evidence

to suggest subtle deficits in emotional recognition of neutral faces in AB- lupus patients. A

summary of the results related to aim 3 are presented in Table 6.

Emotional Recognition

Bivariate Spearman's correlations were used to examine the relationship between disease

duration and emotional recognition performance. I found no relationship between disease

duration and percent of accurate responses for emotional, $r = 0.25$, $p = 0.15$, or neutral faces, $r =$

-0.21, $p = 0.23$, and there was no relationship found when I analyzed the separate emotional

faces (all p values > 0.05). When I split the groups by AB, I again found no significant

relationships in the AB- group (all p values > 0.05). However, as seen in Figure 13, there was a

significant inverse relationship between disease duration and accuracy for neutral faces in the

AB+ group, $r = -0.72$, $p = 0.013$ (significance remains after Bonferroni correction of $p \leq 0.013$),

indicating that those AB+ lupus patients who had the disease longer were less accurate in

identifying neutral faces.

I also conducted Spearman's correlations to examine the relationship between disease

duration and RT to emotional and neutral faces, and found no significant correlations in the lupus

group. When I split the lupus group according to AB, I found no significant relationships in the

AB+ group. There were, however, inverse relationships in the AB- group; as disease duration

increased RT was faster in identifying happy faces, $r = -0.54$, $p = 0.006$ (significance remains

after Bonferroni correction of $p \leq 0.007$), surprised faces, $r = -0.45$, $p = 0.03$, and sad faces, $r = -0.40$, $p = 0.05$.

Moderation Analysis: I conducted a moderation analysis to determine if the relationship between accuracy for emotional faces and AB level depended on disease duration. This analysis was conducted in order to assess for the possibility that emotional processing deficits may emerge as disease duration increases and AB has greater potential to affect brain functioning. Initially, I performed a linear regression, with percent accuracy as the dependent variable and AB level and disease duration as the independent variables. This analysis produced a non-significant effect, $R^2 = 0.02$, $F(1, 32) = 0.32$, $p = 0.73$. I then computed the centered scores for the independent variables and found the product of those centered scores, and then entered the resulting variable into the model as a third independent variable. I again found a non-significant result, $R^2 = 0.07$, $F(1, 31) = 0.77$, $p = 0.52$. I utilized the same model with RT to emotional faces as the dependent variable and found a similar pattern of results; the initial regression model was not a significant predictor, $R^2 = 0.09$, $F(1, 32) = 1.66$, $p = 0.21$, and the moderation regression model was also not significant, $R^2 = 0.12$, $F(1, 31) = 1.44$, $p = 0.25$. Taken together, these models suggest that the relationship between emotional recognition and AB level does not depend on disease duration.

Emotionally modulated attention

I used Spearman's bivariate correlations to identify the presence of a relationship between disease duration and emotionally modulated attention. However, there were no significant relationships between disease duration and RT to emotional targets (all p values > 0.05). Similarly, there were no significant relationships between disease duration and the attentional indices for orienting and disengaging in either lupus group (all p values > 0.05). This

pattern existed for the overall index scores and for the index scores for positive affective stimuli and negative affective stimuli (all p values > 0.05).

Moderation Analysis: I conducted a moderation analysis using the same procedures as I did for the emotional recognition data in order to determine if disease duration affected the relationship between AB level and RT to emotional stimuli. For the RT data, the initial regression analysis was not significant, $R^2 = 0.02$, $F(2, 32) = 0.29$, $p = 0.75$. The analysis that included the moderating variable also did not reach significance, $R^2 = 0.07$, $F(3, 31) = 0.75$, $p = 0.53$. A similar pattern was found for the log RT data; the initial regression produced a non-significant effect, $R^2 = 0.01$, $F(2, 32) = 0.12$, $p = 0.89$, as did the moderation regression, $R^2 = 0.04$, $F(3, 31) = 0.40$, $p = 0.76$. This provides further support that the relationship between emotional processing and AB presence does not depend on disease duration.

Emotional learning

I analyzed the relationship between disease duration and response to conditioned stimuli. No significant relationships were found between disease duration and eye-blink response to CS+, $r = -0.04$, $p = 0.84$, or SCR, $r = 0.24$, $p = 0.17$.

Moderation Analysis: For the moderation analysis, I input max eye-blink response as the dependent variable and AB level and disease duration as the independent variables into a linear regression model. This produced a non-significant model, $R^2 = 0.05$, $F(2, 27) = 0.66$, $p = 0.53$. Following the input of the moderation variable, the model again failed to reach significance, $R^2 = 0.05$, $F(3, 26) = 0.48$, $p = 0.70$. I used this same method with the SCR data, and the initial regression analysis did not reach significance, $R^2 = 0.01$, $F(2, 27) = 0.15$, $p = 0.86$. The model remained non-significant following input of the moderation variable, $R^2 = 0.03$, $F(3, 26) = 0.30$,

$p = 0.83$. Thus, there was no evidence in the present study to suggest that emotional learning in people with lupus is dependent on disease duration.

Aim 4. To determine the relationship between emotional processing, cognitive functioning, and affective symptoms in people with SLE.

To address this aim, I conducted multiple correlation analyses and regression models in order to determine the existence of relationships of emotional processing with general cognitive functioning and mood. A summary of these results is provided in Table 7. First, I analyzed group differences in cognitive functioning and the Bonferroni correction was applied.

Neuropsychological Testing

Table 8 shows the comparison of cognitive performance on core neuropsychological measures between lupus patients and healthy controls, which revealed poorer performance in the lupus group on the NAART ($p = 0.02$), SDMT ($p = 0.04$), LNS ($p = 0.04$), TMT-B ($p = 0.03$), FTT (dominant: $p = 0.03$; non-dominant: $p = 0.05$), COWAT ($p = 0.01$), CVLT-II short delay recall ($p = 0.02$), CVLT-II discrimination ($p = 0.05$), and Rey-Osterrieth Complex Figure copy trial ($p = 0.02$). However, no statistically significant differences were found after the Bonferroni correction was applied at $p \leq 0.003$.

I used one-way ANOVAs to analyze group differences based on anti-NMDAR AB presence. Post-hoc analysis revealed worse performance by AB+ lupus patients, as compared to healthy controls and AB- patients, in TMT-A ($p = 0.02$; $p = 0.04$) and COWAT ($p = 0.0001$; $p = 0.01$). Otherwise, the AB- lupus group exhibited worse performance than healthy controls on the NAART ($p = 0.04$), TMT-B ($p = 0.02$), CVLT-II short delay recall ($p = 0.02$), CVLT-II discrimination ($p = 0.02$), and Rey-Osterrieth Complex Figure copy trial ($p = 0.01$). Thus, many of the results found in the group comparison of lupus patients and healthy controls seem to be driven by performance in the AB- group. The only one of these results that remained statistically

significant following the Bonferroni correction was worse performance on COWAT by the AB+

group, as compared to healthy controls.

For clarity of analysis, I created composite scores from the neuropsychological measures

using factor analysis with 11 components. The results of this analysis produced three factors,

which accounted for 58.2% of the variance of the data set (factor loadings are displayed in Table

9). They were organized as processing speed/executive functioning (SDMT, LNS, TMT-A,

TMT-B, Stroop CW, COWAT), visuospatial functioning (Rey-copy, Rey-delay), and memory

(CVLT-SD, CVLT-LD, CVLT discrimination). The memory factor accounted for 30.6% of the

variance, the processing speed/executive functioning accounted for 20.9%, and the visuospatial

factor accounted for 6.6%. Once the factors were identified, the average z-scores of the

component measures were calculated for each composite score.

Examination of measures of mood and health revealed significantly worse levels of

depression, $t(56) = 2.66$, $p = 0.01$, and trait anxiety, $t(56) = 2.33$, $p = 0.02$, in the lupus group as

compared to HC. No differences were found between AB- and AB+ groups on measures of

mood.

Emotional Recognition

As shown in Figure 14, bivariate Spearman's correlations revealed a significant positive

relationship between accuracy for emotional faces and the composite scores of processing

speed/executive functioning, $r = 0.46$, $p = 0.005$, in the lupus group, and this met the stricter

criteria after the Bonferroni correction of $p \leq 0.017$. By comparison, in the healthy control group,

there was a significant positive relationship between accuracy for emotional faces and the

processing speed/executive functioning factor, $r = 0.43$, $p = 0.042$, but this did not meet the

criteria after the Bonferroni correction. Memory and visuospatial functioning was not related to

emotional recognition in either group. No significant relationships were found in the lupus group

between emotional recognition accuracy and measures of mood (BDI-II, SAI, TAI).

Emotionally modulated attention

I used Spearman's bivariate correlations to examine the relationship between emotionally

modulated attention and measures of cognitive performance and mood and health. Figure 15

shows the relationship of processing speed/executive functioning with RT to emotional targets in

participants with lupus and in healthy controls. In the lupus group, I found a significant inverse

relationship between RT to emotional targets and the processing speed/executive functioning

factor, $r = -0.62$, $p = 0.0001$, indicating that as executive abilities declined RT to targets became

slower. There was also a significant inverse relationship between the visuospatial factor and RT

to emotional targets, $r = -0.48$, $p = 0.004$ (these results met the stricter criteria after the

Bonferroni correction of $p \leq 0.017$). By comparison, in the healthy control group, there was only

a significant inverse relationship the processing speed/executive functioning factor and RT to

emotional targets, $r = -0.40$, $p = 0.003$.

For the measures of mood and health, no significant correlations were found within the

healthy control group (all p values < 0.05). In the lupus group, however, the SAI was positively

correlated with RT to emotional targets, $r = 0.36$, $p = 0.05$, such that increased anxiety was

associated with slower RT. This did not meet the criteria set by the Bonferroni correction ($p \leq$

0.008) and no other significant relationships were found within the lupus group.

See appendix for similar results with log RT data.

Emotional learning

I used Spearman's bivariate correlations to examine the relationship between emotional learning and measures of cognition, mood, and health. No significant correlations were found in the lupus group when examining relationships with max eye-blink or SCR responses.

CHAPTER IV

DISCUSSION

Abnormalities in the structure and function of the amygdala have been demonstrated in animal models of lupus, and structural damage has been observed in white matter integrity within the amygdala during imaging studies in people with SLE (Emmer et al., 2006; Huerta et al., 2006). Moreover, SLE can be characterized cognitively by deficits in processing speed, executive functioning, and memory (Glanz et al., 1997; Kozora et al., 2008; Kozora et al., 2011; Kozora et al., 2012). Mood abnormalities, such as depression and anxiety, are common in people with SLE (Bachen et al., 2009; Nery et al., 2007). Considering this constellation of cognitive, neural, affective, and mood disturbance, I sought to examine the processing of emotional stimuli in people with SLE in relation to anti-NMDAR AB presence, disease duration, cognitive functioning, and mood-related symptoms.

In general, the results did not suggest a deficit in processing emotionally relevant stimuli in people with SLE. However, there was evidence to suggest that lupus patients may process emotional stimuli differently, which especially impacts their ability to process ambiguous emotional stimuli. For instance, they were slowed in their processing of neutral facial expressions and pictures. There was no evidence to suggest this difference was related to the presence of anti-NMDAR ABs or to disease duration. Measures of processing speed and executive functioning were strongly related to emotional processing, but these relationships were similar in healthy controls and in lupus patients.

Group Differences in Emotional Processing

In line with the research goals of this study, I hypothesized that the presence of deficits in emotional processing, which included emotional recognition of facial expressions, attention to

emotionally relevant stimuli, and emotional learning, would be evident in people with SLE.

While there was some evidence to support subtle differences in emotional recognition in people

with SLE, the results did not generally support deficits in emotional recognition in this group.

The results revealed no group differences in emotional recognition, attention to emotional

stimuli, or emotional learning. There were also no interaction effects with the SLE and control

groups and these factors. This is surprising in light of the evidence for amygdala dysfunction

associated with SLE pathology. Amygdala dysfunction, which has been observed in SLE patients

and animal models (Huerta et al., 2006; Kowal et al., 2006; Kowal et al., 2004), often creates

deficits in emotional processing (Adolphs et al., 2002; Adolphs et al., 1994; Adolphs et al., 1999;

Bechara et al., 1995; Broks et al., 1998). However, the results of the present study failed to

provide evidence for deficits in emotional processing, which may have stemmed from amygdala

dysfunction in people with SLE.

    While this study failed to produce robust effects of impairment in emotional processing

in people with SLE, there were subtle differences between SLE patients and the healthy control

group. Analysis of the RT data in the emotional recognition task showed similar responding for

emotional and neutral faces in the SLE group but faster responding to neutral faces in the healthy

control group. There is evidence to suggest that faces with emotional content can produce longer

dwell times in participants viewing such faces when compared to neutral faces (Fox, Russo, &

Dutton, 2002). Thus, the SLE group may not have differentiated the emotional faces from the

neutral faces, suggesting difficulty with emotional identification. However, there were no deficits

with respect to recognition, which may suggest that other brain areas, outside of the amygdala,

may have been recruited to accurately identify the face. Interestingly, a recent study observed

such a coordinated network of brain activity involving the frontal and temporal lobes for both

emotion and neutral expressions (Carvajal et al., 2013). Given the connectivity degradation in SLE, it is quite possible that reaction times were slowed due to a less well-connected network, which would still allow for appropriate identification, but with greater difficulty.

The Effect of Anti-NMDAR AB on Emotional Processing

Given the evidence in the animal research of anti-NMDAR ABs being associated with emotional learning and neuropsychiatric deficits and a loss of amygdala neurons, I hypothesized that SLE patients with circulating serum anti-NMDAR ABs would exhibit greater deficits in emotional processing (Huerta et al., 2006; Omdal et al., 2005). In general, the results of the present study did not support the hypothesis that emotional processing deficits would be present to a greater extent in lupus patients who have circulating anti-NMDAR ABs. Specifically, no interaction effects were seen in emotional recognition, attention to emotional stimuli, or emotional learning, suggesting no differential responding to emotional stimuli between AB+ and AB- lupus patients. Counter to what was expected, slower responding in the AB- group, compared to the healthy control group, was found for neutral and fearful faces, while no such differences were found between the AB+ and healthy control groups.

The presence of anti-NMDAR ABs have been associated with cognitive dysfunction in people with SLE and are known to be toxic to neurons (DeGiorgio et al., 2001). However, results from serum presence of anti-NMDAR AB on cognitive functioning have been mixed. Animal studies examining the effects of these ABs on neuronal functioning have shown that a disruption of the blood brain barrier (BBB) is required for ABs to access the brain parenchyma. Moreover, human studies examining the relationship between CSF anti-NMDAR AB presence and cognitive dysfunction have produced more consistent results (Arinuma et al., 2008; Fragoso-Loyo et al., 2008; Yoshio et al., 2006). As I did not assess CSF AB presence in the current study,

it is difficult to know the extent to which the AB had access to the CNS in the AB+ group. While

I predicted that lupus patients with greater levels of circulating serum anti-NMDAR AB would

be at greater likelihood to have CNS involvement, CNS involvement is not guaranteed. Thus, it

is possible that the SLE patients in this study who were AB+ had intact BBB and have avoided

CNS involvement of their ABs. Moreover, it is possible that lupus patients with relatively lower

levels of circulating anti-NMDAR ABs (i.e., AB-) had compromised BBB, and exhibited similar

cognitive and emotional processing deficits as those patients with greater levels of circulating

AB but who had less BBB permeability.

In animal models of the effect of anti-NMDAR ABs on neuronal tissue and cognitive

functions, epinephrine and LPS were used to produce permeability of the BBB, and they caused

a selective permeability in the amygdala and hippocampus, respectively. LPS is a molecule that

can mimic an immune response, such as that produced in autoimmunity. Thus, in SLE, we would

expect to find a deficit in hippocampal functioning resulting from selective AB effects on

hippocampal tissue. However, that was not found in the present study. In contrast, there was no

difference observed between SLE patients with circulating anti-NMDAR ABs and healthy

controls on measures of memory. Epinephrine, however, was used to produce permeability

within the amygdala, and is a vital hormone released during periods of stress. However, there

was little evidence to show a selective deficit in emotional processing in people with SLE or in

SLE patients with circulating ABs. While memory and emotional processing were not observed

during the present study in SLE patients with circulating ABs, the possibility remains that the

BBB may have been permeated in other brain regions (e.g., PFC) and produced cognitive deficits

(e.g., processing speed and +executive dysfunction) that were not the primary measure of this

study. In fact, deficits in specific executive abilities (i.e., verbal initiation) were observed in AB+

SLE patients in comparison to healthy controls, suggesting that AB presence may be selectively affecting frontal regions and executive functioning.

The Role of Disease Duration

In accord with Aim 2, I predicted that patients who have had lupus for a longer amount of time would have greater difficulty in processing emotionally based stimuli because of the negative impact of the cumulative effect of disease pathology over time (Mackay et al., 2011). Specifically, I thought that the potential for vascular disruption to occur would be greater in those with longer disease duration, and that as a result AB+ lupus patients in particular would exhibit greater difficulties as they had the disease for a longer amount of time. However, disease duration did not prove to impact emotional processing; the results from the emotional recognition, visual search, or fear conditioning tasks did not produce any relationship between disease duration and the respective dependent measures in each task. I used moderation analysis to determine if the relationship between emotional responding and anti-NMDAR AB level depended on disease duration but no such effect was observed in any of the tasks used in this study.

The finding here that emotional processing was not associated with disease duration may be closely related to the results from Aim 2. That emotional processing deficits occur in people with SLE who are anti-NMDAR AB+ relies on the assumption that those ABs gain access to the CNS. Access to the CNS depends on disruption of neuro-vasculature, which is thought to occur to a greater extent as time passes. However, if neuro-vascular changes do not occur then patients who are producing greater amounts of anti-NMDAR ABs would not be susceptible to CNS involvement. Thus, the results from Aims 2 and 3, that emotional processing deficits do not depend on AB presence or disease duration, are consistent with each other. Taken together these

results may indicate good neuro-vascular health in this sample, prohibiting the observance of the

effect of anti-NMDAR AB on emotional processing.

The Influence of Cognitive Functioning and Mood on Emotional Processing

Consistent with the established literature, the results of neuropsychological testing

revealed differences between lupus patients and healthy controls in measures of processing

speed, working memory, motor speed, verbal fluency, short delay verbal recall, verbal memory

discrimination, and visuospatial construction (Kozora et al., 2004). These differences proved to

be driven by poorer functioning in the AB- lupus group. However, the AB+ group exhibited

worse performance on measures of processing speed and verbal initiation than the healthy

controls. The greater contribution of the AB- group in driving the cognitive dysfunction likely

reflects the larger sample size in the AB- group. While lupus patients reported overall higher

levels of depression and trait anxiety, there were no differences between AB- and AB+ patients

on measures of mood.

Because of the integration of mood, cognition, and affect, and the high prevalence of

cognitive and mood disturbance in people with SLE I hypothesized that there would be

relationships between these factors in people with SLE. Specifically, I thought that as measures

of cognition became more impaired emotional processing would also decline, and in a similar

fashion, as mood symptoms increased emotional processing would be more affected. Overall, I

found measures of processing speed and executive functioning to be strongly related to

emotional recognition and attention to emotional stimuli in lupus patients and in healthy controls.

Specifically, better performance on these cognitive measures predicted better accuracy in

identifying emotional facial expressions and faster responding to emotional targets. Surprisingly,

no relationships were found between measures of mood or disease activity and emotional processing.

The results here are not surprising considering the interplay between cognition and emotion. Emotional factors are known to have an impact on cognitive performance in the realms of perception, attention, learning, and memory (Markowitsch et al., 1994; Shi & Davis, 2001; Vuilleumier et al., 2001; Whalen et al., 2001). Emotional states are also known to impact cognitive processing (Gray et al., 2002). Thus, these results are consistent with network models of cognitive and emotional processing (Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012; Pessoa, 2009), and support an underlying neural basis for the interaction of cognitive and affective behaviors.

Neurobiological Implications

Taken together, the results of the present study have not supported deficits in emotional processing in people with SLE and favor spared amygdala functioning in this disease. However, this contrasts previous findings that suggest 1) amygdala neuronal loss in animal models of lupus produces deficits in emotional learning and 2) dysfunction in white matter integrity within the amygdala of human lupus patients. Hence, the question as to why the results of the present study have not supported this basis for the research remains an important question. Since a large basis for this work centered on AB-associated damage to the amygdala in animal models of lupus, it is important to understand the brain regions involved in human emotional processing. In a recent meta-analysis Lindquist et al. (2012) identified networks of brain regions involved in the processing and experience of emotional stimuli and perceptions. Of primary importance, the amygdala showed consistent responding to emotional stimuli with salient exteroceptive properties but was not reactive to internal feelings of emotion. However, the authors also found many other brain regions associated with the processing of emotional stimuli. These include the

ventrolateral PFC, dorsolateral PFC, dorsomedial PFC, inferior orbitofrontal cortex, cingulate

cortex, entorhinal cortex, insula, hippocampus, occipitotemporal cortex, peristriate, parastriate,

and putamen. Many different areas were involved in the processing of the same emotion. For

example, the perception of fear was processed by the amygdala, entorhinal cortex, hippocampus,

and middle temporal lobe. Additionally, the experience of these emotions was associated with

even different neural substrates.

As just mentioned, many brain regions were involved in the processing of emotions, and

these areas included regions of the pre-frontal cortex. Pessoa (2008) argued for a cognitive-

affective control circuit that involves dopaminergic projections from the ventral tegmental area

onto the nucleus accumbens, which then results in a watershed and integrated effect over the

amygdala, orbitofrontal cortex, anterior cingulate cortex, and lateral PFC. In this model,

cognitive and emotional processes are interlinked and executive control acts over both domains,

indicating a profound influence of frontal executive processes on amygdalar processing of

emotional stimuli. Thus, the neuroanatomical considerations involved in emotional stimuli

extent far beyond the amygdala and may account for the correlations between cognitive abilities

and responsiveness to emotional stimuli that were observed in this study. Moreover, this finding

was greater for people with SLE and may reflect diffuse brain dysfunction associated with

disruption in white matter integrity.

The interconnectedness between cognitive and emotional processing regions may allow

for implementation of compensatory strategies in maintaining accurate emotional processing.

The evidence from this study suggests that people with lupus were able to recognize and attend

to emotional stimuli to a similar degree as people without lupus, but it remains unclear whether

the two groups had similar processing strategies. For instance, people with lupus are just as

accurate in identifying emotional faces but they took longer to make their judgment, particularly when the emotion was more ambiguous (e.g., neutral faces). While disease duration did not prove to be an effective predictor of emotional decline, compensatory mechanisms may have helped behavior. Though, under times of duress, taxing cognitive processing, or symptom flare-up, such compensatory mechanisms may break down, which may leave such patients more vulnerable to display emotional processing deficits. Thus, identifying when compensatory processes may be limited or when amygdala damage becomes too severe to compensate for impaired emotional processes may be important factors to investigate.

Treatment Implications

Emotional processing is an important human function because it allows us to navigate through information and events that are most relevant to us. Dysfunction of this process can have a severe impact on our cognitive and social functioning, and on our health. However, the presence of emotional processing deficits was limited in the present study. That being said, certain cognitive functions did emerge as having a strong influence on overall functioning. Namely, processing speed and executive functioning were demonstrated to be deficient in people with SLE through neuropsychological testing and interactions with measures of emotional processing. Moreover, while lupus patients were similarly accurate in their responding to emotional facial expression, they were typically slower, which was especially apparent in response to ambiguous neutral facial expressions. This may has strong implications when navigating social environments. A typical social interaction is inundated with many micro-interactions, such as a gesture or a smirk, that provide information to the observer. Careful observation and understanding of those micro-interactions are important in having positive social interactions and in maintaining close relationships. The combination of slowed information

processing and difficulty in conceptualizing ambiguous social and emotional stimuli may have a negative impact on social and emotional functioning, and may be a contributing factor in the high rates of mood disorder that is found in people with lupus.

The American College of Rheumatology has established a recommended neuropsychological assessment battery for people with SLE ("The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes," 1999); however, this battery does not assess emotional processing and is limited in the level of executive functioning assessment that it incorporates, particularly higher order measures of organization, planning, and reasoning which are dependent on frontal executive processes and can be sensitive to functional interconnectivity. Therefore, important aspects of cognition may be overlooked in a patient group that may have severe deficits. For clinicians who are treating people with lupus, it will be important to establish the presence of a clear cognitive and emotional profile that could prove to be an important diagnostic factor in determining the presence of SLE and in characterizing the neuro-functional profile that an individual patient may be suffering.

While emotional processing deficits were not shown to be impaired in people with lupus in this study, I did find greater levels of depression and anxiety in SLE patients compared to healthy people, and this is consistent with previous research. Thus, the extent to which emotional regulation and mood is disrupted in SLE pathology should be a close consideration for treating clinicians.

Limitations of the Present Study

The present study has several noteworthy limitations. First, the sample was likely undersized, particularly in the AB+ lupus group. While I aimed for an adequate sample size of 20 participants in each group, we failed to reach that mark in the AB+ group. With the prevalence of

AB presence to be roughly 50% in the lupus population, I felt confident that an equal number of

AB+ and AB- lupus participants would be obtained. However, this did not occur and the sample

was more heavily stratified toward inclusion of AB- participants. Thus, statistical power was

certainly lost for analyses aimed at identifying group differences according to AB presence. This

was borne out by measures of estimated power, which failed to reach an adequate mark of 0.80

in any of the group analyses.

Another potential influence to the results was the strict exclusion criteria. This study was

aimed at identifying emotional and cognitive deficits and mood abnormalities in people with

lupus. However, in an attempt to control for possible confounds, lupus patients with active

disease or diagnosed mood disorder were excluded from participation. Thus, the patients that are

at greatest risk for presence of emotional and cognitive deficits were excluded from the study.

This approach could have severely hampered the ability to identify specific deficits associated

with this disease. Along with this, assessing AB presence in serum, as opposed to CSF analysis,

prohibited the ability to know if the AB was accessing brain tissue. Studies have consistently

found cognitive deficits in lupus patients when AB presence was determined in CSF, while

serum analysis has produced mixed results regarding cognitive deficits. Thus, determining AB

presence in CSF would have allowed greater ability to determine the effect on cognitive and

emotional processing when the AB is accessing brain tissue.

Finally, the amygdala has been shown to be preferentially responsive to salient stimuli,

and since fear is arguably the most salient emotion one can experience, the amygdala has been

shown to be responsive to fear. The stimuli that were selected for the experiments in the study

were carefully selected according to emotional content and valence, and arousal was also

considered in the selection process but overtly disgusting, gory, or sexually explicit stimuli were

excluded from inclusion in the set of stimuli. Therefore, it was quite possible that the arousing images selected were less likely to elicit amygdala involvement relative to the arousing images that were excluded. Moreover, by limiting the themes of the images, we may have also inadvertently allowed for greater amygdala habituation, which is commonly observed in imaging studies of the human amygdala (Breiter et al., 1996).

Future Directions

Future studies aimed at understanding neural dysfunction in SLE disease pathology can build off this study. Concerning affective processes in this patient group, attention should shift from potential deficits in emotional processing to regulation of emotional experience, and this would coincide with established clinical recognition of heightened mood and anxiety disorders in people with lupus. Moreover, this would build on data from the present study demonstrating a relationship between cognition and emotional responding. If the shared cognitive-affective executive control circuit is dysfunctional, impaired control over emotional experience and regulation of emotion may also exist. In fact, the locus of dysregulation may not be in the processing of incoming sensory emotional stimuli but may be the regulation of internal emotional feeling and the expression of that emotion. Thus, a person may recognize a snake and become aroused, but if that snake is a non-threatening garden snake, people with lupus may have a difficult time down-regulating their emotional feelings and expression.

Cognitively, the present study demonstrated deficits in processing speed and executive functioning, which is consistent with the established literature on the cognitive profile in SLE. However, to my knowledge the examination of executive functioning has been somewhat limited, with relatively few studies including higher order executive functioning such as planning, organization, abstract reasoning in verbal and non-verbal domains, and novel problem solving. In the present study, group differences were found in visuospatial construction on the

Rey-Osterrieth Complex Figure Test – copy trial. While this finding has been found in past studies, it has largely been interpreted as a deficit in visuospatial abilities. However, this study is known to also require executive abilities such as planning and organization, and is associated with right hemisphere gestalt abilities. Generally speaking, these are the skills that were thought to account for the group differences on this task in this study. However, these functions are difficult to quantitatively measure and future studies could be specifically designed to evaluate for systematic deficits in these areas of executive functioning in people with SLE is warranted.

Finally, the extent to which these deficits can be attributed to neuroanatomical functioning will be important to elucidate dysfunctional circuits in people with SLE. Thus, neuroimaging techniques, such as PET, DTI, MRI, or fMRI, should be incorporated. Particular emphasis should be placed on imaging functional connections between distinct anatomical regions will assist in identifying disrupted connectivity (important in appreciating the gestalt and integrating multiple facets of the environment) and in identifying cortical networks of cognitive and affective processing. For instance, studies with imaging could help to differentiate whether slowed responding to emotion stimuli is caused by reduced amygdala activation and increased compensatory processing, normal amygdala activation with impaired executive functions, or global deficits to emotion-cognitive circuits.

Conclusion

In conclusion, the present study was aimed at identifying emotional processing deficits in people with SLE, and to associate any deficits with the presence of anti-NMDAR ABs, longer disease duration, cognitive deficits, or mood abnormalities. While this study did not provide robust support for the presence of such deficits, mild differences were noted in responding to emotional stimuli in people with SLE, and an association between processing speed and executive functioning was established with emotional processing. These results do not explicitly

support previous findings in animal research demonstrating AB associated amygdala damage and deficit in fear conditioning, but the results are put in the context of the vast complexity of the human cognitive-affective control network and the many neuroanatomical regions involved in the processing of the human emotional experience.

Future studies aimed at clarifying the experience of emotions in people with SLE are needed. Importantly, the contribution of executive cognitive and affective control on emotional processing and emotional regulation would assist in characterizing the presentation of lupus from a mood and affective point of view and would assist clinicians in treated symptoms that can produce severe functional impact on people suffering with this disease.

TABLES AND FIGURES

Table 1.

Neuropsychiatric Syndromes in SLE

Central Nervous	Peripheral Nervous System
Acute Confusional State	Autonomic Neuropathy
Anxiety Disorder	Cranial Neuropathy
Aseptic Meningitis	Guillian-Barre Syndrome
Cerebrovascular Disease	Mononeuropathy
Cognitive Dysfunction	Myasthenia Gravis
Demyelinating Syndrome	Plexopathy
Headache	Polyneuropathy
Mood Disorder	
Movement Disorder	
Myelopathy	
Psychosis	
Seizure Disorder	

Table 2.

Comparison of cognitive performance of NP-SLE 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	-
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	-	-	-	-	-	-	-

* *Note:* NS = Not significant.

** Letter-Number Sequencing = WAIS-III (Kozora et al., 2004; Kozora et al., 2008), WMS-III (Glanz et al., 2005). Digit Symbol Substitution Test = WAIS (Denburg et al., 1987), WAIS-R (Emori et al., 2005; Glanz et al, 2005; Kozori et al., 2004; Kzori et al., 2008; Loukkola et al., 2003). Block Design = WAIS (Denburg et al., 1987), WAIS-R (Emori et al., 2005; Glanz et al., 1997; Glanz et al, 2005; Kozori et al., 2004; Kzori et al., 2008; Loukkola et al., 2003). Information = WAIS (Denburg et al., 1987), 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; Kozora et al., 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).

Table 3.

Comparison of demographic information between healthy controls (HC) and anti-NMDAR AB

negative (SLE AB-) and positive (SLE AB+) lupus patients. Standard deviations are presented in

parentheses.

Variable	Group			Result
	HC	SLE AB-	SLE AB+	
Age	32.78 (12.00)	43.79 (10.80)	37.73 (10.36)	AB- > HC ($p > 0.01$)
Education	14.30 (1.72)	14.00 (2.19)	13.27 (2.06)	NS
Ethnicity				
African American	43.5%	70.8%	36.4%	NS
Caucasian	30.4%	16.7%	30.4%	NS
Hispanic	13%	4.2%	45.5%	NS
Asian	4.3%	0%	0%	NS
Other	8.7%	0%	8.3%	NS
BDI	3.4 (3.4)	7.9 (6.06)	6.4 (7.92)	AB-, AB+ > HC ($p = 0.03$)
Disease Duration	N/A	12.33 (7.88)	11.55 (10.16)	NS
Co-morbidities				
HTN	NA	41.7%	54.5%	NS
Diabetes	NA	0%	9.1%	NS
Smoking	NA	20.8%	9.1%	NS
Medications				
Prednisone (mg)	NA	3.0 (4.54)	2.7 (5.18)	NS
SLEDAI	NA	1.9 (1.57)	1.6 (1.64)	NS
SLE Damage Index	NA	1.0 (1.46)	0.6 (0.92)	NS
Anti-NMDA AB	0.76 (0.72)	0.66 (0.28)	2.53 (0.55)	AB+ > HC, AB- ($p < 0.01$
Anti-dsDNA AB	NA	140.8 (176.3)	185.3 (189.59)	NS
Anti-Ro AB	NA	37.5%	27.3%	NS
Anti-ribosomal P AB	NA	16.7%	9.1%	NS
ACL AB (IgG or IgM)	NA	20.8%	27.3%	NS
Cognitive Dysfunction (self-report)	NA	70.8%	72.7%	NS

Table 4.

Summary of results for Aim 1.

*Note: Presence of * indicates that significance was not hold after Bonferroni correction was*

applied.

Aim 1	Result	Significant
Emotional Recognition		
2(Group) x 2(Emotion) ANOVA on Accuracy	Neutral faces responded to with greater accuracy ($p < 0.01$)	Yes
2(Group) x 7(Emotion) ANOVA on Accuracy	Main Effect of Emotion ($p < 0.01$)	Yes
2(Group) x 2(Emotion) ANOVA on RT	HC faster than SLE ($p = 0.02$) Interaction Effect ($p = 0.01$)	No * Yes
2(Group) x 7(Emotion) ANOVA on RT	Interaction Effect ($p = 0.05$) Faster responding to Neutral Faces by HC ($p = 0.004$)	No * Yes
Accuracy x RT Correlations	All p values > 0.05	No
Emotional Attention		
2(Group) x 2(Emotion) ANOVA on RT	Faster Responding by HC ($p = 0.03$)	Yes
2(Group) x 5(Emotion) ANOVA on RT	Main Effect of Group ($p = 0.03$)	No *
Orienting Index	All p values > 0.05	No
Disengaging Index	All p values > 0.05	No
Emotional Learning		
2(Group) x 2(Condition) on Eye Blink	All p values > 0.05	No
2(Group) x 2(Condition) on SCR	All p values > 0.05	No

Table 5.

A summary of results for Aim 2.

Note: Presence of * indicates that significance was not hold after Bonferroni correction was

applied.

Aim 2	Result	Significant
Emotional Recognition		
2(Group) x 2(Emotion) ANOVA on Accuracy	Neutral Faces elicited greater accuracy ($p = 0.02$)	Yes
2(Group) x 7(Emotion) ANOVA on Accuracy	Main Effect of Emotion ($p < 0.01$)	Yes
2(Group) x 2(Emotion) ANOVA on RT	All p values > 0.05	No
2(Group) x 7(Emotion) ANOVA on RT	Main Effect of Emotion ($p < 0.01$) Faster responding by HC than AB- for neutral faces	Yes Yes
AB x Accuracy Correlations	Surprised faces ($p = 0.03$)	No *
Emotional Attention		
2(Group) x 2(Emotion) ANOVA on RT	All p values > 0.05	No
2(Group) x 5(Emotion) ANOVA on RT	All p values > 0.05	No
Orienting Index	All p values > 0.05	No
Disengaging Index	All p values > 0.05	No
AB x RT Correlations	All p values > 0.05	No
Emotional Learning		
2(Group) x 2(Condition) on Eye Blink	All p values > 0.05	No
2(Group) x 2(Condition) on SCR	All p values > 0.05	No

Table 6.

A summary of results for Aim 3.

Note: Presence of * indicates that significance was not hold after Bonferroni correction was

applied.

Aim 3	Result	Significant
Emotional Recognition		
Disease Duration x Accuracy Correlations	In AB+ for neutral faces (r = -0.72, p = 0.01)	Yes
Disease Duration x RT Correlations	In AB- for happy faces (r = -0.54, p = 0.006),	Yes
	surprised faces (r = -0.45, p = 0.03),	No *
	sad faces (r = -0.40, p = 0.05)	No *
Moderation Analysis	All p values > 0.05	No
Emotional Attention		
Disease Duration x RT Correlations	All p values > 0.05	No
Disease Duration x Orienting Correlations	All p values > 0.05	No
Disease Duration x Disengaging Correlations	All p values > 0.05	No
Moderation Analysis	All p values > 0.05	No
Emotional Learning		
Disease Duration x Eye Blink Correlations	All p values > 0.05	No
Disease Duration x SCR Correlations	All p values > 0.05	No
Moderation Analysis	All p values > 0.05	No

Table 7.

A summary of results for Aim 4.

Note: Presence of * indicates that significance was not hold after Bonferroni correction was

applied.

Aim 4	Result	Significant
Emotional Recognition		
Accuracy x Cognition Measures Correlations	Lupus Group	
	Accuracy and PS/EF	Yes
	(r = 0.46, *p* = 0.0052)	
	HC Group	
	Accuracy and PS/EF	No *
	(r = 0.53, *p* = 0.042)	
Accuracy x Mood Measures Correlations	All *p* values > 0.05	No
Emotional Attention		
RT x Cognition Measures Correlations	Lupus Group	
	RT and PS/EF	Yes
	(r = -0.62, *p* = 0.0001)	
	RT and VS	Yes
	(r = -0.48, *p* = 0.004)	
	HC Group	
	RT and PS/EF	Yes
	(r = -0.40, *p* = 0.003)	
RT x Mood Measures Correlations	Lupus Group	
	SAI (r = 0.36, *p* = 0.05)	No *
Emotional Learning		
Eye Blink x Cognition Measures Correlations	All *p* values > 0.05	No
Eye Blink x Mood Measures Correlations	All *p* values > 0.05	No
SCR x Cognition Measures Correlations	All *p* values > 0.05	No
SCR x Mood Measures Correlations	All *p* values > 0.05	No

Table 8.

Comparison of neuropsychological performance between healthy controls (HC) and anti-NMDAR AB negative (SLE AB-) and positive (SLE AB+) lupus patients. Values are average z score (standard deviation).

Neuropsychological Test	Group			Result
	HC	SLE AB-	SLE AB+	
NAART	0.92 (0.52)	0.48 (0.76)	0.53 (0.90)	HC > AB- ($p = 0.04$)
WAIS-III: Letter Number Sequencing	0.04 (1.09)	-0.56 (1.01)	-0.67 (0.91)	NS
Symbol Digit Modalities Test	0.36 (1.36)	-0.45 (1.66)	-0.86 (1.45)	AB- > AB+ ($p = 0.03$)
Trail Making Test - Part A	-0.26 (1.31)	-0.47 (1.37)	-1.69 (2.42)	HC > AB+ ($p = 0.02$) AB- > AB+ ($p = 0.04$)
Trail Making Test - Part B	-0.70 (1.98)	-4.99 (8.88)	-2.95 (3.44)	HC > AB- ($p = 0.02$)
Stroop Color-Word Test Color-Word Trial	-0.33 (0.88)	-0.84 (1.18)	-0.97 (0.99)	NS
Finger Tapping Test - Dominant	-0.57 (2.36)	-1.45 (1.46)	-2.19 (1.92)	NS
Finger Tapping Test - Non-dominant	-0.75 (1.89)	-1.44 (1.15)	-1.98 (1.12)	NS
Controlled Oral Word Association Test	-0.06 (0.90)	-0.44 (1.01)	-1.39 (0.53)	HC > AB+ ($p < 0.01$) AB- > AB+ (p < 0.01)
Animal Naming	-0.28 (0.89)	-0.47 (1.06)	-0.84 (0.82)	NS
California Verbal Learning Test - II				
Total Learning	-0.24 (0.79)	-0.55 (1.40)	-0.35 (0.92)	NS
Short Delay Recall	-0.13 (1.12)	-0.96 (1.29)	-0.77 (1.03)	HC > AB- ($p = 0.02$)
Long Delay Recall	-0.35 (1.16)	-0.83 (1.19)	-0.86 (1.10)	NS
Discrimination	0.11 (0.89)	-0.83 (1.70)	-0.23 (0.96)	HC > AB- ($p = 0.02$)
Rey-Osterrieth Complex Figure Test				
Copy	-0.95 (1.40)	-3.64 (4.95)	-2.79 (3.25)	HC > AB- ($p = 0.01$)
Delayed Recall	-1.53 (0.98)	-1.69 (1.31)	-1.14 (1.36)	NS

Table 9.

Factor loadings of the components of the factor analysis used in creating composite scores for the neuropsychological measures.

	Factor Loadings		
Components	1: Memory	2: PS/EF	3: VS
CVLT - SD	**1.026**	-.063	.007
CVLT - LD	**.892**	.002	.049
CVLT Discrimination	**.666**	.080	-.019
SDMT	-.124	**.795**	.131
LNS	.232	**.679**	-.047
TMT-A	.132	**.584**	-.262
TMT-B	.006	**.557**	-.047
Stroop CW	.039	**.537**	-.055
COWAT	.186	**.497**	-.188
Rey - Copy	-.082	-.035	**-.868**
Rey - Delay	.062	.076	**-.578**

Figure 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.

Figure 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.

Figure 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).

Figure 4. Mean percent of accurate responses in identifying neutral and emotional faces in healthy controls and participants with lupus during the emotional recognition task. Neutral faces were responded to with greater accuracy overall but there was no difference between groups and no interaction. Bars represent one standard error of the mean.
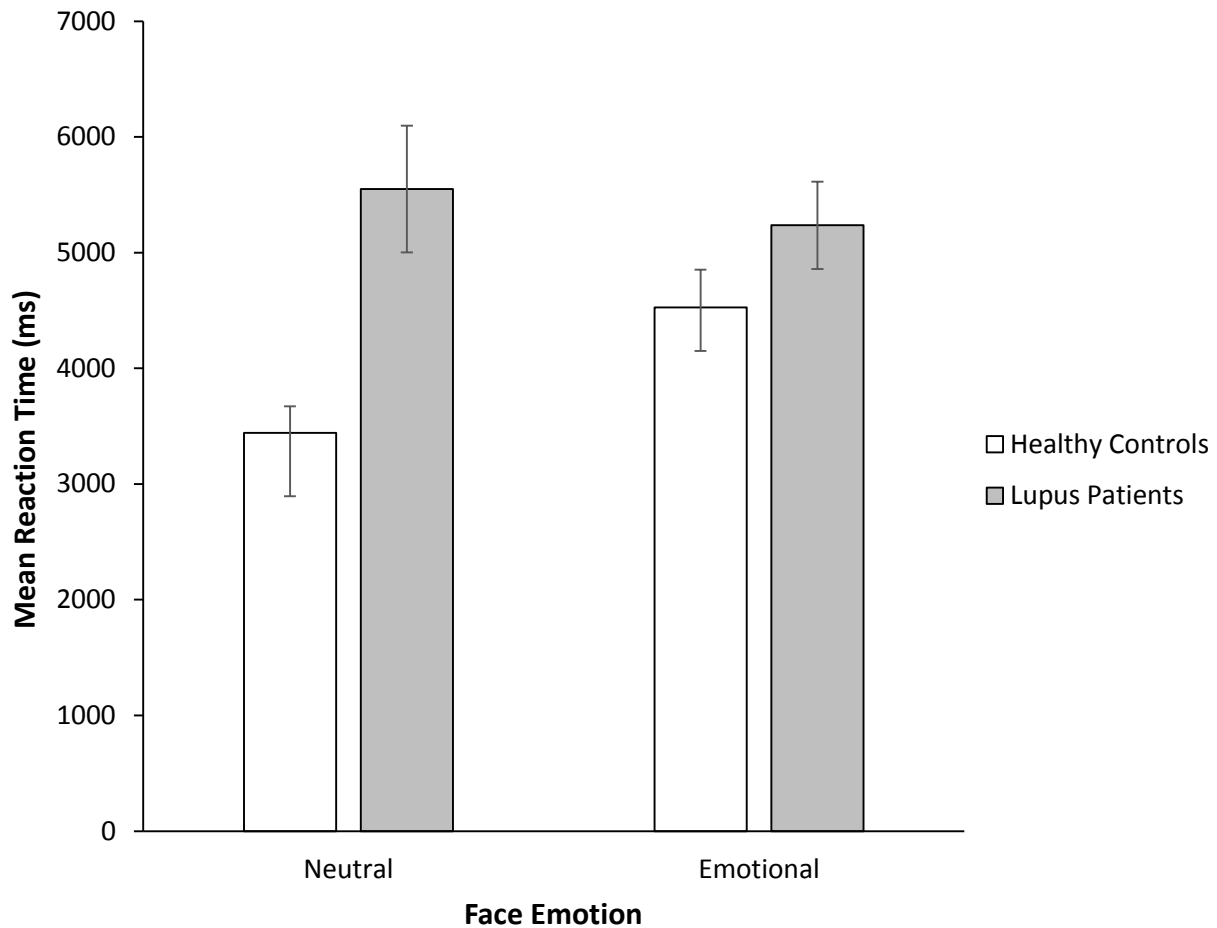
Figure 5. Mean RT differences in ms between healthy controls and participants with lupus when identifying neutral and emotional faces during an emotional recognition task. Healthy controls were faster overall in identifying faces. The extent to which they were faster in their identifications was significantly greater for neutral face types. Bars represent one standard error of the mean.
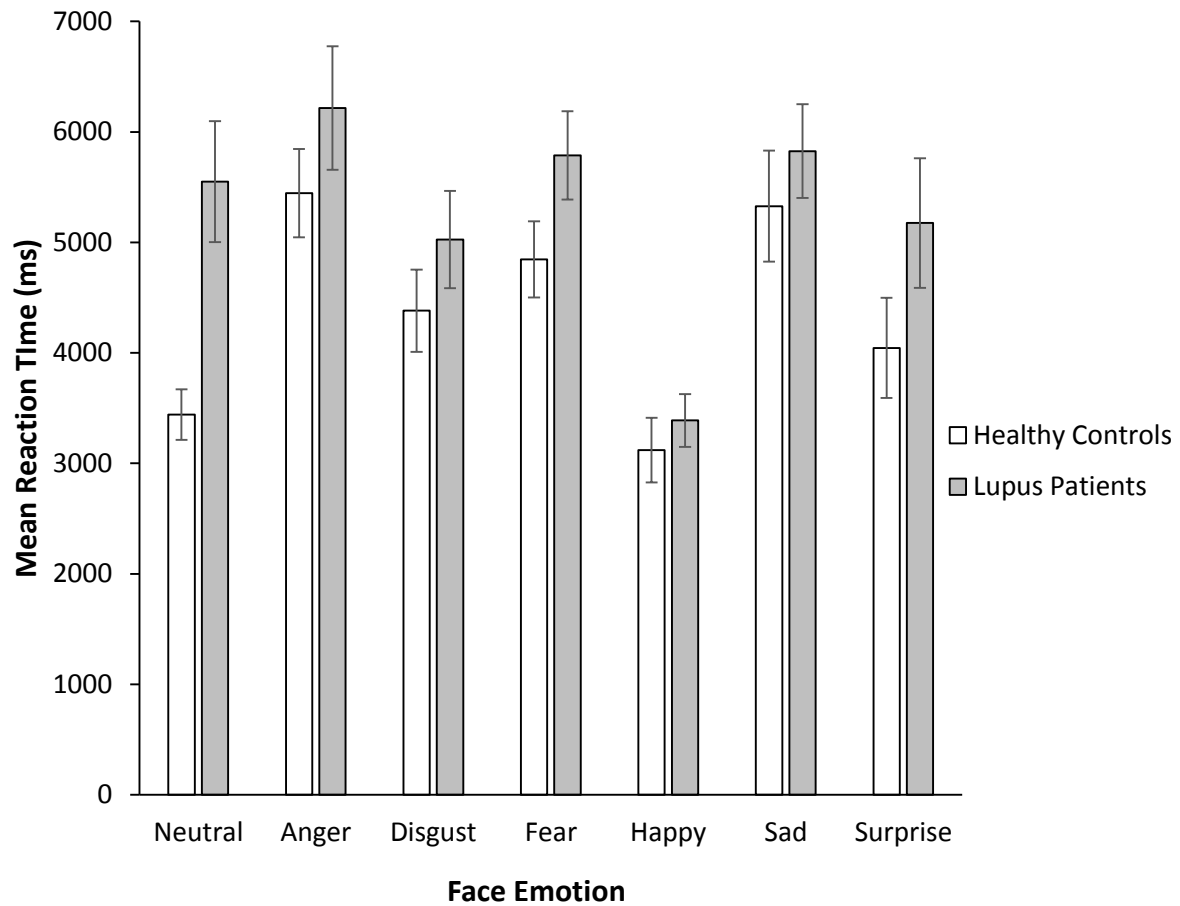
Figure 6. Mean RT in ms between healthy controls and lupus patients for all emotional and neutral face types during the emotional recognition task. Independent measures t-tests revealed faster responding by healthy controls when identifying neutral faces. No significant differences were obtained between groups for any of the emotional faces. Bars represent one standard error of the mean.
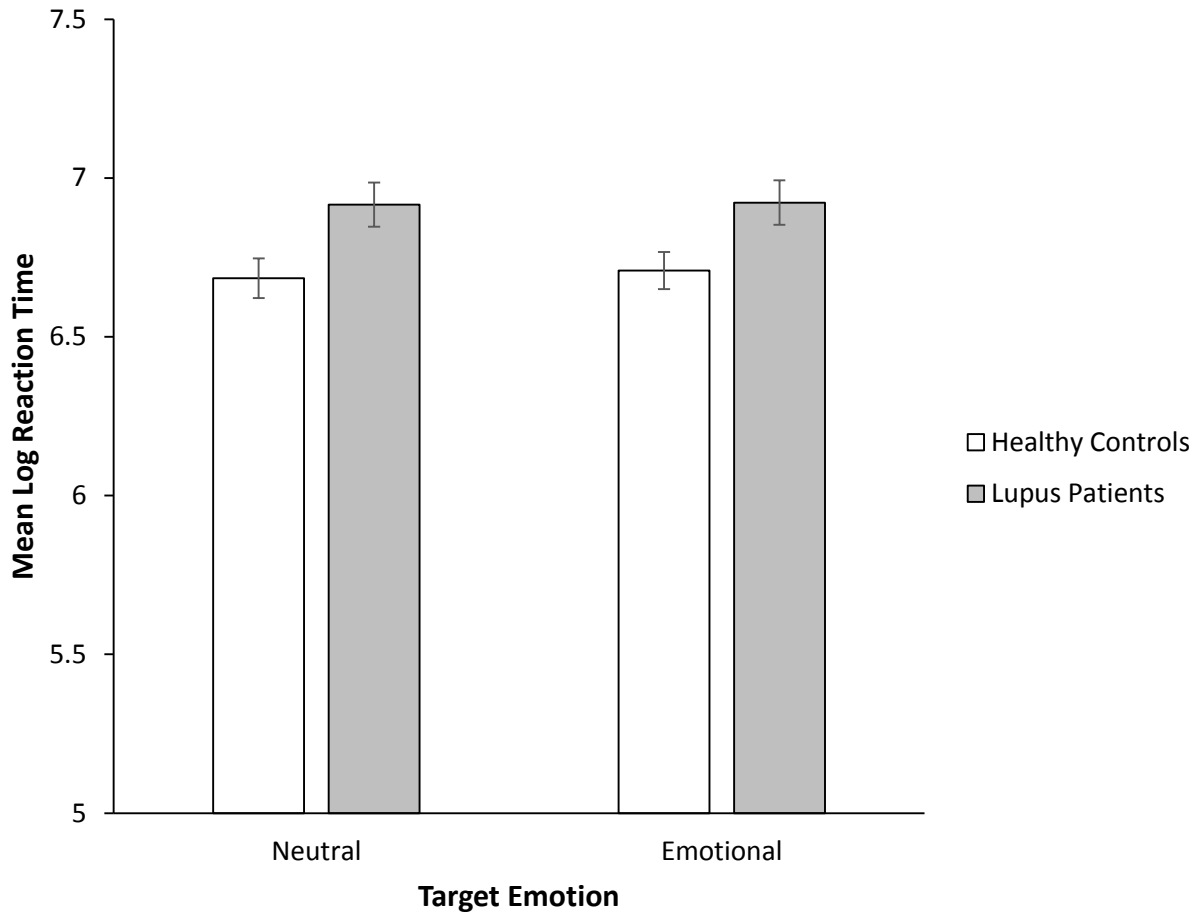
Figure 7. Mean log RT differences between healthy controls and lupus patients in responding to neutral and emotional targets during a visual search attentional task. Results showed significantly faster responding by healthy controls but no main effect of target type and no interaction. Bars represent one standard error of the mean.
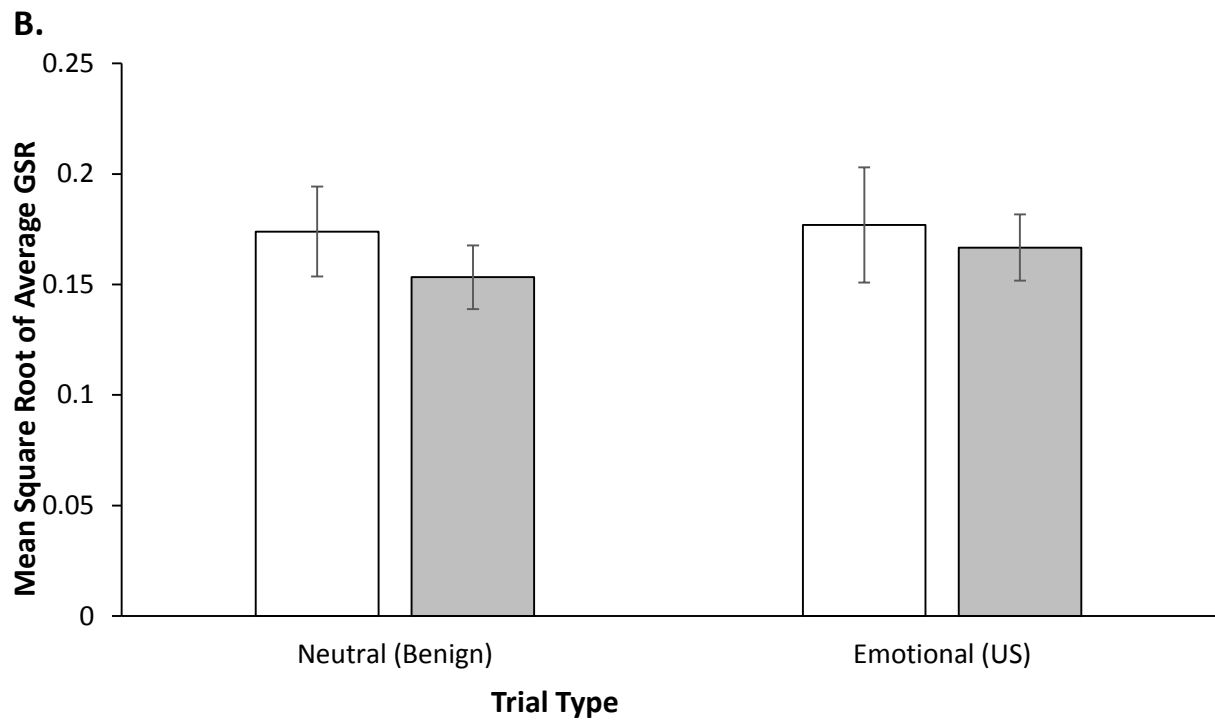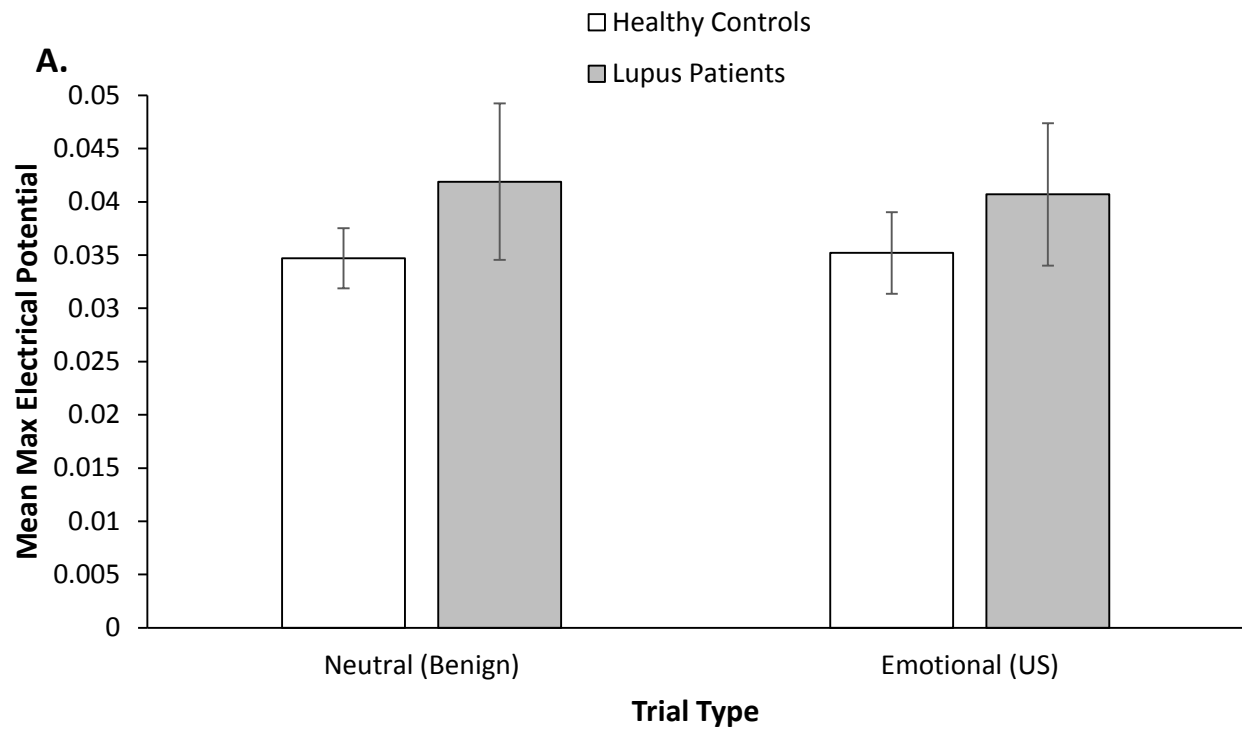
A.

B.

Figure 8. The physiological responses are presented for benign and US trials during a fear-

conditioning task. There were no significant main effects for group or trial type in average

maximum eye blink response (A.) or skin conductance response (B.). There were also no

interaction effects observed for either dependent measure. Bars represent one standard error of
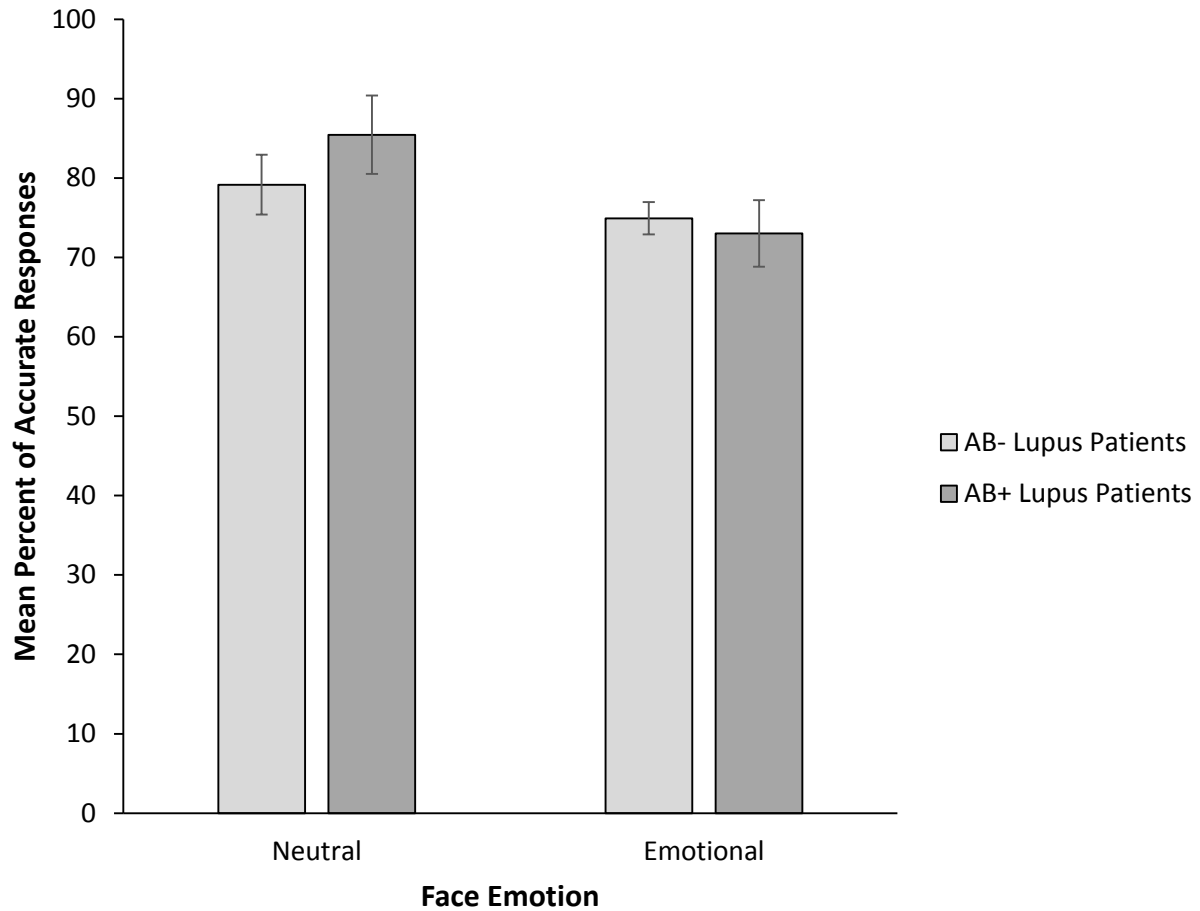
the mean.

Figure 9. Mean percent of accurate responses in identifying neutral and emotional faces for AB-
and AB+ lupus patients. Results showed that neutral faces elicited more accurate responding
overall but there were no differences between groups and no interaction. Bars represent one
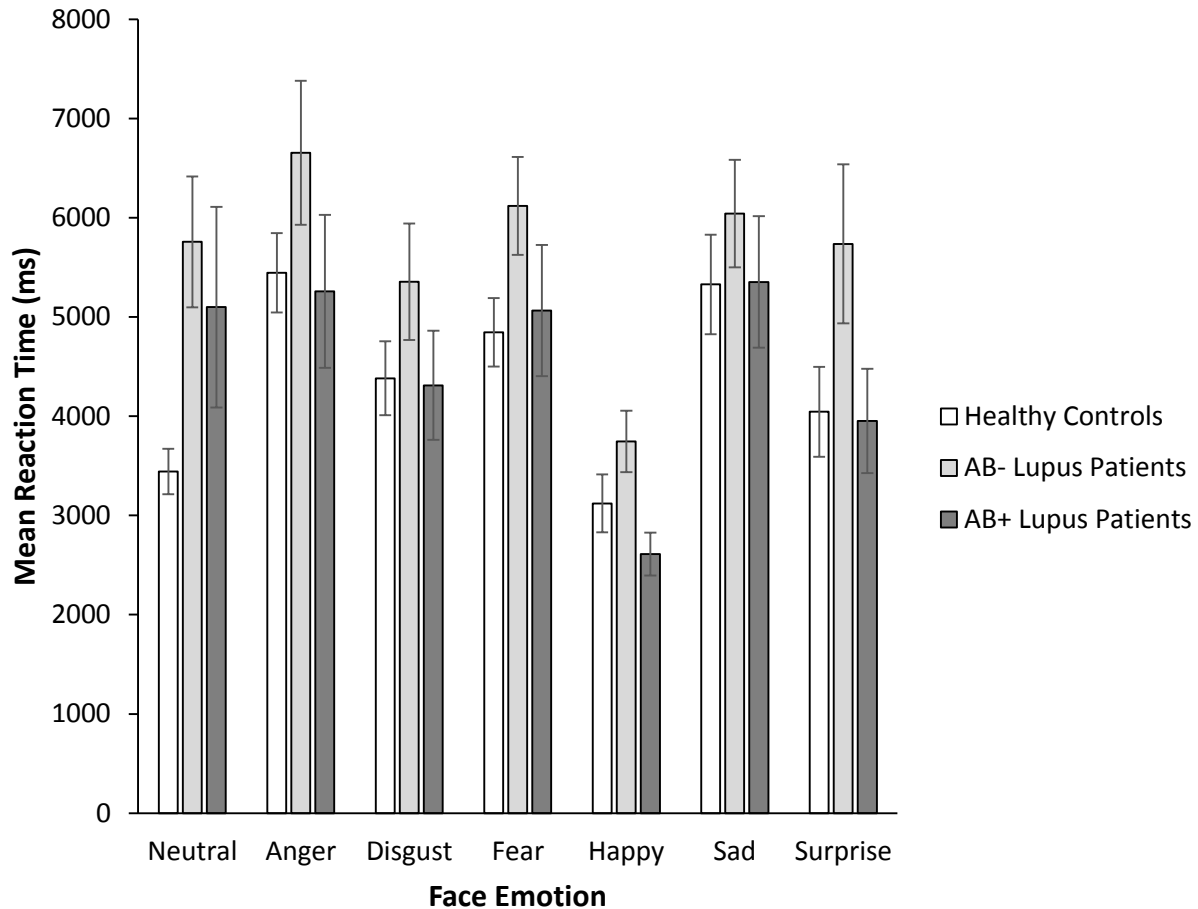standard error of the mean.

Figure 10. Mean RT differences in identifying neutral and emotional faces for healthy controls, AB- lupus patients, and AB+ lupus patients. Results revealed significantly faster responding by healthy controls in comparison to the AB- group for neutral faces, fear faces, and a trend toward faster responding for surprised faces. No significant effects were found between healthy controls and the AB+ group, but there was a trend toward faster responding by healthy controls for neutral faces. Within the lupus groups the AB+ group responded significantly faster to happy faces than the AB- group ($p = 0.03$). Bars represent one standard error of the mean.
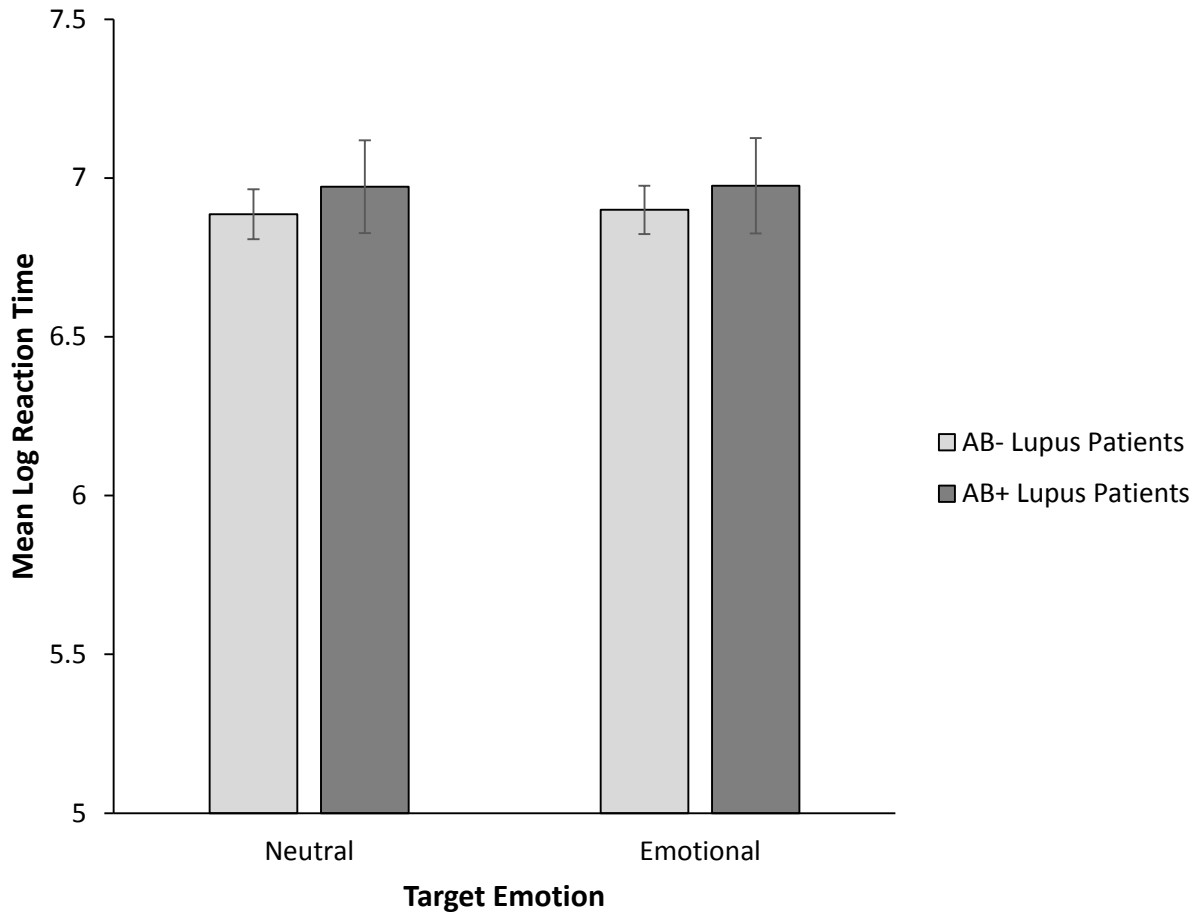
Figure 11. Difference in responding to neutral and emotional targets in a visual search task for

AB- and AB+ lupus patients. Results showed no differences in RT in response to different target

types. There were also no differences between groups and no interaction. Bars represent one

standard error of the mean.
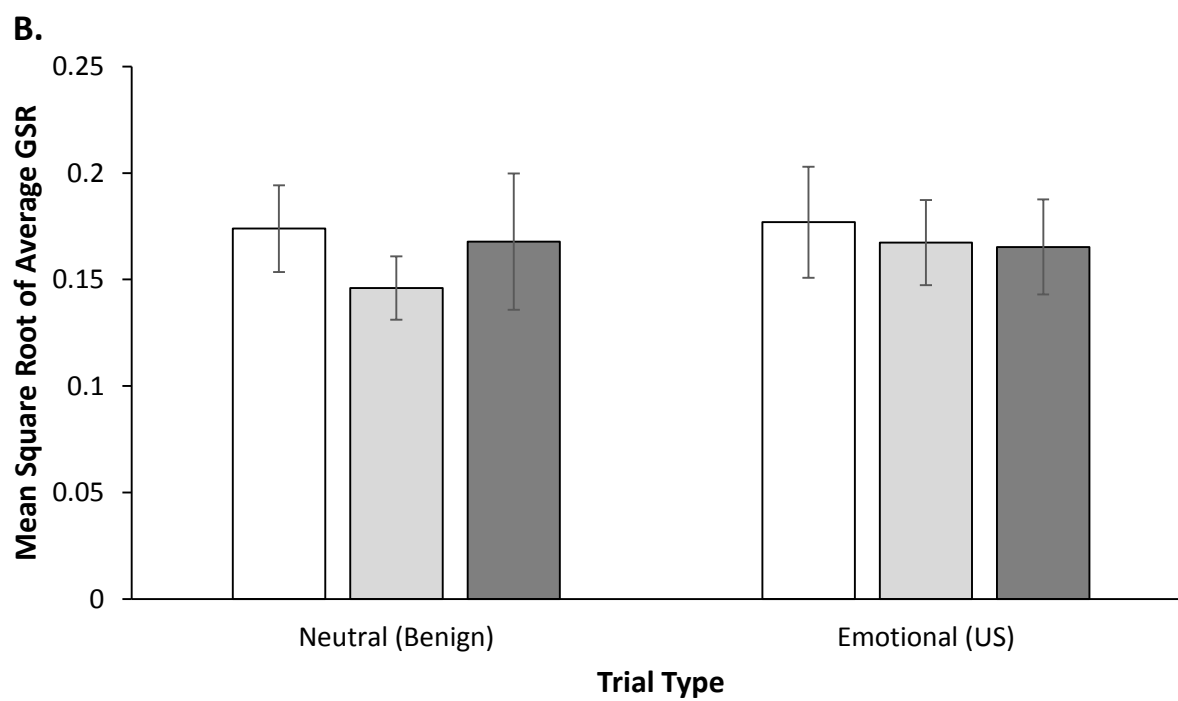
Figure 12. The physiological responses are presented for benign and US trials during a fear-

conditioning task. There were no significant main effects for group or trial type in average

maximum eye blink response (A.) or skin conductance response (B.). There were also no

interaction effects observed for either dependent measure. Bars represent one standard error of

the mean.

Figure 13. Scatterplot of disease duration and percent of accurate responses in identifying neutral

faces in lupus patients with circulating anti-NMDAR ABs. Results show a significant inverse

relationship such that accuracy in identifying neutral faces decreased as disease duration

increased.

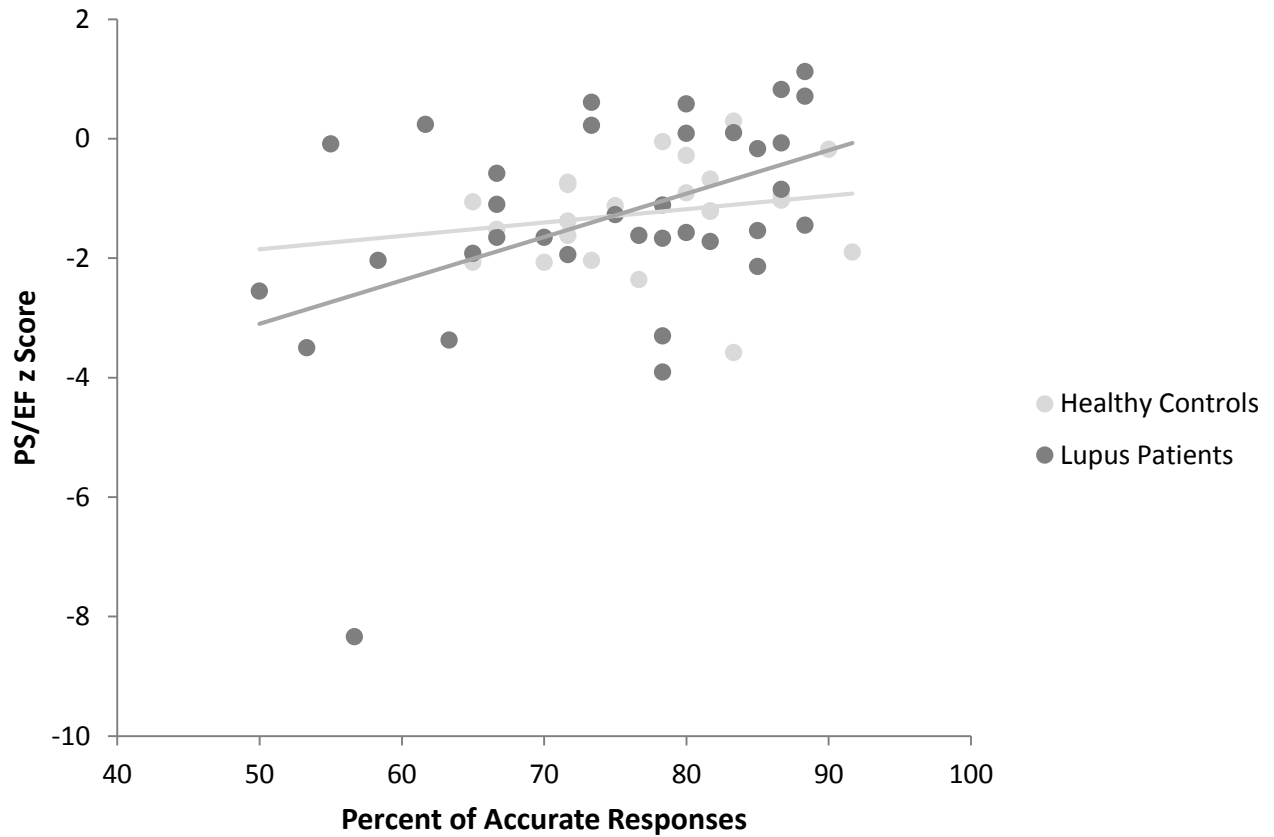*Figure 14.* Scatterplot of the relationship between percent of accurate responding in identifying emotional faces with composite measure of processing speed/executive functioning in healthy controls and participants with lupus.
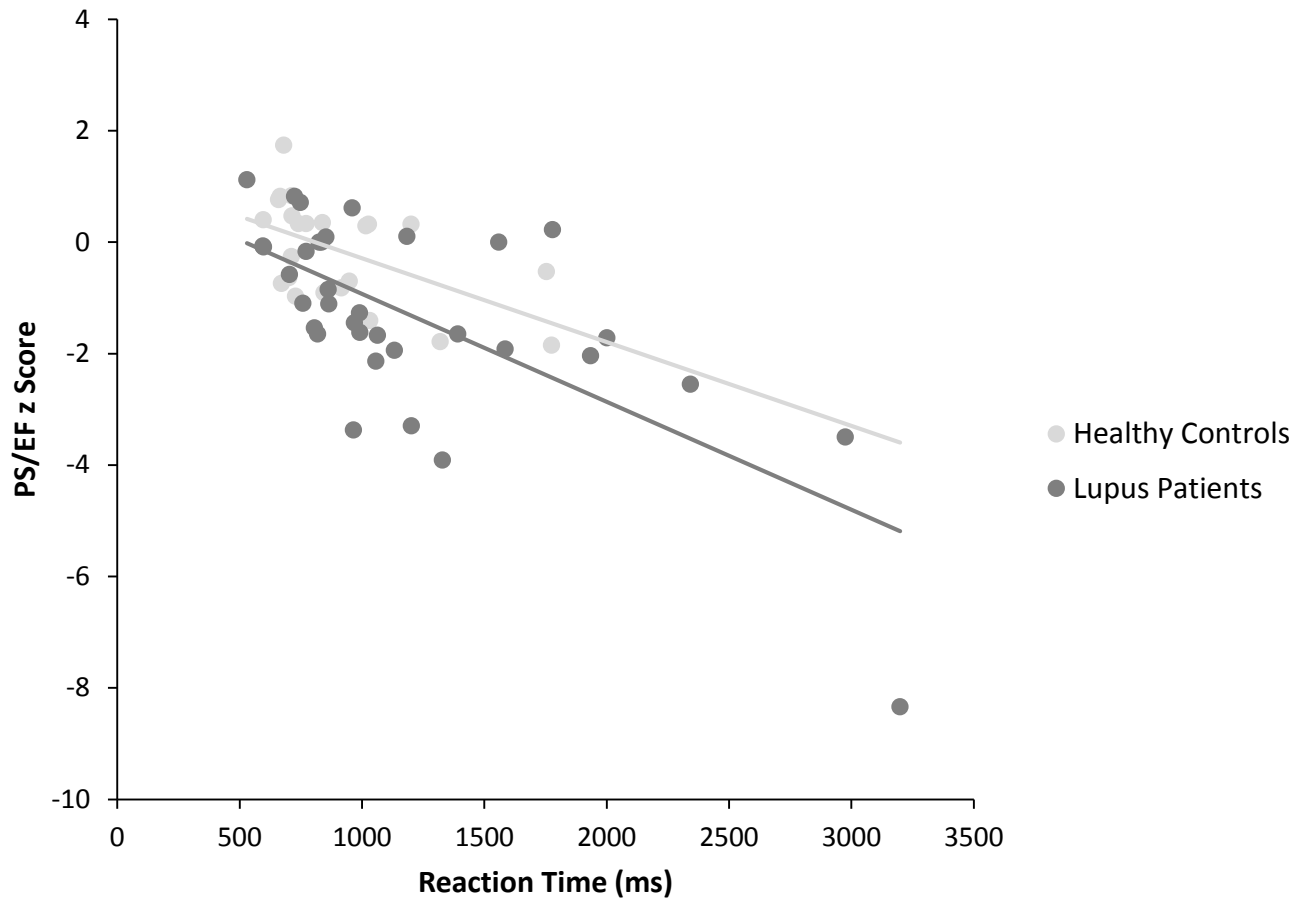
Figure 15. The relationship between RT and the processing speed/executive functioning factor in healthy controls and lupus patients.

APPENDIX

When I looked at the log RT data, I found many similar results as I did in the RT data. Namely, there was significant negative correlations found between processing speed and log RT to emotional and neutral targets within the lupus group, $r = -0.61$, $p < 0.01$, $r = -0.63$, $p < 0.01$, but not in the healthy control group. Significant negative relationships were found in both groups for executive functioning and log RT to emotional and neutral targets (lupus group: emotional, $r = -0.69$, $p < 0.01$, neutral, $r = -0.64$, $p < 0.01$; HC: emotional, $r = -0.53$, $p = 0.09$, neutral, $r = -0.56$, $p = 0.01$). For the memory composite score, significant negative correlations were found in the lupus group, emotional: $r = -0.33$, $p = 0.05$, neutral: $r = -0.34$, $p = 0.05$, but no significant relationships were found in the healthy control group. For the mood and health measures, we found a positive relationship between the STA-Y and log RT to emotional targets within the lupus group, $r = 0.35$, $p = 0.05$; no other significant relationships were observed.

Processing speed proved to be a reliable predictor for log RT to emotional targets, $R^2 = 0.34$, $F(1, 33) = 16.8$, $p < 0.01$, in the lupus group but not in the healthy control group. Executive functioning was a significant predictor in both groups, lupus: $R^2 = 0.39$, $F(1, 33) = 21.25$, $p < 0.01$; HC: $R^2 = 0.35$, $F(1, 21) = 11.25$, $p < 0.01$. Memory was not a significant predictor in the lupus group, $R^2 = 0.04$, $F(1, 33) = 1.39$, $p = 0.25$. For the mood and health measures, we did not find a significant predictor model when all variables were input, but the STA-Y proved to be a significant coefficient in the lupus group. However, it was not found to be a significant predictor when input alone, $R^2 = 0.06$, $F(1, 30) = 2.05$, $p = 0.16$.

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